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CLINICAL ORAL IMPLANTS RESEARCH

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Proceedings of the Sixth ITI Consensus Conference

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Proceedings of the Sixth ITI Consensus Conference

Guest Editors: Daniel Wismeijer and Stephen T. Chen

This Consensus Meeting was supported by the International Team for Implantology

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Proceedings of the 6th ITI Consensus Conference

Abstract

The 6th ITI Consensus Conference was held in Amsterdam on 17–19 April 2018. In preparation for the conference, 21 systematic reviews were written. They were divided into five main topics in dental implantology—surgery, prosthodontics, patient-reported outcomes, complications/risk and digital technologies. Based on these review papers, the working groups prepared consensus statements, clinical guidelines and recommendations for future research.

The International Team for Implantology (ITI) is a not for profit association of professionals in implant dentistry. The objectives of the ITI are the promotion and dissemination of knowledge about implant dentistry and to serve dental professionals by fostering learning, discussion and exchange.

Every 5 years, the ITI conducts a consensus conference to review the current state of evidence in areas of topical interest in dental implantology. The 6th ITI Consensus Conference was held in Amsterdam on 17–19 April 2018. Five major topics comprising surgery, prosthodontics, patient-reported outcomes, complications/risk and digital technologies were identified. In total, 21 systematic reviews were prepared by 80 authors and co-authors in preparation for the consensus workshop (Table 1). The 153 invited participants and observers were divided into five working groups (Figure 1). Their discussion and deliberations over the 3-day workshop culminated in consensus statements, clinical recommendations and recommendations for future research, the results of which are published in this supplement.

FIGURE 1 Participants of the 6th ITI Consensus Conference

TABLE 1 List of systematic reviews

	Authors	Title of review
Group 1: Surgical Group leader: Ronald Jung		
Paper 1	Papaspyridakos P, De Souza A, Vazouras K, Gholami H, Pagni S, Weber, HP	Survival rates of short dental implants (≤6 mm) compared with implants longer than 6 mm in posterior jaw areas: A meta-analysis
Paper 2	Schiegnitz E, Al-Nawas B	Narrow diameter implants: A systematic review and meta-analysis
Paper 3	Jokstad A, Ganeles J	Systematic review of clinical and patient-reported outcomes following oral rehabilitation on dental implants with a tapered compared to a non-tapered implant design
Paper 4	Chappuis V, Avila-Ortiz G, Araújo M, Monje A	Medication-related dental implant failure: Systematic review and meta-analysis
Group 2: Prosthetic Group leader: Dean Morton		
Paper 1	Lin WS, Eckert S.	Clinical performance of intentionally tilted implants versus axially positioned implants: A systematic review
Paper 2	Gallucci G, Hamilton A, Zhou W, Buser D, Chen ST	Implant placement and loading protocols in partially edentulous patients: A systematic review
Paper 3	Roehling S, Schlegel KA, Woelfler H, Gahlert M	Performance and outcome of zirconia dental implants in clinical studies: A meta-analysis
Paper 4	Daudt Polido W, Aghaloo T, Emmett T, Taylor TD, Morton D	Number of implants placed for complete-arch fixed prostheses: A systematic review and meta-analysis
Paper 5	Sailer I, Strasding M, Valente NA, Zwahlen M, Liu S, Pjetursson BE	A systematic review of the survival and complication rates of zirconia-ceramic and metal-ceramic multiple-unit fixed dental prostheses
Paper 6	Pjetursson BE, Valente NA, Strasding M, Zwahlen M, Liu S, Sailer I	A systematic review of the survival and complication rates of zirconia-ceramic and metal-ceramic single-crowns (SCs)
Group 3: PROMS (patient reported outcome measures) Group leader: Jocelyne Feine		
Paper 1	Wittneben JG, Wismeijer D, Brägger U, Joda T, Abou-Ayash, S	Patient-reported outcome measures focusing on aesthetics of implant- and tooth-supported fixed dental prostheses: A systematic review and meta-analysis
Paper 2	Yao CJ, Cong C, Bornstein MM, Mattheos N	Patient reported outcome measures of edentulous patients restored with implant-supported removable and fixed prostheses: A systematic review
Paper 3	Huynh-Ba G, Oates T, Williams MAH	Immediate loading vs. early/conventional loading of immediately placed implants in partially edentulous patients from the patients' perspective: A systematic review
Group 4: Complications/risks Group leader: Lisa Heitz-Mayfield		
Paper 1	Hashim D, Cionca N, Combescure C, Mombelli A	The diagnosis of peri-implantitis: A systematic review on the predictive value of bleeding on probing
Paper 2	Salvi GE, Monje A, Tomasi C	Long-term biological complications of dental implants placed either in pristine or in augmented sites: A systematic review and meta-analysis
Paper 3	Schimmel M, Srinivasan M, McKenna G, Müller F	Effect of advanced age and/or systemic medical conditions on dental implant survival: A systematic review and meta-analysis
Paper 4	Roccuzzo M, Layton DM, Roccuzzo A, Heitz-Mayfield LJ	Clinical outcomes of peri-implantitis treatment and supportive care: A systematic review
Group 5: Digital technologies Group leader: Daniel Wismeijer		
Paper 1	Joda T, Derksen W, Wittneben JG, Kuehl, S	Static computer-aided implant surgery (s-CAIS) analysing patient-reported outcome measures (PROMs), economics and surgical complications: A systematic review
Paper 2	Flügge T, van der Meer WJ, Gimenez Gonzalez B, Vach K, Wismeijer D, Wang P	The accuracy of different dental impression techniques for implant-supported dental prostheses: A systematic review and meta-analysis
Paper 3	Fokas G, Vaughn VM, Scarfe W, Bornstein MM	Accuracy of linear measurements on CBCT images related to pre-surgical implant treatment planning: A systematic review
Paper 4	Tahmaseb A, Wu V, Wismeijer D, Coucke W, Evans, C	The accuracy of static computer-aided implant surgery: A systematic review and meta-analysis

Group 1 addressed the influence of implant design—length, diameter and taper—on survival and success of dental implants. The influence of systemic conditions and medications on implant outcomes was also discussed. Group 2 reviewed the evidence for orientation of implants (axial vs. intentionally tilted), ceramic implants and the numbers of implants required in edentulous indications. Zirconia as a restorative material for single-crown and multiple-unit fixed dental prostheses was examined. In addition, the evidence for combinations of implant placement and subsequent loading was discussed, and a new classification system that combines placement and loading protocols was proposed. Group 3 reviewed the evidence for patient-reported outcome measures on aesthetic outcomes of fixed tooth and implant prostheses, and the patient-reported outcomes for removable and fixed prostheses, and immediate placement and loading. In group 4, the predictive value of bleeding on probing and the outcomes of peri-implantitis treatment followed by supportive care was reviewed. In addition, the outcomes for implants placed in augmented sites and the influence of advanced age and systemic medical conditions was deliberated on. Group 5 examined the outcomes of computer-aided implant surgery, the accuracy of different implant impression techniques, the accuracy of linear measurement of cone beam CT images and the accuracy of static computer-aided implant surgery.

In this special issue of *Clinical Oral Implants Research*, the systematic reviews and the consensus statement/clinical recommendation reports are published. We are pleased to present the proceedings of the consensus conference to advance the science of dental implantology.

ACKNOWLEDGEMENTS

We would like to thank the leaders of the working groups—Drs Ronald Jung, Dean Morton, Jocelyne Feine, Lisa Heitz-Mayfield and Daniel Wismeijer—for their effort in guiding the authors in the preparation of the review papers and for leading the subsequent discussion in their respective working groups. We would like to extend our appreciation to Dr Lisa Heitz-Mayfield, Editor in Chief of this journal, for her invaluable advice during the review process and for preparing this supplement. We are also grateful for the tireless support of Dr Friedrich Buck, Executive Director of the ITI and the entire organizing team at ITI Headquarters. These proceedings were supported by the ITI Foundation, Basel, Switzerland.

CONFLICT OF INTEREST

The authors declare that they are both members of the Board of the International Team for Implantology (ITI), the organiser of the consensus conference, but this fact does not lead to any conflict of interest in regard to the content of this article or the content of the conference.

Keywords

aesthetics, bone augmentation, CBCT, Consensus Conference, dental implant, digital dentistry, edentulous patients, immediate loading, implant failure, loading protocols, medically compromised, narrow diameter implants, patient-reported outcome measures, peri-implantitis, prosthodontics, surgery, systematic review, tapered implants, tilted implants, zirconia implants

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REVIEW ARTICLE

WILEY CLINICAL ORAL IMPLANTS RESEARCH

Survival rates of short dental implants (≤6 mm) compared with implants longer than 6 mm in posterior jaw areas: A meta-analysis

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Abstract

Purpose: To systematically review randomized controlled clinical trials (RCTs) reporting on the long-term survival and failure rates, as well as the complications of short implants (≤6 mm) versus longer implants (>6 mm) in posterior jaw areas.

Materials and Methods: Electronic and manual searches were conducted to identify studies, specifically RCTs, reporting on short dental implants (≤6 mm) and their survival and complication rates compared with implants longer than 6 mm. Secondary outcomes analyzed were marginal bone loss and prosthesis survival rates.

Results: Ten RCTs fulfilled the inclusion criteria and featured a total of 637 short (≤6 mm) implants placed in 392 patients, while 653 standard implants (>6 mm) were inserted in 383 patients. The short implant survival rate ranged from 86.7% to 100%, whereas standard implant survival rate ranged from 95% to 100% with a follow-up from 1 to 5 years. The risk ratio (RR) for short implant failure compared to standard implants was 1.29 (95% CI: 0.67, 2.50, $p = 0.45$), demonstrating that overall, short implants presented higher risk of failure compared to longer implants. The heterogeneity test did not reach statistical significance ($p = 0.67$), suggesting low between-study heterogeneity. The prosthesis survival rates from the short implant groups ranged from 90% to 100% and from 95% to 100% for longer implant groups, respectively.

Conclusion: Short implants (≤6 mm) were found to have *higher variability* and *lower predictability* in survival rates compared to longer implants (>6 mm) after periods of 1–5 years in function. The mean survival rate was 96% (range: 86.7%–100%) for short implants, and 98% (range 95%–100%) for longer implants. Based on the quantity and quality of the evidence provided by 10 RCTs, short implants with ≤6 mm length should be carefully selected because they may present a greater risk for failure compared to implants longer than 6 mm.

KEYWORDS
dental implants, short dental implants

1 | INTRODUCTION

Implants are broadly used for oral rehabilitation in patients who are partially or completely edentulous (Gallucci et al., 2014). There are factors such as presence or absence of sufficient bone volume, keratinized mucosa, smoking habits, periodontal disease, and systemic conditions such as diabetes that can contribute to the long-term success and survival of dental implants.

Presence of adequate bone quality and quantity needs to be evaluated prior to surgical interventions for placing implants. Various procedures such as maxillary sinus floor elevation, bone grafting, guided bone regeneration, distraction osteogenesis, and vertical bone augmentation are being used to enhance bone width and height in atrophied ridges (Gulje et al., 2013). However, there are problems associated with these augmentation techniques such as high cost and treatment time, increased postoperative morbidity, and increased risk of complications (Esposito et al., 2010; Heitz-Mayfield, Needleman, Salvi & Pjetursson, 2014). Therefore, short implants (Atieh, Zadeh, Stanford, & Cooper, 2012), tilted implants (Maló, de Araújo Nobre, Lopes, Ferro, & Gravito, 2015; Maló, de Araujo Nobre, Lopes, Francischone, & Rigolizzo, 2012; Queridinha, Almeida, Felino, de Araújo Nobre, & Maló, 2016), zygoma, or pterygoid implants (Esposito & Worthington, 2013) have been proposed as alternatives to avoid bone augmentation for the accommodation of standard implants, which tends to have greater morbidity and requires longer healing times.

In the implant literature, various authors have defined "short dental implants" differently. Some consider 10 mm or less as being short, while others propose <8, <7, or <6 mm as truly short (Friberg, Jemt, & Lechkolm, 1991; Renouard & Nisand, 2006; Rossi et al., 2016). The survival of short dental implants has been a controversial topic. There have been studies where a lower survival rate has been associated with the use of short implants versus longer implants (Bahat, 1993). On the contrary, a number of systematic reviews and consensus documents have reported that the survival rates of short implants are comparable to those of conventional implants placed in pristine or grafted bone (Atieh et al., 2012; Fan, Li, Deng, Wu, & Zhang, 2017; Lemos, Ferro-Alves, Okamoto, Mendonça, & Pellizzer, 2016; Nisand, Picard, & Rocchietta, 2015; Sanz et al., 2015; Thoma, Zeltner, Hüsler, Hämmerle, & Jung, 2015; Thoma, Haas et al., 2015).

The aim of this study was to systematically review the long-term survival and failure rates, as well as complications of ≤6 mm short implants versus implants longer than 6 mm in posterior jaw areas based on evidence from randomized controlled clinical trials (RCTs).

2 | MATERIAL AND METHODS

A detailed protocol was followed according to the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analyses) statement (Moher et al. 2009). The focused question of the search was in a PICO (Population, Intervention, Comparison, Outcomes) format as follows: "In patient with posterior dental implant restorations, do short implants (≤6 mm) compared to longer implants (>6 mm) demonstrate similar clinical and patient-based outcomes?" The project was registered with PROSPERO (CRD42016049610).

2.1 | Search strategy

An electronic MEDLINE (PubMed) and EMBASE search was performed for clinical studies, including articles published from January 1, 1990, up to June 30, 2017. The search was limited to the English language. The search strategy included the following word combinations: (partially edentulous patients OR posterior partially edentulous OR posterior partial edentulous OR posterior jaw OR posterior dental implant OR posterior implant OR dental implant) AND (short dental implant OR short implant OR reduced length implant) AND (dental implant OR regular implant OR Long implant OR regular length implant OR longer implant OR sinus floor elevation OR sinus lift OR osteotome OR Summers technique OR vertical augmentation OR vertical ridge augmentation OR nerve lateralization) AND (success OR complication OR survival OR Implant Survival OR implant failure OR implant loss OR implant complication OR prosthetic complication OR patient-centered outcome OR patient-based outcome OR peri-implant bone level OR peri-implant bone loss OR marginal bone level OR crestal bone level).

In addition to the electronic search, the bibliographies of all the full-text articles that were selected after title and abstract selection were manually searched. A reference manager software program (Endnote X7, Thompson Reuters) was used and the duplicates were discarded electronically.

2.2 | Inclusion criteria

- Randomized clinical trials.
- Partially edentulous subjects with implant restorations in the posterior mandible or maxilla.
- Implants with rough surfaces and ≤6 mm in length compared to implants ≥7 mm.
- The studies included were at least 10 patients.
- There was a follow-up of at least 1-year post loading.
- The studies included implant rehabilitation of partially edentulous posterior mandible or maxilla.

2.3 | Exclusion criteria

In vitro and preclinical studies, case reports or case series, prospective cohort or retrospective studies were not included. Studies were also not included in the review in case of insufficient information regarding number of patients, follow-up and/or criteria for "short implants." Multiple publications on the same patient population were discarded and only the one with the longest follow-up period included.

2.4 | Selection of studies

Two authors (HG and KV) independently screened the titles derived from this extensive search based on the inclusion criteria. In a subsequent manner, abstracts of all titles agreed on by both authors were obtained and screened for satisfying the inclusion criteria. If title and abstract did not provide sufficient information with regards to the inclusion criteria, the full text was obtained as well. Any disagreements at the above stages of the search were resolved by discussion. At last, the selection based on inclusion/exclusion criteria was made for the full-text articles. The finally selected studies were screened by the two reviewers (HG and KV) and double-checked. Any questions that came up were discussed within the group to achieve consensus.

2.5 | Data extraction and method of analysis

The two reviewers independently extracted the data of all included studies using data extraction tables. The total of extracted data was double-checked, and any questions that came up during the screening and the data extraction were discussed within the group.

The following information was extracted from the selected articles: author(s), study design, year of publication, study setting (university/private practice), number of patients, mean age, age range, drop-out/lost to follow-up, type of comparison (groups), implant design, length, diameter and surface, number of implants placed, number of implants per patient, area of placement, type of prosthesis, loading protocol, prosthesis retention system (screw-retained/cement-retained), follow-up, implant and prosthesis survival rates, marginal bone level, biologic, technical/mechanical complications and patient-centered outcomes.

The primary outcomes included survival rates of dental implants. Secondary outcomes were survival rates of prostheses, complication rates for implants and prostheses as well as radiographic bone levels.

2.6 | Quality assessment

The quality of the included studies was assessed by both reviewers (HG and KV) using the Cochrane Collaboration's tool for assessing risk of bias in randomized trials. Any disagreement was discussed until consensus was achieved.

2.7 | Statistical analysis

Implant survival was evaluated using a risk ratio (RR) with a 95% confidence interval. For studies in which neither the short nor the

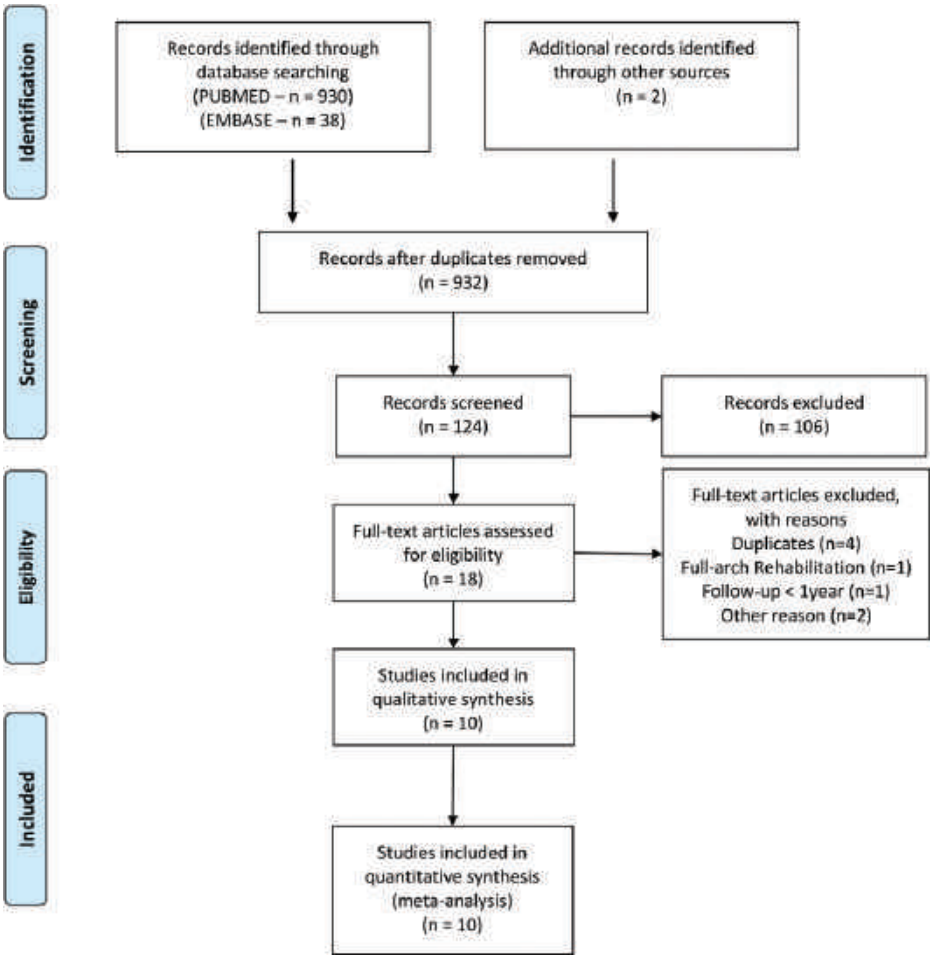

FIGURE 1 Search strategy flow chart

longer implants experienced any failures, a continuity correction was applied. A meta-analysis was performed using a fixed effects model with Mantel-Hansel methods. Mean bone loss was expressed as a weighted mean difference (WMD) and a 95% confidence interval. A meta-analysis was performed using a fixed effects model with inverse-variance methods. Heterogeneity was examined using Cochran's *Q*-statistic and the I^2 statistic. *p*-values < 0.05 were considered statistically significant. The analysis was performed with Stata version 13.1 (StataCorp LLC, College Station, TX).

3 | RESULTS

3.1 | Study characteristics

The electronic search identified 932 titles (Figure 1). After discussion, 808 titles were excluded and the number of finally obtained abstracts was 124. In a subsequent manner, 18 full-text articles were obtained, of which eight were excluded. At last, ten articles representing RCTs met the inclusion criteria and were included in the meta-analysis.

3.2 | Excluded studies

The reasons for excluding studies after the full text was obtained were as follows: four duplicate studies (Esposito, Pellegrino, Pistilli, & Felice, 2011; Esposito et al., 2015; Schincaglia et al., 2015; Thoma, Zeltner et al., 2015; Thoma, Haas et al., 2015), one study with a follow-up of <1 year (Zhang et al., 2017), one study not involving partially edentulous patients (Cannizzaro et al., 2015),one study including less than ten patients (Romeo, Storelli, Casano, Scanferla, & Botticelli, 2014) and one study with an insufficient number of ≤6 mm implants (Al-Hashedi, Taiyeb-Ali, & Yunus, 2016).

3.3 | Included studies

The ten studies that satisfied the inclusion criteria are presented in Table 1. Quality assessment of the included studies is summarized in Table 2. All studies were RCTs published between 2012 and 2017 and conducted at specialty clinics or/and in a university environment. Two studies had a split-mouth design (Esposito, Pistilli, Barausse, & Felice, 2014; Pistilli, Felice, Piattelli et al., 2013; Pistilli, Felice, Cannizzaro et al., 2013) where both treatment modalities were performed in all patients, while seven studies only had one treatment modality being performed in the involved patients in a random way. In one study (Rossi et al., 2016), one-third of the patients were treated with both treatment modalities, while the other two-thirds of patients only received one of the two options in a randomized assignment.

A total of 637 short implants (≤6 mm) were placed in 392 patients, while 653 implants with >6 mm length were inserted in 383 patients. In three studies (Bechara et al.,2016; Felice et al.,2015; Pohl et al.,2017) implants were placed only in the maxilla, whereas in the remaining six studies implants were placed in both jaws. Five studies had a 1-year follow-up (Felice et al., 2015, 2016; Gulje et al., 2013; Pistilli, Felice, Piattelli et al., 2013; Pistilli, Felice, Cannizzaro et al., 2013), four studies presented a 3-year follow-up (Bechara et al., 2016; Esposito et al., 2014; Pohl et al., 2017; Sahrmann et al., 2016), and only one study had a 5-year follow-up (Rossi et al., 2016). With regards to implant length, the short implant group included implant lengths of 4–6 mm with only one study reporting on 4 mm implants (Felice et al., 2016). All other studies included implants of 5 or 6 mm length or both. On the other hand, the control groups in all studies had a variety of implant lengths ranging from 8.5 to 15 mm. Two RCTs reported immediate implant placement as part of their studies (Bechara et al., 2016; Felice et al., 2016), one of them (Bechara et al., 2016) in both groups, the other only in the test group (Felice et al., 2016). Seven of 10 of the included studies reported one or more adjacent implants placed in each patient depending on the span of the edentulous site. When the edentulous area represented more than a single missing tooth, the restoration on multiple adjacent implants was always splinted. Only three studies (Pohl et al., 2017; Rossi et al., 2016; Sahrmann et al., 2016) reported exclusively on implant supported single crowns as the only treatment modality. At last, with regards to retention of restorations, four studies (Bechara et al., 2016; Felice et al., 2015; Pistilli, Felice, Piattelli et al.,2013; Pohl et al., 2017) mentioned combinations of screw- or cement-retained restorations. Three studies (Felice et al., 2016; Gulje et al., 2013; Sahrmann et al., 2016) included only screw-retained restorations while in the remaining three studies only cement-retained restorations were used (Esposito et al., 2014; Pistilli, Felice, Cannizzaro et al., 2013; Rossi et al., 2016).

3.4 | Implant survival rates

Overall, survival rates of short implants (≤6 mm) ranged from 86.7% to 100%, whereas the survival rates for longer implants (>6 mm) ranged from 95% to 100% with a follow-up from 1 to 5 years (Table 3). Two studies reported no implant failures for both groups (Felice et al., 2015; Pohl et al., 2017) during their respective follow-up periods. The study of Guljé et al. (2013) reported a 97% survival rate for the short implants group with two implant failures before and one failure after loading yet prior to the 1-year follow-up. The group with longer implants had a 99% survival rate with one implant lost after loading and prior to the one-year follow-up. In a split-mouth study design, Esposito et al. (2014) found a 92% survival rate for short implants and 97% for longer implants placed in areas previously submitted to vertical augmentation, either with interpositional block grafts or maxillary sinus augmentation depending on indication and anatomic location. Similar to that, Rossi et al. (2016) in a 5-year follow-up study reported lower survival rates for short implants (86.7%) compared to longer implants (96.7%). Some studies reported a minimal difference or an even superior survival rate of short implants compared to longer implants (Bechara et al., 2016; Felice et al., 2016; Pistilli, Felice, Piattelli et al., 2013; Pistilli, Felice, Cannizzaro et al., 2013). In a 3-year follow-up study, Sahrmann et al. (2016) reported 98% survival

TABLE 1 Study and patient characteristics of the included studies [In PDF format, this table is best viewed in two-page mode]

Author/Year	Study design	Number of patients	Number of implants	Number of prostheses	Jaw	Follow-up
Gulje et al. (2013)	RCT	Short: 49 Long: 46	Short: 107 Long: 101	Short: 47 Long: 46	Max/Mand	1 year
Pistilli, Felice, Piattelli et al. (2013)	RCT	Short: 40 Long: 40	Short: 68 Long: 68	Short: 40 Long: 40	Max/Mand	1 year
Pistilli, Felice, Cannizzaro et al. (2013)	RCT Split-mouth	Short: 20 Long: 20	Short: 80 Long: 91	Short: 40 Long: 40	Max/Mand	1 year
Esposito et al. (2014)	RCT Split-mouth	Short: 30 Long: 30	Short: 60 Long: 68	Short: 30 Long: 30	Max/Mand	3 years
Rossi et al. (2016)	RCT	Short/ Long: 45	Short: 30 Long: 30	Short: 29 Long: 30	Max/Mand	5 years
Felice et al. (2015)	RCT	Short: 10 Long: 10	Short: 16 Long: 18	Short: 16 Long: 18	Max	1 year
Felice et al. (2016)	RCT	Short: 75 Long: 75	Short: 124 Long: 116	Short: 75 Long: 73	Max/Mand	1 year
Bechara et al. (2016)	RCT	Short: 33 Long: 20	Short: 45 Long: 45	Short: 35 Long: 33	Max	3 years
Sahrmann et al. (2016)	RCT	Short: 40 Long: 38	Short: 40 Long: 38	Short: 40 Long: 38	Max/Mand	3 years
Pohl et al. (2017)	RCT	Short: 50 Long: 51	Short: 67 Long: 70	Short: 61 Long: 68	Max	3 years

RCT, randomized clinical trial; SC, single crown; FDP, fixed dental prosthesis, SR, screw-retained; CR, cemented-retained; N/A, not applicable.

rate for short and 100% longer implants placed in pristine bone. Our meta-analysis revealed a risk ratio (RR) of 1.29 (95% CI: 0.67, 2.50, $p = 0.45$), for short implant failure compared to longer implants. This means that short implants (≤6 mm) would present a 29% higher risk of failure compared to longer implants. The forest plot with included studies is shown in Figure 2. The heterogeneity test did not reach statistical significance ($p = 0.67$), suggesting low between-study heterogeneity.

3.5 | Marginal bone levels

All studies included in the systematic review reported mean marginal bone levels (MBL) for both implant groups. One study did not report the standard deviation, and instead listed the confidence interval. A meta-analysis for MBL was not performed due the high heterogeneity of MBL between the studies. The mean MBL values of the short implant group ranged from +0.06 to −1.22 mm at the respective follow-up examination. The correspondent values for the longer implants varied from +0.02 to −1.54 mm. Most of the studies reported no statistically significant differences between groups regarding MBL (Felice et al., 2015, 2016; Gulje et al., 2013; Pohl et al., 2017; Sahrmann et al., 2016). On the contrary, four studies found statistically significant differences between groups. However, these differences ranged only from 0.02 to 0.32 mm (Bechara et al., 2016; Esposito et al., 2014; Pistilli, Felice, Piattelli et al., 2013; Rossi et al., 2016).

3.6 | Biologic complications

Most of the studies reported biologic complications related to intra-surgical and post-surgical events (Bechara et al., 2016; Esposito et al., 2014; Felice et al., 2016; Pistilli, Felice, Piattelli et al., 2013; Pistilli, Felice, Cannizzaro et al., 2013; Pohl et al., 2017). Overall, the percentage of patients that experienced biologic complications ranged from 0% to 26% in the short implant group and from 0% to 90% in the longer implant group. Two studies reported that there were no biologic complications (Felice et al., 2016; Sahrmann et al., 2016), while two studies did not clearly assess this variable (Gulje et al., 2013; Rossi et al., 2016). Most of the complications were related to the immediate post-operative period, and included transient paresthesia of the lower lip, Schneiderian membrane perforation, and mandibular graft infection.

3.7 | Prosthesis survival rates

Overall, most of the studies reported high prosthesis survival rates. They varied from 90% to 100% for the short implant group, and from 95% to 100% for the longer implant group. Seven studies reported no prosthesis failures for both groups (Bechara et al., 2016; Felice et al., 2015; Gulje et al., 2013; Pistilli, Felice, Cannizzaro et al., 2013; Pohl et al., 2017; Rossi et al., 2016; Sahrmann et al., 2016). In one study the prosthesis survival rate was not clearly reported (Felice et al., 2015).

TABLE 1 (additional columns)

Test and Control Group (mm long × mm wide implants)	Placement protocol	Prosthesis design	Prosthesis retention	Implant system	Setting
Test: 6 × 4 Control: 11 × 4	Healed sites	Splinted	SR	Osseospeed, Astra Tech	Private practice and university clinic
Test: 5 × 5 Control: 10 × 5	Healed sites	SCs or Splinted	SR or CR	MegaGen	University clinic
Test: 6 × 4 Control: (10, 11.5, 13 or 15) × 4	Healed sites/grafted sites	SCs or Splinted	CR	Southern	Private practice and university clinic
Test: 5 × 6 Control: (7, 8.5, 10 or 11.5 or 13) × 4	Healed sites	SC or Splinted	CR	Rescue MegaGen (test), EZ Plus MegaGen (control)	Private practice and university clinic
Test: 6 × 4.1 Control: 10 × 4.1	N/A	SCs	CR	Straumann	Private practice
Test: (5 or 6) × 5 Control: 10 × 5	Healed sites	SCs or Splinted	SR or CR	Osseotite II- Zimmer Biomet (test) Zimmer Biomet (control)	Private practice and university clinic
Test: 4 × 4 Control: (8.5 or longer) × 4	Healed sites or immediate placement	SC or Splinted	SR	Global D (TwinKon Universal SA2)	Private practice and university clinic
Test: 6 × (4–8) Control: (10, 11.5, 13 or 15) × (4–8)	Healed sites or immediate placement	SCs or FDPs	SR or CR	MegaGen	University clinic
Test: 6 × 4.1 Control: 10 × 4.1	Healed sites	SCs	SR	Straumann	University clinic
Test: 6 × 4 Control: (11, 13 or 15) × 4	Healed sites	SCs	SR or CR	Osseospeed, Astra Tech	Private practice and university clinic

4 | DISCUSSION

The purpose of the present systematic review and meta-analysis was to assess the long-term survival and failure rates of short implants (≤6 mm length) versus longer implants (>6 mm length) in augmented or non-augmented bone and reported in RCTs. Secondary outcomes included the assessment of prosthesis survival, clinical complications as well as peri-implant bone level behavior.

The findings of the present study based on the included 10 RCTs indicate that survival rates of short implants (≤6 mm) ranged from 86.7% to 100%, whereas the survival rates for longer implants (>6 mm) were 95% to 100% with a follow-up from 1 to 5 years. The implant survival of short implants was nominally inferior to that of the longer implants. The risk ratio (RR) for short implant failure compared to longer implants (>6 mm) was 1. 29 (95% CI: 0.67, 2.50, $p = 0.45$)), demonstrating that overall, short implants presented a 29% higher risk of failure compared to longer implants. The heterogeneity test did not reach statistical significance ($p = 0.61$), suggesting low between-study heterogeneity. A recently published RCT with 5-year follow-up compared outcomes with 6 mm short vs 10 mm implants for restoration of single tooth gaps (Naenni et al., 2018). The authors reported implant survival rates of 91% (95% confidence interval: 0.836 to 0.998) for the 6-mm group and 100% for the 10-mm group ($p = 0.036$). It has to be highlighted that this RCT was a continuation of an RCT with 3-year results (Sahrmann et al., 2016), which is part of the present meta-analysis. The 5-year study was not included, because it was published after the cut-off date for inclusion of studies in preparation of the systematic reviews for the 2018 ITI Consensus Conference. A time-dependent reduction in the survival rate of single standing 6 mm short implants in the posterior area is clearly demonstrated.

The results of this systematic review are in accordance with previous similar publications. Thoma, Zeltner et al. (2015) and Thoma, Haas et al. (2015) in a systematic review of RCTs reported higher morbidity with longer implants and extensive grafting in the posterior maxilla compared with short implants. Fan et al. (2017), also in a systematic review of RCTs, focused on the posterior maxilla and compared sinus grafting and longer implants vs short implants. The authors reported similar outcomes for both treatment approaches. Lemos et al. (2016) included both posterior maxillae and mandibles in their meta-analysis and found that short implants exhibited at greater risk of failure compared with longer implants. Nisand et al. (2015) reported similar findings when comparing outcomes for the posterior maxilla and mandible and the options of vertical GBR combined with longer implants vs short implants.

All aforementioned reviews defined short implants as 8 mm or less in length. Conversely, the present review defined short implants as implants of 6 mm length or less. The uniqueness of the present review and meta-analysis lies in the fact that only truly short implants of ≤6 mm in length were compared to longer implants. This distinguishes

TABLE 2 Risk of bias assessment for the included studies [In PDF format, this table is best viewed in two-page mode]

Author (Year of publication)	Adequate sequence generation (selection bias)	Remark	Allocation concealment (selection bias)	Remark	Blinding of participants and personnel (performance bias)	Remark	Blinding of outcome assessment (detection bias)
Pistilli, Felice, Piattelli et al. (2013)	Low risk	A computer-generated restricted random list was created.	Low risk	The information of treatment allocation was enclosed in a sequentially numbered, identical, opaque sealed envelope.	High risk	1. Patients had the right to know what treatment they were receiving. 2. Surgeons had to know the treatment they would provide.	Low risk
Rossi et al. (2016)	Unclear risk	No information provided	Low risk	Sealed numbered envelopes were prepared from the monitor, patients with two sites were allowed to be included in the study	Low risk	1. Patients had the right to know what treatment they were receiving. 2. Surgeons had to know the treatment they would provide.	High risk
Felice et al. (2015)	Low risk	Two computer-generated restricted randomization lists were created. A blocked randomization was applied to include 10 patients in each treatment group.	Low risk	The randomized codes were enclosed in sequentially numbered, identical, opaque, sealed envelopes. Envelopes were opened sequentially after eligible patients were recruited and signed the consent form.	High risk	1. Patients had the right to know what treatment they were receiving. 2. Surgeons had to know the treatment they would provide.	Low risk
Pistilli, Felice, Cannizzaro et al. (2013)	Low risk	A computer-generated restricted random list was created	Low risk	The information of treatment allocation was enclosed in a sequentially numbered, identical, opaque sealed envelope.	High risk	1. Patients had the right to know what treatment they were receiving. 2. Surgeons had to know the treatment they would provide.	Low risk
Bechara et al. (2016)	Unclear risk	Details of random sequence generation provided. Inconsistencies exit as to selection of patients. Eight immediate implants were placed only on the Test group.	Unclear risk	The information of treatment allocation was enclosed in a sequentially numbered, identical, opaque sealed envelope. Inconsistencies exit as to selection of patients.	High risk	1. Patients had the right to know what treatment they were receiving. 2. Surgeons had to know the treatment they would provide.	Low risk
Esposito et al. (2014)	Low risk	A computer-generated restricted random list was created	Low risk	The information of treatment allocation was enclosed in a sequentially numbered, identical, opaque sealed envelope.	High risk	1. Patients had the right to know what treatment they were receiving. 2. Surgeons had to know the treatment they would provide.	High risk
Felice et al. (2016)	Low risk	A computer-generated restricted randomization list was created.	Low risk	The information of treatment allocation was enclosed in a sequentially numbered, identical, opaque sealed envelope.	High risk	1. Patients had the right to know what treatment they were receiving. 2. Surgeons had to know the treatment they would provide.	High risk
Gulje et al. (2013)	Low risk	Randomization was performed using a block randomization sequence.	Unclear risk	The information of treatment allocation was enclosed in a sealed envelope.	High risk	1. Patients had the right to know what treatment they were receiving. 2. Surgeons had to know the treatment they would provide.	High risk
Pohl et al. (2017)	Low risk	A block randomization sequence was used.	Low risk	The randomization was performed at the day of surgery following flap elevation using a sealed envelope.	High risk	1. Patients had the right to know what treatment they were receiving. 2. Surgeons had to know the treatment they would provide.	High risk

TABLE 2 (additional columns)

Remark	Incomplete outcome data (attrition bias)	Remark	Selective reporting (reporting bias)	Remark	Free of other sources of bias	Remark	Overall risk of bias
Two dentists not involved in the treatment of patients performed all clinical measurements without knowing group allocation. Also one dental student not involved in the treatment of all patients performed all radiographic assessments without knowing group allocation. All data analysis was carried out by a biostatistician without knowing the group codes.	Low risk	Drop-out/ Lost to follow information provided.	Low risk	All pre-specified outcomes were reported.	No	1. Reconstructions would be splinted if more than one implants were placed. 2. No sample size calculation was performed.	Low
No information provided	Low risk	Drop-out/ Lost to follow infirmation provided.	Low risk	All pre-specified outcomes were reported.	Yes	All implants were restored with single crowns.	Unclear
One dentist at each center, not involved in the treatment of the patients assessed implant stability and patient satisfaction. One clinician performed radiographic assessments without knowing group allocation. All data analysis was carried out by a clinician with expertise in biostatistics without knowing the group codes.	Low risk	Drop-out/ Lost to follow infirmation provided.	Low risk	All pre-specified outcomes were reported.	No	1. No information if the clinician who performed radiographic assessments was involved in patient treatment. 2. Sinus lift sites could be identified on radiographs	Low
Two dentists not involved in the treatment of patients performed all clinical measurements without knowing group allocation. Also one dental student not involved in the treatment of all patients performed all radiographic assessments without knowing group allocation. All data analysis was carried out by a biostatistician without knowing the group codes.	Low risk	Drop-out/ Lost to follow infirmation provided.	Low risk	All pre-specified outcomes were reported.	No	1. Reconstructions would be splinted if more than one implants were placed. 2. All clinical measurements and radiographic assessments were performed without knowledge of group allocation, however mandibular augmented sites could be easily identified because of the different implant length.	Low
An experienced, calibrated, independent examiner performed a careful clinical examination of the fixtures, peri-implant tissues, and prostheses.	Low risk	Drop-out/ Lost to follow infirmation provided.	Low risk	All pre-specified outcomes were reported.	No	1. Study reports 0% prosthetic complications in 3 years in both groups. 2. Immediate implants were placed only on test group flaplessly with no information of grafting materials being used.	Unclear
One dentist not involved in treatment performed all measurements without knowing group allocation, BUT augmented sites could be easily identified both clinically (different diameters) and radiographically (different opacity). No blinding was possible.	Low risk	Drop-out/ Lost to follow infirmation provided.	Low risk	All pre-specified outcomes were reported.	No	1. Reason for not including two patients in the study despite fulfilling criteria was not mentioned. 2. Reconstructions would be splinted if more than one implants were placed	Unclear
Two clinicians not involved in patient treatment performed clinical measurements without knowing group allocation. One clinician not involved in patient treatment performed all radiographic assessments but the different implant lengths could be easily identified on radiographs. A clinician analyzed the data, but there is no information as to if she was involved in patient treatment.	Low risk	Drop-out/ Lost to follow infirmation provided.	Low risk	All pre-specified outcomes were reported.	No	1. Reconstructions would be splinted if more than one implants were placed. 2. No sample size calculation was performed.	Unclear
1. At each center, only one clinician performed the surgery and clinical observations. 2. Radiographic measurements were made by an experienced and independent radiologist.	Low risk	Drop-out/ Lost to follow infirmation provided.	Low risk	All pre-specified outcomes were reported.	No	1. No information if the sealed envelope was opaque and sequentially numbered. 2. Two to three implants were placed at each site and restorations were always splinted.	Unclear
The use of independent assessor is not mentioned.	Low risk	Drop-out/ Lost to follow infirmation provided.	Low risk	All pre-specified outcomes were reported.	No	1. The study did not address which clinicians carried out the treatments. 2. Reconstructions were not splinted.	Unclear

TABLE 3 Summary of main outcomes of the included studies

Author/year	Implant survival rate, %	Prosthesis survival rate	Mean marginal bone loss (Mean and *SD*)	Biologic complications	Technical complications
Gulje et al. (2013)	Short: 97 Long: 99	Short: 100 Long: 100	Short: 0.06 (0.27) Long: 0.02 (0.6)	N/A	Short: 4 Long: 7
Pistilli, Felice, Piattelli et al. (2013)	Short: 98.5 Long: 97	Short: 97.5 Long: 95	Short: 0.9 Long: 1.08	Short: 20 Long: 56	N/A
Pistilli, Felice, Cannizzaro et al. (2013)	Short: 100 Long: 96.7	Short: 100 Long: 100	Short: 1.05 Long: 1.07	Short: 0 Long: 60	Short: 0 Long: 0
Esposito et al. (2014)	Short: 92 Long: 97	Short: 90 Long: 100	Short: 1.22 (0.49) Long: 1.54 (0.44)	Short: 26 Long: 36	Short: 0 Long: 0
Rossi et al. (2016)	Short: 86.7 Long: 96.7	Short: 100 Long: 100	Short: 0.14 Long: 0.18	N/A	Short: 0 Long: 0
Felice et al. (2015)	Short: 100 Long: 100	Short: 100 Long: 100	Short: 0.70 (0.19) Long: 0.87 (0.21)	Short: 0 Long: 0	Short: 0 Long: 0
Felice et al. (2016)	Short: 96 Long: 97	N/A	Short: 0.53 (0.23) Long: 0.56 (0.33)	Short: 4 Long: 2.6	N/A
Bechara et al. (2016)	Short: 100 Long: 95	Short: 100 Long: 100	Short: 0.20 (0.12) Long: 0.27 (0.14)	Short: 0 Long: 90	Short: 0 Long: 0
Sahrmann et al. (2016)	Short: 98 Long: 100	Short: 100 Long: 100	Short: 0.19 (0.62) Long: 0.33 (0.71)	Short: 0 Long: 0	Short: 3 Long: 0
Pohl et al. (2017)	Short: 100 Long: 100	Short: 100 Long: 100	Short: 0.44 (0.56) Long: 0.43 (0.58)	Short: 4[a] Long: 18[a]	Short: 10 Long: 3

[a]Report from the 1-year follow-up study of Thoma, Zeltner et al. (2015) and Thoma, Haas et al. (2015). N/A, not applicable.

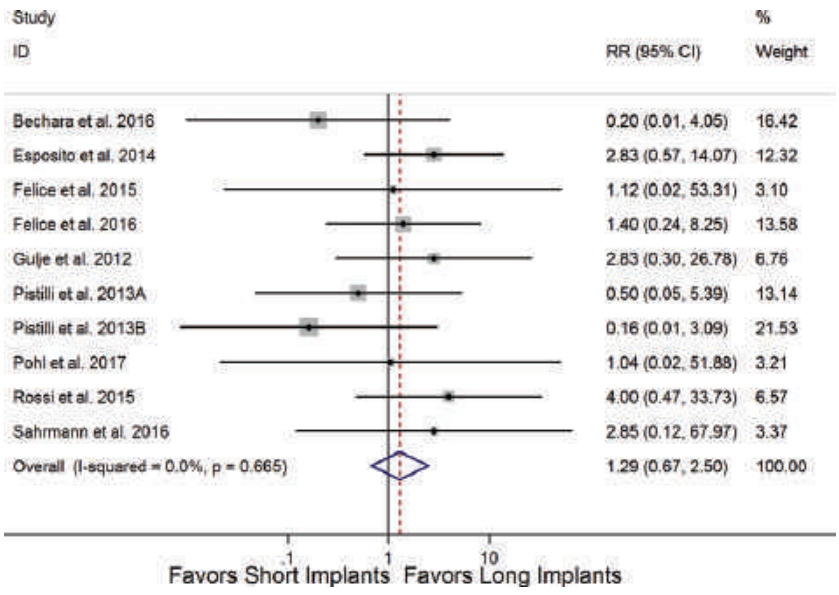

FIGURE 2 Forest plot with included studies. Risk ratios, with continuity correction, by study year

the obtained results from numerous other studies, in which short implants of 8 mm length were assessed and found to perform similarly to those longer than 8 mm (Gallucci et al., 2014; Thoma, Zeltner et al., 2015; Thoma, Haas et al., 2015). To accommodate the highest level of evidence (Moher et al. 2009), only RCTs were included in the present analysis, which adds additional strength to the findings.

Nevertheless, caution is advised when interpreting the results due to a variety of reasons. Two studies (Bechara et al., 2016; Felice et al., 2016) included immediate implant placement in their protocol, differently than the other included studies that performed implant placement only in healed sites. The implants in these two studies, however, were loaded 4 months after surgery, at which stage bone-graft healing was already advanced and the different placement protocols (grafted vs. non-grafted sites) most likely did not negatively affect the implant or prosthesis survival. Limitations also include that even though RCTs were included in the analysis, the risk of bias was difficult to assess in several studies. One study (Esposito et al., 2014) reported that one dentist not involved in the

treatment performed all measurements without knowing group allocation. However, augmented sites could easily be identified both clinically (different diameters) and radiographically (different opacity), possibly indicating a higher risk of reporting bias. Another study (Bechara et al.,2016) featured inconsistencies with regards to patient selection and procedure standardization. For instance, a total of eight implants were immediately placed. However, this modality was only used in the test group (short implant group) without any information about bone grafting procedures in these sites involving immediate implant placement. This may have increased the risk of selection bias. In two studies (Gulje et al., 2013; Pohl et al., 2017) blinding was unclear, whereas in another study (Esposito et al.,2014) different implant diameters were used in the two groups, making blinding impossible and introducing the risk of bias. It also has to be considered that a greater implant diameter combined with a given implant length will increase the overall implant surface available for osseointegration making a true comparison of the performance of short and longer implants difficult. However, eight of the 10 RCTs included in this systematic review compared short and long implants with the same diameters.

Most of the included RCTs were conducted in university settings by the same two research groups and not in private practices. A previous study showed that implant success rates for single crowns and FDPs in general dental practices may be lower than those achieved in well-controlled university or specialty settings (Papaspyridakos, 2015).In addition, most of the included studies revealed limited or no information on the restorative aspects and protocols followed during the planning and prosthodontic treatment phases. The risk of bias assessment with the Cochrane's collaboration tool led to an unclear risk of bias with inadequate reporting of restorative outcomes and/or encountered complications.

Another essential component of the success of dental implant treatment is the reporting of complications and patient satisfaction, along with the implant, peri-implant and prosthodontic outcomes (Papaspyridakos, Chen, Singh, Weber, & Gallucci, 2012). These aspects were not reported in most included studies.

At last, the available evidence in the present review should further be interpreted with caution as four RCTs had a limited sample size ranging from 15 to 40 implants per group, had a limited follow-up time, and represented treatments that were performed predominantly by only two research groups.

Regarding the question about true clinical indications for short implants, posterior partial edentulism in the mandible and maxilla will be the most frequently mentioned ones. While bone augmentation via sinus floor elevation can be predictably achieved in the atrophic posterior maxilla allowing the placement of longer implants. Nevertheless, short dental implants may still be considered a valid alternative with less morbidity and fewer biologic complications based on the findings of this systematic review and meta-analysis.

In the atrophic posterior mandible, vertical bone augmentation procedures are more challenging and less predictable (Kuchler & von Arx, 2014). In such cases, the use of short implants may present the preferable alternative based on the results of this review. The survival rate of short implants in the posterior edentulous mandible is high, based on the included studies.

Even though crown-to-implant ratio seems not to be correlated with crestal bone loss or risk of failure of short implants (Garaicoa-Pazmiño et al., 2014), a comment must be made about the advantage of splinting short dental implants via the final fixed prosthesis. Splinting of short implants in indications where two or more adjacent implants are present, combined with providing the patient with a mutually protected or canine guided occlusion will reduce the mechanical forces on the individual implants and components (Kinsel & Lin, 2009; Taylor, Wiens, & Carr, 2005). Splinting may also reduce the incidence of screw loosening/fracture, porcelain chipping, and implant overload.

Technical/mechanical complications were only reported in three studies (Gulje et al., 2013; Pohl et al., 2017; Sahrmann et al., 2016). Gulje et al. (2013), reported a total of 11 complications: four in the short implant group (three abutment screw loosening and one provisional prosthesis fracture), and seven in the longer implant group (three abutment screw loosening, one provisional prosthesis fracture, and three FDP loosening). Pohl et al. (2017) reported 10 complications in the short implant group (eight events of abutment screw loosening and two incidences of crown de-cementation,) and three complications in the group with longer implants (two incidences with loosening of abutment screws and one crown de-cementation). Sahrmann et al. (2016) reported a 3.8% rate of technical complication (all screw loosening) in the short implant group and no such complications in the longer implant group. Other studies did not find any technical complications (Bechara et al., 2016; Esposito et al., 2014; Felice et al., 2015; Pistilli, Felice, Cannizzaro et al., 2013; Rossi et al., 2016) or did not report this outcome (Felice et al., 2016; Pistilli, Felice, Piattelli et al., 2013).

5 | CLINICAL IMPLICATIONS

Clinical implications from the findings of this meta-analysis include the possibility of using short implants as a valid alternative in selected cases where bone quantity precludes the use of longer implants, which would require potentially extensive bone grafting that increases invasiveness as well as morbidity of the treatment and treatment time. Especially for the posterior mandible where vertical ridge augmentation tends to be a challenging procedure with guarded predictability, the use of short implants seems to offer an excellent alternative. Splinting of multiple short implants appears to be recommended based on the information retrieved from most of the included studies for a better distribution of occlusal forces on the entire implant-prosthodontic complex.

6 | FUTURE RESEARCH

Suggestions for further research include the demand for more longitudinal studies with longer follow-up times on short implants and better standardization of study protocols, especially, important would be the comparison of long-term performance of single versus

splinted implants in posterior jaw areas. In addition, studies would be desirable that compare financial impact, treatment effectiveness, and patient satisfaction for the treatment alternatives of ridge augmentation and placement of longer implants versus the use of short implants without the need for grafting.

7 | CONCLUSIONS

Within the limitations of the present analysis and review, the following conclusions may be drawn:

1. Short implants (≤6 mm) were found to have *higher variability* and *lower predictability* in survival rates compared to longer implants (>6 mm) after periods of 1 to 5 years in function. The mean survival rate was 96% (range: 86.7%–100%) for short implants, and 98% (range 95%–100%) for longer implants.
2. The risk ratio (RR) for short implant failure compared to longer implants was 1.29 (95% CI: 0.67, 2.50, $p = 0.45$), demonstrating that short implants (≤6 mm) demonstrated a 29% higher risk of failure to implants longer than 6 mm.
3. Prosthesis survival for short and longer implants following a period of 1 to 5 years was similarly high. The mean prosthesis survival rate was 98.6% (range: 90%–100%) for short implants, and 99.5% (range: 95%–100%) for the longer implants.
4. Based on the available evidence from RCTs, indications for short implants with ≤6 mm length should be carefully selected because they may present a greater risk for failure over time compared to implants longer than 6 mm.

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CONFLICT OF INTEREST

No conflicts declared.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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REVIEW ARTICLE

WILEY CLINICAL ORAL IMPLANTS RESEARCH

Narrow-diameter implants: A systematic review and meta-analysis

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Abstract

Objectives: Narrow-diameter implants (NDI) are claimed to be a reasonable alternative to bone augmentation procedures. The aim of this comprehensive literature review was to conduct a meta-analysis comparing the implant survival of NDI and standard diameter implants (SDI) and to provide recommendations and guidelines for application of NDI.

Material and methods: An extensive systematic literature search was performed in the PubMed/MEDLINE and the Cochrane Library databases. NDI were classified into Category 1 (implant diameter <3.0 mm, "mini-implants"), Category 2 (implant diameter 3–3.25 mm) and Category 3 (implant diameters 3.3–3.5 mm). Clinical studies at all levels of evidence with at least 10 patients included and a follow-up time of at least 12 months were included. The primary outcome criterion was the survival rates of NDI.

Results: Seventy-six studies were identified for qualitative and 16 studies for quantitative synthesis. Quality assessment illustrated a high risk of bias for the included literature. Mean implant survival rates were 94.7 ± 5%, 97.3 ± 5% and 97.7 ± 2.3% for Categories 1, 2 and 3. Meta-analysis indicated a statistically significant lower implant survival of Category 1 NDI compared to SDI ([OR], 4.54; [CI], 1.51–13.65). For Category 2 and Category 3, no statistical significant differences in implant survival were seen compared to SDI ([OR], 1.06; [CI], 0.31–3.61 and [OR], 1.19; [CI], 0.83–1.70).

Conclusion: NDI of Category 1 performed statistically significantly worse than SDI and were mainly described for the rehabilitation of the highly atrophic maxilla or mandible. Category 2 and Category 3 NDI showed no difference in implant survival compared to SDI. Category 2 NDI were mostly used for the rehabilitation of limited interdental spaces in anterior single-tooth restorations. NDI of Category 3 were described in all regions, including posterior single-tooth restorations. However, resilient long-term data and data on the possible risk of biological and technical complications with wide platform teeth on NDI are missing so far.

KEYWORDS

meta-analysis, narrow diameter, review, small dental implants, survival

1 | INTRODUCTION

High success rates and excellent predictability of dental implant treatment have been demonstrated in countless clinical studies and a multiplicity of indications (Al-Nawas et al., 2012; Moraschini, Poubel, Ferreira & Barboza Edos, 2015; Schiegnitz et al., 2015). In addition, oral rehabilitation with dental implants may provide an increase in oral health-related quality of life (Heydecke, Locker, Awad, Lund & Feine, 2003; Schiegnitz et al., 2017). However, atrophy of the alveolar crest with reduced bone width and height due to trauma, malformation, neoplasia, denture wearing and marginal periodontitis is a challenging limitation for dental implant placement. In these cases, additional surgical procedures can be necessary to augment the insufficient bone volume and reconstruct the detrimental vertical, horizontal or sagittal intermaxillary relationships (Al-Nawas & Schiegnitz, 2014). In this context, a wide variety of augmentation procedures are described in the literature, depending on location and size of defect, such as maxillary sinus floor augmentation and vertical and/or lateral alveolar ridge augmentation (Al-Nawas & Schiegnitz, 2014). However, these augmentation procedures are time and cost-consuming and demand surgical expertise to minimize patients' morbidity and prevent complications such as postoperative pain, infections, nerve damage, bone fractures, hemorrhage, wound dehiscences and implant or augmentation failures. Furthermore, it has to be considered that in medically compromised patients (e.g., patients with a history of radiation in the head and neck region or with antiresorptive medication), augmentation procedures may carry a higher risk of complications (Schiegnitz, Al-Nawas, Kammerer & Grotz, 2014; Walter, Al-Nawas, Wolff, Schiegnitz & Grotz, 2016). Therefore, alternative concepts such as narrow-diameter implants (NDI) are becoming of increasing clinical and scientific interest. The avoidance of augmentation or other invasive surgery using NDI may reduce morbidity for the patient. However, studies evaluating patient-reported outcomes (PRO) such as health-related quality of life (HRQoL) in patients receiving NDI vs. standard diameter implants (SDI) with augmentation procedures are missing so far.

The definition of NDI is inconclusive in published studies, but in general a narrow-diameter implant is taken to have a diameter ≤3.5 mm. This general classification does not give full consideration to the different clinical indications for NDI. Therefore, the classification of Klein et al. (Klein, Schiegnitz & Al-Nawas, 2014) was implemented in this systematic review as it incorporates these parameters. In this classification, NDI are divided into the following three categories:

Category 1: <3.0 mm ("mini-implants")
Category 2: 3.0–3.25 mm
Category 3: 3.30–3.50 mm

For all three categories, numerous clinical studies have been published with promising survival and success rates (Klein et al., 2014). However, clinical evidence comparing NDI to SDI remains controversy. The aim of this comprehensive literature review was to conduct a meta-analysis comparing the implant survival of NDI and SDI. In addition, recommendations and guidelines for application of NDI were provided.

2 | MATERIAL AND METHODS

2.1 | Protocol development

This systematic review and meta-analysis were written and conducted according to the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) statement (Liberati et al., 2009). The following focused question in the Patient, Intervention, Comparison and Outcome (PICO) format was posed (Stone, 2002): "In edentulous or partially edentulous patients, is implant survival, implant success, marginal bone adaptation and oral health-related quality of life outcomes of narrow diameter implants different to implant survival, implant success, marginal bone adaptation and oral health-related quality of life outcomes of standard diameter implants?". The primary outcome criterion was the survival rates of NDI. The secondary outcome criteria were implant success, marginal bone level and oral health-related quality of life. Regarding implant success, different definitions of implant success were used in the included studies. This has to be kept in mind, when interpreting the results of our study.

2.2 | Systematic search strategy and study selection

An extensive search in the electronic databases of the PubMed/MEDLINE and the Cochrane Library was performed in continuation of the review of Klein et al., (2014) for articles published between January 2013 and January 2017. Data from January 1995 to December 2012 were extracted from Klein et al., (2014). Second, the reference lists of related review articles and publications were systematically screened. As studies comparing NDI with SDI with simultaneous bone augmentation are very rare, we included all studies in meta-analysis which compared NDI with SDI without and with simultaneous bone augmentation. The specified key words and inclusion and exclusion criteria for qualitative and quantitative synthesis are displayed in Table 1. Soon, inclusion criteria for qualitative synthesis were studies at all levels of evidence with at least 10 patients and a mean follow-up time of implant survival of at least 12 months after implant placement, which were published in English. Inclusion criteria for quantitative synthesis were studies at all levels of evidence with at least 10 patients in the intervention and comparison group. The two reviewers Eik Schiegnitz [ES] and Bilal Al-Nawas [BA]) independently extracted the data from the studies. The data extracted were sorted as quantitative or qualitative and tabulated for ease of comparison. Articles that did not meet the inclusion criteria were excluded. Any disagreement between the authors regarding inclusion of a certain article and data extraction was resolved by discussion. The PRISMA flow diagram shows the

TABLE 1 Systematic search strategy

Focused question (PICO)	In edentulous or partially edentulous patients, is implant survival, implant success, marginal bone adaption and oral health-related quality of life of narrow-diameter implants different to implant survival, implant success, marginal bone adaption and oral health-related quality of life of standard diameter implants?	
Search strategy	Population	Edentulous OR partially edentulous
	Intervention or exposure	Dental implantation with narrow-diameter implants (NDI)
	Comparison	Other diameters than NDI
	Primary outcome	Implant survival
	Secondary outcome	Implant success, marginal bone level, oral health-related quality of life
	Search combination	"small diameter dental implants" "narrow-diameter dental implants" "narrow dental implants" "small dental implants" "diameter dental implants" "mini-implants"
Database search	Electronic	PubMed, Cochrane library
	Journals	Clinical Oral Implants Research, International Journal of Oral Maxillofacial Implants, Clinical Implant Dentistry and Related Research, Implant Dentistry, Journal of Implantology, Journal of Periodontology, Journal of Clinical Periodontology
Selection criteria	Inclusion criteria for qualitative synthesis	• Clinical studies at all levels of evidence, except expert opinion • At least 10 with NDI-treated patients • Mean follow-up time of implant survival of at least 12 months after implant placement • Published in English
	Exclusion criteria for qualitative synthesis	• Clinical studies with <10 treated patients • Animal studies • Reviews, meta-analyses • Multiple publications on the same patient population • Mini-implants for orthodontic anchorage • Studies with mean follow-up time of implant survival <1 year after implant placement
	Inclusion criteria for quantitative synthesis	• Clinical studies at all levels of evidence, except expert opinion • Intervention group: at least 10 with NDI-treated patients • Comparison group: at least 10 with SDI-treated patients • Mean follow-up time of implant survival of at least 12 months after implant placement • Published in English
	Exclusion criteria for quantitative synthesis	• Clinical studies with <10 treated patients • Animal studies • Reviews, meta-analyses • Multiple publications on the same patient population • Mini-implants for orthodontic anchorage • Studies with mean follow-up time of implant survival <1 year after implant placement

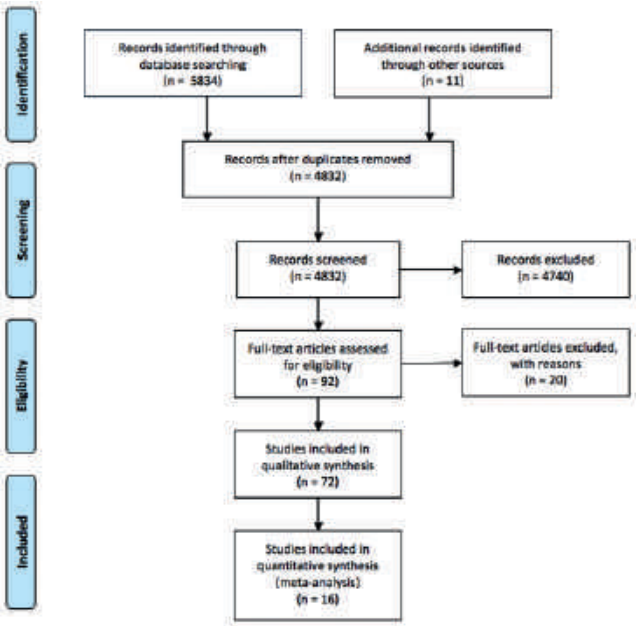

FIGURE 1 PRISMA flowchart

flow of information through the different phases of the review process (Figure 1).

2.3 | Risk of bias/quality assessment

The quality of the included articles in quantitative synthesis was evaluated as described before (Vignoletti et al., 2012; Willenbacher, Al-Nawas, Berres, Kammerer & Schiegnitz, 2016). With this technique, the quality of the included studies was classified according to the Cochrane statements, the CONSORT statements, the MOOSE statement and the STROBE statements. In this way, the studies were checked for the following six criteria: randomization, blinding of the patient and/or the examiner, definition of inclusion and exclusion criteria, selection of a representative population group (at least 20 patients overall and 10 patients in each group), reporting of the follow-up and reasons for dropout and identical treatment between groups except for the intervention (Table 2). As blinding of the patient and/or the examiner is nearly impossible in surgical implant studies, this point was described as not applicable. Studies fulfilling all of the above-mentioned criteria were then categorized with a low potential risk of bias. Studies in which one of the criteria did not match were described as having a moderate risk of bias and studies where two or more of the criteria were missing were as having a high potential risk of bias.

2.4 | Statistical analysis

Meta-analysis was performed applying the statistical software package RevMan (Review Manager [Computer program], version 5.3, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) to calculate the overall estimated effects

TABLE 2 Quality criteria of the included articles

Study	Randomization	Blinding	Appropriate and clearly focused question of the study	Identical treatment except for intervention	Defined criteria for 1. Inclusion 2. Exclusion	Appropriate no. of implants (test/control)	Follow-ups completed/ dropouts/reason for dropout (yes/no)	Conflict of interest was stated	Source of funding	Risk of bias
Temizel, Heinemann, Dirk, Bourauel and Hasan (2017)	No	NA	Yes	Yes	1. Yes 2. Yes	Yes	Yes	No	ND	High
Anitua, Saracho, Begona and Alkhraisat (2016)	No	NA	Yes	Yes	1. Yes 2. No	Yes	No	Yes	ND	High
de Souza et al. (2015)	Yes	NA (Yes)	Yes	Yes	1. Yes 2. Yes	Yes	Yes	Yes	FAPESP (grant no. 11/00688-7, scholarship 11/23347-0)	Low
Anitua et al. (2008)	No	NA	Yes	Yes	1. No 2. No	Yes	No	Yes	Biotechnology Institute (BTI)	High
Pieri et al. (2017)	No	NA	Yes	Yes	1. Yes 2. Yes	Yes	No	Yes	No	High
Aunmeungtong et al. (2017)	Yes	NA (Yes)	Yes	Yes	1. Yes 2. Yes	Yes	Yes	No	ND	Moderate
Andersen, Saxegaard, Knutsen and Haanaes (2001)	No	NA (Yes)	Yes	Yes	1. Yes 2. Yes	Yes	Yes	No	Implant Innovations Inc.	High
Herrmann et al. (2016)	No	NA	Yes	Yes	1. Yes 2. Yes	Yes	Yes	Yes	ND	High
Ioannidis et al. (2015)	Yes	NA	Yes	Yes	1. Yes 2. Yes	Yes	Yes	Yes	ITI Foundation	Low
Schiegnitz et al. (2016)	No	NA	Yes	Yes	1. No 2. No	Yes	Yes	Yes	ND	High
Zweers, van Doornik, Hogendorf, Quirynen and Van der Weijden (2015)	No	NA	Yes	Yes	1. Yes 2. Yes	Yes	Yes	Yes	No	Moderate
Benic et al. (2013)	Yes	NA	Yes	Yes	1. Yes 2. Yes	Yes	Yes	Yes	ITI Foundation	Low
Haas, Mensdorff-Pouilly, Mailath and Watzek (1996)	No	NA	Yes	Yes	1. No 2. No	Yes	No	No	ND	High
Lazzara et al. (1996)	No	NA	Yes	Yes	1. Yes 2. Yes	Yes	Yes	No	ND	High
Romeo et al. (2006)	No	NA	Yes	Yes	1. Yes 2. Yes	Yes	Yes	No	ND	High
Spiekermann, Jansen and Richter (1995)	No	NA	Yes	Yes	1. No 2. No	Yes	No	No	ND	High

ND, not described; NA, not applicable.

and to create the forest plots and funnel plots. Funnel plots are a scatterplot of treatment effect (*x*-axis) against a measure of study precision (*y*-axis) (Egger, Davey Smith, Schneider & Minder, 1997). The overall estimated effect was categorized as significant where $p < 0.05$.

3 | RESULTS

3.1 | Study selection and study characteristics

A total of 5845 records were identified through the electronic search and manual search (Figure 1). After exclusion of duplicates and screening of titles and abstracts, 92 studies were left for full-text assessment. At last, 72 studies were included in the qualitative analysis and 16 studies in the quantitative analysis. The selected studies were subdivided into three categories according to the diameter of the investigated implants: 22 studies reporting on implants of Category 1 (Table 3) with 1280 patients and 5,441 NDI, 19 studies reporting on implants of Category 2 with 823 patients and 1,133 NDI (Table 4) and 35 studies reporting on implants of Category 3 with 3,842 patients and 5,612 NDI (Table 5). Altogether in the included articles, 12,186 NDI were inserted. The study of Anitua, Orive, Aguirre, Ardanza & Andia, 2008 was included in all three categories, and the studies of Anitua et al., 2010 and Mangano et al., 2013 were included in Category I and Category II. Data on the influence of NDI on oral health-related quality of life were rarely documented. Therefore, this secondary outcome could not be addressed.

3.2 | Quality assessment/risk of bias

Quality assessment showed a huge variety across the included studies in quantitative analysis (Table 2). Three studies showed a low potential risk of bias, two studies a moderate risk of bias and 11 studies a high potential risk of bias (Figure 2). Therefore, a high risk of bias for the included literature was seen. This has to be kept in mind when interpreting the results of the review.

3.3 | Implant survival, implant success and marginal bone level

3.3.1 | Category 1

The most prevalently used implant type in Category 1 was one-piece implant with a diameter between 1.8 and 2.4 mm (Table 6). Mean follow-up was 34 ± 20 months and ranged between 12 and 78 months (Table 3). Mean survival rate was 94.7 ± 5% (range 80%–100%). The most frequently described indications were the edentulous arch and single non-load-bearing teeth in the anterior region. Types of final restorations were mainly complete overdentures. Most of the studies reported survival rates; only one study indicated an implant success rate of 92.9%. Mean marginal bone loss ranged from 0.6 mm to 1.43 mm. Regarding the applied surgical protocol, procedures ranged from minimally invasive transmucosal implant insertion to the raising of a full-thickness flap. Most of the studies described an immediate loading protocol for the overdenture. Regarding the secondary outcome criteria oral health-related quality, several clinical studies showed an increase in terms quality of life after treatment with NDI of Category 1 (Elsyad, 2016; Enkling, Saftig, Worni, Mericske-Stern & Schimmel, 2017; Preoteasa, Imre & Preoteasa, 2014).

3.3.2 | Category 2

In Category 2, 17 of 19 studies investigated SDI with a diameter of 3.0 mm (Table 6). Mean follow-up was 29 ± 17 months (range 12 to 63 months), and mean survival rate was 97.3 ± 5% (range 80.5%–100%). The leading indication and the mainly used final restorations for these implants were single-tooth restoration in the anterior region. Implant success rates were described in three studies and constituted 100%. The included studies indicated a mean marginal bone loss between 0.09 mm and 1.6 mm. Concerning the secondary outcome criteria of oral health-related quality of life, none of the investigated studies addressed this point.

3.3.3 | Category 3

In Category 3, the most prevalent implant type was of two-piece design with a diameter of 3.3 mm (Table 6). Analysis of the included studies indicated a mean survival rate of 97.7 ± 2,3% (range 91% to 100%) after a mean follow-up of 39 ± 24 months (range 12–109 months). There were several studies representing long-term survival for NDI of category 3 (Arisan, Bolukbasi, Ersanli & Ozdemir, 2010; Hasegawa et al., 2017; Mangano et al., 2014; Romeo et al., 2006; Schiegnitz et al., 2016). The indications were often imprecisely defined, but also included the load-bearing posterior region. Types of final restorations were mixed. Implant success rates ranged between 91.4% and 100%. Mean marginal bone loss ranged from 0.1 mm to 2.17 mm. As in Category 2, the secondary outcome criteria oral health-related quality of life was not evaluated.

3.4 | Meta-analysis of implant survival of NDI vs. implant survival of SDI 2

Meta-analysis showed a significant difference in implant survival between NDI of Category 1 and SDI (odds ratio [OR], 4.54; confidence interval [CI], 1.51–13.65; Figure 3). Begg and Mazumdar's funnel plot for this meta-analysis is shown in Figure 4. Meta-analysis of studies comparing implant survival in NDI of Category 2 and SDI revealed no statistically significant difference ([OR], 1.06; [CI], 0.31–3.61; Figure 5). Begg and Mazumdar's funnel plot indicated a low risk for publication bias for this meta-analysis (Figure 6). In addition, no statistically significant difference was seen comparing implant survival of NDI of Category 3 and SDI ([OR], 1.19; [CI], 0.83–1.70; Figure 7). Begg and Mazumdar's funnel plot for this meta-analysis is

displayed in Figure 8. When interpreting these results of the meta-analysis, the Forrest plots show that the effects among most of the categories are driven mostly by one study and the confidence intervals are large for most of the analyses due to the paucity of events and heterogeneity of study design and outcome measure. Therefore, drawing definite conclusions out of these data is not recommended.

4 | DISCUSSION

Patient preference for minimally invasive treatment options such as rehabilitation without bone augmentation is generally high (Pommer et al., 2014). Therefore, the aim of this systematic review was to perform a meta-analysis comparing the implant survival of NDI and SDI. NDI were classified into Category 1 (<3.0 mm, "mini-implants"), Category 2 (3.00–3.25 mm) and Category 3 (3.30–3.50 mm) as described before (Klein et al., 2014). Quality assessment of the included studies showed an enormous variety, as prospective randomized studies were rare. In addition, survival follow-up times showed a wide variation. Reasons for implant failures and implant success were missing in most of the included studies. Therefore, that the best possible available external evidence evaluated has a high risk of bias compared to other reviews that include only randomized studies should be kept in mind when considering the results of this review.

According to the results of our meta-analysis, the mean survival rates of NDI of Category 1 were promising (94.7 ± 5%). However, this is significantly lower than the survival rates of SDI. These results may not be surprising, as these mini-implants were generally inserted in highly atrophic edentulous jaws that represent surgically challenging situations. Studies comparing survival and success of NDI compared to SDI with augmentation procedures in high atrophic situations are missing so far. Mean marginal bone loss of Category 1 NDI ranged from 0.6 mm to 1.43 mm, similar to those of SDI (Di Girolamo, Calcaterra, Gianfilippo, Arcuri & Baggi, 2016; Helmy, Alqutaibi, El-Ella & Shawky, 2017). In a recent systematic review, the use of mini-implants to retain complete overdentures was examined (Lemos et al., 2017). The results showed a similar survival rate of 92.32% after a mean follow-up time of 30 months for the mini-implants. Marginal bone loss values were described in the majority of the studies below 1.5 mm. Regarding patient-centered outcomes, several clinical studies illustrated an increase in terms of aesthetics, satisfaction and quality of life after rehabilitation treatment with mini-dental implants (Aunmeungtong, Kumchai, Strietzel, Reichart & Khongkhunthian, 2017; Elsyad, 2016; Enkling et al., 2017; Preoteasa et al., 2014). In conclusion, application of a minimum of 4 or 6 mini-implants in mandibular or maxillary arches for retaining overdenture prostheses is considered a promising alternative treatment when insertion of SDI is due to extreme bone atrophy is not possible (Bidra & Almas, 2013; Lemos et al., 2017). Due to the one-piece design, most of the studies reported immediate restoration and immediate loading protocols. Regarding the suitable retention system (e.g., bar, ball or locator), there is no strong evidence for the superiority of one system over the others regarding patient satisfaction, survival, peri-implant bone loss and other clinical factors (Carlsson, 2014; Laverty, Green, Marrison, Addy & Thomas, 2017).

Regarding NDI of Category 2, mean implant survival was 97.3 ± 5% after a mean follow-up of 29 ± 17 months. Meta-analysis indicated comparable implant survival between NDI of Category 2 and SDI. These NDI were mainly inserted to replace the maxillary lateral or mandibular incisor teeth. These sites often present limited interdental space or a thin alveolar crest. Placing an implant too close to the adjacent teeth may result in loss of proximal bone height, which can negatively influence the final position of the papillae and supracrestal soft tissues (King et al., 2016; Tarnow, Cho & Wallace, 2000). Therefore, in evaluating anterior single-tooth restorations, aesthetic outcome and stability of peri-implant soft tissues are the main foci of interest besides implant survival. However, these outcome parameters were seldom assessed. Pieri, Siroli, Forlivesi & Corinaldesi, (2014) showed high mean pink aesthetic scores and stable facial soft tissues after a follow-up of 3 years. King et al., (2016) indicated stable soft tissues and clinically insignificant changes in probing depth and gingival zenith stores. These promising results should be confirmed by larger multicenter studies. Regarding the surgical protocol and the loading protocol, there were insufficient data in the included studies to recommend the superiority of one of the protocols.

NDI of Category 3 showed a mean survival rate of 97.5 ± 2.4% after a mean follow-up of 39 ± 24 months. Meta-analysis of the literature showed comparable survival rates for Category 3 NDI and SDI. The indications in the included studies were often mixed and ill-defined. However, there were several studies showing promising results for NDI of Category 3 for the posterior jaw. A recent review on the clinical performance of narrow-diameter titanium–zirconium implants (TiZr) indicated that these implants could be reliable for restorations in the posterior region, even when replacing single missing molars (Badran et al., 2017; F. E. Lambert et al., 2015; Tolentino et al., 2016). However, long-term data are rare so far.

After finalization of the systematic literature review, several further clinical studies were published (Cabrera-Dominguez, Castellanos-Cosano, Torres-Lagares & Machuca-Portillo, 2017; A. B. de Souza et al., 2017; Froum, Shi, Fisselier & Cho, 2017; Giannakopoulos et al., 2017; Grandi, Svezia & Grandi, 2017; Malo, de Araujo Nobre, Lopes & Ferro, 2017; Shi et al., 2017). These studies support the concluded results of our systematic review, and no relevant differences in clinical conclusions were found. For example, a 36-month split-mouth randomized controlled clinical study showed that 3.3-mm NDI placed to support single crowns in the posterior region did not differ to 4.1-mm SDI in regard to marginal bone level, implant survival and success rates (de Souza et al., 2017). A retrospective cohort study with a mean follow-up time of 120 months confirmed high long-term survival rates, high patient satisfaction, acceptable complication rates and marginal bone loss for 3.3 mm NDI (Shi et al., 2017).

TABLE 3 Summary of included studies of Category 1, continuation of Klein et al. (2014) [In PDF format, this table is best viewed in two-page mode]

Study	Study type	No. of patients	Implant design	Diameter (category)	Length (mm)
Enkling et al. (2017)	PS	20	One-piece	1.8 (I)	13–15
Temizel et al. (2017)	**PS**	**32**	**One-piece (I) Two-piece (C)**	**1.8–2.4 (I) 3.3–3.7 (C)**	**13–15 (I) 11–13 (C)**
Zygogiannis, Wismeijer and Parsa (2016)	PS	10	One-piece	1.8–2.4 (I)	10–15
Schwindling and Schwindling (2016)	RS	25	One-piece	1.8, 2.1, 2.4 (I)	10–18
Anitua et al. (2016)	**RS**	**20 (II) ND (C)**	**Two-piece**	**2.5 (I) ND (I)**	**10 –15 (I) ND (C)**
Lambert, Botilde, Lecloux and Rompen (2016)	PS	20	One-piece	2.0, 2.5 (I)	10–13
de Souza et al. (2015)	**RCT**	**120**	**One-piece**	**2.0 (I) 4.0 (C)**	**10**
Mundt, Schwahn, Stark and Biffar (2015)	RS	133	One-piece	1.8, 2.1, 2.4 (I)	10–18
Maryod, Ali and Shawky (2014)	PS	36	One-piece	1.8 (I)	15
Preoteasa et al. (2014)	PS	23	One-piece	1.8, 2.1, 2.4 (I)	10–18
Mangano et al. (2013)	PS	16	One-piece	2.7 (I)	10–13
Tomasi, Idmyr and Wennstrom (2013)	PS	21	One-piece	1.8, 2.1, 2.4 (I)	7–14
Elsyad, Gebreel, Fouad and Elshoukouki (2011)	PS	28 (49–75; 63)	One-piece	1.8 (I)	12–18
Jofre, Cendoya and Munoz (2010), Jofre, Hamada, Nishimura and Klattenhoff (2010)	RCT	45 (45–90)	One-piece	1.8 (I)	15
Anitua et al. (2010)	RS	51 (19–90; 55)	One-piece	2.5 (I)	10–15
Balaji, Mohamed and Kathiresan (2010)	RS	11 (20–52; 29)	One-piece	2.4 (I)	13
Anitua et al. (2008)	**RS**	**ND**	**Two-piece**	**2.5 (I) 3.75 (C)**	**10–15 7.5–18**
LaBarre, Ahlstrom and Noble (2008)	RS	ND	ND	1.8–2.4 (I)	ND
Morneburg and Proschel (2008)	PS	67 (53–83; 69)	One-piece	2.5 (I)	9, 12, 15
Froum, Cho, Cho, Elian and Tarnow (2007)	RS	27	One-piece	1.8–2.4 (I)	7–14
Shatkin, Shatkin, Oppenheimer and Oppenheimer (2007)	RS	531	ND	1.8–2.4 (I)	ND
Vigolo and Givani (2000)	RS	44 (18–74; 35)	Two-piece	2.9 (I)	8.5, 10, 13, 15

Studies included in meta-analysis are highlighted with bold characters; MAX, maxilla; MAN, mandible; ND, no data available or data cannot be separated; PS, prospective study; RS, retrospective study; RCT, randomized controlled trial. I, Category 1 (narrow diameter implants); II, Category 2 (narrow diameter implants); C, Control (standard diameter implants).

TABLE 3 (additional columns)

No. of implants	Indication (jaw region)	Follow-up (months: range; mean)	Implant failures; survival rate	Implant success rate	Mean marginal bone loss (mm)
80	Edentulous jaw (MAN)	12	0; 100%	ND	ND
99 (I) 35 (C)	**Edentulous jaw (MAN)**	**24**	**0; 100% (I) 1; 97.1% (C)**	**ND**	**ND**
110	Edentulous jaw (MAN)	18	0; 100%	ND	−1.05 ± 0.81 (mesial, 18 months) −1.02 ± 0.7 (distal, 18 months)
99	Edentulous jaw (MAN)	33 (2–87)	8; 91.9%	ND	ND
37 (II) 160 (C)	**Fixed prostheses (MAN + MAX)**	**78 (0–116) ND (C)**	**1; 97.3% (II) 1; 99.3% (C) $p = 0.267$**	**ND**	**−0.70 ± 0.55 (mesial, 78 months) −0.72 ± 0.56 (distal, 78 months)**
30	Temporary restorative option (MAN + MAX)	42	1; 96.6%	ND	ND
236 (I) 152 (Ia with 4 NDI) 84 (Ib with 2 NDI) 80 (with 2 SDI)	**Edentulous jaw (MAN)**	**12**	**31; ND 16; 89% (Ia) 15; 82% (Ib) 1; 99% (C)**	**ND**	**ND**
MAX: 336 MAN: 402	Edentulous jaw (MAX, MAN)	MAX: 27.1 MAN: 29.4	MAX: 15; 94.3% (5-year) MAN: 11; 95.7% (5-year)	ND	ND
144	Edentulous jaw (MAN)	36	7 of 120; 94.2%	ND	ND
110	Edentulous jaw (MAX, MAN)	36	8; 92.7%	ND	ND
22	Fixed Partial Prostheses (MAN + MAX)	24	0; 100%	ND	ND
80	Edentulous jaw (MAX, MAN)	12	16; 80%	ND	ND
112	Edentulous jaw (MAN)	36	4; 96.4%	92.9%	−1.26 ± 0.6 (36 months)
90	Edentulous jaw (MAN + MAX)	15–24	0; 100%	ND	−1.43 ± 1.26 (24 months, ball-retained) −0.92 ± 0.75 (24 months, bar-retained)
31	ND (MAN + MAX)	48	1; 98.9%	ND	−1.26 ± 0.5 (24 months)
11	Anterior single-tooth restoration(MAN + MAX)	24	1; 90.9%	ND	−0.6 (24 months)
38 1654	**ND ND**	**29**	**1; 97.4% (I) 9; 99.5% (C)**	**ND ND**	**ND ND**
626	ND	72	46; 92,6%	ND	ND
134	Edentulous jaw (MAN)	72	6; 95.5%	ND	−0.7 ± 0.4 (24 months)
48	Anterior single-tooth restoration (MAN + MAX)	12–64	0; 100%	ND	ND
2514	ND (MAN + MAX)	35	145; 94.2%	ND	ND
52	Single-tooth restorations and partial prostheses (MAX + MAN)	60	3; 94.2%	ND	−0.8 mm (0.5–1.1 mm) (60 months)

TABLE 4 Summary of included studies of Category 2, continuation of Klein et al. (2014) [In PDF format, this table is best viewed in two-page mode]

Study	Study type	No. of patients	Implant design	Diameter (category)	Length (mm)	No. of implants
Pieri et al. (2017)	**RS**	**127**	**Two-piece**	**3.0 (II) 4.0–4.5 (C)**	**11–15**	**113 (II) 126 (C)**
Aunmeungtong et al. (2017)	**RCC**	**60**	**One-piece**	**3.0 (II) 3.75 (C)**	**12 (II) 10 (C)**	**40 (II) 20 (C)**
King et al. (2016)	PS	38	Two-piece	3.0 (II)	11–15	62
Maiorana et al. (2015)	PS	69	Two-piece	3.0 (II)	11–15	97
Pieri et al. (2014)	PS	50	Two-piece	3.0 (II)	11–15	50
Lauritano, Grassi, di Stasio, Lucchese and Petruzzi (2014)	RS	21	One-piece	3.0 (II)	≤12	84
Mangano et al. (2013)	PS	16	One-piece	3.2 (II)	10–13	15
Mazor, Lorean, Mijiritsky and Levin (2012)	RS	33 (23–76; 49.2)	Two-piece	3.0 (II)	13	66
Oyama, Kan, Rungcharassaeng and Lozada (2012)	PS	13 (18–84; 32.9)	Two-piece	3.0 (II)	ND	17
Galindo-Moreno et al. (2012)	PS	69 (32 ± 17)	Two-piece	3.0 (II)	11; 13; 15	97
Zembic et al. (2012)	RS	47 (17–76; 31)	One-piece	3.0 (II)	13, 15	57
Sohn et al. (2011)	RS	36 (42–72; 53)	One-piece	3.0 (II)	12, 15	62
Anitua et al. (2010)	RS	51 (19–90; 55)	Two-piece	3.0 (II)	10–15	58
Degidi, Nardi and Piattelli (2009a)	PS	40 (55 ± 17)	Two-piece	3.0 (II)	11;13,15	93
Degidi, Nardi and Piattelli (2009b)	RCT	60 (18–55; 32)	Two-piece	3.0 (II)	13; 15	60 30 (immediate loading) 30 (one-stage loaded)
Reddy, O'Neal, Haigh, Aponte-Wesson and Geurs (2008)	RS	17 (19–74)	One-piece	3.0 (II)	ND	31
Anitua et al. (2008)	**RS**	**ND**	**Two-piece**	**3.0 (II) 3.75 (C)**	**10–15**	**69 (II) 1654 (C)**
Andersen et al. (2001)	**PS**	**55**	**Two-piece**	**3.25 (II) 3.75 (C)**	**13–15**	**60 32 (II) 28 (C)**
Polizzi, Fabbro, Furri, Herrmann and Squarzoni (1999)	RS	21 (13–58; 30)	Two-piece	3.0 (II)	10, 13, 15	30

Studies included in meta-analysis are highlighted with bold characters; MAX, maxilla; MAN, mandible; ND, no data available or data cannot be separated; PS, prospective study; RS, retrospective study; RCT, randomized controlled trial. I, Category 1 (narrow diameter implants); II, Category 2 (narrow diameter implants); C, Control (standard diameter implants).

TABLE 4 (additional columns)

Indication (jaw region)	Follow-up (months: range; mean)	Implant failures; survival rate	Implant success rate	Mean marginal bone loss (mm)
Posterior splinted partial fixed restoration (MAX, MAN)	**60**	**2; ND (II) 4; ND (C) $p = 0.37$**	**ND**	**−0.95 ± 0.84 (II) −1.2 ± 0.86 (C) $p = 0.06$ (60 months)**
Edentulous jaw (MAN)	**12**	**0; 100% (II) 0; 100% (C)**	**0; 100% (II) 0; 100% (C)**	**−0.53 ± 0.41 (IIa) −0.60 ± 0.45 (IIb) −1.33 ± 0.6 (C) (12 months)**
Anterior region (MAX, MAN)	36	2; 96.8%	ND	−0.23 (36 months)
Anterior region (MAX, MAN)	36	4; 95.9%	ND	−0.09 (36 months)
Anterior region (MAX, MAN)	36	0; 100%	100%	−0.24 ± 0.15 (36 months)
Anterior region (MAN)	12	10; 80.5%	ND	ND
Fixed Partial Prostheses (MAN, MAX)	24	0; 100%	ND	ND
Single-tooth restoration (MAN + MAX)	12 ± 1.9	0; 100%	ND	ND
Single-tooth restoration of incisors (MAN + MAX)	12	0; 100%	ND	−0.38 ± 0.36 (12 months)
Anterior region (MAN + MAX)	12	4; 95.9%	ND	−0.7 ± 1.0 (12 months)
Single-tooth restoration in anterior region (MAX + MAN)	13 (9.8–20.8)	1; 98%	ND	−1.6 ± 1.2 (12 months)
Maxillary lateral incisors and mandibular incisors (MAN + MAX)	23 ± 4.3	0; 100%	100%	−0.53 ± 0.37 (12 months)
Mixed Indications (MAN + MAX)	48	1; 96.8%	ND	−1.26 ± 0.5 (24 months)
Fixed partial posterior restorations (MAX, MAN)	48	0; 100%	ND	−1.16 ± 0.9 (48 months)
Single lateral incisor (MAX)	36	0; 100% 0; 100% (immediate loading) 0; 100% (one-stage loaded)	ND	−0.85 ± 0.7 (immediate loading, 36 months) −0.75 ± 0.6 (one-stage loaded, 36 months)
Single-tooth restoration in anterior region (MAN + MAX)	12	1; 96,7%	ND	−0.7 (12 months)
ND	**29**	**0; 100% 9; 99.5%**	**ND**	**ND**
Anterior region (MAX)	**36**	**2; 93.8% 0; 100%**	**ND**	**−0.5 ± 0.0 (II; 36 months) −0.4 ± 0.2 (C; 36 months)**
Single-tooth restoration of incisors (MAN + MAX)	63	1; 96,7%	ND	Minimal marginal bone loss after 12 months

TABLE 5 Summary of included studies of Category 3, continuation of Klein et al. (2014) [In PDF format, this table is best viewed in two-page mode]

Study	Study type	No. of patients	Implant design (one-piece: I; two-piece: II)	Diameter	Length (mm)
Hasegawa et al. (2017)	RS	242	Two-piece	3.3 (III) 3.75–5 (C)	10–15 (III) 7–18 (C)
Schiegnitz et al. (2016)	**RS**	**90**	**Two-piece**	**3.3 (II) 4.1 (C1) 4.8 (C2)**	**8–14**
Woo, Kim, Kang, Kim and Yang (2016)	RS	66	Two-piece	3.5 (III)	8–11
Herrmann et al. (2016)	**RS**	**107 (III) 204 (C)**	**Two-piece**	**3.3 (III) 4.1–4.8 (C)**	**8–14 (III) 12–14 (C)**
Zembic, Tahmaseb, Jung and Wismeijer (2016)	PS	20	Two-piece	3.3 (III)	8–12
Tolentino et al. (2016)	RCT	10	Two-piece	3.3 (III) TiZr vs. Ti	
Moraguez, Vailati, Grutter, Sailer and Belser (2017)	PS	10	Two-piece	3.3 (III)	10–12
Muller et al. (2015)	RCT	91	Two-piece	3.3 (III)	8–14
Al-Nawas et al. (2015)	PS	359	Two-piece	3.3 (III)	8–14
Temmerman, Keestra, Coucke, Teughels and Quirynen (2015)	PS	28	Two-piece	3.5 (III)	8–15
Ioannidis et al. (2015)	**RCC**	**20 (III) 20 (C)**	**Two-piece**	**3.3 (III) 4.1 (C)**	**≥ 8**
Quirynen et al., 2015 (Quirynen et al., 2015)	RCT	89	Two-piece	3.3 (III) TiZr vs. Ti	8–14
Zweers et al. (2015)	**RS**	**119**	**Two-piece**	**3.3 (III) 4.1 (C)**	**8–14 (III) 10–14 (C)**
Lambert et al. (2015)	PS	20	Two-piece	3.3 (III)	ND
El-Sheikh and Shihabuddin (2014)	PS	20	Two-piece	3.3 (III)	8–12
Mangano et al. (2014)	PS	279	Two-piece	3.3 (III)	8–14
Tolentino et al. (2014)	PS	42	Two-piece	3.3 (III) TiZr vs. Ti	8–12
Benic et al. (2013)	**RCC**	**40**	**Two-piece**	**3.3 (TiZr, III) 4.1 (Ti, C)**	**8–14**
Cordaro, Torsello, Mirisola di Torresanto and Baricevic (2013)	RS	10	Two-piece	3.3 (III)	10–12
Lee et al. (2013)	RS	338	Two-piece	3.3–3.5 (III)	10–13
Barter, Stone and Bragger (2012)	PS	22	Two-piece	3.3 (III)	ND

(Continues)

TABLE 5 (additional columns)

No. of implants (category)	Indication (jaw region)	Follow-up (months: range; mean)	Implant failures; survival rate	Implant success rate	Mean marginal bone loss (mm)
132 (III) 775 (C)	Mixed indications (MAN, MAX)	71.3 (12–137)	4; 97% (III) 19; 97% (C) $p = 0.762$	ND	ND
24 (III) 138 (C1) 27 (C2)	**Mixed indications (MAN, MAX)**	**62 ± 3.1**	**1; 95.8% (III) 6; 95.7% (C1) 0; 100% (C3)**	**ND**	**ND**
98	Posterior edentulous region (MAN, MAX)	37.45 ± 12.80	0; 100%	ND	−0.14 ± 0.39 (37.45 months)
154 (III) 396 (C)	**Mixed indications (MAN, MAX)**	**22.4 ± 8.2 (III) 28.4 ± 10.1 (C)**	**4; 97.4% (III) 6; 98.5% (C)**	**ND**	**ND**
40	Edentulous jaw (MAX)	12	1 of 38; 97.3%	ND	−0.7 ± 1.1 (12 months)
20	Single restorations in the posterior region (MAN)	12	0; 100%	100%	−0.32 ± 0.27 (TiZr) −0.35 ± 0.24 (Ti) $p = 0.60$ (12 months)
20	Fixed dental prostheses for incisors (MAX)	60	0; 100%	ND	−2.17 ± 0.38 (60 months)
182 91 (TiZr) 91 (Ti)	Edentulous jaw (MAN)	60	1; 98.9% (TiZr) 2; 97.8% (Ti)	95.8% (TiZr) 92.6% (Ti)	−0.60 ± 0.69 (TiZr) −0.61 ± 0.83 (Ti) (60 months)
603	Mixed indications (MAN, MAX)	24	10 of 409; 97.6%	97.4%	No bone loss was at 81.2% of implants
100	Mixed indications (MAN, MAX)	36	0; 100%	ND	−0.18 ± 0.55 (36 months)
20 (III) 20 (C)	**Anterior and premolar single crowns (MAN, MAX)**	**36**	**0; 100% (III) 0; 100% (C)**	**ND**	**−0.10 (III) −0.21 (C) (36 months)**
75 (TiZr) 75 (Ti)	I (MAN)	36	1; 98.7% (TiZr) 2; 97.3% (Ti)	98.7% (TiZr) 97.3% (Ti)	−0.78 ± 0.75 (TiZr) −0.60 ± 0.71 (Ti) (36 months)
238 150 (III) 88 (C)	**Edentulous jaw (MAN)**	**36**	**0; 100% (III) 0; 100% (C)**	**ND**	**−0.32 (III) −0.14 (C) $p = 0.002$ (36 months)**
39	Temporary implants in anterior regions (MAX, MAN)	12	2 of 38; 94.7%	94.7%	−0.35 (12 months)
40	Posterior fixed partial dentures (MAN, MAX)	12	0; 100%	ND	−0.49 to 0.6 (12 months)
324	Mixed indications (MAN, MAX)	64.8	4 of 320; 98.7% at 10-year follow-up	ND	−0.69 ± 0.28 (120 months)
21 (TiZr) 21 (Ti)	Single restorations (MAN, MAX)	12	1; 95.2% (TiZr) 1; 95.2% (Ti)	95.2% (TiZr) 95.2% (Ti)	ND
20 (III) 20 (C)	**Anterior and premolar single crowns (MAX, MAN)**	**12**	**0; 100% (III) 0; 100% (C)**	**ND**	**−0.41 ± 0.66 (III) −0.40 ± 0.53 (C) $p = 0.696$ (12 months)**
40	Edentulous jaw (MAX)	13.5 (12–16)	0; 100%	97.5%	−0.55 ± 0.5 (13.5 months)
541	Fixed dental prostheses (MAN, MAX)	58.8	9; 98.1% (12-year survival)	91,8%	0.07 ± 0.20 (annual change)
22	Mixed indications (MAN, MAX)	24	1; 95.2%	ND	−0.33 ± 0.54 (24 months)

(Continues)

TABLE 5 (Continued) [In PDF format, this table is best viewed in two-page mode]

Study	Study type	No. of patients	Implant design (one-piece: I; two-piece: II)	Diameter	Length (mm)
Malo and de Araujo Nobre (2011)	RS	147	Two-piece	3.3 (III)	10; 11.5; 13; 15
Yaltirik, Gokcen-Rohlig, Ozer and Evlioglu (2011)	RS	28	Two-piece	3.3 (III)	10, 12, 14
Al-Nawas et al. (2011)	RCT	89	Two-piece	3.3 (III) TiZr vs. Ti	8–14
Arisan et al. (2010)	RS	139	Two-piece	3.3 (III) 3.4 (III)	8–14 9.5–15
Veltri, Ferrari and Balleri (2008)	RS	12	Two-piece	3.5 (III)	9, 13, 15, 17
Anitua et al. (20082008**)**	**RS**	**ND**	**Two-piece**	**3.3 (III) 3.75 (C)**	**8.5–18 7.5–18**
Cordaro, Torsello, Mirisola Di Torresanto and Rossini (2006)	RS	31	Two-piece	3.5 (III)	10; 12
Romeo et al. (2006)	**RS**	**188**	**Two-piece**	**3.3 (III) 4.1 (C)**	**10, 12**
Zarone, Sorrentino, Vaccaro and Russo (2006)	PS	30	Two-piece	3.3 (III)	10, 12, 14
Zinsli, Sagesser, Mericske and Mericske-Stern (2004)	PS	149	Two-piece	3.3 (III)	8, 10, 12
Hallman (2001)	PS	40	Two-piece	3.3 (III)	8, 10, 12
Haas et al. (1996)	**RS**	**607**	**Two-piece**	**3.3 (III) 4.0 (C)**	**10, 13, 15**
Lazzara et al. (1996)	**RS**	**ND**	**Two-piece**	**3.3 (III) 3.3 (III) 4.0 (C) 4.0 (C)**	**ND**
Spiekermann et al. (1995)	**RS**	**136**	**Two-piece**	**3.3 (III) 4.0 (C) 4.0 (C)**	**ND**

Studies included in meta-analysis are highlighted with bold characters; MAX, maxilla; MAN, mandible; ND, no data available or data cannot be separated; PS, prospective study; RS, retrospective study; RCT, randomized controlled trial. I, Category 1 (narrow diameter implants); II, Category 2 (narrow diameter implants); C, Control (standard diameter implants).

Caution in the use of NDI has been recommended in posterior regions because of concerns regarding reduced osseointegration surface, an increased probability of fracture compared with SDI and disadvantageous peri-implant crestal bone resorption due to stress values affecting the crestal cortical bone, which are reciprocal to the implant diameter (Pieri, Forlivesi, Caselli & Corinaldesi, 2017). Regarding bone stability, the included studies showed comparable peri-implant bone loss for NDI compared to SDI. However, longer follow-up studies are needed to confirm these results. A recent study of Pieri et al. that investigated fixed partial denture treatment in posterior mandibular and maxillary jaws with NDI of Category 2 or SDI showed higher implant survival and lower biological complications for SDI, however, not statistically significant (Pieri et al., 2017). In contrast, a higher

TABLE 5 (additional columns - continued)

No. of implants (category)	Indication (jaw region)	Follow-up (months: range; mean)	Implant failures; survival rate	Implant success rate	Mean marginal bone loss (mm)
247	Posterior region (MAN + MAX)	60	12; 95.1%	ND	1.74 ± 0.9 mm (120 months)
48	Mixed indications (MAX + MAN)	60	3; 93.75%	ND	ND
178, 89 (TiZr), 89 (Ti)	Edentulous jaw (MAN)	12	3; 98.3% 1; 98.9% (TiZr) 2; 97.8% (Ti)	96.6% 94.4%	−0.3 ± 0.5 (12 months) −0.3 ± 0.6 (12 months)
316, 235, 81	ND	109 (60–124)	14; 92.3% 5; 97.9% 9; 88.9%	91.4%	−1.3 ± 0.1 (120 months)
73	Edentulous jaw (MAX)	12	0; 100%	ND	0.30 ± 0.13 (12 months)
804, 1654	**ND ND**	**29**	**8; 99% (III) 9; 99.5% (C)**	**ND ND**	**ND ND**
44	Incisors (MAN)	23 (18–42)	0; 100%	94%	ND
122, 208	**ND (MAN + MAX) ND (MAN + MAX)**	**84**	**III MAX: 1; 98.1% III MAN: 2; 96.9% C MAX: 1; 98.8% C MAN: 2; 97.9%**	**III MAX: 96.1% III MAN: 92% C MAX: 97.6% C MAN: 93.8%**	**III: 1.5 ± 1.5 mm C: 1.4 ± 1.1 mm (84 months)**
34	Edentulous jaw (MAX)	39	0; 97.06%	94.12%	1.2 ± 0.6 mm (24 months)
298	Mixed indications (MAX + MAN)	60	9; 98.7%	ND	ND
160	ND (MAN + MAX)	12	1; 99.4%	96.3%	−0.35 ± 1.05 (12 months)
1920, 198, 1722	**ND (MAN + MAX)**	**27**	**86; 95.5% 14; 92.9% (III) 72; 95.8% (C)**	**ND**	**ND**
82, 120, 147, 279	**ND (MAN) ND (MAX) ND (MAN) ND (MAX)**	**60**	**3 of 76; 96% 5 of 112; 95,5% 7 of 139; 95% 22 of 267; 92%**	**ND**	**ND**
127, 99, 38	**ND**	**60**	**8; 91% 7; 95% 3; 97%**	**ND**	**0.34 ± 0.52 mesial, 0.36 ± 0.49 distal 0.26 ± 0.35 mesial, 0.29 ± 0.34 distal 0.53 ± 0.53 mesial, 0.54 ± 0.619 distal (60 months)**

risk of prosthetic complications was seen for NDI. These complications include abutment and implant fracture, screw loosening or fracture, and ceramic fracture (Allum, Tomlinson & Joshi, 2008; Assaf, Saad, Daas, Abdallah & Abdallah, 2015). This increased biomechanical risk is explained by minor mechanical properties of the components due to their smaller dimensions and material composition (Assaf et al., 2015). As always, the patients have to be informed in detail about all possible treatment options with their possible advantages and disadvantages and the practitioner should have the knowledge to offer all of these treatment options.

As a consequence of new product developments in the dental implant market with new designs such as two-piece 2.9 mm implants, we suggest a new classification for NDI that considers

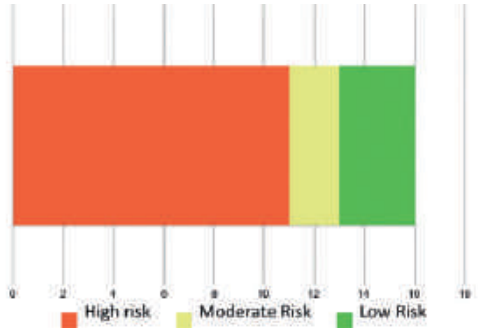

FIGURE 2 Risk of bias across studies

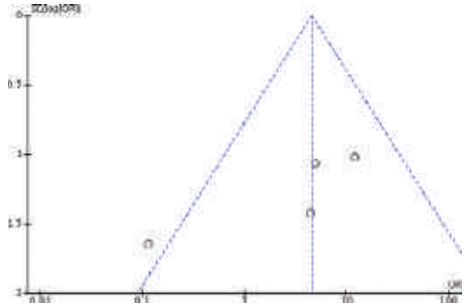

FIGURE 4 Funnel plot calculated for selected studies reporting on NDI (Category I) vs. SDI

TABLE 6 The number of inserted dental implants for the different diameter categories

Category	Diameter (mm)	Number of studies	Number of implants
1	1.8	3	346
	1.8–2.4	10	4,504
	2.0	1	236
	2.4	1	11
	2.5	5	270
	2.7	1	22
	2.9	1	52
2	3.0	17	1,086
	3.2	1	15
	3.25	1	32
3	3.3	29	4,440
	3.3, 3.4	1	316
	3.5	4	315
	3.3–3.5	1	541

more precisely the described indications in the recent literature. However, due to the high risk of bias and heterogeneity in the included studies, further clinical studies have to prove the long-term success of NDI.

Category 1: Implants with a diameter of < 2.5 mm ("mini-implants"), described mostly for the highly atrophic edentulous arch and for single non-load-bearing teeth in the frontal region.

Category 2: Implants with a diameter of 2.5 mm to <3.3 mm, described mostly for single-tooth restoration in the anterior region (mainly to replace the maxillary lateral or mandibular incisor teeth).

Category 3: Implants with a diameter of 3.3 mm to 3.5 mm, described for all regions, including posterior single-tooth restorations.

To date, most implants of category 1 are one-piece implants. One-piece implants with a diameter of more than 3.0 mm are rarely described in the literature.

5 | CONCLUSION

Within the limits of this meta-analytic approach to the literature with the identified high risk of bias and heterogeneity in the included studies therein, the included studies describe NDI as a possible treatment alternative with promising survival rates. Their clinical advantage might be in the extension of treatment options. NDI of Category 1 performed statistically significantly worse than SDI and were mainly described for the rehabilitation of the highly atrophic maxilla or mandible. Category 2 and Category 3 NDI indicated no difference in implant survival compared to SDI. Implants of Category 2 were mostly used for the rehabilitation of limited interdental spaces in anterior single-tooth restorations. NDI of Category 3 were described in all regions, including posterior single-tooth restorations. However, long-term data are rare and there is a lack of data on peri-implant tissue values and prosthetic considerations, for example, the possible risk of biological and technical complications with wide platform teeth on NDI. These parameters have to be evaluated in future clinical studies.

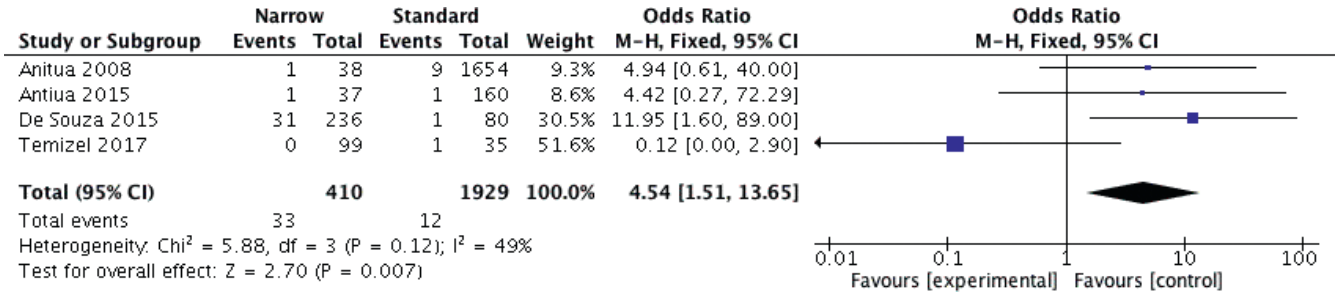

FIGURE 3 Forest plot of survival of NDI (Category I) vs. SDI

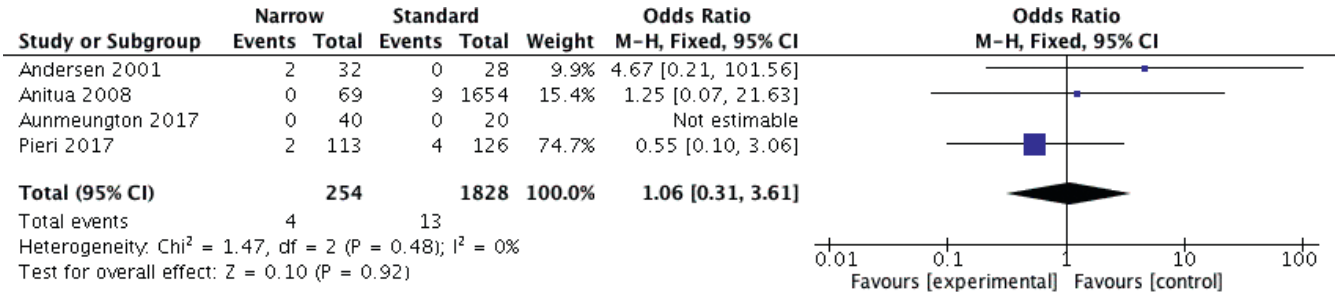

FIGURE 5 Forest plot of survival of NDI (Category 2) vs. SDI

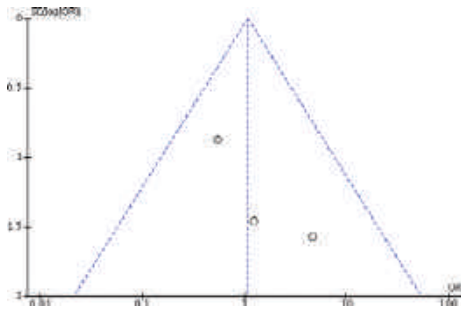

FIGURE 6 Funnel plot calculated for selected studies reporting on NDI (Category II) vs. SDI

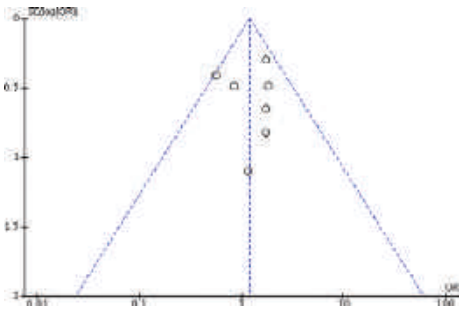

FIGURE 8 Funnel plot calculated for selected studies reporting on NDI (Category III) vs. SDI

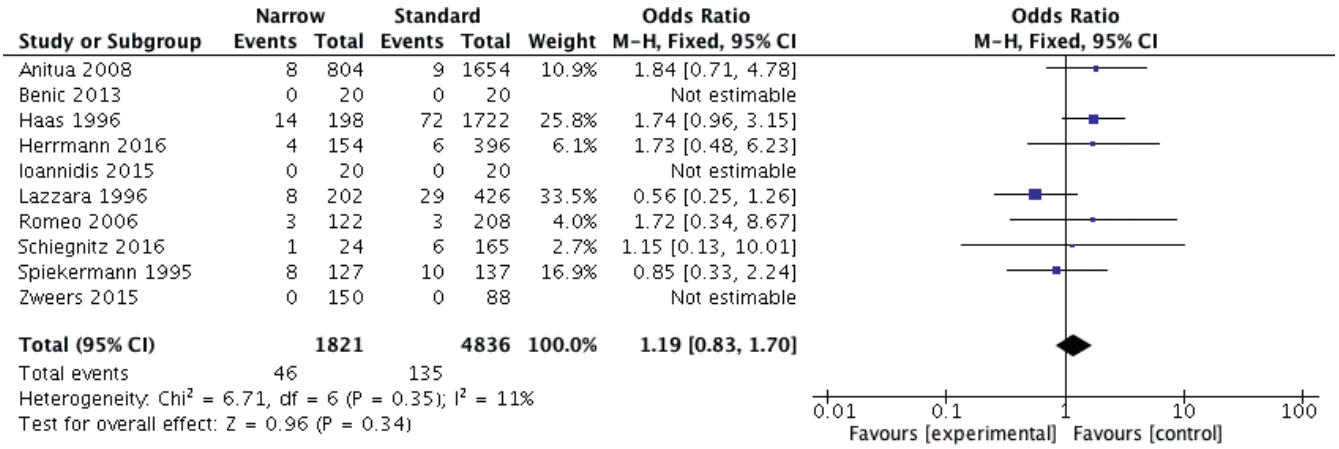

FIGURE 7 Forest plot of survival of NDI (Category 3) vs. SDI

CONFLICT OF INTEREST

Dr. Eik Schiegnitz reports lectures, personal fees and/or grants from Dentsply, Geistlich, Medartis, Septodont and Straumann outside the submitted work. Prof. Dr. Bilal Al-Nawas reports lectures, personal fees and/or grants from Camlog, Dentsply, Geistlich, Medartis, Nobel Biocare, Straumann and Zimmer outside the submitted work.

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REVIEW ARTICLE

WILEY CLINICAL ORAL IMPLANTS RESEARCH

Systematic review of clinical and patient-reported outcomes following oral rehabilitation on dental implants with a tapered compared to a non-tapered implant design

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Abstract

Background: Dental implants are available in different shapes.

Aims: This systematic review aims to address whether tapered compared to non-tapered implants demonstrate similar clinical and patient-reported outcomes. The review follows the preferred reporting items for systematic reviews and meta-analyses (PRISMA) format.

Materials & Methods: We searched electronic databases including MEDLINE through PubMed and the Cochrane Central Register of Controlled Trials for randomized clinical trials (RCT) that compare tapered versus non-tapered implants with at least 10 treated participants and a minimum mean follow-up time of 3 years. There were no restrictions to a particular treatment indication or outcome measures. Two authors independently conducted screening, risk of bias assessment, and data extraction of eligible trials in duplicate. We applied the Cochrane risk of bias assessment tool to consider risk of bias.

Results: We identified 18 different RCTs, of which three reported outcomes at 3 years or greater. The three trials described the results of 245 participants with 388 implants at 3 years, from the initially 306 participants with 494 implants at baseline. The three trials compared, respectively, two, two, and three different commercially available implant brands and reported only clinically insignificant differences. We judged all three trials to be at moderate risk of bias. The low number and heterogeneity of RCTs did not allow for meta-analyses.

Discussion and conclusion: Appropriate professional judgment in clinical decision making must include a comprehensive diagnosis of the patient's jawbone quality and quantity and consideration of osteotomy protocol in accordance with the patient's treatment preferences, where the shape of the dental implant is only one contributory factor.

KEYWORDS

clinical decision making, humans, osteotomy, randomized controlled trials

1 | INTRODUCTION

The dental implant market has increased tremendously over the last 15 years, reflected by the number of available implant brands. In 2003, some 80 manufacturers produced an estimated 220 different implant brands (Jokstad et al., 2003). Today, the numbers have proliferated to an estimated 500 manufacturers producing 4,000 different implant brands. Different resources on the Internet attempt to keep track of the plethora

of brands with varying success. To the authors' knowledge, the most comprehensive resource (Osseosource.com) identifies about 2,000 different dental implants. A noteworthy trait is that in 2003, there were about 12 implant brands identified by having a "tapered" implant body (Jokstad et al., 2003), while today, about 50% of all implant brands on the market are "tapered." For example, the cited Web site (Osseosource.com) lists 908 tapered and 1,082 cylindrical root-formed dental implants. Even though the exact number of manufacturers and implant brands is unknown, it is clear that the industry has responded to the demand from the clinicians to manufacture dental implants marketed as "tapered," "conical," "ovoid," "root formed," or derivatives of these terms.

The alleged clinical benefits of using tapered rather than non-tapered implants under different clinical circumstances focus on enhanced "primary stability." This quantity is represented by measurements of implant insertion torque, named by some previously as implant placement resistance, alternatively by resonance frequency analysis (RFA). Special emphasis is on implants placed in soft bone (O'Sullivan, Sennerby & Meredith, 2000) or extraction sockets (Martinez, Davarpanah, Missika, Celletti & Lazzara, 2001), eventually in combination with implant site preparation using twist drills with a diameter less than the diameter of the implant, dubbed, for example, as "soft-bone protocols" or as "under-preparation" (O'Sullivan, Sennerby, Jagger & Meredith, 2004). The long-term clinical and patient-reported outcomes following oral rehabilitation using dental implants with a tapered design compared to a non-tapered appear not to have been systematically reviewed and critically appraised.

A tapered dental implant, often named "conical" in several non-English languages, is identifiable by displaying some convergence of the implant outer walls toward the apex of the endosseous part of the implant body, that is, the portion of the implant body intended to be positioned within the bone. Implants with diverging walls coronally from the crestal bone are not considered as "tapered" in the literature. For example, the ITI Type F-implant, perhaps better known today as the Straumann tissue-level implant, was originally described by its developers as having a "cup-" (Sutter & Schroeder, 1988), alternatively a "trumpet-shaped" (Scacchi, 2000) coronal neck, but is not considered tapered.

The literature provides little guidance on how to define the "tapered" dental implant. There are no textbook chapters or review papers specific to this topic. The term "tapered dental implant" is not defined in any international standards, including ISO-16443-2014 (ISO, 2014). The Glossary of Prosthodontic Terms (GPT-9) has defined "taper" in context with the axial walls of a tooth preparation, but nothing relative to dental implants (Academy of Prosthodontics, 2017). A third authoritative source, that is, The Glossary of Oral and Maxillofacial Implants, describes definitions of three different dental implant body designs, that is, cylindrical, stepped, and tapered (Laney, 2007a,b,c). While the explanations for cylindrical and stepped dental implants seem precise, the description of a tapered dental implant is clearly unsatisfactory for the purpose of this systematic review (SR). That is, "*Shape of an implant body when viewed in profile, lengthwise. A tapered implant usually narrows apically*" (Laney, 2007c). The first sentence applies to any geometric contour; while the second sentence would have been correct if "usually" had been omitted. For the purpose of this SR, we considered it necessary to develop a distinct definition of a "tapered dental implant." We therefore amended the definition for a stepped implant, that is, "*Specific implant shaft design that incorporates concentric steps that narrow in width toward the apex of the implant*" (Laney, 2007b). In the current SR, a tapered implant is recognized as a *cylindrical implant where the endosseous part narrows in diameter toward the apex*. This definition encompasses any dental implant where the diameter at the bone crest level is wider than the diameter at the apical end, and regardless of the vertical cervical–apical position of the narrowing along the longitudinal axis of the implant body. Hence, the definition encompasses all implants where the taper is located in the cervical, middle, or apical parts only, as well as implants that taper continuously from the cervical platform to the apex (Figure 1).

The objective of this SR was to address the question: In patients with dental implant restorations, do tapered compared to non-tapered implants demonstrate similar clinical and patient-reported outcomes?

2 | MATERIAL AND METHODS

2.1 | Protocol and registration

The protocol of this review was registered in the PROSPERO database in 2016 (registration number CRD42016049607) (www.crd.york.ac.uk/PROSPERO).

2.2 | Eligibility criteria

The criteria for study inclusion were a randomized clinical trial (RCT) comprising a comparison between a tapered versus non-tapered implant design with at least 10 treated study participants and a minimum mean follow-up time of 3 years. Exclusion criteria were RCTs (i)

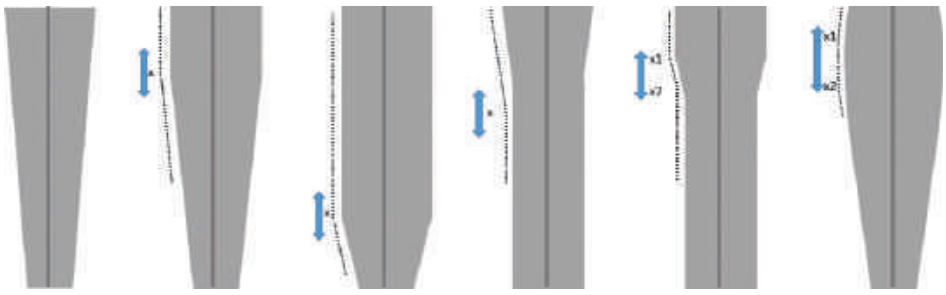

FIGURE 1 Examples of variations of tapering, which the definition in the current systematic review designates as "tapered" dental implants

using zygomatic or orthodontic implants, (ii) trials lacking any objective outcome measurements, (iii) trials with focus on post-restoration interventions of adverse treatment outcomes, for example, of peri-implantitis, dehiscence, fenestration, repairs, and (iv) trials that included study participants undergoing reconstructions due to extensive loss of oromaxillofacial tissues, for example, caused by trauma, cancer, or congenital defects. Only full publications in peer-reviewed scientific journals in English were considered for inclusion.

2.3 | Information sources and search

We searched MEDLINE through PubMed (URL: https://www.ncbi.nlm.nih.gov/pubmed, the Cochrane Central Register of Controlled Trials (CENTRAL) (URL: http://onlinelibrary.wiley.com/cochranelibrary/search and the personal bibliographical database of one of the authors (A.J.). The search strategy in Pubmed was as follows: *((jaw, edentulous [Mesh Term]) OR (edentulous) OR (edentulism)) AND (((((dental implantation, endosseous[MeSH Terms]) OR "dental implants"[MeSH Terms]) OR endosseous implant*) OR dental implant*))AND (taper* OR conical NOT connection*) AND (Success OR survival OR Function OR esthetic* OR complicat* OR maintenance OR Bone OR patient satisfaction OR quality of life OR treatment outcome[MESH Terms]).*

The Gray literature was assessed by searches in the abstract database of IADR (International Association for Dental Research) (URL: https://live.blueskybroadcast.com/bsb/client/_new_default.asp?action=HOME&Client=404900) as well as Google Scholar (URL: http://scholar.google.com). The final digital searches were completed in December 2017.

Digital searches were complemented with hand searching the reference lists of the publications identified digitally, and by browsing the most recent issues of the following scientific journals: Clinical Implant Dentistry and Related Research, Clinical Oral Implants Research, European Journal of Implantology, Implant Dentistry, International Journal of Oral Maxillofacial Implants, International Journal of Oral Maxillofacial Surgery, International Journal of Periodontics and Restorative Dentistry, International Journal of Prosthodontics, Journal of Clinical Periodontology, Journal of Dental Research, Journal of Oral Implantology, Journal of Oral and Maxillofacial Surgery, Journal of Oral Rehabilitation, and Journal of Periodontology.

2.4 | Study selection and data collection process

Two individuals screened for study eligibility of studies independently, and subsequently reached a consensus for inclusions. In situations with multiple publications from a single clinical study, the report with the longest follow-up time was selected for data extraction. However, earlier reports were appraised if particular details about materials and methods were lacking in the selected articles. We contacted the corresponding authors of the primary publications that reported an observation time less than 3 years to inquire about any existence of further publications.

2.5 | Data items

Data extracted from the individual studies included items 18–20 in the PRISMA checklist (Appendix S1), that is, (i) characteristics of the individual studies, (ii) risk of bias within the individual studies, and (iii) the results of individual studies. Characteristics of the individual studies included identification of the lead author and description of the study participants' condition, the years when the implants were placed, and whether the study was conducted in a single or multiple universities, public health, or private practice settings. The number of study participants and implants placed with the mean follow-up time was supplemented with a description of implant type(s) with details on design of taper. Details of the actual intervention included the following: (i) status of the pre-implant surgery situation, (ii) implant surgery details, (iii) the post-surgery details, and (iv) type of superconstruction.

2.6 | Risk of bias in individual studies

Elements that possibly could limit the study internal and external validity included an assessment of the stated study objective versus its conclusions, the choice and quality of statistical tests, and the source of funding of the study. The Cochrane risk of bias assessment tool (Higgins et al., 2011) was applied to estimate risk of bias of individual trials.

2.7 | Summary measures

The primary outcomes were complications associated with the surgery and restorative phase, implant and restoration success and survival, maintenance needs patient-reported function, satisfaction, quality of life, and aesthetics; all outcomes measured at 3 years or greater after implant placement. Secondary outcomes were peri-implant bone loss and peri-implant soft tissue indices established at 3 years or greater after implant placement.

2.8 | Synthesis of results and risk of bias across studies

The pre-hoc objective was to undertake meta-analyses and estimate risk ratios and differences in means. As the review progressed, it became clear that the evidence base was too weak for such statistical analyses. Hence, this SR does not include summary measures or formal statistics to examine possible publication bias or selective reporting.

2.9 | Additional analyses

No subgroup analyses were planned.

3 | RESULTS

3.1 | Study selection

We identified initially approximately 230 reports (Figure 2). After screening the abstracts, the great majority (n = 107) were considered not eligible according to the inclusion criteria. The predominant reasons were not an RCT trial (n = 59) or that the term "taper" or

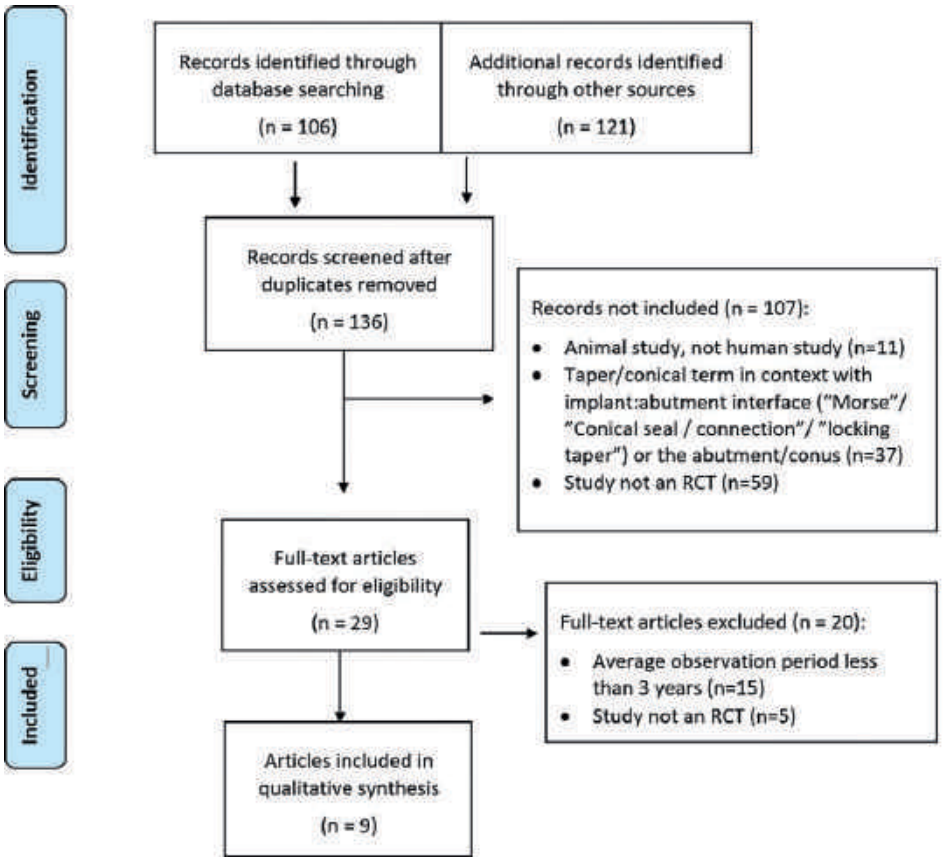

FIGURE 2 Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flowchart*. Reports on tapered versus non-tapered dental implant. *Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. PLoS Med 2009;6:e1000097

"conical" were descriptors of the interface between the implant and the abutment, for example, in context with "Morse taper," "conical seal/connection," or "locking taper," alternatively a description of the (non-endosseous) implant abutment or conus (*n* = 37). A third reason for ineligibility was that the study did not include human study participants (*n* = 11). The remaining 29 articles were read in full. Nine of these articles were selected for data extraction. The major reason for non-inclusion was a mean follow-up of less than 3 years (*n* = 15), and/or that the study was not an RCT (*n* = 5). The nine papers reported data from two industry-funded international multicenter parallel-group RCTs initiated in January 2006 (Cecchinato, Lops, Salvi & Sanz, 2015; Ferrus et al., 2010; Huynh-Ba et al., 2010; Sanz et al., 2010, 2014; Tomasi et al., 2010) and in April 2006 (Arnhart et al., 2012; Kielbassa et al., 2009), respectively, and from one non-sponsored split-mouth RCT conducted in a single university clinic in Rome, Italy and initiated in January 2010 (Pozzi, Tallarico & Moy, 2014) (Table 1).

It was planned initially to estimate by use of kappa statistics the strength of agreement between the two reviewers on abstract screening, full-text screening, and methodological quality assessment. However, the low yield of *n* = 3 RCTs that both raters agreed to include, hence inferring a $\kappa = 1$, rendered other formal calculations of kappa statistics inconsequential.

TABLE 1 Identified RCT trials (*n* = 3) from identified reports (*n* = 9)

RCT # 1, Implants placed between 2006.01 and 2008	
1. Cecchinato et al. (2015)	3-year data
2. Sanz et al. (2014)	3-year data
3. Tomasi et al. (2010)	<3-year data
4. Huynh-Ba et al. (2010)	<3-year data
5. Ferrus et al. (2010)	<3-year data
6. Sanz et al. (2010)	<3-year data
RCT #2, Implants placed between 2006.04 and 2007.05	
1. Arnhart et al. (2012)	3-year data
2. Kielbassa et al. (2009)	<3-year data
RCT # 3, Implants placed between 2010.01 and 2010.06	
Pozzi et al. (2014)	3-year data

3.2 | Study characteristics

The reports of the two parallel-group RCTs described outcomes after 3 years and the single split-mouth RCT after 3.5 years (Table 2). The first trial evaluated *Fixture Microthread Osseospeed* implants (Astra Tech, Mölndal, Sweden) with a straight versus a conical neck

TABLE 2 Study characteristics

RCT	Setting	Patient situation	N orig.	Implant product	Time (years)	N exam.	Outcomes (P)rimary (S)econdary
#1	Multicenter (4): University clinic, Madrid, Spain; Bern, Switzerland, Gothenburg, Sweden & Private practice, Rome, Italy	Partial & Single Maxilla Anterior.	95p. 101i.	(Astra Tech) Fixture MicroThreadOsseoSpeed Cyl: Cylindrical neck: ø3.5/4 mm Lengths 8/9 mm(51i.) Con: Conical neck: ø4.5-3.5(cervical)/5.0-4.5(apical) mm Lengths 11/13 mm(50i.) (Tapering in cervical third of body)	3	84p. 84i.	Primary: Thickness of the facial bone wall; clinical assessment[a] Secondary: • Crestal bone-level change; periapical radiographs • Soft tissue inflammation (0/1); clinical assessment and periodontal probe • Papilla fill (Jemt score); clinical assessment and periodontal probe • Soft tissue recession; clinical assessment and periodontal probe • BuccalBone; cone-beam computer tomography
#2	Multicentre (12): University clinics, Graz, Wien, Austria; Liege, Belgium; Berlin, Freiburg, Witten, Germany; Jerusalem, Israel; Milano, Rome, Italy; Madrid, Seville, Spain; Bern, Switzerland	Edentulous & Partial & Single Mandible & Maxilla.	177p. 325i.	(Nobel Biocare) ø3.5/4.3 mm Lengths 8-16 mm T1a: NobelActive(117i.) T1b: NobelActive (OnePiece) (82i.) T2: Nobel Replace-Tapered (126i.) (Both tapered, but different tapering)	3	127p. 236i.	Primary: Marginal bone-level change; periapical radiographs Secondary: • Implant survival and success according to criteria described by van Steenberghe (1997) • All adverse events • Soft tissue parameters, sulcus bleeding (0,1,2), plaque score (0,1) & papilla fill (Jemt score); clinical assessment and periodontal probe
#3	University Clinic, Rome, Italy	Partial or Bilateral single Mandible Posterior.	No drop-out	(Nobel Biocare) Lengths 10/11.5 mm T1: NobelActive: ø3.9 mm T2: Nobel Speedy Groovy: ø4.1 mm (Both tapered, but different tapering)	3.5	34p. 68i.	Primary: Success of implants and prostheses Secondary: • Marginal bone-level change; periapical radiographs • Periodontal-indices/soft tissue parameters, sulcus bleeding (0-3), plaque score (0,1) & papilla fill; clinical assessment and plastic periodontal probe • Implant stability;(RFA) at 4 months

[a]Per clinicaltrials.gov, registration NCT00711282.

Con, conical; Cyl, cylindrical; i, implant; p, patient; RFA, resonance frequency analysis; T, test group.

immediately following tooth extractions (Cecchinato et al., 2015; Ferrus et al., 2010; Huynh-Ba et al., 2010; Sanz et al., 2010, 2014; Tomasi et al., 2010). The two other RCTs compared *NobelActive* implants (Nobel Biocare, Gothenburg, Sweden) versus *NobelReplace* (Arnhart et al., 2012; Kielbassa et al., 2009), respectively, *NobelSpeedy* (Pozzi et al., 2014) implants placed in healed sites. All three implant designs display a taper, but differ with regard to degree of taper and configuration of the screw threads. The rates of dropouts of study participants ranged between none among 34 patients with 68 implants (Pozzi et al., 2014) and approximately 30% in one of the larger multicenter trials that started with originally 177 study participants (Arnhart et al., 2012; Kielbassa et al., 2009).

3.3 | Risk of bias within studies

According to the Cochrane bias tool, all three RCTs were deemed to have low risk of selection and performance bias (Table 3). A power calculation was described satisfactorily in all three RCTs. Detection bias was considered moderate as no precautions were described regarding masking of the radiographs to avoid distinguishing between the implant designs. The relatively high dropout rates in the two multicenter trials (Arnhart et al., 2012; Cecchinato et al., 2015) imply a possible attrition bias, and may raise concern about the representativeness of the findings. The risk of reporting bias was considered low for all three RCTs. The two multicenter trials (Cecchinato et al., 2015; Ferrus et al., 2010; Huynh-Ba et al., 2010; Sanz et al., 2010, 2014; Tomasi et al., 2010) and (Arnhart et al., 2012; Kielbassa et al., 2009) were funded by the manufacturer of the implants that were tested. None of the RCTs reported any details about fiducial arrangements with the patients, that is, whether they received free professional care and/or components or paid full fees. One of the studies did not report whether it had been approved by an independent research ethics board (Pozzi et al., 2014). In sum, all three RCTs were considered to have moderate bias.

3.4 | Results of individual studies

The clinical performance of both tapered as well as non-tapered implants placed in healed sites (Arnhart et al., 2012; Pozzi et al., 2014) and in extraction sockets (Cecchinato et al., 2015) appears to be good after 3 years, with only minor clinically relevant differences in reported outcomes (Table 4). None of the RCTs reported any patient-reported outcome measurements (PROMs). The variable experimental clinical variables in the identified studies preclude making any strong conclusions about potentially influential factors on the reported clinical outcomes. One particular detail of importance that unfortunately is missing in all three RCTs is the lack of detail about the implant site osteotomy procedures and qualities. RCT #1 (Cecchinato et al., 2015; Ferrus et al., 2010; Huynh-Ba et al., 2010; Sanz et al., 2010, 2014; Tomasi et al., 2010) cite "in accordance with the guidelines described in the Astra Tech Manual surgical procedures." RCT #2 (Arnhart et al., 2012; Kielbassa et al., 2009) lacked all details about this aspect, likely because of the heterogeneous treatment indications and extensive range of participating clinical settings. RCT #3 described "Drill sequence was chosen according to the manufacturer's instructions in relation to the bone quality," which may or may not include underprepared implant sockets (Pozzi et al., 2014).

3.5 | Risk of bias across studies

The risk of bias across studies appears to be low. All three RCTs reported clinically relevant outcomes, although a lack of patient-reported outcomes was identified.

4 | DISCUSSION

4.1 | Summary of evidence

The main finding of this SR is that the evidence basis is currently insufficient to conclude whether tapered implants have any benefits compared to non-tapered dental implants in terms of survival or success rates at 3 years or greater. The limited evidence of long-term clinical outcomes signifies that the question of whether tapered dental implants have any merits compared to non-tapered remains uncertain for a range of potential clinical indications.

4.2 | Agreements and disagreements with other reviews

Similar conclusions were made in two recent comparable SRs focused on the effects of implant design on clinical outcomes (Esposito, Ardebili & Worthington, 2014; Jokstad et al., 2016). The first SR includes only RCTs of dental implants indicated because of different clinical conditions, including single space and partially edentate situations in both jaws (Esposito et al., 2014), while the second SR presents data from all clinical studies where implants have been compared in a fully edentulous maxilla (Jokstad et al., 2016).

4.3 | Limitations

A pro-hoc decision was made to not include reports of clinical studies with less than a mean follow-up time of 3 years. Consequently, we did not extract the data from twenty clinical studies (Table 5), which are not to say that the information in these studies is unimportant. One prevailing reason why many clinicians seem to favor tapered implants is to maximize the "primary stability" of the implant body in extraction sites and in soft bone, with the expectation that "high values" lower the risk of adverse outcomes associated with an immediate or early loading of the implant. Hence, many publications with a focus on implants with a tapered design address the subject from the perspective of an implant that potentially remain immobile during the healing process, particularly in type 4 bone and extraction sockets. It is intriguing that the prevailing idea of good "primary stability" represented by insertion torque or RFA does not appear to correlate well with measurements of actual implant micromotion in-vitro enabled by the adoption of new measurement technologies

TABLE 3 Bias assessment

RCT	Study design	Study objective (sic)	Statistics	REB	Funding	Seq. generat	Allocate conceal	Blinding pat	Blinding outcom	Incomplete data	Select reporting	Other	Sum
#1 Parallel – 2 arms	Implant A vs Implant B 2 × 50p	To study the peri-implant soft tissues response, by evaluating both the recession and the papilla indexes of patients treated with implants with two different configurations.	• Mann–Whitney-U • Wilkinson signed rank	"Approved by the local ethics review boards"	Astra Tech AB, Sweden	Low	Low	Low	High	High	Low	Moderate	Moderate
#2 Parallel – 3 arms	Implant A vs Implant B vs Implant C 64p, 53p & 60p	To compare two versions of a variable-thread dental implant design to a standard tapered dental implant design in cases of immediate functional loading	• Mixed Model-covariance • Kruskal–Wallis • Mann-Whitney-U • Spearman's correlation • Wilcoxon signed rank • Cox regression	"Approved by independent Institutional Review Boards by all participating centers"	Nobel Biocare Services, Switzerland ref. (T-117)	Low	Low	Low	High	High	Low	Moderate	Moderate
#3 Split	Implant A vs Implant B 2 × 34p	To compare the clinical and radiological outcomes of two implant designs with different prosthetic interfaces and neck configurations.	• Paired-t • Fisher's exact • Mann-Whitney-U	".. the Helsinki Declaration" No IRB reported	Not receive any materials/ products or financial support	Low	Low	Low	High	Low	Low	Moderate	Moderate

TABLE 4 Study results

	Pre-surgery details	Surgery details	Post-surgery details	Prosthes	Outcomes (C)ylindrical (T)apered	PROMs	Major findings
RCT #1	Tooth extracted, socket state defined	Immediate placement, no grafting, healing abutment, semi-submerged healing 4 months	Prosthesis delivery 22 weeks following implant placement	Allceram/ metal-ceram/ zirconia-crown	Primary: Facial bone thickness (mm) Raw data not show Secondary: • Crestal bone-level change (mm) Cyl: 0.0 Con: +0.3 • Soft tissue inflammation (0/1) Raw data not shown • Papilla fill (mean Jemt score) Cyl: 2.0 Con: 2.1 • Soft tissue recession (mm) Cyl: 0.2 Con: 0.2	None reported	• Both implant types allowed proper soft and hard tissue healing to occur with infrequent mucosal inflammation and maintained marginal bone levels • Both interproximal papilla filling and the mid-facial mucosa stability were not influenced by implant type
RCT #2	Site healed at least 6 months. 3% of the implants were placed in bone quality IV (Lekholm& Zarb classification)	«Per manufacturer instruction»	Immediate temporary→ healing → permanent restore within 1 year	Crown/partial FDP/full FDP-cement/ screw	Primary: Marginal bone level change (mm) T1:0.9 T2:0.2 T3:0.9 Secondary: • Implant survival (%) T1a:96 T1b:96 T2:96 • Implant success (%) T1a:94 T1b:96 T2:95 • All adverse events (*n*) T1a:21 T1b:11 T2:18 • Sulcus bleeding T1a:15 T1b:10 T2:30 • Papilla (mean Jemt score) T1a:1.6 T1b:1.7 T2:1.6 • Plaque (%) T1a:29 T1b:38 T2:47	None reported	• No significant differences in cumulative survival rates were seen among implant type. • The bone remodeling up to 3 years was comparable for implants A1 and B, while the one-piece implant A2 had significantly less overall bone loss
RCT #3	Site healed at least 6 months. Bone quality not reported.	Ab, Flap, drill per manufacturer instruction, no grafting, bone crest placement, submerged healing 8 weeks	Healing abutment connection → 1 week, impression	Metal-ceram-crown	Primary: Success of implants & prostheses (%) T1: 100 T2:100% Secondary: • Marginal bone level change (mm) Vert:T1: 0.7 T2: 1.3 Hor. T1:0.2 T2: 0.6 • Periodontal-indices/soft tissue parameters, sulcus bleeding, plaque score & papilla index; Raw data lacking • Implant stability (ISQ) T1: 82 T2:82	None reported	• Vertical bone loss was statistically different (0.58 ± 0.10 mm) between the two implant types

Con, conical; Cyl, cylindrical; FDP, fixed dental prosthesis; RCT, randomized clinical trial.

(Freitas, Bonfante, Giro, Janal & Coelho, 2012; Pagliani et al., 2013; Sennerby et al., 2015).

The term "tapered implant" includes a range of different designs (Figure 1), which we attempted to embrace within our definition described in the introduction section of this SR. However, the static strain that is induced in the cortical and trabecular bone, respectively, given the different designs will vary, and from this perspective, one may argue that adopting the term "tapered" implant as all-inclusive is unsatisfactory. Even though the current literature basis is rather limited as reflected in the current SR, it will be helpful to refer to a better identification concept than "tapered" versus "cylindrical" or "non-tapered," especially for future authors of SRs and meta-analyses. Recent new descriptors in advertisements and the research literature are "cylindrico-conical," "cylindrical-conical," and "reverse conical neck". A proposal for a classification that perhaps better can differentiate between the current estimated 4,000 implant brands would be to describe coronal neck, defined as the portion meant to be in contact with cortical bone plus the coronal, central and apical thirds meant to be located in the trabecular bone.

The influence on clinical outcomes of one particular design element of an implant body, such as the taper, cannot be determined separately from other design elements, for instance, the thread and apical morphology and the implant surface roughness (Jokstad et al., 2003). A case illustration is the Brånemark System Conical Self-Tapping Fixture launched in the early nineties by Nobel Pharma, the predecessor of Nobel Biocare. (U.S. FDA K925760, approved 1993). The machined coronal part of the implant body flared out to produce a wider diameter at the implant platform. After some years, the product was discontinued from sale in the market because of poor clinical performance. Yet, another implant with a comparable macro-geometry of the coronal part, but with an external serrated surface micro-roughened by titanium oxide blasting, was launched a few years later by Astra Tech (U.S. FDA K931767, approved 1994). This product, the Fixture ST, demonstrated far superior clinical outcomes (Norton, 1998), and its design is reflected in many of today's implants marketed by different manufacturers.

4.4 | Implications for clinical practice

4.4.1 | Limitation of space

A logical indication where the placement of a tapered rather than a non-tapered implant is when there is limited space, whether there is a likelihood of perforating the labial plate or of damaging an adjacent vital structure or a neighboring tooth (Fleming, 1994). None of the RCTs identified in the current SR were designed with such study objective. Moreover, existing SRs on best management of implant fenestration have not interpreted the extracted data relative to implant design in their primary studies (Chiapasco & Zaniboni, 2009; Merli et al., 2016; Storgård Jensen & Terheyden, 2009). Nevertheless, regardless of any scientific research or precise data, it seems reasonable that many clinicians likely prefer tapered implants because they often will fit into an edentulous space better than straight-walled implants. There is also anecdotal experience in clinical practices where patients routinely partake in shared treatment decision making that psychological and emotional aspects influence the decision process as a tapered shape resembles more a natural tooth form coupled with a perceived less risk of injuring adjacent vital structures.

4.4.2 | Time-to-loading

The principal quest for tapered implant designs originates from the desire to provide immediate placement following tooth extractions, eventually also in combination with an immediate restoration. Initially, claims were made that an implant placed immediately following an extraction could conserve peri-implant bone and preserve the adjacent soft tissues including the papilla as long as the clinician adhered to particular protocols. As the extraction socket morphology and the implant body were seldom analogous, early strategies included the placement with a combination of membranes with or without grafting materials, alternatively to use a wide diameter implant. The use of wide-bodied implants produced unpredictable, outcomes, which opened for stepped and subsequently taper implants as alternatives, especially when there was a risk of perforating the labial plate in the aesthetic zones (Garber, Salama & Salama, 2001). In this context, it should be recognized that the current recommendation for the selection of implant dimensions and positioning is primarily dictated by the prosthetic emergence profile in areas of aesthetic priority (Buser, Martin & Belser, 2004).

4.4.3 | Bone quality and quantity

"Poor bone quality" is often associated with an argument that a tapered implant should be preferred rather than a non-tapered to secure a high "primary stability," which is synonymous to implant immobility at the time of surgical placement. Only three of the RCTs identified in this SR compare implants placed in the posterior maxilla (Mangano et al., 2017; Markovic et al., 2013; Simmons et al., 2017) and only clinically insignificant differences between the designs are reported. There is on the other hand a substantial number of non-RCTs that report outcomes of regular as well as experimental transient implants placed in the posterior maxilla that allude to particular benefits of specific implant design features. There is also an additional vast volume of research papers stemming from laboratory and animal experiments where tapered versus non-tapered implants have been compared. The extrapolation to recommendations for clinical practice of the data from these many otherwise excellent research papers is fraught with difficulties. As a start, the term "poor bone quality" is often, but incorrectly equated to type IV bone, according to a widespread categorical scoring system for jaw anatomy (Lekholm & Zarb, 1985). However, "poor" does not appear in the original description of type IV bone, but rather "*A thin layer of cortical bone surrounding a core of low density trabecular bone.*" The authors continue with a warning that it is only by

TABLE 5 Studies that were not included, and reason for non-inclusion (*n* = 20)

Reference	Study design	Study objective (sic)	Reason
Waechter et al. (2017)	RCT-split (SignoVinces: Geometry A – Integra cylindrical vs Geometry B- Duo tapered)	To compare the clinical outcomes of tapered and cylindrical implants and to study their effect on bone site characteristics and peri-implant health during healing.	<3 years. (90 days)
McCullough and Klokkevold (2017)	RCT-split (Megagen: Geometry A –Anyridge tapered vs Geometry B- EZPlus cylindrical)	To evaluate the role of macro-thread design on implant stability in the early post-operative healing period using resonance frequency analysis.	<3 years. (8 weeks)
Mangano et al. (2017)[a]	RCT-split (Megagen: Geometry A –Anyridge tapered vs Geometry B- EZPlus cylindrical)	To evaluate the effects of fixture design and surface on the early bone formation around immediately loaded implants inserted in the human posterior maxilla	<3 years. (8 weeks)
Simmons et al. (2017)[a]	RCT, 3 arms (Denstply: Geometry A -Osseospeed ± under-preparation vs Geometry B-Osseospeed TX-tapered apex)	To compare a parallel wall design implant to a tapered apex design implant when placed in the posterior maxilla using two different surgical protocols.	<3 years. (1 year)
Stanford et al. (2016)[a]	RCT, 2 arms (Dentsply: Geometry A-Osseospeed EV vs Geometry B-Osseospeed TX-tapered apex)	To evaluate implant system design, surgical and prosthetic aspects, and the effect on marginal bone levels of two related implant systems.	<3 years. (1 year)
Torroella-Saura et al. (2015)[a]	RCT-split (Implant A-Biocom cylindrical vs Implant B-MIS-Seven tapered)	To evaluate the effect of two different designs, tapered vs cylindrical, on the primary stability of implants placed with an immediate loading protocol in edentulous mandibles to support fixed prostheses within occlusal contacts during the first 48 h.	<3 years. (3 months)
Linkevicius, Puisys, Svediene, Linkevicius and Linkeviciene (2015)[a]	RCT-split (Implant A-Certain-Prevail cylindrical vs Implant B-Tapered-Laser-Lok)	To compare how laser-micro-textured implants and implants with platform switching maintain crestal bone stability in thin peri-implant tissues.	<3 years. (1 year)
Kan, Roe and Rungcharassaeng (2015)	Retrospective study with concurrent controls	To examine the effects of implant morphology (tapered vs cylindrical) and the final drill-implant diameter discrepancy (FD-IDD) of six implant systems on the incidence of rotational instability during immediate implant placement and provisionalization in the aesthetic zone.	Not a RCT
Pera et al. (2014)	CCT, 2 arms (Biomet 3i: Geometry A-Osseotite cylindrical & Geometry B-Osseotite-NT tapered)	To report the 6-year outcomes for patients rehabilitated with an immediate loading protocol of the maxilla (Columbus Bridge Protocol).	Not a RCT
Kim et al. (2013)[a]	RCT, 2 arms (Implant A-Osstem TSIII HA vs Implant B-Zimmer TSV)	To compare clinical outcomes and stability following immediate loading of two types of tapered implants in the partially edentulous posterior maxilla and mandible.	<3 years. (1 year)
Kadkhodazadeh, Heidari, Abdi, Mollaverdi and Amid (2013)[a]	RCT, 3 arms (Implant A –AllFit-SSO cylindrical vs Implant B-SPI-Element cylindrical vs Implant C-SPI-Contact tapered)	To use intra-oral radiographs to evaluate changes in marginal bone levels around three different implant designs after 1 year.	< 3 years, (1 year)
Markovic et al. (2013)	Prospective case series×2 (Implant A - BlueSky-Bredent & Implant B-Straumann-Standard plus)	To investigate the relationship between surgical techniques and implant macro-design (self-tapping/non-self-tapping) for the optimization of implant stability in the low-density bone present in the posterior maxilla using resonance frequency analysis	Not an RCT
Kim, Lee, Kim, Park and Moon (2010)[a]	RCT-split (AstraTech-OsseoSpeed Fixture: Geometry A-Cylindrical vs Geometry B-Conical)	To evaluate and to compare the effect of the conical neck design on marginal bone loss around two types of implants, one with a straight shape and the other with a conical neck design, when both implants were provided with micro-threads to the top of the fixture	<3 years. (1 year)

(Continues)

TABLE 5 (Continued)

Reference	Study design	Study objective (sic)	Reason
Park et al. (2010)[a]	RCT, 2 arms (Implant A -Osstem vs Implant B-Straumann-Standard)	To compare the implant stability and clinical outcomes obtained with two types of non-submerged dental implants that have different thread designs and surface treatments	<3 years. (1 year)
Lang et al. (2007)	RCT, 2 arms (Straumann: Geometry A- Standard plus cylindrical vs Geometry B- TE tapered)	To compare the clinical and patient-based outcomes of immediately placed cylindrical and tapered screw-shaped implants with focus on early aspects of implant stability, the need for augmentation and post-surgical transmucosal healing	<3 years. (12 weeks)
Östman et al. (2005)	Prospective case series (Nobel Biocare: Brånemark Mk4/Replace-Selectin underprepared sites) compared to historical reference group data	To evaluate the clinical outcome and stability of directly loaded oxidized titanium implants after a modified surgical protocol and inclusion by primary implant stability	Not an RCT
O'Sullivan et al. (2004a)	Prospective case series x2, (Nobel Biocare: Geometry A-Brånemark standard in underprepared sites & Geometry B-Brånemark Mk4)	To compare selected parameters associated with implant insertion using two different methods of enhancing implant primary stability and to identify any relationship between these parameters and changes in the stability of each implant during the initial 6-month healing period following implant insertion	Not an RCT
Åstrand et al. (2003)	RCT, 2 arms (Geometry A-Brånemark Mk2 vs Geometry B-Brånemark Mk4)	To compare the outcome of using the tapered Brånemark System Mark IV fixture with the outcome of using earlier Brånemark fixtures in a controlled study	<3 years. (1 year)
Friberg et al. (2003)	RCT-split, 2 arms (Geometry A-Brånemark standard vs Geometry B-Brånemark Mk4)	To compare the early behavior of a modified (prototype Mk IV, Brånemark System, Nobel Biocare AB, Gothenburg, Sweden: test) implant with that of the standard Brånemark implant (control) in regions of mainly type 4 bone	<3 years. (1 year)
Gatti and Chiapasco (2002)	RCT, 2 arms (Geometry A-Brånemark-conical vs Geometry B-Brånemark Mk2)	To compare the long-term outcome of immediately loaded implant-retained mandibular overdentures supported by four screw-type one-piece transmucosal implants with that of four screw-type two-piece implants inserted in the interforaminal area of the mandible	<3 years. (2 years)

[a]Corresponding author contacted to confirm that no further data existed.

explorative drilling "*that the true bone quality present in the jaw can be determined*" given that on the radiographs of that period, the trabecular bone was masked by the cortical bone layer. "Poor quality bone" is difficult to define from the perspective of the likelihood of an osseointegration of a surgically placed dental implant, and investigators have struggled to identify its foremost and secondary determinants among mechanical properties such as density, hardness, and stiffness as well as morphological characteristics such as height of cortical passage and trabecular bone pattern characteristics such as trabecula number, thickness, and separation in combination with biomarkers of physiological properties such as healing ability and regenerative ability. Added to this complexity is that the prevailing non-destructive method to measure implant immobility is by RFA, which does not yet seem to be a reliable predictor of future osseointegration (Atieh, Alsabeeha & Payne, 2012; Manzano-Moreno, Herrera-Briones, Bassam, Vallecillo-Capilla & Reyes-Botella, 2015).

4.5 | Primary stability

Retaining the implant immobility after surgical placement, that is, "primary stability," during the healing process is a surrogate outcome and not a criterion of clinical success (Chang, Lang & Giannobile, 2010; Shadid, Sadaqah & Othman, 2014). One may even question whether "primary stability" per se has any prognostic value at all, given that extreme values of "primary stability" can be achieved with unconventional and outdated implant designs such as the "basal implants," for example, the *Bicortical Screw*, the "fin implants," for example, the *Tatum "D" implant*, or the "expanding implants," for example, the *Sargon implant*.

Alternative methods to better retain immobility after surgical placement of conventionally designed dental implants have been suggested (Martinez et al., 2001), including under-preparation in diameter of an osteotomy, or the placement of a tapered implant into a cylindrical osteotomy, thereby compressing the cortical bone

coronally (O'Sullivan et al., 2000). Several in vitro studies show that the relative gain of under-preparation in terms of increased insertion torque or RFA values can be increased by 50%–100%, dependent on the discrepancy between the osteotomy and implant body diameters (Campos et al., 2015). In contrast, the comparative studies in Table 5 describe the differences between the tapered versus non-tapered designs up to maximum 10% at baseline in terms of implant insertion torque (O'Sullivan, Sennerby & Meredith, 2004; Kielbassa Kielbasa 2009, Park et al., 2010; Torroella-Saura et al., 2015; Stanford et al., 2016) or RFA values (Friberg et al., 2003; Kim, Lee, Lee & Yi, 2013; Markovic et al., 2013; McCullough & Klokkevold, 2017; O'Sullivan, Sennerby, Jagger & Meredith, 2004; Östman, Hellman & Sennerby, 2005; Park et al., 2010; Simmons et al., 2017; Waechter et al., 2017). Moreover, the minor differences at baseline decrease to clinically insignificant after 8 weeks (McCullough & Klokkevold, 2017) and 12 weeks (Park et al., 2010), or to no differences after 90 days (Waechter et al., 2017), 6 weeks (Simmons et al., 2017), 3 months (Markovic et al., 2013; Torroella-Saura et al., 2015), and 6 months (Östman et al., 2005; Simmons et al., 2017).

The biological effects of the different methods of increasing "primary stability" are difficult to quantify in humans. It is reasonable to assume that there is an upper threshold beyond which overcompression of bone during placement will be detrimental to implant success (Cha et al., 2015). It has been shown in animal models that bone compression by undersized osteotomies show different patterns of osseointegration depending on the extent of compression (Tabassum, Meijer, Walboomers & Jansen, 2011). Recent animal model data suggest, however, that bone condensation should perhaps be avoided as it may not contribute positively to implant osseointegration (Wang et al., 2017).

In sum, the literature in general implies that among the three major determinants for whether a cylindrical/tapered/hybrid dental implant placed in an osteotomy made by an appropriate cylindrical/tapered/hybrid rotary instrument will remain immobile in the jaw bone is by ranking (i) bone quality and quantity > (ii) osteotomy preparation > (iii) implant geometry elements and -surface.

5 | CONCLUSIONS

A systematic search for best evidence to clarify whether patients with dental implant restorations benefit from receiving tapered compared to non-tapered implants in terms of clinical and patient-reported outcomes at 3 years or greater identified three RCTs that report only clinically insignificant differences. Several RCTs that report outcomes up to 2 years describe minimal differences about primary stability at implant placement and at their last respective follow-up examinations.

Retaining the implant immobility after surgical placement, that is, "primary stability," during the healing process is recognized as a critical element in implant therapy and can be challenging in conditions of poor bone quality or when providing immediate implant placement with or without immediate function. Appropriate professional judgment in clinical decision making must include a comprehensive diagnosis of the patient's jawbone quality and quantity and consideration of osteotomy protocol in accordance with the patient's treatment preferences, where the shape of the dental implant is only one contributory factor.

CONFLICTS OF INTEREST

No conflict of interest is declared.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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REVIEW ARTICLE

WILEY CLINICAL ORAL IMPLANTS RESEARCH

Medication-related dental implant failure: Systematic review and meta-analysis

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Abstract

Objectives: The aim of this systematic review was to investigate the association between the intake of systemic medications that may affect bone metabolism and their subsequent impact on implant failures.

Material and methods: Electronic and manual literature searches were conducted. Implant failure (IF) was the primary outcome, while biological/mechanical and the causes/timing associated with IF were set as secondary outcomes. Meta-analyses for the binary outcome IF and odds ratio were performed to investigate the association with medications.

Results: A final selection of 17 articles was screened for qualitative assessment. As such, five studies focused on evaluating the association of implant failure and non-steroidal anti-inflammatory drugs (NSAIDs), two on selective serotonin reuptake inhibitors (SSRIs), two on proton pump inhibitors (PPIs), seven on bisphosphonates (BPs), and one on anti-hypertensives (AHTNs). For PPIs, the fixed effect model estimated a difference of IF rates of 4.3%, indicating significantly higher IF rates in the test compared to the control group ($p < 0.5$). Likewise, for SSRIs, the IF was shown to be significantly higher in the individuals taking SSRIs ($p < 0.5$) as estimated a difference of 7.5%. No subset meta-analysis could be conducted for AHTNs medications as only one study fulfilled the inclusion criteria, which revealed an increased survival rate of AHTN medication. None of the other medications yielded significance.

Conclusions: The present systematic review showed an association of PPIs and SSRIs with an increased implant failure rate. Hence, clinicians considering implant therapy should be aware of possible medication-related implant failures.

KEYWORDS

biological complications, dental implant, drug, endosseous implant, epidemiology, failure, medication

1 | INTRODUCTION

Increasing life expectancy of global demographical trends revealed not only an estimated increase in a world population of 50 million annually (Srinivasan et al., 2017), but as populations are aging, the prevalence of disabling disease and the related intake of medications increases steeply with age (Collaborators, 2017). Even though implant-supported rehabilitations are a highly successful treatment option with predictable long-term success rates after 10 and 20 years (Chappuis et al., 2013; Chappuis et al., 2018), the possible

The present systematic review was prepared as part of the 6th International Team of Implantology (ITI) Consensus Meeting hold in Amsterdam in April, 2018.

impact of disabling systemic diseases on implant rehabilitation has been described in systematic reviews (Beikler and Flemmig, 2003; Bornstein et al., 2009; Diz et al., 2013; Donos and Calciolari, 2014; Mombelli and Cionca, 2006; Scully et al., 2007). These uncontrolled medical conditions may have an effect at the local or systemic level and have been associated with an increased risk of breakdown of the peri-implant tissues (Heitz-Mayfield & Huynh-Ba, 2009; Heitz-Mayfield, Needleman, Salvi & Pjetursson, 2014; Lang et al., 2011; Lang et al., 2004; Monje, Catena & Borgnakke, 2017). Systemic diseases as obesity, arthritis, and other chronic diseases induce a low-grade systemic inflammatory condition associated with high levels of circulating pro-inflammatory cytokines that favor the chemotaxis and activations of monocytes, neutrophils, and adipose tissue macrophages, which may ultimately contribute to the establishment of bone loss and peri-implant disease (Hill, Reid Bolus & Hasty, 2014; Straub et al., 2015; Wei, Tarling, McMillen, Tang & LeBoeuf, 2015).

In addition to uncontrolled systemic diseases itself, the systemic intake of medication such as thiazide diuretics, β-blockers, anti-inflammatory drugs, proton pump inhibitors, or serotonin reuptake inhibitors have shown to further modulate bone metabolism (Abrahamsen and Vestergaard, 2013; Brater, 1998, 2011; de Vernejoul et al., 2012; Geusens et al., 2013; Haney & Warden, 2008; Vestergaard, 2008; Wiens et al., 2006). These medication-related side effects are less understood and may exert an important influence on implant-related outcomes. Therefore, in recent demographical trends with an aging population, a comprehensive assessment and understanding of the patient's medical background is important, as related medication-specific side effects are able to influence bone metabolism (Insua, Monje, Wang & Miron, 2017; Kremers et al., 2016).

Osteocytes play a crucial role in bone turnover processes, such as osseointegration, and are a major source of receptor activator of nuclear factor-kappaB ligand (RANKL) in bone (O'Brien, Nakashima & Takayanagi, 2013), which is required for osteoclast differentiation and activation (Kong et al., 1999). Hence, in case of medication-induced disruption of osteocyte metabolic activities, adequate peri-implant bone remodeling in early stages of healing may be jeopardized. Likewise, anti-hypertensive medications, such as beta-blockers or angiotensin-converting enzyme inhibitors, have been shown to inhibit the normal physiologic function of osteoclasts on bone by blocking surface β-2 adrenergic receptors, which may result in shifting the balance toward bone formation by blocking the renin-angiotensin system (Brater, 1998, 2011). Furthermore, the action of serum serotonin reuptake inhibitors (SSRIs) on certain receptors and serotonin transporters, such as 5-HT1B, 5-HT2B or 5-HT2C, may result in a direct detrimental effect on bone metabolism by increasing osteoclast differentiation (Haney & Warden, 2008; Vestergaard, 2008), which may negatively impact the process of osseointegration.

A comprehensive assessment and understanding of the patient's medical background and current medications is important for life-long implant-supported rehabilitations. Therefore, the aim of this systematic review was to investigate the association between the intake of medications that may affect bone metabolism and implant outcomes.

2 | MATERIAL AND METHODS

This systematic review was conducted according to the guidelines of the Preferred Reporting Items of Systematic Reviews and Meta-analyses (PRISMA) statement (Moher, Liberati, Tetzlaff, Altman, & PRISMA Group, 2009). The review protocol was registered in PROSPERO (International Prospective Register of Systematic Reviews) hosted by the UK's National Institute for Health Research (NHS), University of York, Centre for Reviews and Dissemination, under the code CRD42017067170 (https://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42017067170)

2.1 | Focused questions

1. Is there an association between medication intake and implant outcomes (i.e., implant failure)? (Primary question)—If answer is "yes," then:
2. What are these medications and the respective dosage associated with implant failure? (Secondary question)
3. Does implant failure occur in the early stages of healing or after osseointegration is attained (i.e., biological complications) (Secondary question)
4. Are these patients associated with more mechanical complications?
5. Are there any other confounders associated with implant failure in medicated patients? (Secondary question)
6. What is the strength of the evidence for associations between medication intake and implant failure? (Secondary question)

2.2 | PECO question (population, exposure, comparison, and outcome measures) (Stone 2002).

P: Completely or partially edentulous human adults wearing implant-supported prostheses.
E: Regular intake of oral, intramuscular, or intravenous medications/drugs that may affect bone metabolism.
C: Individuals not taking any known relevant medication (Non-specific medication dependent for the treatment of a medical condition.)
O: Dental implant failure (primary outcome), peri-implant marginal bone loss (secondary outcome), and biological (i.e., peri-implant mucositis or peri-implantitis) or mechanical complications reported at the implant or patient level (secondary outcomes).

2.3 | Eligibility criteria

Prospective or retrospective cohort, case–control, cross-sectional, or randomized controlled trials exploring the association of medication intake and implant failure in humans were considered for inclusion.

2.3.1 | Literature search protocol

Electronic and manual literature searches were conducted independently by two authors (AM, VC) in several databases, including

PubMed, MEDLINE (OVID), EMBASE (OVID), Cochrane Central Register of Controlled Trials (Cochrane Library), Cochrane Oral Health Group Trials Register (Cochrane Library), Web of Science (Thomson Reuters), and SciVerse (Elsevier). Studies published up to May 2017 were considered, without any language restrictions. For the PubMed library, combinations of controlled terms (MeSH and EMTREE) and keywords were used whenever possible, and other terms not indexed as MeSH and filters were also applied. The search strategy used was ((((“dental implants” OR ((“dental implantation, endosseous”) OR “dental implantation, endosseous”[MeSH Terms]) AND “abnormalities, drug-induced”[MeSH Terms]) OR “serotonin uptake inhibitors”[MeSH Terms]) OR “anti-inflammatory agents, non-steroidal”[MeSH Terms]) OR “adrenergic beta-antagonists”[MeSH Terms]) OR “angiotensin-converting enzyme inhibitors”[MeSH Terms]) OR “proton pump inhibitors”[MeSH Terms]) OR “bisphosphonates”[MeSH Terms]) OR “bisphosphonate-associated osteonecrosis of the jaw”[MeSH Terms]) AND “survival analysis”[MeSH Terms] AND ((Classical Article[ptyp] OR Clinical Study[ptyp] OR Clinical Trial[ptyp]) AND “humans”[MeSH Terms]). Moreover, a less specific screening using non-MeSH index terms was conducted to ascertain the articles to be evaluated. The screening strategy was as follows: ((((medication-related[Title/Abstract] OR drug-related[Title/Abstract]) OR bisphosphonate-related[Title/Abstract]) AND dental implant failure[Title/Abstract]) OR dental implant survival[Title/Abstract]) OR ((“dental implants”[MeSH Terms] OR (“dental”[All Fields] AND “implants”[All Fields]) OR “dental implants”[All Fields] OR (“dental”[All Fields] AND “implant”[All Fields]) OR “dental implant”[All Fields]) AND biological complication[Title/Abstract]) OR ((“dental implants”[MeSH Terms] OR (“dental”[All Fields] AND “implants”[All Fields]) OR “dental implants”[All Fields] OR (“dental”[All Fields] AND “implant”[All Fields]) OR “dental implant”[All Fields]) AND technical complication[Title/Abstract]). On the other side, for the EMBASE Library, the key terms used were as follows: (‘dental implant’/exp OR ‘dental implants’) OR (‘endosseous implant’ OR ‘endosseous implants’) AND (‘medication-related’/exp OR ‘medications-related’) OR ‘drug-related’/exp OR ‘drugs-related’ AND ‘implant failure’/de AND ‘human’/de AND ‘article’/it. For searching the remaining electronic databases, combinations of ‘medication-related’ OR ‘drug-related’ AND ‘dental implant’ AND ‘failure’ OR ‘survival’, limited to titles and abstracts.

Additionally, the “grey literature” available at the New York Academy of Medicine Grey Literature Report (http://greylit.org) and the register of clinical studies hosted by the US National Institutes of Health (www.clinicaltrials.gov) was searched to further identify potential candidates for inclusion. Moreover, the authors conducted manual searches in selected journal issues published between January 2017 and August 2017 (i.e., *Journal of Dental Research*, *Journal of Clinical Periodontology*, *Journal of Periodontology*, *Journal of Oral and Maxillofacial Implants*, *Clinical Oral Implants Research*, *Clinical Implant Dentistry and Related Research*, *The International Journal of Periodontics & Restorative Dentistry*, *and the International Journal of Oral and Maxillofacial Surgery)*. Bibliographies of identified relevant publications were also cross-searched.

2.4 | Literature selection and data extraction protocol

Corresponding authors were contacted for clarifying information about studies lacking clear information. Two independent examiners (AM and VC) extracted the data. Data of interest were extracted based on the general study characteristics (authors and year of publication, type of study), population characteristics (number of participants), implant and prosthetic characteristics (number of implants, implant location, type of prosthetic loading, follow-up period after implant placement), and primary and secondary outcomes.

2.5 | Risk of bias

The methodological and reporting quality of all selected full-text reports was assessed according to the STROBE statement for observational studies (Shea et al. 2009; von Elm et al. 2007). Moreover, the Assessment of Multiple Systematic Reviews guidelines (AMSTAR) was followed (Shea et al. 2009).

2.6 | The Newcastle–Ottawa Scale for assessing the quality of non-randomized studies (NOS)

Assessment of the quality of non-randomized, non-interventional studies is essential for proper evaluation of the evidence provided by each study. We followed the Newcastle–Ottawa System (NOS) protocol (Wells et al. 2011). The items evaluated were selection of study groups, comparability of participants, and outcome. Each included study received a maximum score of 13 points for cohort studies and 10 points for case–control studies (Table S1). The Cohen’s kappa coefficient was calculated to assess inter-rater agreement (AM and GAO).

2.7 | Statistical analysis

The statistical analysis was performed with the statistical software package R 3.1.1 (The R Project for Statistical Computing, www.r-project.org). The feasibility of conducting specific quantitative analyses (meta-analyses) was explored. If feasible, the additional package “meta” was used. Meta-analyses for the binary outcome implant failure (IF) were performed. The numbers of implants in both experimental and control groups were extracted directly from the data; the numbers of failures had to be calculated from the reported failure rates. As aforementioned, studies with missing information were excluded from the quantitative analysis.

The odds ratio of failure in the test group (individuals in-taking medications) vs. failure in the control group (individuals not taking any known relevant medication) was analyzed. Estimated odds ratios together with 95% confidence intervals were calculated for every included study as well as for the pooled set of studies. The studies were pooled using the inverse variance method. Both fixed and random weights were applied, yielding two different estimates

of the population odds ratio. The heterogeneity among the included studies was measured computing I^2 and a p value for the null of homogeneous studies. This p value was compared to the level of significance of 5%.

3 | RESULTS

3.1 | Study selection (Figure 1)

A total of 430 entries were identified through the electronic search, and after removal of duplicates. The initial pool was not supplemented with any further article identified through manual search or cross-reference assessments. Of these 430, forty articles were assessed for full-text evaluation, resulting in a final selection of 17 articles for qualitative assessment (Table 1) (Alissa et al., 2009; Al-Sabbagh, Robinson, Romanos & Thomas, 2015; Chrcanovic, Kisch, Albrektsson & Wennerberg, 2017a,b; Famili, Quigley & Mosher, 2011; Grant, Amenedo, Freeman & Kraut, 2008; Jeffcoat et al., 1995; Koka, Babu & Norell, 2010; Memon, Weltman & Katancik, 2012; Reddy, Jeffcoat & Richardson, 1990; Siebert, Jurkovic, Statelova & Strecha, 2015; Urdaneta, Daher, Lery, Emanuel & Chuang, 2011; Winnett, Tenenbaum, Ganss & Jokstad, 2016; Wu et al., 2014, 2016, 2017; Zahid, Wang & Cohen, 2011). A total of 23 articles did not meet the eligibility criteria and were subsequently excluded (Table 2).

The studies included for qualitative assessment were pooled according to the medication category. As such, five studies were focused on evaluating the association of implant failure and non-steroidal anti-inflammatory drugs (NSAIDs) (Alissa et al., 2009; Jeffcoat et al., 1995; Reddy et al., 1990; Urdaneta et al., 2011; Winnett et al., 2016), two on selective serotonin reuptake inhibitors (SSRIs) (Chrcanovic et al., 2017b; Wu et al., 2014), two on proton pump inhibitors (PPIs) (Chrcanovic et al., 2017a; Wu et al., 2017), seven on oral bisphosphonates (BPs) (Al-Sabbagh et al., 2015; Famili et al., 2011; Grant et al., 2008; Koka et al., 2010; Memon et al., 2012; Siebert et al., 2015; Zahid et al., 2011), and one on anti-hypertensives (AHTNs) (Wu et al., 2016).

3.2 | Studies methods

With regard to research methodology, the vast majority of the included articles (12) were based on retrospective cohort studies (RC) (Chrcanovic et al., 2017a,b; Famili et al., 2011; Grant et al., 2008; Koka et al., 2010; Memon et al., 2012; Urdaneta et al., 2011; Winnett et al., 2016; Wu et al., 2014, 2016, 2017; Zahid et al., 2011), three were randomized controlled trials (RCT) (Alissa et al., 2009; Jeffcoat et al., 1995; Reddy et al., 1990), one prospective cohort (PC) (Siebert et al., 2015), and one case–control (CC) (Al-Sabbagh et al., 2015).

3.3 | Association of medication-related implant failure

Overall, five groups could be pooled according to the medication type. For hypertension-related medication-associated implant failure (i.e., beta-blockers or ACE inhibitors), only one study could be identified and accordingly, no subset meta-analysis could be carried out. For NSAIDs, the analysis could not be performed, as the vast majority of studies reported no failures in any of the control or experimental groups. For PPIs, the homogeneity of the two included studies was rejected at the 5% level (I^2 = 0.93, p < .01). Hence, the results should be interpreted carefully. Both the fixed effects and the random effects model estimated a difference of implant failure (IF) rates of 4.29% and 4.53%, meaning significantly higher IF rates in the test compared to the control group (p < .01) (Figure 2). Likewise, for SSRIs, the homogeneity of the two studies was rejected at the level 5% (p < .01). Both the fixed effects and the random effects model estimated a large positive difference of 7.48% and 7.50%, rendering significantly higher IF rates in the test compared to the control group (p < .01) (Figure 3). With regard to IF associated with the intake of BPs, one study (Al-Sabbagh et al., 2015) was excluded from the analysis due to missing IF in the control group. Using the IF rate as the primary outcome in the analysis, studies with a 0 IF rate in either the experimental or the control group were assigned a weight of 0, because the estimated standard deviation is 0. The remaining six studies were weighted and the estimated differences were −0.13 in the fixed effects model and 0.86 in the random effects model (Figure 4). These results must be interpreted cautiously due to a high heterogeneity of I^2 = 98% (p < .01 for the test of homogeneity among the included studies).

No analysis was conducted for secondary outcomes. Implant survival (IS) was redundant to the primary outcome IF, whereas marginal bone loss (MBL) and timing of failure (TF) were reported in too few studies.

3.4 | Odds ratio for implant failure according to the medication intake

No subset meta-analysis could be conducted for AHTNs medications as only one study fulfilled the inclusion criteria, which revealed an increased survival rate of AHTN medication. For PPIs, the homogeneity of the two studies could not be rejected at the 5% level (I^2=0, p = 0.78). Both the fixed effects and the random effects model estimate an odds ratio of a failure in the experimental group against a failure in the control group of 2.02. The corresponding 95% confidence interval does not contain 1.00, so there is a significant effect of the medication (p < .05) (Figure 2). Likewise, for SSRIs, the homogeneity of the two studies could be rejected at the 5% level (I^2 = 0, p = .36). The fixed effects model estimated an odds ratio of IF in the experimental group against failure in the control group of 2.92; the random effects model resulted in 3.00 (Figure 3). Thus, a significant effect of the experimental medication was found (p < .05). When analyzing oral BPs, one study (Al-Sabbagh et al., 2015) was excluded from the analysis due to missing IF in the control group, as previously mentioned. For the remaining six studies, the homogeneity could not be rejected at the 5% level (I^2 = 27, p = .24). The fixed effects model estimated an odds ratio of failure in the experimental group against failure in the control group of 1.11, while the random effects model indicated an

TABLE 1 On the medication-related implant failure: systematic review [In PDF format, this table is best viewed in two-page mode]

Authors (year)	Study design	Mean follow-up	Systemic condition	Medication	Dosage (mg/ml)	Therapy length (months)	Administration method	Subjects (*n*)	Age (years)
Wu et al. (2016)	RC	17.1 ± 16.6	Hypertension	AM (beta-bloquers - 18.9%, thiazide diuretics - 5.4%, ACE inhibitors - 29.7%, ARBs - 24.3%, others - 21.6%)	NR	NR	Oral	142	57.7 ± 12.1
			ASA I-II	NSM	N	N	N	586	
Alissa et al. (2009)	RCT	6	ASA I-II	NSAIDs (Ibuprophen)	600 mg	4×/day 7 d	Oral	29	NR
				NSM	N	N	N	29	
Jeffcoat et al. (1995)	RCT	12	ASA I-II	NSAIDS (Flurbiprofen)	50 mg	2× day 3 mo	Oral	29	47.2
				Flurbiprofen	100 mg	2× day 3 mo	Oral		
				NSM	N	N	N		
Winnett et al. (2014)	RC	NR	NC	NSAIDS (Ibuprophen)	600 mg	4× day 2w	Oral	60	NR
				NSM	N	N	N	44	
Urdaneta et al. (2011)	RC	70.7	Arthristis, CDV prevention	NSAIDS (Ibuprophen, celecoxib, acetylsalicydic, rofecoxib, nabumetone, naproxen, etodolac)	Ibuprophen (600–1600 mg), celecoxib (200 mg), acetylsalicydic (325 mg), rofecoxib (25 mg), nabumetone (500 mg), naproxen (375 mg), etodolac (400 mg)	Daily	Oral	13	NR
			ASA I-II	NSM	N	N	n	68	
Wu et al. (2016)	RC	16.6 ± 16.3	Gastric function abnormalitis	PPI	NR	NR	Oral	58	56.6 ± 13.7
			ASA I-II	NSM	N	N	n	741	
Wu et al. (2014)	RC	36	Depressive condition	SSRIs (citalopram, dapoxetine, escitalopram, fluoxetine, fluvoxamine, indalpine, paroxetine, sertraline, venlafaxine, zimeline)	NR	NR	Oral	50	56.4 ± 13.7
			ASA I-II	NSM	N	N	N	440	
Reddy et al. (1990)	RCT	4	ASA I-II	NSAIDS (Flurbiprofen)	100 mg	2× day 4 mo	Oral	NR	NR
				NSM	N	N	N		
Chrcanovic et al. (2017)	RC	94.8 ± 78.7	Gastric function abnormalitis	PPI	NR	NR	NR	67	60.4 ± 15.9
			ASA I-II	NSM	N	NR	NR	932	
Chrcanovic et al. (2017)	RC	90.11 ± 74.23	Depresive condition	SSRIs	NR	NR	NR	18	55.9 ± 18.5
			ASA I-II	NSM	N	N	NR	282	
Al-Sabbagh et al. (2014)	CC	84.6	Osteoporosis	BP	NR	>3	Oral	20	515
			ASA I-II	NSM			N	183	
Siebert et al. (2013)	PC	12	Osteoporosis	Zoledronic	5 mg/year	NR	IV	12	54 ± 12
			ASA I-II	NSM	N	N	N	12	

(Continues)

TABLE 1 (additional columns)

Gender (M/F)	Implants (*n*)	Failure (month)	Marginal bone loss (mm)	Implant survival rate(%)	Implant failure rate (%)	HR (95% CI)	Biological complications	Comments
375/353	327	NR	NR	99.4	0.6	0.12 (0.03–0.49)	NR	1. BA was performed more often in AH drug users (OR = 0.71) 2. Age, gender, implant length, implant torque, implant loading and BA did not affect SR 3. HT patients not taking AH drugs had a failure of 4.7% 4. Smoking was associated with increased implant failure (HR: 3.59)
	1172	NR	NR	95.9	4.1	1	NR	
NR	41	N	1.09 ± 0.99	100	0	NR	0	1. The multiple linear regression test showed that MBL was not SS associated with: age, gender, anatomic location, treatment group and examiner
	48	N	1.19 ± 0.96	100	0	NR	0	
NR		N	0.65	100	0	NR	NR	1. Quantitative digital substraction radiography was used to assess bone mass loss 2.Placebo and low-dose flurbiprophen lost a mean of 11.2 ± 3.89 and 14.6 ± 3.69 mg, respectively. 3. High-dose flurbiprophen lost a mean of 2.60 ± 4.13 mg 4. Smooth surface dental implants
		N	1.6	100	0	NR		
		N	1.1	100	0	NR		
NR	273	Early:72%; late:28%	NR	56	44	NR	NR	1. Retrospective data based on university setting. 2. The NSAIDs experienced 3.2× more case of radiographic bone loss 1/2 and 1.9× greater than 1/2 of the implant height
	203	Early:65%; late:35%		62	38	NR		
NR	61	NR	0.06	100	0	NR	NR	1. Study on extra-short locking-taper implants 2. Main goal was to analyze crestal bone gain 3. Crestal bone gain was significantly correlated with type of opposing structure, tooth, type of restoration, crown cemented on prefabricated titanium abutment, hydroxiapatite coating, implant site and daily intake of NSADS ($p = 0.04$) 4. Similar bone gain was observed in men/woman, maxilla/mandible
	265		0.42	97.74	2.26	NR	NR	
369/430	133	NR	NR	93.2	6.8	2.73 (1.10–6.78)	NR	1. Large RC study with different implan ttypes, protocols and grafting procedures 2. NSAIDs were taken more by PPI users (OR = 1.73) 3. Smoking was associated with IF ($p = 0.001$) 4. Patients gender, age implant length, and bone augmentation had no significant association with IF
	1,640			96.8	3.2	1		
198/292	94	4–14 mo	NR	89.4	10.6	6.28 (1.25–31.61)	NR	1. Large RC study with different implan ttypes, protocols and grafting procedures 2. Smoking habit ($p = 0.01$)and small implant diameters ($p = 0.02$) were associated with higher IF 3. Bone augmentation was associated with higher implant failure
	882			95.4	4.6	1		
NR	NR	NR	NR	100	0	NR	NR	1. Main goal was to assess the peri-implant bone remodeling testing the feasability of digital substraction radiography 2. No data on patientients demographics nor implant characteristics 3. Individuals intaking the NSAIDs experienced greater peri-implant bone density during healing
				100	0	NR		
479/520	250	Early:late = 1.34:1	NR	88	12	2.81 (1.13–6.93)	NR	1. Retrospective database on university setting. 2. Multilevel mixed effects parametric survival analisys conducted for the association between PPI and IF 3. Multifactorial analysis detected bruxism (HR = 2.86), smoking (HR = 2.36, short implant length (HR = 1 to >10 mm HR = 0.39), prophylactic antibiotic regimen (HR = 0.49) and location (anterior maxilla as the highest HR = 1; anterior mandible the lowers HR = 0.53) 3.
	3309	NR		93.5	4.5	1		
145/155	48	Early = 31.4%; late = 51.4%	NR	87.5	12.5	4.10 (0.67–24.96)	NR	1. Retrospective data based on university setting. 2. Kaplan Meier showed SS in the cumulative survival rate ($p < 0.001$) 3. Multilevel mixed effects equations did not detect SS association with IF. 4. Multivariate generalized estimating equations logistic regression model showed SS association with IF and smooth implants (HR = 1; rough surface = HR = 0.08) and location (anterior maxilla presented the highest HR = 1; anterior mandible the lowest HR = 0.12) 5. Time in function demonstrated to SS influence IF ($p < 0.001$)
	883			96.5	3.3	1		
40.9%/59.1%	472	N	NR	100	0	0	NR	CC study conducted at the university setting - Lack of control for confoundings - No report on data regarding the control group - Poorly defined eligibility criteria
	46	NR	NR	NR	NR	NR	NR	
0%/100%	60	NR	NR	100	0	0	NR	Prospective case-control study on immediate placement therapy - Common implant characteristics: 3.7 × 16 mm - Patients received pre-implant therapy ATB - No mention on MBL, although authors state no SS difference between groups
	60	NR	NR	100	0	0	NR	

(Continues)

TABLE 1 (Continued) [In PDF format, this table is best viewed in two-page mode]

Authors (year)	Study design	Mean follow-up	Systemic condition	Medication	Dosage (mg/ml)	Therapy length (months)	Administration method	Subjects (*n*)	Age (years)
Grant et al. (2008)	RC	48	Osteoporosis	Prior to implant placement: Fosamax (66), Actonel (21), Boniva (2) After implant placement: Fosamax (27), Actonel (5) Boniva (1)	NR	38	Oral	115	40
			ASA I-II	N	N	N	N	343	
Koka et al. (2010)	RC	>36	Osteoporosis (32)/ osteopenia (18)	BP	NR	NR	Oral	55	71
			NR	NSM	N	N	N	82	66
Zahid et al. (2011)	RC	66	Osteoporosis	BP		26	Oral	26	56
			ASA I-II	N	N	N	N	274	
Memon et al. (2012)	RC	54	Osteoporosis	Risedronate (23), Ibandronate (5), Alendronate (72)	NR	<1 y (20), 1–3 y (19), >3 y (15), unespecified (46)	Oral	100	66 ± 9
			ASA I-II	N	N	N	N	100	63 ± 9
Famili et al. (2014)	RC	12	Osteoporosis (21)/ osteoarthritis (1)	Fosamax/Boniva/Actonel	NR	NR	Oral	22	≥50 (120)/ <50 (91)
			ASA I-II	NSM	N	N	N	98	

ASA, American Society of Anesthesiologists; BP, bisphosphonate; HRT, hormone replacement therapy; MBL, marginal bone level; N, none; NR, not reported; NSM: no specific medications; RC, randomized, controlled.

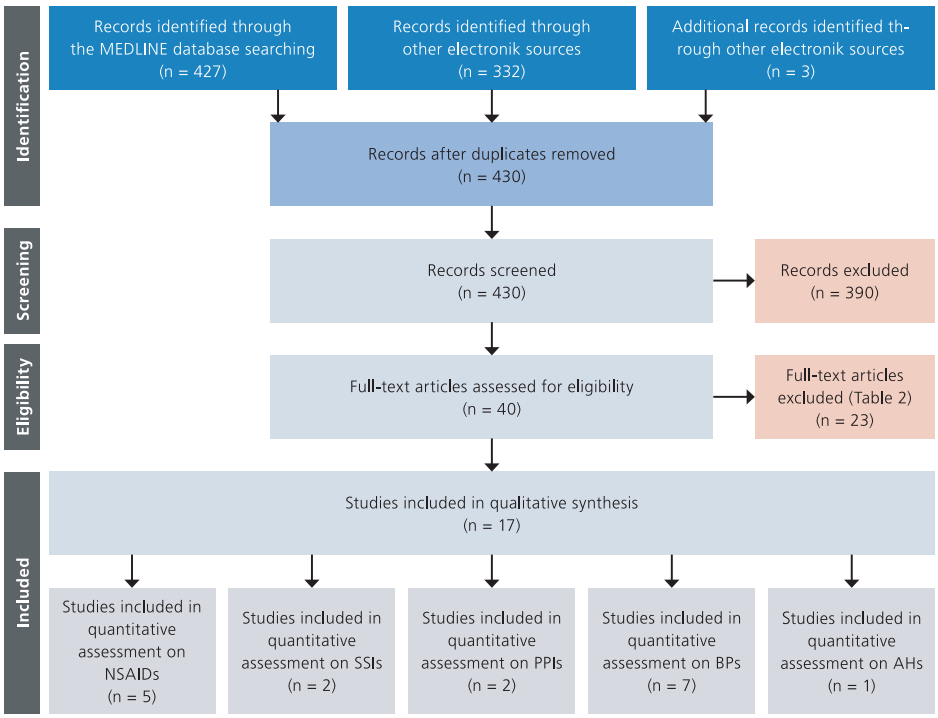

FIGURE 1 PRISMA flowchart of the screening process

TABLE 1 (additional columns - continued)

Gender (M/F)	Implants (*n*)	Failure (month)	Marginal bone loss (mm)	Implant survival rate(%)	Implant failure rate (%)	HR (95% CI)	Biological complications	Comments
0%/100%	468	<6	NR	99.5	0.5	NR	NR	Retrospective cohort study with poor data regarding implant outcomes - Patients were reached through mail to answer a survey to be examined - Implants in the case group had early failure - None of the 115 included in the case group had osteonecrosis as consequence of implant therapy - Diabetes and steroids could be other confounding factors
	1450	NR	NR	99	1	NR	NR	
0%/100%	121	NR	NR	99.17	0.83	NR	NR	Retrospective cohort study with vague data acquisition - Failures in the non-BP group ocurred concomitant to the intake of steroids, calcium and vitamin D and in smokers and diabetics - Failures in the BP group ocurred in patients intaking HRT-estrogen, cacium and vitamin D
	166	NR	NR	98.19	1.81	NR	NR	
38.1%/62.9	51	<2	NR	94.11	5.88	NR	NR	Restrospective radiographic study - Poor descriptive and statistic analysis - Possible confounders: smoking (8.5% - OR = 1.28), bone graft (26.2 OR = 1.31) and thread exposure (10.9% - OR = 3.25) - Statistically significant associations were found between the use of BP and thread exposure (p = 0.001) - No cases of osteonecrosis as consequence of implant therapy were registered
	610	NR	NR	97.1	2.6	NR	NR	
0%/100%	153	Early (10)	0.66 ± 0.70	93.5	6.5	NR	NR	Retrospective-chart based study - MBL evaluated at stage 2 - MBL was only available from 73 patients in both groups - Multiple implant systems were evaluated - Failures by BP: Alendronate (6) ibandronate (3) and risedronate (10) - By proportion, ibandronate had the highest percentage of failures (25%)
	132	Early (6)	0.80 ± 0.65	95.5	4.5	NR	NR	
0%/100%	75	Early	NR	98.7	1.3	NR	NR	Retrospective Unviersity-based study on females with/-out osteoporosis - Vague definition on success rate - Authors did not identify confounders - No data regarding the number of patients according to the BP - Lack on data in regards to the time period taking BP - Poor demographics
	272	N	NR	100	0	NR	NR	

TABLE 2 Excluded papers based on full text evaluation

Author (year)	Medication	Reason for exclusion
Nisi et al. (2015)	Bisphosphonate	No data on implant failure
Holzinger et al. (2014)	Bisphosphonate	Data on BRONJ after implant therapy
Lopez-Cedrun et al. (2013)	Bisphosphonate	Data on BRONJ after implant therapy
Kim and Kwon et al. (2010)	Bisphosphonate	Case report
Lazarovici et al. (2010)	Bisphosphonate	Data on BRONJ after implant therapy
Kwon et al. (2014)	Bisphosphonate	Data on BRONJ after implant therapy
Grant et al. (2008)	Bisphosphonate	No data on implant failure
Favia et al. (2015)	Bisphosphonate	No data on implant failure
Mattheos et al. (2013)	Bisphosphonate	Case report
Kwon et al. (2016)	Bisphosphonate	No data on implant failure
Kwon et al. (2016)	Bisphosphonate	Single-arm case study
Jacobsen et al. (2013)	Bisphosphonate	No data on implant failure
Tam et al. (2014)	Bisphosphonate	Single-arm case study
Lazarovici et al. (2010)	Bisphosphonate	Data on BRONJ after implant therapy
Shabestari et al. (2010)	Bisphosphonate	Single-arm case study
Goss et al. (2010)	Bisphosphonate	Data on BRONJ after implant therapy
Bell and Bell (2010)	Bisphosphonate	Single-arm case study
Gomez-Moreno et al. (2016b)	Anticoagulant	Report on bleeding complications
Gomez-Moreno et al. (2016a)	Anticoagulant	Report on bleeding complications
Karbuda et al. (2007)	COX-2 inhibitor	Report on analgesic and inflammatory response
Chrcanovic et al. (2016c)	Anticoagulant	Multivariate analysis
Chrcanovic et al. (2016a)	NSM	Multivariate analysis
Chrcanovic et al. (2016b)	Anticoagulant	Multivariate analysis

BRONJ, Bisphosphonate-related osteonecrosis of the jaw; COX, Cyclooxygenase; NSM, No-specific medication.

odds ratio of 1.21. Hence, an effect of the experimental medication could not be concluded ($p > .05$ for the null of no effect) (Figure 4).

3.5 | Quality assessment

After the screening process, we found 13 studies included in the qualitative assessment that could be analyzed with NOS (Table S1). A Cohen's kappa inter-rater agreement rate of .92 was reached. After discussing the disagreements between the examiners (AM and GAO), a mean NOS score of 6.38 ± 2.43 was obtained.

4 | DISCUSSION

4.1 | Principal findings

Although survival in implant dentistry does not represent a challenge anymore, failures and complications still occur (Brugger et al., 2015). The present systematic review revealed an insight into the possible effect of some medications on implant failure. Interestingly, PPIs used to reduce the production of acid by blocking the enzyme in the wall of the stomach that produces acid (Colmenares & Pappas, 2016) and SSRIs used for depression and anxiety conditions (Galli, Macaluso & Passeri, 2013) exhibited an increased risk of implant failures. On the other side, unexpectedly, the use of oral BPs for the treatment of osteoporosis did not yield significance when analyzing their impact on implant failure. This finding is of special interest as oral BPs intake was reported to be associated with a significantly higher risk to develop osteonecrosis of the jaw due to the blocking of osteoclastic activity (Edwards et al., 2007). To the best of authors' knowledge, this systematic review was the first one in highlighting the potential implications of medications upon implant longevity. Nevertheless, findings from this study cannot be conclusive due to the studies' design and consequently, the number of inherent uncontrolled confounders. Accordingly, it is encouraged to prospectively study the effect of these medications upon early and late implant failure controlling other known risk factors for the stability of the peri-implant tissues.

4.2 | Are our findings biologically plausible?

The effect and interaction of some medications with bone homeostasis has been extensively documented in preclinical studies (David, Nguyen, Barbier & Baron, 1996; Galli et al., 2013; Haney & Warden, 2008; Insua et al., 2017; Nyman, Schroeder & Lindhe, 1979; Robinson, Tashjian & Levine, 1975; Rzeszutek, Sarraf & Davies, 2003; Vestergaard, 2008). Recently, in vivo clinical reports have been of great interest in the field of implant dentistry due to the likely role of these medications upon osseointegration (Winnett et al., 2016; Wu et al., 2014, 2016, 2017). The present meta-analysis yielded statistical significance to feature the possible relevance of PPIs and SSRIs on IF.

Proton pump inhibitors aim at inhibiting the acid output to the stomach for the treatment of gastroesophageal reflux or gastric ulcers. The underlying mechanism that could negatively impact osseointegration leans on the impaired effective calcium uptake through the intestines (Kopic & Geibel, 2010, 2013). Calcium is an essential mineral for the proper formation and maintenance of the skeleton as it may impact upon the bone mineral density (Tai, Leung, Grey, Reid & Bolland, 2015). In point of fact, a calcium intake of at least 1,000–1,200 mg/day has been recommended to minimize the risk of

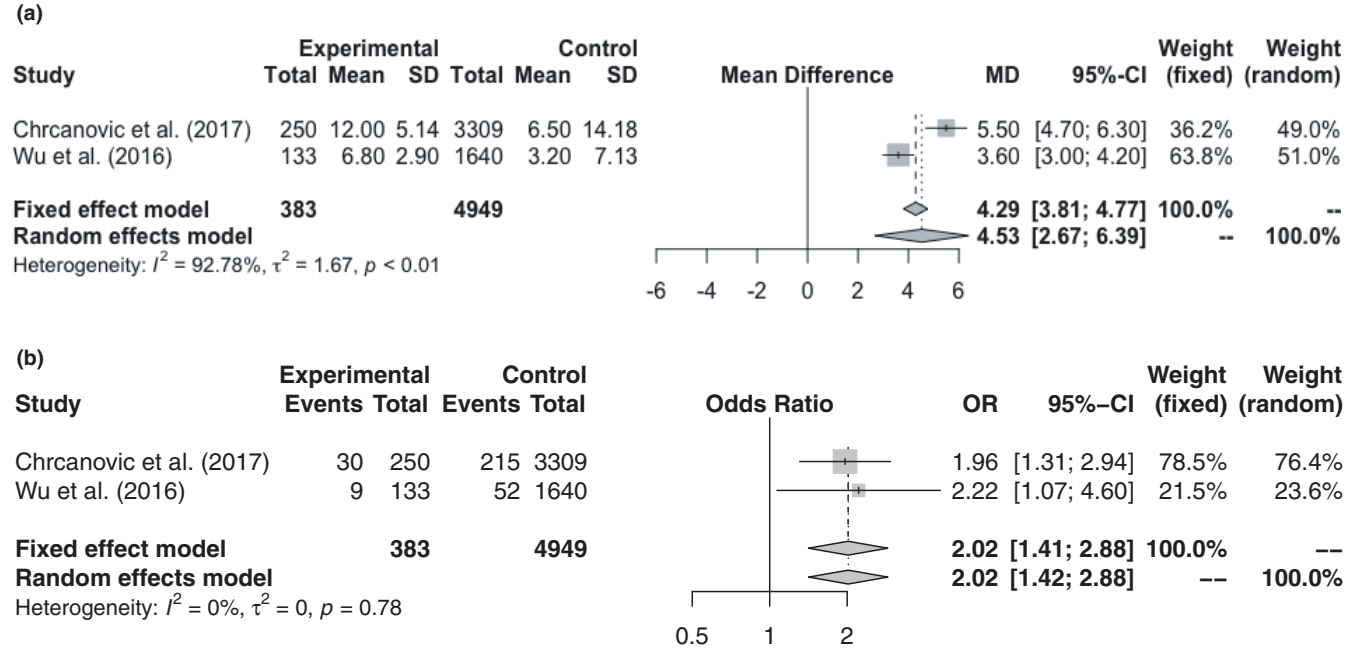

FIGURE 2 (a) Meta-analysis of mean and 95% confidence interval of implant failure for patients taking proton pump inhibitors (PPIs). (b) Meta-analysis of mean and 95% confidence interval of odds ratios for patients taking proton pump inhibitors (PPIs)

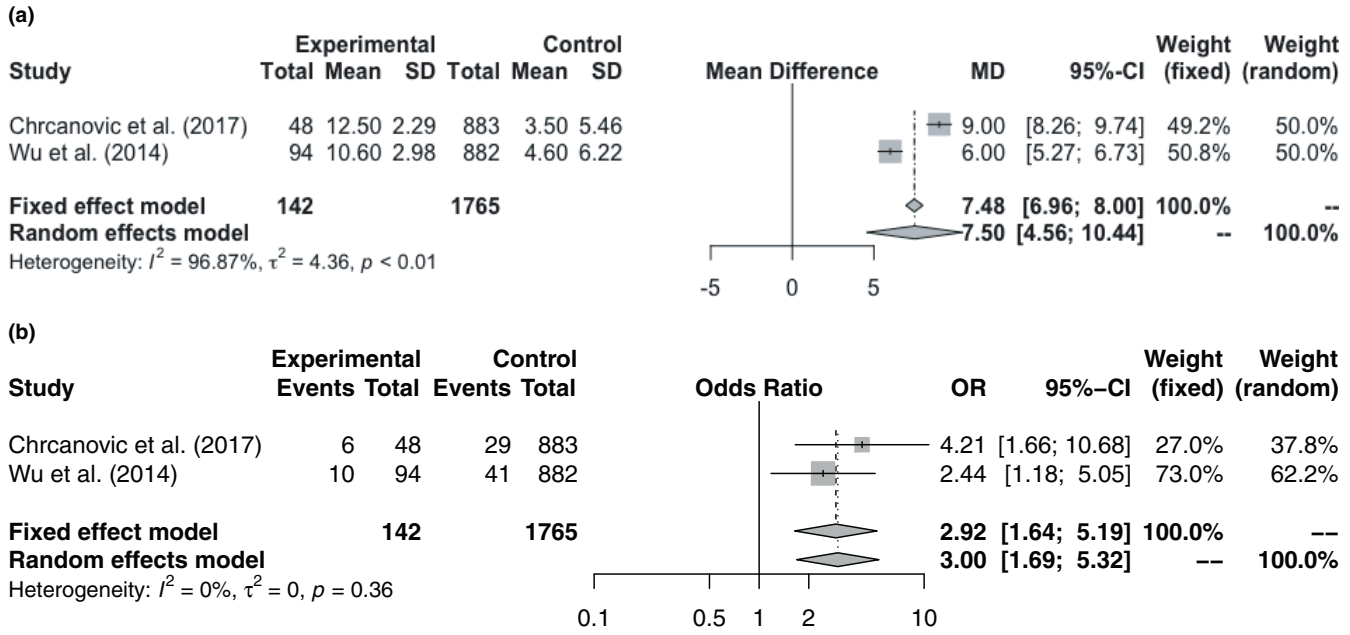

FIGURE 3 (a) Meta-analysis of mean and 95% confidence interval of implant failure for patients taking serum serotonin reuptake inhibitors (SSRIs). (b) Meta-analysis of mean and 95% confidence interval of odds ratios for patients taking serum serotonin reuptake inhibitors (SSRIs)

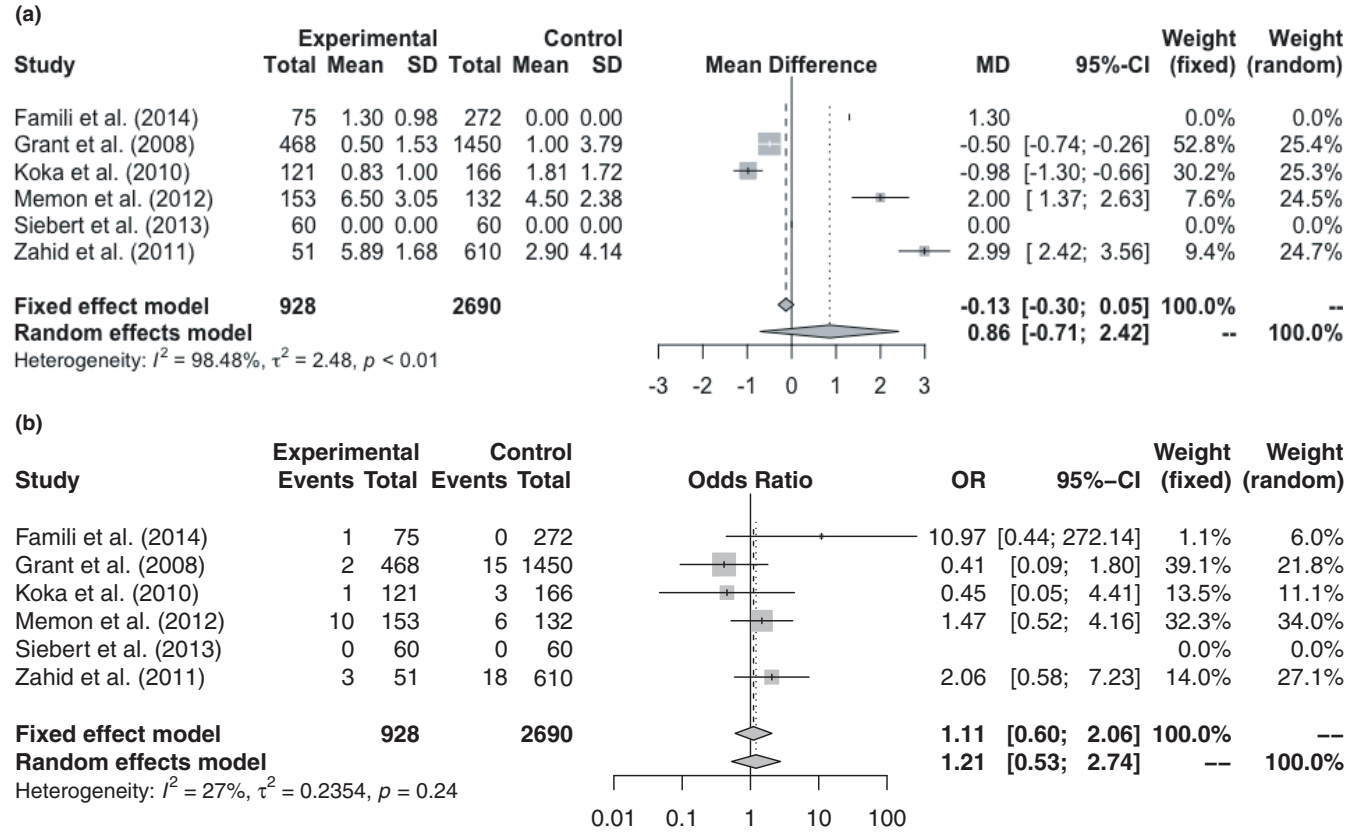

FIGURE 4 (a) Meta-analysis of mean and 95% confidence interval of implant failure for patients taking bisphosphonates (BPs). (b) Meta-analysis of mean and 95% confidence interval of odds ratios for patients taking bisphosphonates (BPs)

osteoporosis (Tang, Brooks, Wetmore & Shireman, 2015). O'Connell, Madden, Murray, Heaney and Kerzner (2005) examined for 7 days the intake of omeprazole 20 mg QD and found out a reduced calcium absorption when compared to a placebo medication in postmenopausal women. A further study confirmed that urine calcium excretion was reduced when in-taking omeprazole 20 mg TD (Graziani et al., 1995). Hence, understanding the effect of PPIs on calcium reduction and the detrimental result upon bone homeostasis highlight the clinical implications of the intake of PPIs on IF.

Along the same lines, SSRIs used for depressive or anxiety conditions have been further identified to play a pivotal role on the osteoblast/osteoclast balance. As such, serotonin can regulate osteoclast activation and differentiation as osteoclasts derive from hematopoietic cell precursors (Battaglino et al., 2004). As a matter of fact, the activity of the serotonin transporter and receptor is present in bone. Consequently, SSRIs have demonstrated to have detrimental effect on bone mineral density and trabecular microarchitecture through their anti-anabolic skeletal effects (Kahl et al., 2006). For this reason, it might be hypothesized to negatively influence the process of osseointegration. Recently, a preclinical in vivo study has elucidated the effect of SSRIs on osteoblast differentiation and bone regeneration in rats. Interestingly, SSRI medication significantly reduced osteogenic differentiation and mineralization with concomitant reduction of osteoblast marker genes including alkaline phosphatase, Osterix, and osteocalcin, indicating its putative impact on the regulation of bone metabolism (Nam et al., 2016). Hence, such cellular findings would be in concordance with the results obtained by Wu et al. (2014), who demonstrated that patients in-taking SSRIs experienced an increased risk of IF (hazard ratio: 6.28; 95% confidence interval: 1.25–31.61; $p = .03$). In addition, it should also be considered that the higher risk of implant failures may is influenced as well by the psychological condition of the patient rather than by the intake of SSRI.

On the other side, medications reported in the literature to possibly interfere with osseointegration or bone homeostasis such as NSAIDS or oral BPs have failed to show statistical significance. As aforementioned, these findings must be cautiously interpreted, as there are other confounding factors such as the absence of an effect on implant survival due to the given dosages. The largest and longer term study analyzing failing osseointegration of 197 implants revealed that patients using NSAIDs peri-operatively experienced 44% IF, while 38% IF rate was occurred in patients, who did not take NSAID peri-operatively. Moreover, the NSAIDs cohort experienced 3.2 times more cases of radiographic bone loss >30% of the overall height and 1.9 times more cases of cluster failures (Winnett et al., 2016). Accordingly, it might be speculated that the intake of peri-operative NSAIDs may inhibit the inflammatory bone metabolism, especially in vulnerable populations while having minimal clinical effect in healthy patient populations (Winnett et al., 2016). In contrast, the use of AHTNs has been suggested to have a beneficial impact on implant longevity. The biological plausibility of this finding rests on the fact that AHTNs drugs can affect bone metabolism by inhibiting osteoclasts catabolic effects on bone by blocking their β2 adrenergic receptors (beta-bloquers), to enhance bone formation by increasing calcium absorption at the distal convoluted tubule (thiazides) or by shifting the balance toward bone formation by blocking the renin-angiotensin system (ACE inhibitors) (Wu et al., 2016). In addition, oral BPs did not show to substantially contribute to IF. This is an interesting finding, as this medication mainly used for osteoporosis or cancer therapy is likely the most widely documented medication affecting the skeletal bone characteristics (Brufsky & Mathew, 2015; Rachner, Khosla & Hofbauer, 2011; Sambrook & Cooper, 2006). Briefly, BPs inhibit the digestion of bone by promoting the apoptosis or cell death of osteoclast, thereupon decreasing the rate of bone resorption along the therapy (Migliorati, Siegel & Elting, 2006). One of the most common complications in our field has been the increased risk of osteonecrosis of the jaw as a consequence of dental extraction or otherwise oral surgery (Ruggiero et al., 2009). Authors want to reiterate that when interpreting these results must be exercised cautiousness due to the lack of homogeneity with regard to the dosage and timing in-taking oral BPs reported in the studies, but apparently seems not to represent a contraindication for implant therapy in osteoporotic patients. Contrarily, bone malignancies/metastases involving the intake of intra-venous BPs represent an absolute contraindication for implant therapy.

4.3 | Limitations and future directions

The findings of the present study should be interpreted with great caution. First of all, due to the nature of the included study designs in the present systematic review, no "cause-effect" relationship can be established, but "association" and thus, findings from the present review encourage to investigate in a prospective manner the impact of medications on implant outcomes controlling other known confounders (i.e., smoking, plaque control, or other local and systemic contributing factors) that could potentially interfere in the implant stability. Moreover, the timing of implant failure must be adequately reported. In this sense, this would help to gain perspective on possible underlying mechanisms that elicit implant failure. Along these lines, it is encouraged to investigate the effect of polymedication on osseointegration and implant failure. Furthermore, a major limitation that was found when investigating the biological complications was the lack of standardization with regard to the definition of peri-implant disease. Hence, it is strongly advised to follow the guidelines recommended by the European Federation of Periodontology and the American Academy of Periodontology to report on biological complications using clinical and radiographic assessments.

5 | CONCLUSIONS

Findings from the present systematic review showed an association of proton pump inhibitors and selective serotonin reuptake inhibitors with implant failure. Hence, the effect of these medications should

be further investigated in future studies as potential confounders for implant outcomes.

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CONFLICT OF INTEREST

The authors do not have any direct financial interests with the products and instruments listed in this manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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CONSENSUS REPORT

WILEY CLINICAL ORAL IMPLANTS RESEARCH

Group 1 ITI Consensus Report: The influence of implant length and design and medications on clinical and patient-reported outcomes

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Abstract

Objectives: The aim of Working Group 1 was to address the influence of different local (implant length, diameter, and design) and systemic (medications) factors on clinical, radiographic, and patient-reported outcomes in implant dentistry. Focused questions on (a) short posterior dental implants (≤6 mm), (b) narrow diameter implants, (c) implant design (tapered compared to a non-tapered implant design), and (d) medication-related dental implant failures were addressed.

Materials and methods: Four systematic reviews were prepared in advance of the Consensus Conference and were discussed among the participants of Group 1. Consensus statements, clinical recommendations, and recommendations for future research were based on structured group discussions until consensus was reached among the entire expert Group 1. The statements were then presented and accepted following further discussion and modifications as required by the plenary.

Results: Short implants (≤6 mm) revealed a survival rate ranging from 86.7% to 100%, whereas standard implant survival rate ranged from 95% to 100% with a follow-up from 1 to 5 years. Short implants demonstrated a higher variability and a higher Risk Ratio [RR: 1.24 (95% CI: 0.63, 2.44, $p = 0.54$)] for failure compared to standard implants.

Narrow diameter implants (NDI) have been classified into three categories: Category 1: Implants with a diameter of <2.5 mm ("Mini-implants"); Category 2: Implants with a diameter of 2.5 mm to <3.3 mm; Category 3: Implants with a diameter of 3.3 mm to 3.5 mm. Mean survival rates were 94.7 ± 5%, 97.3 ± 5% and 97.7 ± 2.3% for category 1, 2 and 3.

Tapered versus non-tapered implants demonstrated only insignificant differences regarding clinical, radiographic, and patient-reported outcomes.

The intake of certain selective serotonin reuptake inhibitors and proton pump inhibitors is associated with a statistically significant increased implant failure rate. The intake of bisphosphonates related to the treatment of osteoporosis was not associated with an increased implant failure rate.

Conclusions: It is concluded that short implants (≤6 mm) are a valid option in situations of reduced bone height to avoid possible morbidity associated with augmentation procedures; however, they reveal a higher variability and lower predictability in survival rates. Narrow diameter implants with diameters of 2.5 mm and more demonstrated no difference in implant survival rates compared to standard diameter implants. In contrast, it is concluded that narrow diameter implants with diameters of less than 2.5 mm exhibited lower survival rates compared to standard diameter implants. It is further concluded that there are no differences between tapered versus non-tapered dental implants.

Certain medications such as selective serotonin reuptake inhibitors and proton pump inhibitors showed an association with a higher implant failure rate.

KEYWORDS
biological complications, clinical decision-making, dental implants, drug, endosseous implant, epidemiology, failure, humans, medication, meta-analysis, narrow diameter, osteotomy, randomized controlled trials, review, short dental implants, small dental implants, survival

1 | INTRODUCTION

The objectives of Group 1 of the 6th ITI Consensus Conference were to provide statements and recommendations for clinicians and researchers related to short implants (≤6 mm), narrow diameter implants (≤3.5 mm), implant designs (tapered versus non-tapered), and certain medications on clinical, radiographic, and patient-reported outcomes in implant dentistry.

For Working Group 1, four systematic reviews have been prepared and reviewed before the Consensus Conference. Based on the data and the meta-analysis of the individual, systematic reviews and basis on thorough discussions among the participants of Group 1 and among the entire plenum of the conference consensus statements and clinical recommendations were carefully formulated. In addition, recommendations for future research were also prepared by the working group. The four systematic reviews are listed below:

1. Survival rates of short dental implants (≤6 mm) compared with implants longer than 6 mm in posterior jaw areas: A meta-analysis.
   Panos Papaspyridakos, Andre De Souza, Konstantinos Vazouras, Hadi Gholami, Sarah Pagni, Hans-Peter Weber
2. Narrow diameter implants: A systematic review and meta-analysis
   Eik Schiegnitz, Bilal Al-Nawas
3. Systematic review of clinical and patient-reported outcomes following oral rehabilitation on dental implants with a tapered compared to a non-tapered implant design
   Asbjørn Jokstad, Jeffrey Ganeles
4. Medication-related dental implant failure: Systematic review and meta-analysis
   Vivianne Chappuis, Gustavo Avila-Ortiz, Mauricio Araújo, Alberto Monje

2 | SURVIVAL RATES OF SHORT DENTAL IMPLANTS (≤6 MM) COMPARED WITH IMPLANTS LONGER THAN 6 MM IN POSTERIOR JAW AREAS: A META-ANALYSIS

2.1 | Preamble

Short implants have been proposed as an alternative to eliminate or reduce the need for vertical bone augmentation procedures, which are often associated with additional costs, longer treatment time, increased postoperative morbidity, and greater risk for complications. However, the long-term efficacy of short dental implants has been a topic of controversy in the dental implant literature. Whereas some studies reported lower survival rates for short compared to longer implants, other reports, including a number of systematic reviews, more recently concluded that survival rates of short implants are similar to longer implants placed in pre-existing or grafted bone. The majority of studies does not include direct comparisons of the performance of short and longer implants. The interpretation of the literature is also complicated by the fact that authors have defined "short dental implants" differently. Some have considered <10 mm as short, whereas in other studies, short implants were 8 mm or less, 7 mm or less, or 6 mm or less.

The purpose of this study was to systematically review randomized controlled clinical trials (RCTs) reporting on long-term survival as well as complication rates of short implants (≤6 mm) versus longer implants (>6 mm) in posterior jaw areas of partially edentulous patients.

The main goal and primary outcome of this systematic review and meta-analysis was to compare long-term survival rates between short implants (≤6 mm) and longer implants (>6 mm) in posterior jaw areas.

Secondary outcomes were as follows:

- Radiographic bone levels
- Prosthesis survival
- Implant complications

The present systematic review is based on 10 randomized clinical trials including 775 patients (392 with short and 383 with longer implants) representing a total of 1,290 implants (637 short and 653 longer implants). The follow-up period ranged from 1 to 5 years.

Sufficient data were available to perform a meta-analysis of the primary outcome (implant survival). Only descriptive analyses were possible for the secondary outcomes radiographic bone levels, prosthesis survival, and biologic complication rates for implants.

When interpreting the results, it is important to realize that only three of the 10 studies evaluated the performance of short and longer implants in a randomized manner in sites allowing the placement of both types of implants. The other seven studies compared the use of short implants to longer implants in conjunction with augmentation procedures. In other words, these seven studies compare different treatment approaches and not necessarily implant lengths per se. This difference needs to be kept in mind when comparing the results of these studies.

2.2 | Consensus statements

2.2.1 | Consensus statement 1

Short implants (≤6 mm) exhibit similar survival rates compared to longer implants (>6 mm) after periods of 1–5 years in function. The mean survival rate was 96% (range: 86.7%–100%) for short implants, and 98% (range 95%–100%) for longer implants. The meta-analysis showed a risk ratio of 1.29 (95% CI: 0.67, 2.50, $P = 0.45$) for failure when short implants were used.

This statement is based on a meta-analysis of 10 RCTs including 775 patients (392 patients with short, 383 with longer implants) and 1,290 implants (637 short, 653 longer implants).

2.2.2 | Consensus statement 2

Time in function may reduce the survival rate of short implants more than that of longer implants.

This statement is based on one RCT with a follow-up of 5 years including 45 patients and 60 implants (30 short, 30 longer). This is additionally confirmed by a recently published RCT with a 5-year patient follow-up that could not be included as it was published after the cut-off date for inclusion in the systematic review.

2.2.3 | Consensus statement 3

Short and longer implants present similar amounts of radiographic interproximal bone level changes. Following a period of 1–5 years, the radiographic interproximal bone level changes for the short implants ranged from +0.06 to −1.22 mm, whereas the corresponding values for the longer implants ranged from +0.02 to −1.54 mm.

This statement is based on 10 RCTs including 775 patients (392 patients with short, 383 with longer implants) and 1,290 implants (637 short, 653 longer implants).

2.2.4 | Consensus statement 4

The rate of surgical and postsurgical complications is higher in the longer implant group (mean: 32.8%; range: 0–90%) compared to the short implants (mean: 6.8%; range: 0–26%).[1] In the longer implant group, the majority of complications were associated with bone grafting procedures.[2]

2.2.5 | Consensus statement 5

Prosthesis survival for short and longer implants following a period of 1–5 years is similarly high. The mean prosthesis survival rate was 98.6% (range: 90%–100%) for the short implants, and 99.5% (range: 95%–100%) for the longer implants.

This statement is based on nine RCTs including 625 patients (317 patients with short and 308 with longer implants).

2.3 | Clinical recommendations

2.3.1 | What are the current indications for short implants?

Short implants are a valid option in situations of reduced bone height when it is important to avoid possible morbidity associated with augmentation procedures or to reduce treatment time. They may also be preferred when the possibility of damage to adjacent structures can be significantly reduced. Adjacent structures include maxillary sinuses, blood vessels and nerves, tooth structures and existing implants.

2.3.2 | Should longer implants be the first choice?

The selection of the length of an implant depends on site-specific local anatomical and patient conditions. When sufficient bone height exists, implants longer than 6 mm are preferred when they can be placed without increasing surgical risk.

2.3.3 | Can short implants be immediately loaded?

The loading times for short implants reported in the literature ranged from 6 weeks to 6 months. At the present time, no evidence-based recommendation can be made for immediate loading.

2.3.3 | Does implant diameter affect the survival of short implants?

Based on the findings from the studies included in this review, short implants with a diameter of 4 mm or greater should be used.

2.3.4 | Should adjacent short implants be splinted?

Based on the findings from the studies included in this review, the clinical recommendation is made to splint restorations involving adjacent short implants.

2.3.5 | What are the occlusal considerations for restorations on short implants?

Although the reviewed literature does not give specific recommendations regarding occlusion, a greater risk of occlusal overload of short implants has to be considered. Caution is especially advised when indicating short implants in patients presenting with single missing molars and/or parafunctional habits. Changes in occlusion should be assessed and adjusted as necessary during regular maintenance visits.

[1]This statement is based on eight RCTs including 590 patients (298 patients with short, 292 with longer implants) having 1,022 implants (500 short, 522 longer implants).

[2]This statement is based on six RCTs including 305 patients (134 patients with short and 171 with longer implants) and confirms previous consensus reports.

2.4 | Recommendations for future research

- Prospective long-term clinical studies on the performance of short implants (>5 years)
- Randomized clinical trials comparing short and longer implants in intact bone sites without the need for vertical bone augmentation.
- RCTs or long-term controlled clinical studies on the effect of splinting
- Studies on optimal implant design for short implants

3 | NARROW DIAMETER IMPLANTS: A SYSTEMATIC REVIEW AND META-ANALYSIS

3.1 | Preamble

Narrow diameter implants (NDI) are used in clinical situations including narrow bony ridges as an alternative to bone augmentation procedures and in sites with reduced interdental gap width. The aim of the systematic review was to assess the survival rates of NDI made from titanium or titanium alloy and to provide recommendations and guidelines for the application of NDI.

There is a need for clarity and standardization in the description of the diameter of an implant. For the purpose of this study, the maximal endosseous implant diameter has been used, including implant threads, as provided by the implant manufacturer. The available literature describes the use of different types of NDI, but it appears generally accepted that a NDI is one with a diameter of ≤3.5 mm.

Since the previous classification of NDI (Klein, Schiegnitz, & Al-Nawas, 2014), there have been new developments in the field of NDI and therefore, the following modification to this classification is proposed:

Category 1: Implants with a diameter of <2.5 mm ("Mini-implants")
Category 2: Implants with a diameter of 2.5 mm to <3.3 mm
Category 3: Implants with a diameter of 3.3 mm to 3.5 mm

At the present time, most implants of <2.5 mm diameter are one-piece implants. One-piece implants with a diameter of >3.0 mm are rarely described.

From 5,845 records retrieved initially, 72 studies were included in the qualitative analysis and 16 studies in the quantitative analysis. Quality assessment of the included literature showed considerable variation, with a high risk of bias. It should be noted that important aspects relating to clinical outcomes are not reported: There are no data on patient-reported outcome measures, loading protocols, biological or technical complications, all of which could impact on the actual clinical performance and longevity of the provided treatment.

It is important to note that there are no studies comparing NDI without bone augmentation procedures to SDI with bone augmentation procedures.

3.2 | Consensus statements

3.2.1 | Consensus statement 1

Mean survival rate of Category 1 implants was 94.5% ± 5% (Range 80%–100%) after observation periods of 12–78 months. The most frequently described applications of these implants were for transitional restorations, overdentures, and single anterior tooth replacement.

This statement is based on 20 clinical trials (eight RS, 10 PS, and two RCTs) with 1,220 patients and 5,367 implants. The majority of the included papers exhibited a high risk of bias.

3.2.2 | Consensus statement 2

Mean survival rates of Category 2 implants were 97.3% ± 4% (Range 80.5%–100%) after observation periods of 12–63 months. The most frequently described application was for single anterior tooth replacement.

This statement is based on 21 clinical trials (10 RS, 9 PS, and 2 RCTs) with 883 patients and 1,207 implants. The majority of the included papers exhibited a high risk of bias.

Compared to SDI, Category 2 NDI exhibit comparable survival rates in meta-analysis ([OR], 1.06; [CI], 0.31–3.61). This statement is based on four clinical trials (2 RS, 1 PS, and 1 RCT). The majority of the included papers exhibited a high risk of bias.

3.2.3 | Consensus statement 3

Mean survival rates of Category 3 implants were 97.7% ± 2% (Range 91%–100%) after observation periods of 12–109 months. The applications of these implants were not always precisely defined, but also included the replacement of posterior teeth in either arch.

This statement is based on 35 clinical trials (17 RS, 12 PS, and six RCT) with 3,842 patients and 5,612 implants. The majority of the included papers exhibited a high risk of bias.

Compared to SDI, Category 3 NDI exhibit comparable survival rates in meta-analysis ([OR], 1.19; [CI], 0.83–1.70). This statement is based on 10 clinical trials (eight RS, and two RCT). The majority of the included papers exhibited a high risk of bias.

3.2.4 | Consensus statement 4

There is insufficient evidence on the success rates for all NDIs. Clinical parameters and treatment protocols are often not sufficiently described and no controlled comparative long-term studies are available, resulting in a high risk of bias.

3.3 | Clinical recommendations

3.3.1 | What are the potential advantages of using NDI?

- NDI should be considered when it is important to ensure maintenance of adequate tooth-implant and implant-implant distances in

sites with reduced mesio-distal width.
- The use of NDI can be considered to reduce the need or complexity of lateral bone augmentation procedures to reduce morbidity.
- The use of NDI may allow simultaneous rather than staged bone augmentation procedures.
- The use of NDI may provide increased prosthetic flexibility in certain clinical situations.

3.3.2 | What are the potential disadvantages of using NDI?

Biological

- One-piece NDI with ball attachments might be difficult to manage at the onset of dependency.
- The use of NDI may compromise optimal prosthetic designs allowing the maintenance of peri-implant tissue health.

Mechanical

- Reducing implant diameter brings an increased risk of implant or component fracture.
- Caution is recommended for the use of NDI in patients with parafunctional habits and malocclusions.

3.3.3 | Should NDI be splinted?

Given the reduced implant strength and bone contact offered by NDI, it may be advisable to use splinted restorations based on the individual clinical situation.

3.3.4 | What are the indications for each classification of NDI?

Category 1 implants can be considered for:
- Support of definitive complete mandibular overdentures
- Support of interim prostheses, both fixed and removable

Category 2 implants can be considered for:
- Support of definitive complete mandibular overdentures
- Support of single tooth replacement in the anterior zone with narrow interdental width (maxillary lateral incisors and single mandibular incisors)

Category 3 implants can be considered for:
- Support of definitive complete overdentures
- Support of single tooth replacement in sites with reduced interdental and/or buccal-lingual width
- Support of multiple unit restorations

Personalized informed consent should include the possibility of more technical and biological complications.

3.4 | Recommendations for future research

- Future studies should compare the success and patient-reported outcome measures between NDI without augmentation procedure and SDI with an augmentation procedure.
- Future studies should document long-term results of potential technical and biological complications
- Future studies should compare new materials and implant designs.
- Future studies should investigate the aesthetic outcome of NDI.

4 | SYSTEMATIC REVIEW OF CLINICAL AND PATIENT-REPORTED OUTCOMES FOLLOWING ORAL REHABILITATION ON DENTAL IMPLANTS WITH A TAPERED COMPARED TO A NON-TAPERED IMPLANT DESIGN

4.1 | Preamble

Approximately 50% of all implants on the market are tapered. In this systematic review, a tapered implant is recognized as a cylindrical implant where the endosseous part narrows in diameter toward the apex. The rationale for using this implant design is to improve primary stability and subsequent treatment success.

The present systematic review evaluated the scientific evidence related to implant survival and success to address the question: In patients with dental implant restorations, do tapered compared to non-tapered implants demonstrate similar clinical and patient-reported outcomes?

Twenty-nine articles were identified of which three RCTs reported outcomes at 3 years. The three RCTs described the results of 245 patients with 388 implants at three years and reported clinically insignificant differences. The three RCTs each reported different clinical outcomes and the data were not comparable. None reported patient-reported outcomes or maintenance needs. All three RCTs have a moderate risk of bias. Meta-analyses were not conducted.

4.2 | Consensus statements

4.2.1 | Consensus statement 1

The evidence shows that both tapered and non-tapered implants demonstrate satisfactory performance with respect to marginal bone levels at 3 years. This statement is based on the evidence of three RCTs, (245 patients with 388 implants).

4.2.2 | Consensus statement 2

There is currently insufficient evidence to conclude if tapered compared with non-tapered implants demonstrate similar clinical and

patient-reported outcomes. This statement is based on the evidence from three RCTs, (245 patients with 388 implants).

4.3 | Clinical recommendations

4.3.1 | Is there a recommendation for any specific implant design with regard to taper?

Based on Consensus statements 1 and 2, both tapered and non-tapered implants can be used according to the operator's preference.

4.3.2 | Are there particular clinical situations in which any specific implant design with regard to taper is preferred?

Tapered implants can be considered in clinical situations to avoid injuring anatomical structures or causing apical fenestrations.

Appropriate professional judgment and clinical decision-making must include a comprehensive diagnosis of the patient's jawbone anatomy, bone quality and quantity, and osteotomy protocol.

4.3.3 | Is utilizing a tapered implant an effective strategy to increase insertion torque?

In situations where increased insertion torque is desired, tapered implants may be considered. The shape of the dental implant is only one contributing factor to achieve high insertion torque; however, the clinical significance of implant shape on long-term results is unclear.

4.4 | Recommendations for future research

- Clinically validate a nomenclature and classification system to describe and compare different configurations of "tapered" implants (Figure 1).
- Clinical studies that aim to compare tapered versus non-tapered implant designs should include details of bone quality and quantity, the osteotomy preparation protocols, (osteotomy shape, degree of under sizing, method of osteotomy (twist drill, piezo, condensation, etc.)).
- Establish whether insertion torque and resonance frequency analysis are valid indicators of the risk of micromotion as a function of the implant design.

5 | MEDICATION-RELATED DENTAL IMPLANT FAILURE: A SYSTEMATIC REVIEW AND META-ANALYSIS

5.1 | Preamble

Current global trends indicate that the general population's expectancy of life is increasing worldwide. These demographic changes have been associated with an increase in the intake of medications for the treatment of highly prevalent medical conditions. Some of these medications may influence tissue metabolism and, therefore, the outcomes of implant therapy in certain cohorts. Interestingly, the impact of medication that may particularly alter bone homeostasis upon implant therapy outcomes has not been systematically explored.

The main goal of this systematic review was to assess the association of implant failure rate as the primary outcome with intake of oral or parenteral medications that may affect bone metabolism.

Secondary outcomes were:

- Timing of implant failure.
- Marginal bone loss.
- Biological and Mechanical/Technical complications.

The present systematic review includes 17 investigations, one CCT had to be excluded due to missing reports on implant failures rates. The 16 remaining studies consisted of three RCTs, one PC and 12 RC including a total of 4,827 patients with 13,247 implants.

A total of five different categories of medications were identified upon completion of the systematic search: nonsteroidal anti-inflammatory medication (NSAIDs), antihypertensive medication (AHTNs), selective serotonin reuptake inhibitors (SSRIs), proton pump inhibitors (PPIs), and bisphosphonates (BPs). Sufficient data were available to perform meta-analyses of the primary outcomes for SSRIs, PPIs, and BPs. The heterogeneity of the study design and methodology in the selected studies did not allow for meta-analyses for any of the secondary outcomes. Limitation of this systematic

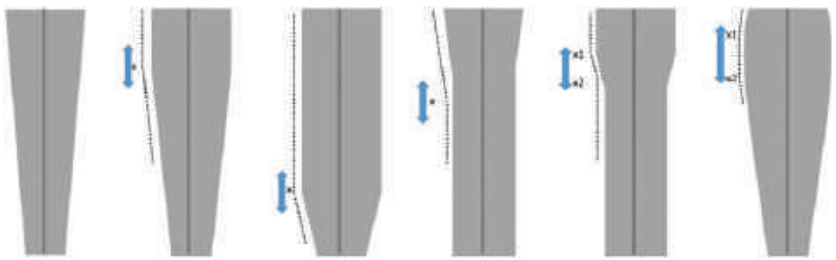

FIGURE 1 Different types of configurations and geometrie for tapered implants available on the dental market

review is related to differences in study design and medication regimens, in addition to confounding factors, such as comorbidity and polypharmacy among others reported in the literature. Therefore, the findings of this systematic review should be interpreted with caution.

5.2 | Consensus statements

5.2.1 | Consensus statement 1: General Statement

Limited evidence on the effect of long- and short-term medication intake on dental implant therapy outcomes indicates that there may be an association between implant failure rate and the intake of certain medications that influence bone metabolism.

5.2.2 | Consensus statement 2: nonsteroidal anti-inflammatory drugs (NSAIDs)

The association between nonsteroidal anti-inflammatory drug (NSAID) intake and implant failure rate is unclear.

This statement is based on the analysis of five studies (i.e., three RCTs, including a total of 191 patients, and two retrospective cohort studies, including a total of 81 patients) that revealed marked heterogeneity of the pharmacological regimen in the selected studies and a majority of studies reporting no implant failures in either the test or control groups, or both groups.

i.e., Ibuprofen, Flurbiprofen, Celecoxib, Acetylsalicylic, Rofecoxib, Nabumetone, Naproxen, Etodolac and others.

5.2.3 | Consensus statement 3: antihypertensive medication (AHTNs)

The association between the long-term intake of certain AHTNs and implant failure rate is unclear.

This statement is based on very limited available evidence of one retrospective study including 728 patients. Noteworthy, AHTNs exhibited a lower implant failure rate compared to the control population not taking AHTNs in this study.

i.e., Beta-blockers, Thiazide diuretics, Angiotensin-converting enzyme inhibitors, Angiotensin II receptor blockers and others.

5.2.4 | Consensus statement 4: selective serotonin reuptake inhibitors (SSRIs)

The intake of certain SSRIs is associated with a statistically significant increased implant failure rate.

This statement is based on the quantitative analysis of two retrospective cohort studies including a total of 790 patients, which suggested that implant failure rate was higher in subjects taking SSRIs as compared to a control population (Odd ratio: 2.92; average difference: 7.48%, C.I. [95%] = 6.96–8.00 with a $p < 0.01$, between 36 and 90 months of follow-up).

i.e., Citalopram, Dapoxetine, Escitalopram, Fluoxetine, Fluvoxamine, Indalpine, Paroxetine, Sertraline, Venlafaxine and Zimeline and others.

5.2.5 | Consensus statement 5: proton pump inhibitors (PPIs)

The intake of PPIs is associated with a statistically significant increased implant failure rate.

This statement is based on the quantitative analysis of two retrospective cohort studies including a total of 1,798 patients, which suggested that implant failure rate was higher in subjects taking PPIs as compared to a control population (Odds ratio: 2.02; average difference: 4.29%, C.I. [95%] = 3.81–4.77 with a $p < 0.01$, between 16 and 94 months of follow-up).

i.e., Omeprazole, Lansoprazole, Pantoprazole, Dexlansoprazole, Esomeprazole, Rabeprazole and others.

5.2.6 | Consensus statement 6: bisphosphonates (BPs) related to osteoporosis

The intake of BPs related to the treatment of osteoporosis was not associated with an increased implant failure rate.

This statement is based on the quantitative analysis of six cohort studies (i.e., five retrospective on oral BPs and one prospective using intravenous BPs including a total of 1,239 patients), which suggested that implant failure rate was higher in subjects taking BPs as compared to a control population (average difference: −0.13%, C.I. [95%] = −0.3 to 0.05, between 12 and 66 months of follow-up). Caution should be taken when interpreting these data due to the inherent risks associated with the occurrence of medication-induced osteonecrosis in patients taking BPs.

The effect of BP on implant outcomes in patients undergoing treatment of neoplastic diseases therapy was not evaluated, because implant therapy is usually contraindicated in this population.

i.e., Risedronate, Ibandronate, Alendronate, Zoledronic acid and others.

5.3 | Clinical recommendations

5.3.1 | What are the implications of the increasing intake of medication by the general population in daily practice?

Clinicians and patients considering implant therapy should be aware of possible medication-related implant failures. Hence, a comprehensive assessment and understanding of the patient's medical background and current medications, as well as a personalized informed consent, should be considered integral components of all phases of contemporary implant therapy (initial and supportive therapy).

5.3.2 | What considerations should be taken in daily clinical practice pertaining medication intake-related implant failure?

Clinicians should consider the association between increased implant failure rate and the intake of proton pump inhibitors (PPIs) or selective serotonin reuptake inhibitors (SSRIs) in their routine risk assessment as part of comprehensive implant therapy.

Clinicians should proceed with caution when implant therapy is considered in patients taking bisphosphonates (BPs) related to osteoporosis.

Standard implant therapy is contraindicated in patients receiving high-dose bisphosphonates (BPs) for the treatment of neoplastic diseases.

5.4 | Recommendations for future research

- To elucidate potential mechanisms of action that would explain the effect of certain medications on bone and soft tissue homeostasis around implants exhibiting different macro- and microscopic features via the conduction of *in vivo* preclinical studies.
- To investigate potential cause–effect relationships between the intake of certain medications and implant outcomes through prospective clinical trials evaluating clinical, radiographic, microbiological, histological, PROMs, and other parameters. This will expand our knowledge and increase the success of implant therapy..
- To evaluate the effect of confounders, such as the disease itself, comorbidities, behavioral aspects, and polypharmacy, on implant therapy outcomes in prospective clinical trials including target populations.

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REVIEW ARTICLE

WILEY CLINICAL ORAL IMPLANTS RESEARCH

Clinical performance of intentionally tilted implants versus axially positioned implants: A systematic review

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Abstract

Objectives: The aim of this review was to determine the clinical performance of dental implants that are intentionally tilted when compared with implants that are placed following the long axis of the residual alveolar ridge.

Materials and methods: A systematic review of the scientific literature using a predefined research question (PICO) and search strategy was undertaken. This search included five electronic databases. Two independent reviewers examined electronic databases and performed a manual review following search strategy to accomplish the item generation and reduction. Included articles were evaluated to determine the level of evidence. Data were extracted only from level I and level II studies, based on the Oxford Centre for Evidence-based Medicine—Levels of Evidence (March 2009). If included studies were homogeneous in nature, data were to be accumulated. However, if included studies were heterogeneous in nature, only descriptive data would be reviewed and analyzed.

Results: A total of 811 articles were identified through the PICO question and search strategy. Detailed review of the abstracts and articles resulted in further item reduction, and 46 articles were included for full-text review. A total of 42 articles were then selected for inclusion in the systematic review. The identified articles included two level I and 20 level II studies. In addition, 15 level IV, one gray literature, and four previous systematic reviews with meta-analyses were also used in the study. The extracted data from the included studies demonstrated heterogeneity that prevented quantitative assessment, and only one level II study directly compared tilted and axially placed implants. Assessment of the descriptive data demonstrated no differences in implant survival, marginal bone loss, prosthesis survival, or patient-reported outcome measures (PROMs) whether implants are placed axially or with intentional inclination of the coronal aspect of the implant toward the distal aspect of edentulous jaws.

Conclusions: Based upon the systematic review of the literature, an analysis of the descriptive data suggested no differences in clinical performance between implants that are placed in an axial position relative to the residual alveolar ridge when compared with implants that are intentionally tilted toward the distal aspect of edentulous jaws.

KEYWORDS

clinical assessment, clinical research, clinical trials, diagnosis, prosthodontics tilted, axial

1 | INTRODUCTION

Natural teeth are supported in alveolar bone by the periodontal ligament. Most descriptions of the periodontal ligament identify the different supporting fiber groups that maintain the natural tooth in its position within the jaw. Force application to the tooth will create different types of forces within the ligament itself. A vertical force on a natural tooth will cause some of the periodontal ligament fibers to stretch, creating tensile force between the ligament and the surrounding bone while forces applied in an angular fashion will create compressive forces in some areas and tensile forces in other areas within the ligament space (Alhashimi, Frithiof, Brudvik, & Bakhiet, 2001; Feller et al., 2015; Lv et al., 2009).

Dental implants are maintained in bone by direct deposition of mineralized bone on the surface of the dental implant. (Albrektsson & Zarb, 1993; Albrektsson, Zarb, Worthington, & Eriksson, 1986; Branemark, 1983) Although there are areas of fibrous connective tissue that also contact the implant, the predominant structure at the interface of implant and bone is calcified material. As a tissue, bone is far more than simply mineralized structure as it is dependent upon connective tissue, vascular supply and cells that are responsive to the need for osseous remodeling. Without constant bone remodeling, the survival of bone at the surface of an alloplastic device, the dental implant, would be very short-lived.

Dental implants, like natural teeth, also experience complex force applications. It may be reasonable to suggest that the unique configuration of a dental implant, often exhibiting a screw shaped macrostructure and a highly complex microstructure with a series of peaks and valleys related to the manufacturing process and surface treatment of the implant, creates a more complex set of forces than those that are seen on the natural tooth.(Brunski, 1988) Compressive, tensile, and shear forces represent the major categories of force that need to be maintained in a relative equilibrium to achieve and maintain osseointegration (Brånemark, Ohrnell, Skalak, Carlsson, & Brånemark, 1998; Brånemark & Skalak, 1998).

Biomechanical descriptions of stress distribution at the interface of implant and bone demonstrate a different pattern regarding force application to natural teeth. With natural teeth, the goal is to place forces down the long axis of the teeth. With implants, this force application may be somewhat irrelevant because the complex forces of compression, tension, and shear exist macroscopically at each thread of the implant and microscopically at every undulation of the microscopic surface of the implant. Early descriptions of implant placement in such a way as to create axial loading of the implant were derived from theories that were applicable to natural teeth. Over time, some clinicians recognized that efforts to create a vertical osteotomy to house the implant in a similar way to that of the natural teeth were frequently a futile effort. Discussions of slight angulations grew as the recognition that off axis loading of implants was not associated with chronic implant failure. In fact, the form of the residual alveolar ridge, particularly in the anterior maxilla and mandible, is such that it virtually mandates off axial loading for dental implants when placed in those areas.

Immediately placed and restored dental implants were among the earliest descriptions of dental implant usage. Those early descriptions however predated the description of osseointegration and instead utilized implants that were supported by connective tissue. (Schnitman & Shulman, 1980). With the recognition that direct bone to implant contact was possible, a new level of predictability and durability was achieved. (Adell, Lekholm, Rockler, & Brånemark, 1981) The earliest descriptions of osseointegration called for the avoidance of physical contact with any recently placed implant. The thought was that if contact could be eliminated by placing the implant beneath the oral mucosa or through the oral mucosa (Buser, Belser, & Lang, 1998) with relief provided to the tissue surface of the overlying prosthesis, healing of the bone to the implant could occur predictably. The early descriptions of osseointegration were specific relative to the design, at a micro- and macrostructural level, material, surgical technique, and prosthetic technique. (Albrektsson et al., 1986) Those early descriptions recommended an undisturbed healing time of 3–6 months depending upon the anatomic location of implant placement.

Patient response to this somewhat lengthy healing phase was acceptable but fell short of enthusiastic. With time, the microstructure and macrostructure of the implants were modified to allow shorter healing times that thereby allowed earlier functional loading of dental implants. One treatment approach that gained clinical acceptance involved the use of extra implants, more than four or five implants in each jaw, whereby the additional implants would be used to support prostheses until the traditionally distributed four or five implants were allowed to osseointegrate (Balshi & Wolfinger, 1997). Schnitman, Wohrle, & Rubenstein (1990), Schnitman, Wohrle, Rubenstein, DaSilva, & Wang (1997) described this technique and also described anticipation of failure of those extra implants that were used to immediately support the prosthesis. Instead, the survival rate of the immediately loaded implants, at the time of planned loading of the traditionally placed implants, was considered acceptable (Schnitman et al., 1997).

An alternative treatment approach was described by Krekmanov, Kahn, Rangert, & Lindstrom (2000) whereby the distal implants were intentionally tilted in a posterior direction thereby reducing the length of prosthetic cantilevers while still maintaining an optimal number of replacement teeth. The secondary benefit of this treatment approach was to reduce the number of implants that would be necessary to secure a dental prosthesis. The investigators found that both aims were met without any adverse effect on the survival of the implants. Malo, Rangert, & Nobre (2003) combined the use of intentionally tilted posterior implants with a minimal number of implants that were functionally loaded on the day of implant placement. This treatment approach was described as the “all-on-four” technique. The investigations found a high level of predictability for this treatment in both jaws.

With time, different implant manufacturers began to create transmucosal abutments that were at an angle to the central long axis of the implant. (Brosh, Pilo, & Sudai, 1998; Clelland, Lee, Bimbenet, & Brantley, 1995; Kao, Gung, Chung, & Hsu, 2008; Tian et al., 2012)

No consistent scientific studies identified problems with angled abutments. This observation led to an appreciation that intentional nonaxial loading could allow more strategic positioning of implants while taking advantage of the nonaxial positioning of the implant. Anatomic structures could be engaged by tilting implants in such a way as to create more separation between anterior and posterior implants thereby creating a foundation that could support fixed dental prostheses while using fewer dental implants (Krekmanov et al., 2000).

The primary aim of this systematic review of the literature was to determine the clinical performance of dental implants that are intentionally tilted toward distal aspect of edentulous jaws when compared with implants that are placed following the long axis of the residual alveolar ridge, in the edentulous patients. The secondary aim was to determine the biomechanical stability of implant-retained prostheses that depend upon angulated transmucosal abutments to effectively realign the implant with the prosthesis that it supports.

2 | MATERIALS AND METHODS

A systematic review of the scientific dental implant literature was conducted to address the question of performance of implants that are either loaded through axial forces or through the intentional tilting of the implant for strategic purposes. PRISMA was followed in reporting this systematic review.

The following focused question using the PICO format was developed. In patients who require replacement of all teeth in one or both dental arches using dental implants to support/retain fixed dental prostheses using intentionally tilted or angulated (toward the posterior portion of the mouth) posterior dental implants will be compared to traditionally placed axial dental implants to determine factors and outcomes relating to implant and prosthesis prognosis, biological and prosthesis complications, and patient-reported outcome measures (PROMs). A systematic review was performed using PubMed, Cochrane Central Register of Controlled Trials or EMBASE databases. Gray literature was searched through electronic screening using the New York Academy of Medicine Grey Literature report (http://greylit.org) and through Google Scholar.

Population-based search terms including dental implant, oral implant, endosseous implant, edentulous, immediate load, immediate loading, immediate provisional utilization, or immediate function were used. Considering the intervention that was performed the following terms were used: tilted, angulated, tipped, implant restoration, implant supported prosthesis, implant supported fixed dental prosthesis, implant supported FDP, all on four, or provisional. The comparison group was searched using the terms: vertical, straight, planned, traditional, parallel or axial. The outcomes that were searched were: implant prognosis, implant survival, implant success, prosthetic complications, prosthetic survival, prosthetic success, need for grafting, treatment time, patient satisfaction, clinician satisfaction, provisional, interim or definitive. The complete search strategy was listed in Table 1.

Manual searching was performed of the following journals: Clinical Oral Implants Research, International Journal of Oral Maxillofacial Implants, Clinical Implant Dentistry and Related Research, Journal of Prosthetic Dentistry, Journal of Prosthodontics, and International Journal of Prosthodontics. In addition, personal communications were solicited of authors involved in previous studies for any of these search terms.

Inclusion and exclusion criteria were identified and agreed upon prior to identification of articles for this review. The two authors agreed upon the search terms and search strategy prior to initiation of the study. Upon completion of item generation all titles were reviewed and an initial item reduction was performed based upon study irrelevance. A review of the abstracts associated with each article that was deemed relevant was then performed for the secondary item reduction. The final item reduction occurred after the reading of the full-text articles. Kappa agreement of inter-rater reliability was performed during the item reduction process. Agreement was established through direct communication and discussion of articles. All the included studies were reviewed and determined their levels of evidence. Level I study was defined as individual good quality RCT with narrow confidence interval and systematic review (with homogeneity) of RCTs. Level II study was defined as individual cohort study (including low-quality RCT) and systematic review (with homogeneity) of cohort studies. Level III study was defined as individual case–control study and systematic review (with homogeneity) of case–control studies. Level IV study was defined as case series and poor-quality cohort and case–control studies. Level V study was defined as expert opinion without explicit critical appraisal (Oxford Centre for Evidence-based Medicine, 2009).

Meta-analysis was planned if a sufficient number of homogeneous level I studies were available to address the PICO question. In the event that there were not sufficient numbers of homogeneous level I studies or if all level I studies were heterogeneous in nature the plan was to use descriptive statistics for the available level I studies. Once the level I studies were exhausted the same approach was to be used with level II studies. Any studies that were assessed as levels III or IV would be used for descriptive purposes only or could be used to provide further support or to refute the data obtained from the previous analyses. Likewise, any gray literature that was identified would be used to support or refute the findings from the level I and level II studies.

3 | RESULTS

Using the search terms described in the materials and methods a total of 811 articles were identified. Among the 811 articles identified via electronic and hand-search, 765 were excluded with author agreement subsequent to title and abstract review. A total of 46 articles that were identified as particularly relevant to this study design were then assembled for full-text evaluation. Upon the evaluation of the full-text a total of 42 articles were identified (Figure 1).

TABLE 1 Systematic search strategy

Focus Question	In patients who require replacement of all teeth in one or both dental arches using dental implants to support/retain fixed dental prostheses using intentionally tilted or angulated (toward the posterior portion of the mouth) posterior dental implants will be compared to traditionally placed axial dental implants to determine factors and outcomes relating to implant and prosthesis prognosis, biological and prosthesis complications, and patient-reported outcome measures (PROMs).
Search strategy	
Population	1. Dental implant [MeSH Terms] OR oral implant OR endosseous implant 2. Jaw, Edentulous [MeSH Terms] OR Mouth, Edentulous [MeSH Terms] OR Fully Edentulous OR complete edentulous OR full-arch OR partially edentulous OR partial edentulism OR complete edentulism OR terminal dentition OR failing dentition OR Full Arch 3. Immediate load OR Immediate loading OR Immediate provizionalization Or Immediate function
Intervention or Exposure	4. tilted OR tipped OR angulated OR tilting OR tipping 5. implant restoration OR implant supported prosthesis OR implant supported fixed dental prosthesis OR implant supported FDP OR implant supported FPD OR all-on-four OR all-on-4 OR provisional OR four-implant
Comparison	6. vertical OR straight OR planned OR traditional OR parallel OR axial OR upright
Outcome	7. implant prognosis OR implant survival OR implant success OR prosthetic complications OR prosthetic survival OR prosthetic success OR need for grafting OR treatment time OR patient satisfaction OR clinician satisfaction OR provisional OR Definitive OR interim
Search combination	1 OR 2 OR 3 AND (4 OR 5) AND 6 AND 7
Database search	
Language	English
Electronic database	PubMed (Medline) Cochrane Central Register of Controlled Trials (CENTRAL) EMBASE
Manual journal search	Clinical Oral Implants Research International Journal of Oral Maxillofacial Implants Clinical Implant Dentistry and Related Research Journal of Oral Implantology Implant Dentistry Journal of Prosthetic Dentistry Journal of Prosthodontics International Journal of Prosthodontics Personal communications on Grey Literatures
Selection criteria	
Inclusion criteria	Randomized controlled trials (RCT) Nonrandomized studies (NRS) Multicenter studies Published between 2003 and 2017 Follow-up period of at least 12 months Humans Adult (19+)
Exclusion criteria	Failure to identify inclusion criteria Methodology, technique, or review article Multiple publications on the same patient population Lack of identifiable information specific to prosthodontic procedures Patient pool of 10 or less Non-English language Animal studies Histologic or nonclinical outcomes Failure to report treatment outcomes on the dental implants or prostheses

Kappa agreement of inter-rater reliability was performed. Cohen's κ was run to determine if there was agreement between the two authors' judgments during the first, second, and final item reduction. During the first item reduction (title review), there was good agreement between the 2 authors' judgments, κ = 0.8016 (95% CI, 0.738–0.866). During the second item reduction (abstract review), there was very good agreement between the 2 authors' judgments, κ = 0.872 (95% CI, 0.782–0.963). During the final item reduction (full-text review), there was very good agreement between the 2 authors' judgments, κ = 0.954 (95% CI, 0.865–1) (Altman, 1991; McHugh, 2012).

The identified articles were then sorted into the different levels of evidence. (Table 2). The Cochrane Collaboration tool was used to

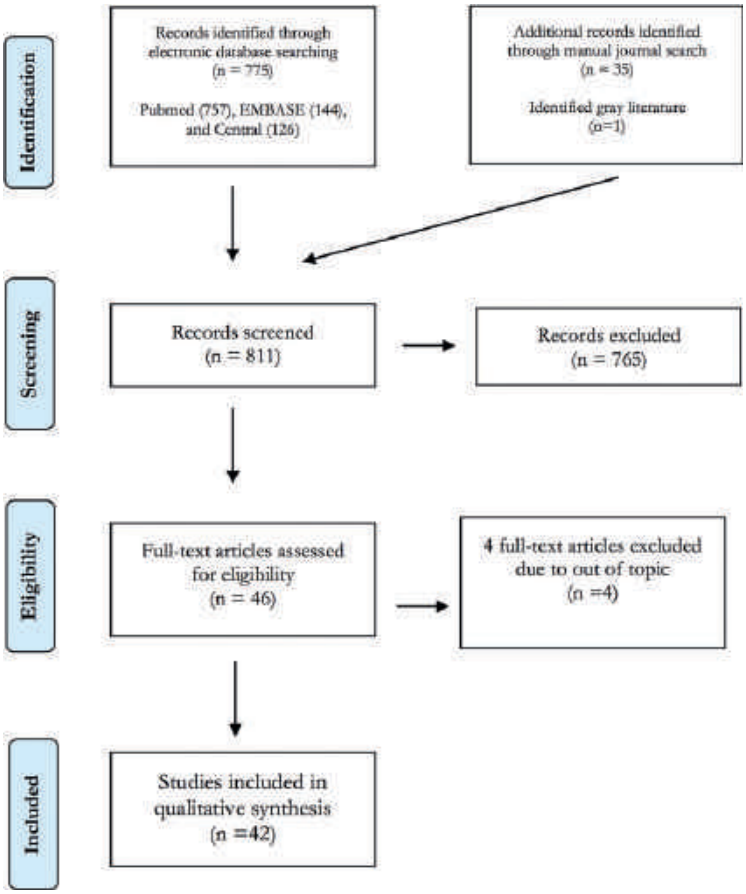

FIGURE 1 Search strategy (PRISMA flow diagram)

assess the quality of randomized controlled trials (RCTs) (Table 3), and the Newcastle-Ottawa Scale (NOS) was used to assess the quality of nonrandomized studies (Table 4). Level I and level II studies were reread and data were extracted from these studies (Tables 5–10). Likewise, the studies were evaluated to determine the final value of these articles to the literature review and data analysis that was drawn from it.

Upon final assessment of 42 articles it was determined that there were two level I studies. (Crespi, Vinci, Capparé, Romanos, & Gherlone, 2012; Tallarico, Meloni, Canullo, Caneva, & Polizzi, 2016) However, these studies did not aim to directly compare tilted to axial implants. One randomized controlled trial compared definitive acrylic resin prostheses with or without a cast metal framework that were immediately loaded and supported by axial and tilted implants. (Crespi et al., 2012) Although this study was not designed specifically to compare the tilted versus axial implants, 3-year overall implant survival rate was reported at 100% for axially positioned implants and at 96.59% for tilted implants, with a prosthetic survival rate of 100%. In addition, no statistically significant differences were found in marginal bone loss between tilted (maxilla: 1.11 ± 0.32 mm and mandible: 1.12 ± 0.35 mm) and axial implants (maxilla: 1.10 ± 0.45 mm and mandible: 1.06 ± 0.41 mm) at 3 years ($p > 0.05$). The second randomized controlled trial compared four implants supported prostheses (two axial and two tilted, all-on-4 protocol) to six-implants supported prostheses (all axial implants, all-on-6 group). (Tallarico, Meloni, et al., 2016) It showed that the all-on-6 group underperformed in comparison to the all-on-4 group relative to implant survival while the all-on-4 group exhibited more complications. Neither the numbers of implant failures nor the numbers of complications were statistically significant, and consequently, the performance of the two comparison groups was considered to be statistically equivalent.

Twenty level II studies were evaluated and were likewise heterogenous in nature. The level II studies that were available on this topic were not specifically focused on the performance of the implants per se but were instead studies that evaluated the targeted number of implants that would be placed per arch. Most studies focused on the clinical performance of four implants placed in the edentulous maxilla or mandible. Only one level II study focused on the direct comparison between axially placed and tilted implants (Krennmair et al., 2016). In this particular 3-year prospective clinical trial, 21 patients with four axially placed implants (axial group: two anterior and two posterior implants) and 20 patients with four implants (tilted group: two anterior axially placed and two distal tilted implants) were all restored with implant supported mandibular full-arch fixed dental prostheses. 37 out of 41 patients (19 patients in the axial group and 18 patients in the tilted group) and 148 out of 164 implants were followed at the 1-, 2-, and 3-year evaluation (dropout rate: 11.8%) presenting 100% implants and prostheses survival rates. The study showed that there were no

TABLE 2 Studies Included for Data Extraction

Levels of Evidence	Numbers	Studies
Level I	2	Crespi et al. (2012) Tallarico, Meloni et al. (2016)
Level II	20	Capelli et al. (2007) Francetti et al. (2008) Testori et al. (2008) Tealdo et al. (2008) Agliardi et al. (2010) Hinze et al. (2010) Francetti et al. (2012) Grandi et al. (2012) Weinstein et al. (2012) Malo, Nobre, and Lopes (2012) Di et al. (2013) Krennmair et al. (2014) Pera et al. (2014) Browaeys et al. (2015) Gherlone, Ferrini, Crespi, Gastaldi, and Capparé (2015) Ayna et al. (2015) Krennmair et al. (2016) Piano et al. (2016) Najafi et al. (2016) Li et al. (2017)
Level IV	15	Babbush, Kutsko, and Brokloff (2011) Paulo Malo, de Araújo Nobre, Lopes, Moss, and Molina (2011) Butura, Galindo, and Jensen (2011) Galindo and Butura (2012) Cavalli et al. (2012) Maló, de Araújo Nobre, Lopes, Francischone, and Rigolizzo (2012) Krennmair, Seemann, Weinländer, Krennmair, and Piehslinger (2013) Maló, de Araújo Nobre, and Lopes (2013) Thomas J Balshi, Wolfinger, Slauch, and Balshi (2014) Sannino, Bollero, Barlattani, and Gherlone (2015) Tallarico, Canullo, et al. (2016) Sannino and Barlattani (2016) Drago (2016) Niedermaier et al. (2017) Babbush, Kanawati, and Kotsakis (2016)
Previous Systematic reviews and Meta-Analysis	4	Ata-Ali, Peñarrocha-Oltra, Candel-Marti, and Peñarrocha-Diago (2012) Menini et al. (2012) Del Fabbro and Ceresoli (2014) Chrcanovic, Albrektsson, and Wennerberg (2015)

statistical significant differences between axial and tilted groups regarding clinical implant and prosthesis outcomes, including survival rates, biological and mechanical complications, peri-implant marginal bone resorption, pocket depth, bleeding index and gingival index.

In most studies, the posterior implants were titled toward the distal between 30 and 45 degrees from the long axis of residual ridges, and the dental implants were placed with minimal insertion torque of 30 Ncm. 17 and 30 degrees transmucosal prosthetic abutments were used to align the angulations of prosthetic screw access. Immediate loading protocol with screw-retained provisional resin prostheses was commonly used to provide patients the interim prostheses. The survival rate of tilted implants varied in the included studies, with the lowest reported survival rate at 89.4% during first 12 months follow-up (Tealdo et al., 2008) to the highest reported survival rate at 100% during 5 years follow-up (Ayna, Gülses, & Açil, 2015) and 97.50% at 7 years follow-up (Li, Di, Zhang, & Lin, 2017). In the authors' assessments, there were no differences in the implant survival rates between tilted and axial implants. When comparing the marginal bone loss around the implants, no significant differences were found between tilted and axial implants in most included studies. Although most studies did not report the survival rates for the interim prosthesis, 100% survival rates of definitive prosthesis were commonly documented. Two studies reported the remake of definitive prosthesis due to the loss of dental implants (Di et al., 2013; Najafi, Siadat, Akbari, & Rokn, 2016).

For the interim prosthesis, the most commonly reported prosthetic complication included fracture of interim prosthesis, (Agliardi, Panigatti, Clerico, Villa, & Malo, 2010; Francetti et al.,

TABLE 3 Risk of Bias for Randomized Controlled Trials by the Cochrane Collaboration's tool. Levels of risk or bias: high, unclear, and low

Study	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias) (patient-reported outcomes)	Blinding of outcome assessment (detection bias) (Mortality)	Incomplete outcome data addressed (attrition bias)	Selective reporting (reporting bias)	Other sources of bias
Crespi et al. (2012)	High	Low	High	Unclear	High	Low	Low	High
Tallarico, Meloni, et al., (2016)	High	Low	High	Unclear	High	Low	Low	High

2008; Francetti, Romeo, Corbella, Taschieri, & Del Fabbro, 2012; Grandi, Guazzi, Samarani, & Grandi, 2012; Krennmair, Seemann, Weinländer, Krennmair, & Piehslinger, 2014), screw loosening, (Krennmair et al., 2014; Testori et al., 2008) and fracture of veneering material.(Hinze, Thalmair, Bolz, & Wachtel, 2010; Krennmair et al., 2014) For the definitive prosthesis, the fracture of metal framework was uncommon, and was reported in 2 incidences from 2 articles. (Francetti et al., 2012; Pera et al., 2014) Other most commonly reported complications on definitive prostheses included fracture or wear of veneering material or artificial teeth, the need for readaptation of prosthesis to tissue to compensate for continuing resorption, abutment or prosthetic screw loosening, prosthetic screw fracture, and loss of screw access restoration (Ayna et al., 2015; Di et al., 2013; Francetti et al., 2012; Hinze et al., 2010; Krennmair et al., 2014; Najafi et al., 2016; Pera et al., 2014).

Patient-reported outcome measures (PROMs) were reported in different studies to demonstrate the overall clinical efficacy when combining anterior axial implants and posterior tilted implants in treating edentulous patients. (Ayna et al., 2015; Capelli, Zuffetti, Del Fabbro, & Testori, 2007; Di et al., 2013; Francetti et al., 2008; Krennmair et al., 2014; Li et al., 2017; Pera et al., 2014; Testori et al., 2008; Weinstein, Agliardi, Fabbro, Romeo, & Francetti, 2012) Patients generally reported satisfactory outcomes regarding aesthetics, phonetics, ease of maintenance, and functional efficiency. However, the survey instruments were greatly varied in different studies, and rarely was a reliable and validated psychometric instrument used to collect these patient-reported outcomes.

One article was identified from the authors knowledge of submitted or planned journal articles. (Eckert, 2017) This article qualified as gray literature. The study was a single cohort study that demonstrated 1,903 implants (Bone Level Tapered implants 4.1 mm or 3.3 mm; Straumann) placed over a 16-months time period. In this study anterior implants were placed along the axis of the residual ridge and posterior implants were intentionally tilted toward the distal approximately 30° or more. The treatment protocol indicated a plan to utilize the minimum number of implants necessary to achieve the immediate loading treatment protocol. The average number of implants placed in the maxilla was 4.3 implants per maxilla while the average number in the mandible was 4.1 implants. Immediate loading protocol was followed after implant surgery with screw-retained acrylic resin prostheses in 440 of 441 planned arches. The mean observation time in this study was 260 days. Of the 1,903 implants that were placed, all but six of the implants received angled abutments. In the posterior, the implants were intentionally tilted to the distal and a 30° angled abutment was used to create an apparent screw access opening slightly forward and more vertical than the implant angle would have established. The anterior implants followed the angulation of the alveolar ridge and this resulted in a forward angle of the anterior implant relative to the occlusal plane. In the anterior maxilla, 30° angled abutments were required for most implants. In the mandible the majority of the anterior implants were corrected using 17° angled abutments. No difference in implant performance, axial vs tilted, was identified. This study also reported no significant differences in implant survival based upon insertion torque.

TABLE 4 Quality assessment and risk of bias for nonrandomized trials by the Newcastle-Ottawa Scale. Higher scores indicate lower risk of bias in a study

	Selection				Comparability		Outcome			
Study	Representativeness of the exposed cohort	Selection of the nonexposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Control for main factor	Control for additional factor	Assessment of outcome	Follow-up long enough for outcomes to occur	Adequacy of follow-up of cohorts	Total scores (9/9)
Capelli et al. (2007)	0	★	★	★	★	0	★	0	0	5
Francetti et al. (2008)	0	★	★	★	★	0	★	0	0	5
Testori et al. (2008)	0	★	★	★	★	0	★	0	0	5
Tealdo et al. (2008)	0	★	★	★	★	★	★	0	★	7
Agliardi et al. (2010)	0	★	★	★	★	★	★	0	0	6
Hinze et al. (2010)	0	★	★	★	★	0	★	0	★	6
Francetti et al. (2012)	0	★	★	★	★	0	★	★	★	7
Grandi et al. (2012)	0	★	★	★	★	0	★	0	0	5
Weinstein et al. (2012)	0	★	★	★	★	0	★	0	★	6
Malo et al. (2012)	0	★	★	★	★	0	★	0	0	5
Di et al. (2013)	0	★	★	★	★	0	★	0	★	6
Krennmair et al. (2014)	0	★	★	★	★	★	★	0	★	7
Pera et al. (2014)	0	★	★	★	★	★	★	★	★	8
Browaeys et al. (2015)	0	★	★	★	★	★	★	★	★	8
Gherlone et al. (2015)	0	★	★	★	★	0	★	0	★	6
Ayna et al. (2015)	0	★	★	★	★	★	★	★	★	8
Krennmair et al. (2016)	0	★	★	★	★	★	★	★	★	8
Piano et al. (2016)	0	★	★	★	★	0	★	0	0	5
Najafi et al. (2016)	0	★	★	★	★	★	★	0	★	7
Li et al. (2017)	0	★	★	★	★	0	★	0	★	6

TABLE 5 Study design of the included Level I and Level II studies

Publication year	First author	Study level	Numbers of patients	Study jaw	Patient's age (years)	Follow-up duration	Implants used in the study
2012	Crespi R	1	36 (22 women and 14 men)	Maxilla: 24 Mandible: 2	54.6 (range: 41–81)	3 years	PAD System; Sweden-Martina
2016	Tallarico M	1	40 (19 women and 21 men)	Maxilla: 40	63 (range:42–87)	5 years (mean of 63.8 months, ranging 60–84 months)	NobelSpeedy Groovy implants; Nobel Biocare AG
2007	Capelli M	2	65 (43 women and 22 men)	Maxilla: 41 Mandible: 24	59.2 (range: 28–83)	Up to 52 months	Osseotite NT; Biomet 3i
2008	Francetti L	2	62 (34 women and 28 men) Assessed—44 patients only	Mandible: 44	56 (range: 35–77)	44 patients follow-up >1 year, (mean of 22.4 months, ranging 6–43 months)	Brånemark System MK IV NobelSpeedy Groovy
2008	Testori T	2	41 (26 women and 15 men) Assessed—30 patients	Maxilla: 30	59.2 ± 9.5 (range 38–84)	30 patients follow-up >1 year, (mean of 22.1 months, ranging 3–42 months)	Osseotite NT Implant; Biomet 3i
2008	Tealdo T	2	21 (10 women and 11 men)	Maxilla: 21	58	Mean of 20 months, ranging 13–28 months	Osseotite and Osseotite NT; Biomet 3i
2010	Agliardi E	2	173 (93 women and 80 men) Assessed—154 patients	Enrolled: Maxilla: 72 Mandible: 101 Assessed: Maxilla: 61 Mandible: 93	57.3 ± 8.5 (range 42–74)	154 patients follow-up >1 year. Maxilla: mean of 26.9 ± 12.5 months, ranging 12–55 months Mandible: mean of 31.3 ± 14 months, ranging 12–59 months	Brånemark Systems MKIV: 92 NobelSpeedy Groovy: 404
2010	Hinze M	2	37 (19 women and 18 men)	Maxilla: 19 Mandible: 18	64.6 (range 39–84)	1 year	NanoTite Tapered Implants; Biomet 3i
2012	Francetti L	2	47 (22 women and 25 men)	Maxilla: 16 Mandible: 33	53 (range 44–63)	Maxilla: mean of 33.8 months, ranging 22–40 months Mandible: mean of 52.8 months, ranging months 30–66 months	Brånemark System MK IV: 92 NobelSpeedy Groovy: 104
2012	Grandi T	2	47 (25 women and 22 men)	Mandible: 47	62.3 ± 9.4 (range 52–78)	18 months	Tapered implants (JDEvolution, JDentalCare, Modena, Italy)
2012	Weinstein R	2	20 (12 women and 8 men)	Mandible: 20	60.8 ± 8.8 (range 44–77)	Mean of 30.1 ± 8.6 months, ranging 20–48 months,	Brånemark System MKIV: 12 NobelSpeedy Groovy: 68

(Continues)

TABLE 5 (Continued)

Publication year	First author	Study level	Numbers of patients	Study jaw	Patient's age (years)	Follow-up duration	Implants used in the study
2012	Maló P	2	142 (86 women and 56 men)		53.7 (range 20–78)	Mean of 26 months, ranging 1–107 months.	MkIII implant (Nobel Biocare) MkIV implant (Nobel Biocare) NobelSpeedy implant (Nobel Biocare)
2013	Di P	2	69 (32 women and 37 men)	Maxilla: 38 Mandible: 48	56.78 (range 37–74)	Mean of 33.7 months, ranging 12–56 months,	Brånemark Mk III: 52 NobelSpeedy Groovy: 292 (TiUnite, Nobel Biocare).
2014	Krennmair S	2	24 (10 women and 14 men)	Mandible: 24	61.5 ± 11.9 (range 38–84)	24 months	Camlog; Screw-Line Promote plus; Wimsheim, Germany
2014	Pera P	2	37 (20 women and 17 men)	Maxilla: 37	55.1 (range 43–71)	Mean of 72.5 months, ranging 72–76 months,	Osseotite; Biomet 3i: 56 Full Osseotite; Biomet 3i: 108
2015	Browaeys H	2	20 (14 women and 6 men)	Maxilla: 9 Mandible: 11	55 (range 35–74)	3 years	Mk III Groovy: for mandible, $n = 44$ Nobel Speedy Groovy: for maxilla, $n = 44$
2015	Gherlone EF	2	14 (8 women and 6 men)	Maxillae: 6 Mandible: 8	56.3 (range 43–80)	12 months	Winsix; BioSAFin, Ancona, Italy
2015	Ayna M	2	27 (19 women and 8 men)	Mandible: 27	64.4 ± 10.8 (range 43–77)	5 years	Nobel Speedy
2016	Krennmair S	2	37 Axial group: 19 (12 women and 7 men) Tilted group: 18 (10 women and 8 men)	Mandible: 37	Axial Group 66.7 ± 9.6 (range 43–84) Tilted Group 62.6 ± 9.7 (range 42–77)	3 years	Camlog; Screw-line, Promote, Wimsheim
2016	Piano S	2	21	Maxilla	66 years (range 56–81 years)	2 years	Straumann SLActive Bone Level implants
2016	Najafi H	2	30 (14 women and 16 men)	Maxilla: 14 Mandible: 25	59.3 ± 11.7 (range 28–89)	32.5 ± 13.6 months	Brånemark System MKIII or MKIV Nobel Speedy Groovy Nobel Replace selec
2017	Li S	2	17 (7 women and 10 men)	Maxilla: 7 Mandible: 13	39.4 (range 28–45)	Mean of 5 years, ranging 2–7 years	Brånemark System MK III: 44 Nobel Speedy Groovy: 8 Nobel Active: 28

(Continues)

TABLE 6 Surgical and prosthetic protocol used in the included Level I and Level II studies

Publication year	First author	Total implants placed	Tilted implants placed	Axial implant placed	Tilted implant inclination (degrees)	Implant insertion torques (Ncm)	Loading protocol	Abutment angles	Definitive prosthesis loading at	Prosthesis design
2012	Crespi R	176	Maxilla: 48 Mandible: 40	Maxilla: 48 Mandible: 40	Mandible: 30°–35° Maxilla: 30°-35°	>40	Immediate Within 24 hr and with definitive prosthesis	Anterior Implant: 17° Posterior implant: 30°	24 hr	Screw-retained acrylic resin prosthesis: 21 Screw-retained cast metal-frame prosthesis: 23
2016	Tallarico M	200 All-on-4: 80 All-on-6: 120				35–45	Immediate A prefabricated, screw-retained, fully acrylic or metal-reinforced acrylic resin provisional restoration, without any cantilever, delivered immediately.	Distal: 17° or 30° Mesial: 0° or to implant level	Patient returned for impression at 4 months and delivery at 5 months.	Definitive prosthesis with CAD/CAM titanium or zirconia frameworks and layered with either pink and/or white material (not specified).
2007	Capelli M	342 Maxilla: 246 Mandible: 96	130 Maxillary: 82 Mandible: 48	212 Maxillary: 164 Mandible: 48	Maxilla: 30°–35° Mandible: 25°–35°	30–50	Immediate Provisional full-arch restorations made of a titanium framework and acrylic resin teeth were delivered within 48 hr of surgery	If implant inclination exceeded 30 degrees, angulated abutments were used.	3 months	Complete full-arch prostheses were fabricated with a titanium framework combined with new acrylic resin teeth composed of 12 elements
2008	Francetti L	248	124	124	30°	40–50	Acrylic temporary prosthesis with 10 teeth was delivered within 48 hr	Distal: 30° Mesial: Straight	After 4–6 months	CAD-CAM Procera system
2008	Testori T	246	82	164	30°–35°	30	Immediate The provisional screw-retained prosthesis was delivered within 48 h from surgery using temporary provisional cylinders with fiber-reinforced acrylic teeth.		3 months	Seven Screw-retained, fabricated with a titanium framework (CRESCO Astra Tech Implant System) with acrylic resin teeth; the remaining 33 prostheses were porcelain-cemented restorations with a cast mesiostructure connecting all the implants on each side.
2008	Tealdo T	111	47	64		>40	Immediate Screw-retained fixed provisional prostheses supported by palladium-alloy frameworks within 24 hr after surgery, no cantilevers distal to the distal implants.	Conical abutments (0°, 17°, 25°, and 45°)	18 weeks	All of the definitive prostheses consisted of palladium-alloy frameworks; the occlusal surfaces were designed completely in porcelain or acrylic resin artificial teeth. All of the definitive prostheses were screw retained.

(Continues)

TABLE 6 (Continued)

Publication year	First author	Total implants placed	Tilted implants placed	Axial implant placed	Tilted implant inclination (degrees)	Implant insertion torques (Ncm)	Loading protocol	Abutment angles	Definitive prosthesis loading at	Prosthesis design
2010	Agliardi E	692	346	346	Maxilla: 30°–45° Mandible: 30°	>30	Immediate Acrylic provisional prosthesis	Maxilla: Distal: 30° (*n* = 144) Mesial: 0° (*n* = 127) 17° (*n* = 20) Mandible: Distal: 30° (*n* = 202) Mesial: 0° (*n* = 202)	4–6 months	CAD-CAM Proceras System (Nobel Biocare, Stockholm, Sweden)
2010	Hinze M	148 Maxilla: 76 Mandible: 72	74	74	30°	>30	Immediate Within 24 hr, 10 units screw-retained full-arch acrylic resin provisional restorations.		6 months	Complete full-arch prostheses were supported by metal frameworks combined with high-density acrylic resin.
2012	Francetti L	196 Maxilla: 64 Mandible: 132	98	98	30°	40–50	Immediate An acrylic temporary prosthesis with 10 teeth was delivered within 48 hr of implant placement.	Distal: 30° Mesial: 0°	4–6 months	CAD-CAM Procera system and consisting of 12 teeth
2012	Grandi T	188	94	94		>45	Immediate 10-unit screw- retained, provisional fixed dental prosthesis with a metal framework (nonprecious alloy) within 48 hr after surgery	Distal: 30° (*n* = 94) Mesial: 0° (*n* = 82) 17° (*n* = 12)	6 months	
2012	Weinstein R	80	40	40	30°	50	Immediate An acrylic temporary prosthesis with 10 teeth was delivered within 48 hr of surgery with centric and lateral contacts limited at the intercanine zone.	Distal: 17° or 30° Mesial: 0°	4–6 months	CAD- CAM Procera system (Nobel Biocare AB).
2012	Maló P	227 Maxilla: 133 Mandibule: 94			Maxilla: up to 45° Mandible: 30°–45°	35	Immediate A high-density acrylic resin prosthesis with titanium cylinders was manufactured at the dental laboratory and inserted on the same day, usually 2–3 hr postsurgically.	Distal: 30° Mesial: 0°, 17° or 30°	6 months	Depending on patient desires, the definitive prosthesis featured either a titanium framework and all-ceramic crowns or a titanium framework and acrylic resin prosthetic teeth.

(Continues)

TABLE 6 (Continued)

Publication year	First author	Total implants placed	Tilted implants placed	Axial implant placed	Tilted implant inclination (degrees)	Implant insertion torques (Ncm)	Loading protocol	Abutment angles	Definitive prosthesis loading at	Prosthesis design
2013	Di P	344	172	172	Maxilla: up to 45°	>35 N	Immediate 10–12 units interim all acrylic prostheses (without metal frameworks) delivered approximately 6 hr after implant placement.	0° (*n* = 113) 17° or 30° (*n* = 231)	6 months	12 acrylic resin teeth units with a metal framework
2014	Krennmair S	96	48	48		>30	Immediate A simple metal bar was connected to the copings to obtain reinforcement of the interim prostheses, and they were inserted within 24 hr.	Distal: 30° (*n* = 12) 20° (*n* = 36) Mesial: 0° (*n* = 48)	3 months	Cobalt-chromium screw-retained prostheses. All prostheses consisted of 12 acrylic veneering (1 molar per side) with the extension varying in size.
2014	Pera P	164				>40	Immediate The screw-retained provisional prostheses with metal frameworks were placed within 24–36 hr of the surgery.	Distal: 17°, 25°, 30° 0°: *n* = 6 17°: *n* = 77 25°: *n* = 75 30°: *n* = 6	4 months	Metal framework with acrylic resin or a microfilled hybrid composite resin
2015	Browaeys H	80	40	40	Between 20° and 40°	< 50	Immediate. Within 48 hr, the 10-unit provisional resin-based prosthesis was delivered and installed in the mouth	Distal: 30° Mesial: 0°	3–4 months	The final prosthetic work was performed by the referring dentist, but no other details provided.
2015	Gherlone EF	56	28	28	30° to 35°	>40	Immediate 5 hr after implant placement, screw-retained full-arch interim prosthesis by only all acrylic resin frameworks were positioned.	Distal: 30° Mesial: 17°	4 months A digital scan body was used to finalize definitive prosthesis. (Lava COS; 3M)	Definitive prostheses were made by acrylic resin masticatory surfaces and metal frameworks for increased strength and rigidity
2015	Ayna M	108	54	54	45°	>35	Immediate All implants were immediately loaded within 24 hr.	Distal: 30° Mesial: 0°		The patients were assigned to the different groups (ceramics/acrylic) according to their own choice. (14 acrylic, and 13 ceramics)
2016	Krennmair S	148	36	112		>30	Conventional loading Patient returned for impression and uncovering at 2 months.	Axial implant: 0 degree Tilted implant:20° and 30°	Patient returned for impression and uncovering at 2 months.	Screw-retained Cobalt-Chromium acrylic resin prosthesis. All prostheses consisted 12 acrylic veneering.

(Continues)

TABLE 6 (Continued)

Publication year	First author	Total implants placed	Tilted implants placed	Axial implant placed	Tilted implant inclination (degrees)	Implant insertion torques (Ncm)	Loading protocol	Abutment angles	Definitive prosthesis loading at	Prosthesis design
2016	Piano S	84	42	42	≤ 30°	>25	Immediate The framework was created by laser welding the titanium copings to the preproduced CAD/CAM titanium bars, and acrylic resin was used for the overdenture veneering. 12–14 units. Delivered within 48 hr.	Distal: 0° (*n* = 22) 25° (*n* = 16) Mesial: 0° (*n* = 26) 25° (*n* = 20)	3 months	After 3 months, the interim prostheses were relined, if any soft tissues remodeling occurred. Acrylic resin was used for prosthesis relining. A direct resin addition technique was performed.
2016	Najafi H	156	78 Maxillae: 28 Mandible: 50	78 Maxillae: 28 Mandible: 50	45°	≥35 Ncm for the immediate loading group <35 Ncm for delayed group	Immediate group: On the third day after surgery, the final metal resin prosthesis was delivered Delayed group : During the second surgery, which was carried out after four months, the abutments were connected and the remaining prosthetic procedures were the same as those in the IL group	Distal: 30° Mesial: 0°		It appeared that authors used the original interim as the definitive prosthesis.
2017	Li S	80	40	40	30°–40°	35–45	Immediate 10–12 units heat-cured acrylic resin prostheses without metal frameworks were delivered to the patients approximately 6 hr after surgery.	Distal: 17° or 30° Mesial: 0°, 17° or 30°	4–6 months	High-precision CAM metal framework with a wrap-around heat-cured acrylic resin, as well as 12 acrylic resin teeth units, or all-ceramic crown units

TABLE 7 Implant outcomes in the included Level I and Level II studies

Publication year	First author	Overall implant survival	Percentages of surviving tilted implants	Percentages of surviving axial implants	Implant survival differences	Marginal bone loss (mean ± *SD*) (mm) on all implants	Marginal bone loss (mean ± *SD*) (mm) on tilted implants	Marginal bone loss (mean ± *SD*) (mm) on axial implants	Marginal bone loss differences
2012	Crespi R	3 years Maxilla: 98.96% Mandible: 97.5%	3 years Maxilla: 97.97% Mandible: 95% Overall: 96.59%	3 years Maxilla: 100% Mandible: 100%			At 1 year: Maxilla: 1.05 ± 0.29 Mandible: 1.05 ± 0.32 At 2 year: Maxilla: 1.07 ± 0.46 Mandible: 1.09 ± 0.29 At 3 years: Maxilla: 1.11 ± 0.32 Mandible: 1.12 ± 0.35	At 1 year: Maxilla: 1.10 ± 0.35 Mandible: 1.04 ± 0.30 At 2 year: Maxilla: 1.08 ± 0.41 Mandible: 1.04 ± 0.35 At 3 years: Maxilla: 1.10 ± 0.45 Mandible: 1.06 ± 0.41	No statistically significant differences ($p > 0.05$) in crestal bone loss were found in either arch between tilted and axial implants at 12, 24, and 36 months.
2016	Tallarico M	5 years All-on-6: 95% All-on-4: 98.75%			Not statistically significant differences ($p = 0.246$) between All-on-4 and All-on-6 groups	5-year All-on-4: 1.7 ± 0.42 All-on-6: 1.51 ± 0.36			Not statistically different between All-on-4 and All-on-6 groups at 5 years. ($p = 0.117$)
2007	Capelli M	Maxillary: 97.59% up to 40 months (mean follow-up, 22.5 months) Mandibular: 100% with up to 52 months of follow-up (mean follow-up, 29.1 months).	3 years 98.46%	3 years 98.58%			1 year Maxillary: 0.88 ± 0.59 ($n = 42$ implants) Mandible: 0.75 ± 0.55 mm ($n = 32$ implants)	1 year Maxillary: 0.95 ± 0.44 ($n = 84$ implants) Mandible: 0.82 ± 0.64 mm ($n = 32$ implants)	No significant difference in crestal bone loss between tilted and upright implants was detected at the 12-month follow-up evaluation in either jaw.
2008	Francetti L	1 year 100%	1 year 100%	1 year 100%			1 year 0.7 ± 0.5	1 year 0.7 ± 0.4	No significant difference in marginal bone loss was found between tilted and axial implants at 1-year evaluation.
2008	Testori T	3 year 97.58%	3 year 97.10%	3 year 97.90%			1 year 0.8 ± 0.5	1 year 0.9 ± 0.4	Marginal bone loss around axial and tilted implants at 12-month evaluation was similar
2008	Tealdo T	1 year 92.8%	1 year 89.40%	1 year 95.30%	No statistically significant differences between tiled and axial implants	1 year 0.84	1 year Mesial: 0.92 Distal: 1.04	1 year Mesial: 0.62 Distal: 0.86	

(Continues)

TABLE 7 (Continued)

Publication year	First author	Overall implant survival	Percentages of surviving tilted implants	Percentages of surviving axial implants	Implant survival differences	Marginal bone loss (mean ± *SD*) (mm) on all implants	Marginal bone loss (mean ± *SD*) (mm) on tilted implants	Marginal bone loss (mean ± *SD*) (mm) on axial implants	Marginal bone loss differences
2010	Agliardi E	1 year Maxilla: 98.4% Mandible: 99.7%	1 year 99.70%	1 year 98.84%		1 year Maxilla: 0.9 ± 0.7 (*n* = 204 implants) Mandible: 1.2 ± 0.9 (*n* = 292 implants) Such difference was not statistically significant.			No significant differences in bone loss were found between axially placed and tilted implants.
2010	Hinze M	1 Year Maxilla: 96.6% Mandible: 98.7%	1 Year 94.60%	1 Year 96%	No significant differences in bone loss were found between axially placed and tilted implants.		1 year 0.76 ± 0.49	1 year 0.82 ± 0.31	No significant differences in bone loss were found between axially placed and tilted implants.
2012	Francetti L	100%	100%	100%			Mandible: 6 m: 0.47 ± 0.22 12 m:0.48 ± 0.23 18 m: 0.64 ± 0.37 24 m: 0.67 ± 0.38 36 m: 0.69 ± 0.52 48 m: 0.81 ± 0.40 60 m: 0.39 ± 0.18 Maxilla: 6 m: 0.35 ± 0.27 12 m: 0.32 ± 0.28 18 m: 0.72 ± 0.23 24 m: 0.63 ± 0.38 36 m: 0.85 ± 0.34	Mandible: 6 m: 0.52 ± 0.22 12 m: 0.57 ± 0.42 18 m: 0.67 ± 0.35 24 m: 0.90 ± 0.49 36 m: 0.92 ± 0.43 48 m: 0.92 ± 0.55 60 m: 0.51 ± 0.17 Maxilla: 6 m: 0.38 ± 0.34 12 m: 0.40 ± 0.27 18 m: 0.61 ± 0.49 24 m: 0.44 ± 0.37 36 m: 0.85 ± 0.74	No significant difference in marginal bone loss was found between axial and tilted implants; and between mandible and maxilla, at each comparable time frame.
2012	Grandi T	18 months 100%	18 months 100%	18 months 100%		6 m: 0.31 ± 0.12 12 m: 0.58 ± 0.11 18 m: 0.7 ± 0.11	6 m: 0.36 ± 0.14 12 m: 0.6 ± 0.16 18 m: 0.74 ± 0.14	6 m: 0.27 ± 0.17 12 m: 0.57 ± 0.13 18 m: 0.68 ± 0.14	No significant differences in bone loss were found between axially placed and tilted implants at the 6-month, the 12-month and the 18-month follow-up
2012	Weinstein R	1 Year 100%	1 Year 100%	1 Year 100%			1 Year: 0.7 ± 0.4 (*n* = 36 implants)	1 Year: 0.6 ± 0.3 (*n* = 36 implants)	Marginal bone loss around axial and tilted implants was similar at 12-month evaluation. Such difference was not statistically significant ($p > 0.05$)
2012	Maló P	2-year estimate Maxilla: 97.7% 3 Year estimate Mandible: 94.8%				1 year: Maxilla: 1.3 ± 0.4 Mandible: 1.4 ± 0.3 3 year: Maxilla: 1.6 ± 0.4 5 year: Mandible: 1.7 ± 0.6			

(Continues)

TABLE 7 (Continued)

Publication year	First author	Overall implant survival	Percentages of surviving tilted implants	Percentages of surviving axial implants	Implant survival differences	Marginal bone loss (mean ± *SD*) (mm) on all implants	Marginal bone loss (mean ± *SD*) (mm) on tilted implants	Marginal bone loss (mean ± *SD*) (mm) on axial implants	Marginal bone loss differences
2013	Di P	56 months Overall: 96.2% Maxilla: 92.8% Mandible: 99.0%	56 months 93.60%	56 months 98.83%	The implant survival rate was significantly elevated in mandibular versus maxillary implants		56 months 0.8 ± 0.4	56 months 0.7 ± 0.2	Marginal bone level changes were statistically similar on the upright and the tilted implants
2014	Krennmair S	2 years 100%	2 years 100%	2 years 100%		12 m: 0.18 ± 0.20 24 m: 0.40 ± 0.29			Marginal bone level changes were statistically between 12 and 24 months. $p < 0.001$
2014	Pera P	6 years 97.58%				1 year: 1.14 6 year: 1.52	1 year: 1.01 ± 0.75 3 year: 1.32 ± 1.20 6 Year: 1.44 ± 1.24	1 year: 1.24 ± 0.90 3 year: 1.51 ± 1.22 6 Year: 1.58 ± 1.22	No significant differences in bone loss were found in tilted versus upright implants.
2015	Browaeys H	3 years 100%	3 years 100%	3 years 100%		61 implants (out of 80) were taken into account for statistical analysis of bone level changes: 1 year: 1.13 ± 0.94 3 years: 1.61 ± 1.40	1 year: 1.14 ± 1.14 3 years: 1.67 ± 1.22	1 year: 1.13 ± 0.71 3 years: 1.55 ± 0.73	This difference was statistically significant ($p < 0.001$) between 1 year and 3 years follow-up, indicative of ongoing bone loss Bone loss was not significantly different between straight and tilted implants ($p = 0.605$) after 3 years
2015	Gherlone EF	12 months 100%	12 months 100%	12 months 100%			12 months Maxilla: 1.07 ± 0.81 Mandible: 1.10 ± 0.89	12 months Maxilla: 1.07 ± 0.99 Mandible: 1.02 ± 0.72	No statistically significant differences ($p > 0.05$) in crestal bone loss between tilted and upright implants was detected at 12-month follow-up evaluation in either jaws.
2015	Ayna M	5 Years 100%	5 Years 100%	5 Years 100%			1 year region 35: 0.89 ± 0.11 region 45: 0.93 ± 0.13 5 Year region 35: 1.24 ± 0.13 region 45: 1.30 ± 0.13	1 year region 32: 0.47 ± 0.14 region 42: 0.52 ± 0.11 5 Year region 32: 0.78 ± 0.10 region 42: 0.78 ± 0.10	Bone loss was significantly more pronounced around the distal implants (regions 35 and 45), with the differences amounting to a factor of 2–3 ($p < 0.0001$ throughout).

(Continues)

TABLE 7 (Continued)

Publication year	First author	Overall implant survival	Percentages of surviving tilted implants	Percentages of surviving axial implants	Implant survival differences	Marginal bone loss (mean ± *SD*) (mm) on all implants	Marginal bone loss (mean ± *SD*) (mm) on tilted implants	Marginal bone loss (mean ± *SD*) (mm) on axial implants	Marginal bone loss differences
2016	Krennmair S	3 years 100%	3 years 100%	3 years 100%		1 year: 1.11 ± 0.4 2 year: 1.26 ± 0.42 3 year: 1.40 ± 0.41	Tilted Group At 1 year: Posterior implant 1.0 ± 0.5 At 2 year Posterior implant 1.2 ± 0.5 At 3 years Posterior implant 1.4 ± 0.4	Axial Group At 1 year: Anterior: 1.1 ± 0.4 Posterior: 1.1 ± 0.3 At 2 year: Anterior: 1.3 ± 0.3 Posterior: 1.2 ± 0.3 At 3 years: Anterior 1.4 ± 0.4 Posterior 1.4 ± 0.3 Tilted Group At 1 year: Anterior: 1.2 ± 0.4 At 2 year: Anterior: 1.4 ± 0.5 At 3 years: Anterior 1.5 ± 0.5	There were also no differences for marginal bone reduction for posterior and for anterior implants (region) comparing between axial group and tilted group. The time effect proved as statistically relevant for marginal bone reduction in anterior and posterior region ($p < 0.01$).
2016	Piano S	2 years 100%	2 years 100%	2 years 100%		2 years 0.34 ± 0.45	2 years 0.34 ± 0.46	2 years 0.35 ± 0.44	No significant difference between mean marginal bone loss of anterior and posterior implants was found ($p = 0.89$).
2016	Najafi H	13 months delayed: 99% immediate: 100% Maxilla: 98.2% Mandible: 100%	13 months 100%	13 months 98.71%		13 months: Maxilla: 0.88 ± 0.17 Mandible: 0.81 ± 0.2 Delayed Loading: 0.81 ± 0.16 Immediate Loading: 0.87 ± 0.25	13 months 0.82 ± 0.24	13 months 0.84 ± 0.27	No statistically significant difference was observed between the mean marginal bone loss of axial and tilted implants ($p > 0.05$), maxillary and mandibular implants ($p > 0.05$), or immediately loaded and delayed loaded groups ($p > 0.05$).
2017	Li S	7 years 98.75%	7 years 97.50%	7 years 100%		1 year: 0.8 ± 0.4 7 year: 1.2 ± 0.3	1 year: 0.9 ± 0.4 3 year: 0.9 ± 0.4 5 year: 1.1 ± 0.4 7 year: 1.2 ± 0.4	1 year: 0.8 ± 0.4 3 year: 0.9 ± 0.4 5 year: 1.0 ± 0.3 7 year: 1.2 ± 0.3	No statistical difference in all follow-ups ($p > 0.05$)

TABLE 8 Prosthesis survival in the included Level I and Level II studies

Publication year	First author	Prosthesis survival
2012	Crespi R	100%
2016	Tallarico M	100%
2007	Capelli M	100%
2008	Francetti L	100%
2008	Testori T	100%
2008	Tealdo T	100%
2010	Hinze M	100%
2012	Francetti L	100%
2012	Grandi T	100%
2012	Maló P	100%
2013	Di P	96.5% (Due to the loss of 2 implants at the same side in 3 patients)
2014	Krennmair S	100%
2014	Pera P	100%
2015	Browaeys H	100%
2015	Gherlone EF	100%
2015	Ayna M	100%
2016	Krennmair S	100%
2016	Piano S	100%
2016	Najafi H	96.1% for the delayed loading group 100% for the immediate loading group 92.2% for the maxillary group 100% for the mandibular group
2017	Li S	100% (20/20) for definitive prostheses 85% (17/20) for provisional prostheses

4 | DISCUSSION

The current systematic review was conducted to determine the clinical performance of intentionally tilted implants versus axially positioned implants. During the item reduction process, inter-rater reliabilities (Cohen's κ) were calculated to measure agreement among the two data collectors. Substantial inter-rater agreements were obtained in the different stages of item reduction process, indicating high degree of agreement between two authors in the identification process for included studies. Based on the evaluation criteria in a previous systematic review, RCTs were assessed with the Cochrane Collaboration's tool. Articles were judged to be at low risk of bias if there was adequate sequence generation, allocation concealment and blinding, and if one or more criteria were not met, then the study would be determined at high risk of bias. For the nonrandomized studies, the studies were considered at low risk of bias in the case of Newcastle-Ottawa Scale (NOS) scores of 7 stars or higher. (Soto-Peñaloza, Zaragozí-Alonso, Peñarrocha-Diago, & Peñarrocha-Diago, 2017) Among all the studies evaluated, both level I studies and 12 out of 20 level II studies showed high risk of bias (Tables 3 and 4).

The results of this study indicate that the implants that are generally described as "titled" are the distal implants whereas the implants that are described as axially placed and loaded are located in the anterior portions of the jaw. With the intentionally titled implant being located in the posterior portion of the jaw, these implants are subject to higher occlusal force simply because their proximity to the condyle is closer than are anterior implants. As such it would not be surprising to see some effect on implant performance that is routinely subject to a higher immediate loading. Based upon the systematic review of the literature, an analysis of the descriptive data suggested no differences in implant performance relative to anatomic location.

The level I and II articles reviewed in this systematic review appear to demonstrate no difference in clinical performance when compared to historical literature. The level I and II articles were sufficiently heterogeneous relative to the design of the studies as to prevent quantitative data accumulation/synthesis. Nonetheless there was consistent descriptive confirmation that the tilted implants demonstrated no difference relative to implant survival of the axially loaded implants (Table 7). Based on the high prosthesis survival rates (Table 8), the biomechanical stability is high. Although catastrophic complication in the definitive prosthesis, such as the fracture of metal framework, was uncommon, high prevalence of prosthetic complications was reported for both interim and definitive prostheses (Table 9). The fracture of interim acrylic prosthesis, and fracture or wear of veneering material or artificial teeth in both interim and definitive prostheses can be resolved with chairside or laboratory repairs, and occlusal adjustment in conjunction with the use of an occlusal guard. The prosthetic screw loosening or fracture can be resolved by refining the occlusal contacts and re-tightening or replacement of prosthetic screws. The need for periodic postinsertion observation and prosthetic maintenance is recommended for the edentulous patients receiving interim and definitive implant prostheses, supported by both intentionally tilted implants and axially positioned implants.

Patient-reported outcome measures (PROMs) (Table 10) showed the patient's satisfaction toward aesthetics, phonetics, ease of maintenance, and functional efficiency after the completion of treatment with definitive implant prostheses supported by both intentionally tilted implants and axially positioned implants. However, the variations of self-developed survey instruments made the comparisons across studies challenging. For the future studies, a reliable and validated psychometric instrument is recommended for collecting patient-center outcomes to ensure the quality of the results of studies. For instance, Oral Health Impact Profile (OHIP-49) (Slade & Spencer,

TABLE 9 Biological and prosthesis complications in the included Level I and Level II studies

Publication year	First author	Biological complication	Prosthesis complication	Complication comparison
2012	Crespi R	1 patient, a 76-year-old nonsmoking woman, reported severe discomfort, pain, and swelling in the anterior maxilla 3 months after surgery.	2 all acrylic resin prostheses showed fracture of acrylic resin 3% of sites showed occlusal screw lessening within first 6 months	The same clinical outcome was seen for patients treated with the so-called All-on-Four protocol, regardless of whether the acrylic resin restorations were reinforced with metal.
2016	Tallarico M	All-on-4 group 1 patient with pain and swelling without suppuration during osseointegration, around distal implants. 1 patient with peri-implantitis after the definitive prosthesis delivery, within the first year of loading All-on-6 group 1 patient with pain and swelling without suppuration during osseointegration, around distal implants. 2 patients with peri-implantitis after the definitive prosthesis delivery, within the first year of loading	All-on-4 group: 2 prosthetic screws loosening in provisional restorations 1 fracture of the acrylic provisional prostheses. 3 fractures of the veneering material of the definitive implant supported complete FDP All-on-6 group: 1 fracture of the acrylic provisional prostheses. 1 fracture of the veneering material of the definitive implant supported complete FDP	Both group experienced some technical and biological complications with no statistically significant differences between groups (p = 0.501).
2008	Francetti L	One patient reported a light hypoesthesia on the left side of the lower lip after surgery which resolved after 6 months.	The most frequent prosthetic complication was the fracture of the acrylic prosthesis that occurred in seven cases (11%). No fracture of the definitive prostheses reported.	
2008	Testori T	No biological complication was reported	Only screw loosening, which occurred in seven provisional prostheses (17.5%), affecting prosthesis stability. The screw loosening occurred on three tilted and four axially placed implants.	
2008	Tealdo T		No loose abutment screws or fractures of prosthesis frameworks reported in the study.	
2010	Agliardi E	None of the patients reported any postsurgical biological complication.	Fracture of the acrylic prosthesis that occurred in 24 cases (15.6%), of which 14 in the mandible (15%) and 10 in the maxilla (16.4%).	

(Continues)

TABLE 9 (Continued)

Publication year	First author	Biological complication	Prosthesis complication	Complication comparison
2010	Hinze M	The only biological complication observed was extensive bruising in 2 patients.	Technical complication: 1. Fracture of acrylic veneer material in 4 provisional prostheses (10.8%). 2. 1 definitive reconstruction displayed fracture of the veneer material (3.7%). 3. Loss of the screw access hole restoration occurred in 9.5% of the anchors. 4. Occlusal screw loosening was observed in 6% of cases,	
2012	Francetti L	Three axial mandibular implants in two patients showed peri-implantitis, with about 3 mm of marginal bone loss, suppuration, and bleeding on probing Peri-implantitis was detected after 3 years of loading in one implant placed in a 50-year-old female patient, and after 18 months in two implants placed in a 60-year-old male patient. Both patients were nonsmokers.	Fracture of the acrylic prosthesis that occurred in 5 cases (15%) in the mandible and in 3 cases in the maxilla (19%) 1 fracture of the final mandibular framework has been recorded in 1 female patient after 3 years of loading (3%).	
2012	Grandi T	No other immediate postsurgical complications. Two patients had an episode of peri-implant microsites and were treated with nonsurgical debridement of the affected implants.	3 patients (6.3%) had a fracture of the provisional restoration, but all of the definitive prostheses remained stable throughout the study period without any complications.	
2012	Weinstein R	No complication was recorded during surgical and prosthetic procedures.	No adverse event occurred.	
2012	Maló P	Peri-implant pathology was associated with 6 implants (in 6 patients: 3 in the maxilla and 3 in the mandible) distributed within, the dehiscence subgroup 5 implants) and the fenestrations subgroup 1 implant).	6 prostheses fractured. 2 in the maxilla and 4 in the mandible) in 6 patients with bruxism. Abutment screws loosened in 13 patients. No other aesthetic or functional complications.	

(Continues)

TABLE 9 (Continued)

Publication year	First author	Biological complication	Prosthesis complication	Complication comparison
2013	Di P	All implant failures occurred at 8–10 weeks after placement. No biological complications occurred.	Three fixed prostheses were changed to removable dentures until new implants could be placed in 2–3 months, and fixed prostheses were again immediately placed because two implants were lost on the same side in three patients. Three abutment screws loosened and five artificial teeth separated from the acrylic resin base. Fracture occurred near the implant metal coping in three provisional restorations. No fracture occurred near the cantilever area.	
2014	Krennmair S	Swelling, hematoma and some minor discomfort were reported in individual cases 2 patients with 4 implants had an episode of peri-implant mucositis at the 1st year evaluation 1 patient presented with gingival hyperplasia at 2 implants	Provisional Prosthesis: 2 Abutment screw loosening (8.3%), 5 provisional prostheses fractured (20.8%), 6 acrylic teeth fractured (20.8%), 3 acrylic teeth were repaired in office (12.5%) and 4 prostheses needed denture rebasing/reduction (16.7%). Definitive Prosthesis: No metal framework/denture fractures; however, there were 9 acrylic teeth fractures (1st year: 7 teeth fractures in 5 patients; 2nd year: 2 teeth in 1 patient) repaired in the laboratory, 6 acrylic teeth repairs in office (1st year: 2 teeth in 2 patients; 2nd year: 4 teeth in 2 patients) and 18 patients had their prostheses rebased (1st year: 13; 2nd year: 5) as a result of soft tissue shrinkage.	
2014	Pera P		Minor fractures of acrylic (n = 7) Major fractures of acrylic (n = 2) Fracture of the metal framework (n = 1) Loosening of the prosthetic screws (n = 6)	
2015	Browaeys H		No complications such as fractures occurred during the surgical phase or the delivery of the immediate restoration.	
2015	Gherlone EF		No occlusal screw loosening was observed.	

(Continues)

TABLE 9 (Continued)

Publication year	First author	Biological complication	Prosthesis complication	Complication comparison
2015	Ayna M		All acrylic restorations showed some extent of abrasion that was, however, neither aesthetically nor functionally relevant. Veneer fractures occurred in 4 patients, all with acrylic suprastructures (28.6%). Three of those fractures (all on canine teeth) were superficial and could be repaired in situ; only one reached the metal framework, and the denture had to be repaired in the laboratory. Besides a single loosening of a fixation screw, there were no prosthetic complications in patients with ceramic suprastructures.	
2016	Krennmair S	Total Incidence Axial Implant group: Anterior implant Mucositis: 14 Gingival Hyperplasia: 4 Fistula: 2 Recession: 7 Total: 27 Posterior implant Mucositis: 4 Gingival Hyperplasia: 2 Fistula: 0 Recession: 6 Total: 12 Tilted Implant group: Anterior implant Mucositis: 8 Gingival Hyperplasia: 3 Fistula: 0 Recession: 3 Total: 14 Posterior implant Mucositis: 4 Gingival Hyperplasia: 4 Fistula: 2 Recession: 8 Total: 18	Total Incidence Axial Implant group: Abutment screw loosening: 4 Acrylic tooth fracture: 8 Acrylic tooth repaired in office: 7 Acrylic denture base fracture: 2 denture rebasing/reduction: 15 denture cleaning (discoloration): 28 screw access acrylic repair: 7 Opposing denture teeth fracture: 6 Opposing denture rebasing: 2 Total: 79 Tilted Implant group: Abutment screw loosening: 8 Acrylic tooth fracture: 6 Acrylic tooth repaired in office: 4 Acrylic denture base fracture: 2 denture rebasing/reduction: 17 denture cleaning (discoloration): 20 screw access acrylic repair: 8 Opposing denture teeth fracture: 5 Opposing denture rebasing: 0 Total: 70	In total there were 39 biological complications (183 mucositis, 63 gingival hyperplasia, 23 fistula, 133 recessions) in the axial group I and 32 biological complications (123 mucositis, 73 gingival hyperplasia, 23 fistula, 113 recessions) in the tilted group II. (no significance) The overall incidence of prosthetic maintenance per patient/year did not differ between axial group (1.36) and tilted group (1.36).

(Continues)

TABLE 9 (Continued)

Publication year	First author	Biological complication	Prosthesis complication	Complication comparison
2016	Piano S		No screw loosening, fracture or abutment fracture, or framework fractures were observed during the follow-up period. No subject lost the retention of the prosthesis during the follow-up period.	
2016	Najafi H		The most common mechanical complication was acrylic tooth chipping (16 jaws, 41%). Other complications were abutment screw loosening (one jaw, 2.5%), prosthetic screw loosening (two jaws, 5.1%) and prosthetic screw fracture (two jaws, 5.1%)	
2017	Li S	One implant (1.25%) showed peri-implantitis (the same implant failure due to peri-implant pathology) with a pocket of 5 mm and concurrent bone loss >2 mm with bleeding on probing.	5 patients (29.4%) showed mechanical complications in provisional or definitive prostheses. Provisional Prosthesis: 3 provisional prostheses fractured (15%, the same 3 failed prostheses). Artificial teeth separation occurred in 2 mandibular and 1 maxillary provisional prostheses (15%. One patient (5.88%) had phonetic changes 2 weeks after surgery. Definitive Prosthesis: Loose abutment screws were observed in 2 mandibular definitive prostheses (10%)	

TABLE 10 Patient-reported outcome measures (PROMs) in the included Level I and Level II studies

Publication year	First author	Patient-centered outcome
2007	Capelli M	Patient completed a satisfaction evaluation questionnaire regarding aesthetics, phonetics, ease of maintenance, and functional efficiency. The questionnaire was repeated at each annual evaluation. All patients were satisfied with the phonetics, aesthetics, and psychological and functional aspects once treatment was completed.
2008	Francetti L	At each follow-up, patient's satisfaction for aesthetics and function was evaluated by a questionnaire. Satisfaction for both aesthetics and function increased over time.
2008	Testori T	28 patients (70%) completed the questionnaire for satisfaction evaluation after 1-year follow-up. (5 points Likert scale) Aesthetics (teeth and smile) was judged as excellent or very good by 75% of patients, good by 21.4% of them and sufficient by one patient (3.6%). Mastication function was considered excellent or very good by 69.2% of patients and good by 30.8%. Ease of maintenance was considered excellent or very good in 35.7% of cases, good in 42.9%, sufficient in 14.3% of cases, and poor by 7.1% of patients. Phonetics was judged excellent or very good in 85.7% of cases and sufficient in 14.3%. All patients affirmed that their quality of life had improved after the treatment.
2012	Weinstein R	The patients' satisfaction for function, aesthetics, and phonetics was assessed by means of a questionnaire. The answers were based on a 5-point Likert-type scale, ranging from 1 ("poor") to 5 ("excellent"). Eighteen patients filled in the questionnaire for satisfaction evaluation after 12 months follow-up: aesthetics (teeth aspect and color, and smile appearance) was judged as excellent or very good by 66.7% of patients, while phonetics and mastication were considered excellent or very good by 77.8 and 88.9% of patients, respectively.
2013	Di P	Each patient's response to the treatment outcome in the context of function, aesthetics, and phonetics was assessed via a questionnaire administered at the 6- and 12- month recall visits. The scoring for each subject was as follows: 5 = excellent, 4 = very good, 3 = good, 2 = sufficient, and 1 = poor. All patients were satisfied with the function and aesthetic aspects of their prostheses (an excellent rating for 95.6% of patients). Phonetic change occurred in three patients within 2 weeks of implant placement. Although patients showed different levels of oral hygiene and maintenance at follow-up, all oral hygiene methods provided satisfactory periodontal maintenance. The water sprayer was preferred by most patients.
2014	Krennmair S	5-point Likert scale questionnaire Patients provided high subjective satisfaction rates at 1st year and 2nd year examination for the following items: in general with restoration, chewing, prosthesis stability, speech, and aesthetic outcomes. Patients' subjective satisfaction score rating assessed by 5 items was high at the 1- (score: 4.6 ± 0.4) and 2-year evaluation (score: 4.7 ± 0.36).
2014	Pera P	Patients anecdotally reported good satisfaction with regard to the functionality and aesthetic appearance of their prostheses
2015	Ayna M	The subjective improvement as expressed by the Oral Health Impact Profile (OHIP) score was dramatic. An initially substantial impairment (approximately 30 out of a maximum of 56 points, suggesting an intermediate burden) was practically canceled after denture integration, and the score increased only slightly during observation. There were no differences between patients with acrylic and ceramic dentures.
2017	Li S	No details were provided. However, the following descriptions were given: The mastication function and aesthetics as well as the quality of life of GAP patients were tremendously improved by immediate implant and restoration, which was in line with the low complaint about aesthetics and function. The immediate loading procedure significantly reduced the treatment time and overall cost for Chinese patients.

1994) and its short form (OHIP-14) (Slade, 1997) are among the most commonly used survey instruments for the assessment of subjective treatment outcome in dentistry with good reliability and validity. Only one included study utilized German version of the OHIP-14 to assess the impact of the all-on-4 treatment approach on quality of life in the patient population with edentulous mandible, and the patient's quality of life significantly improved after treatment (Ayna et al., 2015).

The unpublished report, (Eckert, 2017) describes no significant difference in implant performance relative to insertion torque of the implants. The authors hypothesize that insertion torque is a design feature of an implant that is not specifically related to the relative micromotion that occurs during functional loading. In essence, when immediate loading occurs, the dental prosthesis serves to protect the implants through rigid fixation thereby reducing micromotion and allowing the biological process of osseointegration to occur.

The concept that the anterior implants are generally placed in such a way as to create axial loading, forces down the long axis of the implant with the implant being perpendicular to the occlusal plane, might be called into question. From the descriptive information that is available, it appears that the anterior implants are placed within the alveolar bone, a situation that often has the implant inclined toward the facial thereby not being subject to axial load. Perhaps there is no true axial loading of any of the implants but, without the presence of a periodontal ligament, the concept of axial loading may not be a critical factor toward the performance of dental implants.

Future research on this topic should continue to assess the long-term clinical performance of implants used to support and retain fixed prostheses in the edentulous jaws. Careful attention should be paid to the angulation of implants which is indirectly identified through the use of angled transmucosal abutments. Those abutments would only be necessary if the angle of the implant must be redirected to accommodate the prosthesis. Consistent documentation of the use of angled abutments and correlation between those implant abutments and the anatomic location of the abutments may prove valuable. In addition, the ongoing documentation of clinical performance of implants relative to insertion torque should continue however the demand for high insertion torque in all clinical settings may be called into question.

5 | CONCLUSIONS

Based upon this systematic review of the scientific literature related to the use of intentionally tilted dental implants when compared to axially loaded implants, the following observations are made

- Level I studies that are designed to directly compare the performance of tilted implants to that of axially loaded implants were not identified.
- An analysis of the descriptive data from Level I and Level II studies suggests no differences in clinical performance of implants whether placed in an axial or in a tilted configuration.
- Lower-level studies and a large population unpublished study appear to confirm the observations regarding the clinical performance of tilted implants in comparison to axially loaded implants.
- Insufficient information is available regarding the most appropriate number of implants needed to provide immediate support and retention of a definitive prosthesis however there are numerous low-level studies that demonstrate acceptable performance when four implants are used to support and retain full-arch fixed prostheses.

CONFLICT OF INTEREST

Dr. Lin reports personal fees from Straumann, grants from Ivoclar, grants from ITI, grants from Straumann, outside the submitted work. Dr. Eckert reports personal fees from Straumann, personal fees from Osstell, personal fees from Ivoclar, personal fees from Rodo, personal fees from Quintessence Publishing, personal fees from ClearChoice Management System, outside the submitted work.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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REVIEW ARTICLE

WILEY CLINICAL ORAL IMPLANTS RESEARCH

Implant placement and loading protocols in partially edentulous patients: A systematic review

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Abstract

Objectives: To systematically review the evidence for the clinical outcome of fixed implant prostheses treated with different combinations of implant placement and loading protocols in partially edentulous patients.

Materials and methods: An electronic search was performed in Medline, Embase, and Central to identify studies investigating the outcome of implants subjected to immediate placement + immediate restoration/loading (Type 1A), immediate placement + early loading (Type 1B), immediate placement + conventional loading (Type 1C), early placement + immediate restoration/loading (Type 2-3A), early placement + early loading (Type 2-3B), early placement + conventional loading (Type 2-3C), late placement + immediate restoration/loading (Type 4A), late placement + early loading (Type 4B), late placement + conventional loading (Type 4C) with implant-supported fixed dental prostheses (IFDPs) in partially edentulous patients. Only human studies with at least 10 cases and a minimum follow-up time of 12 months, reporting on solid-screw-type implants with rough surfaces and an intra-osseous diameter between 3 and 6 mm, were included. A cumulative survival rate for each type of the implant placement and loading protocols was weighted by the duration of follow-up and number of implants.

Results: The search provided 5,248 titles from which 2,362 abstracts and 449 full-text articles were screened. A total of 69 publications that comprised 23 comparative studies (15 randomized controlled trials, 7 controlled clinical trials) and 47 noncomparative studies (34 prospective cohort studies, 13 retrospective cohort studies) were included for analysis. Considerable heterogeneity in study design was found, and therefore, a meta-analysis of controlled studies was not possible. The weighted cumulative survival rate of each type of placement and loading protocol was 98.4% (Type 1A), 98.2% (Type 1B), 96.0% (Type 1C), 100% (Type 2-3B), 96.3% (Type 2-3C), 97.9% (Type 4A), 98.3% (Type 4B), and 97.7% (Type 4C). Type 1C, Type 2-3C, Type 4B, and Type 4C were scientifically and clinically validated (SCV). Type 1A, Type 1B, and Type 4A were clinically documented (CD), and Type 2-3A and Type 2-3B were clinically insufficiently documented (CID).

Conclusions: Evaluating outcomes in oral implantology by combining the placement and loading protocols are paramount. The selected loading protocol appears to influence the outcome of immediate implant placement.

KEYWORDS

dental implants, early loading, early placement, immediate loading, immediate placement

1 | INTRODUCTION

Various surgical and prosthodontic protocols used in oral implantology are directly associated with the long-term outcome of implant prosthesis (Cochran et al., 2011; Moraschini, Poubel, Ferreira, & Barboza Edos, 2015; Ormianer et al., 2012; Payer et al., 2010; Polizzi et al., 2000; Zuffetti et al., 2016). In this context, implant placement protocols have been differentiated by the duration of the healing period following tooth extractions prior to implant placement. Likewise, implant loading protocols have been differentiated by the duration of the healing period following implant placement prior to the initial delivery of a provisional or definitive implant restoration.

Different implant placement options have been clinically applied as defined by the last three ITI Consensus Conferences in 2003, 2008, and 2013 (Chen & Buser, 2009; Chen, Wilson, & Hammerle, 2004; Hammerle, Chen, & Wilson, 2004). These options include the following: (a) *immediate implant placement* on the day of extraction (Type 1), (b) *early implant placement* after 4–8 weeks of soft tissue healing (Type 2), (c) *early implant placement* after 12–16 weeks of partial bone healing (Type 3), and (d) *late implant placement* after complete bone healing of at least 6 months (Type 4).

Each of the different implant placement protocols present unique clinical considerations (Buser, Chappuis, Belser, & Chen, 2017; Quirynen, Van Assche, Botticelli, & Berglundh, 2007). A reduction in overall treatment time with immediate and early implant placement protocols presents an attractive solution for patients and clinicians. However, immediate implant placement is thought to be significantly influenced by the local alveolar anatomy following tooth extraction (Levine et al., 2017). Dimensional changes following tooth extraction occur and are not mitigated by immediate implant placement (Araujo, Sukekava, Wennstrom, & Lindhe, 2005), which may lead to compromised long-term aesthetic outcomes (Chen & Buser, 2014; Hammerle, Araujo, Simion, & Osteology Consensus, 2012). The degree of dimensional changes may be influenced by the thickness of the labial buccal bone following tooth extraction (Chappuis, Araujo, & Buser, 2017; Chappuis et al., 2013; Matarasso et al., 2009). Thicker buccal bone leads to less dimensional ridge alterations and may provide more predictable results for immediate implant placement.

The reported ridge alterations following tooth extraction can be clearly visualized when performing early implant placement after 4–8 weeks of soft tissue healing (Belser et al., 2009; Buser, Bornstein, et al., 2008; Buser, Chappuis, Bornstein et al., 2013; Buser, Chappuis, Kuchler et al., 2013; Buser, Chen, Weber, & Belser, 2008; Buser et al.,

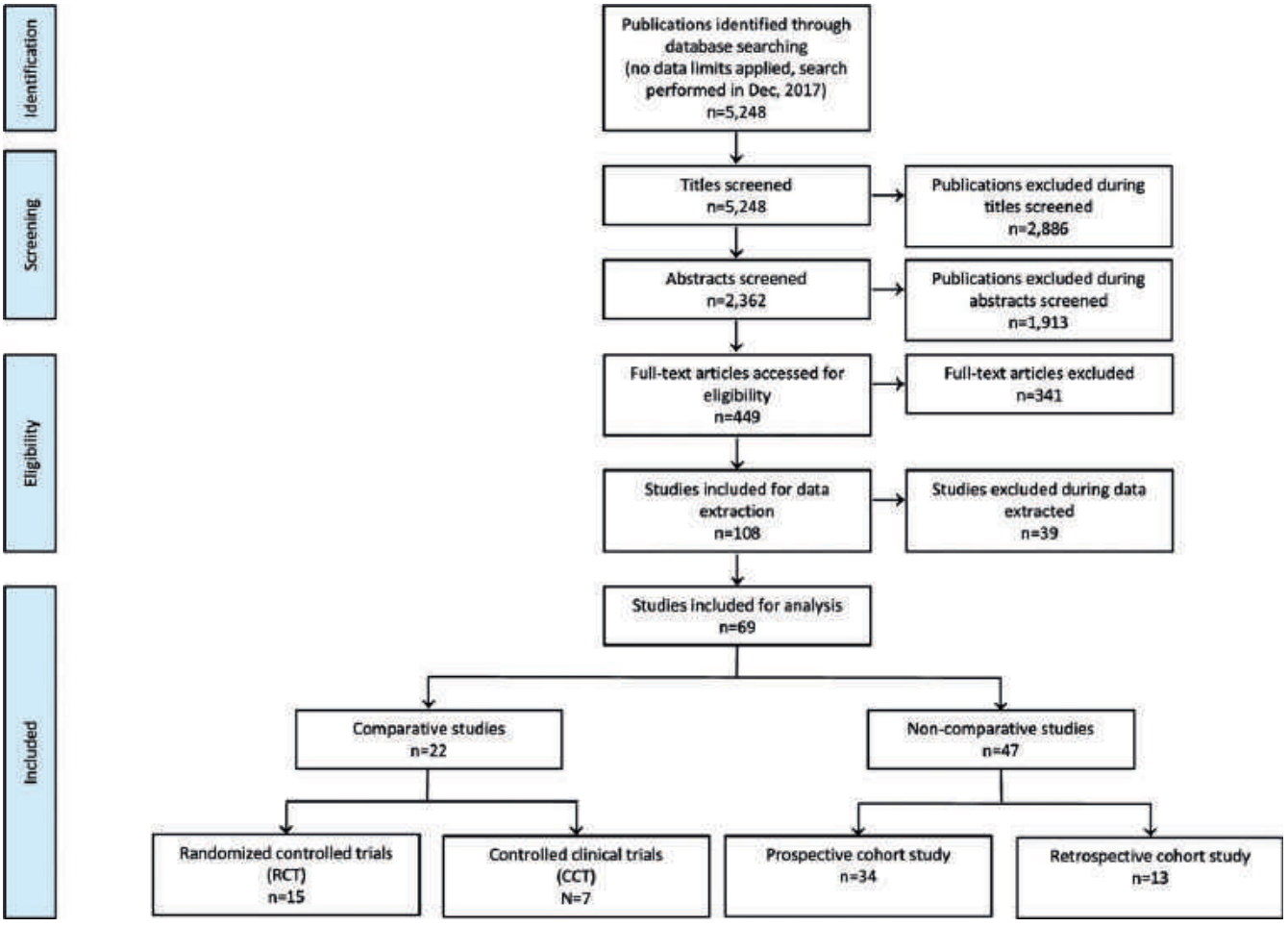

FIGURE 1 Search strategy and post-extraction dimensional changes

2009; Buser et al., 2011; Chappuis et al., 2018). At re-entry, there is often a bone defect at the facial aspect where the alveolar buccal bone wall is either thin or missing (Chen & Darby, 2017). This is more marked in the anterior maxilla than posterior sites and varies according to the initial thickness of the buccal plate at the time of tooth extraction. This approach is often associated with a local contour augmentation at the time of implant placement using guided bone regeneration (GBR) to compensate for these ridge alterations, and has been shown to provide long-term peri-implant tissue stability (Buser, Bornstein et al., 2008; Buser, Chappuis, Bornstein et al., 2013; Buser, Chappuis, Kuchler et al., 2013; Buser, Chen et al., 2008; Buser et al., 2009; Buser et al., 2011; Chappuis et al., 2017; Sanz et al., 2012; Schropp, Wenzel, Spin-Neto, & Stavropoulos, 2015; Schropp, Wenzel, & Stavropoulos, 2014; Soydan, Cubuk, Oguz, & Uckan, 2013).

Different implant loading options, as defined by the last three ITI Consensus Conferences in 2003, 2008, and 2013, have also been clinically applied (Benic, Mir-Mari, & Hammerle, 2014; Chiapasco, 2004; Cochran, Morton, & Weber, 2004; Gallucci, Morton, & Weber, 2009; Gallucci et al., 2014; Ganeles & Wismeijer, 2004; Grutter & Belser, 2009; Morton, Jaffin, & Weber, 2004; Papaspyridakos, Chen, Chuang, & Weber, 2014; Roccuzzo, Aglietta, & Cordaro, 2009; Schimmel, Srinivasan, Herrmann, & Muller, 2014; Schrott, Riggi-Heiniger, Maruo, & Gallucci, 2014; Weber et al., 2009). The definition of loading protocols has been slightly modified over the years and is currently accepted as follows: (a) *Immediate loading* of dental implants is defined as being earlier than 1 week after implant placement, (b) *Early loading* of dental implants between 1 week and 2 months after implant placement, and (c) *Conventional loading* of dental implants >2 months after implant placement (Gallucci et al., 2014; Weber et al., 2009).

Likewise, reduced overall treatment times with immediate and early loading protocols, together with the potential to avoid a removable provisional prosthesis, present attractive solutions for clinicians and patients. Surface modification of dental implants has accelerated the bone response during implant healing (Buser et al., 2004). High survival rates for each of the various loading protocols have been reported (Benic et al., 2014; Gallucci et al., 2014; Sanz-Sanchez, Sanz-Martin, Figuero, & Sanz, 2015; Schrott et al., 2014). However, bone turnover during the healing period may compromise implant stability and reduce the ability of an implant to resist significant lateral forces prior to adequate osseointegration (Neugebauer, Traini, Thams, Piattelli, & Zoller, 2006).

Throughout history, implant placement and loading protocols have been analyzed separately from one another. However, the implant placement technique and its related surgical outcome at the time of placement are determinant factors for selecting the loading protocol. For instance, primary implant stability is known to be one of the key factors for success associated with placement and loading protocols (Schrott et al., 2014). Hence, it appears that many treatment factors need to align with careful patient and site assessment to select the ideal placement/loading option.

TABLE 1 Studies excluded during data extraction

Reason for exclusion	Number	Studies
Insufficient information to separate partially and completely edentulous patients	6	Degidi, Nardi, and Piattelli (2012), Horwitz and Machtei (2012), Malchiodi, Ghensi, Cucchi, and Corrocher (2011), Malchiodi et al. (2010), Siebers, Gehrke, and Schliephake (2010), Vandeweghe et al. (2012)
Insufficient information to separate implant failure from partially and completely edentulous patients	5	Bekcioglu, Sagirkaya, Karasoy, and Cehreli (2012), Danza, Guidi, and Carinci (2009), Glauser et al. (2001), Kopp et al. (2013), Penarrocha-Diago, Carrillo-Garcia, Boronat-Lopez, and Garcia-Mira (2008)
Less than 10 partially edentulous patients	1	Polizzi and Cantoni (2015)
Not screw-type implant	2	Kopp et al. (2013), Mangano et al. (2014)
Intra-osseous Implant diameter more than 6.0 mm	1	Atieh et al. (2013)
Insufficient information to separate machined surface implants and rough surface implants	1	Wagenberg, Froum, and Eckert (2013)
Insufficient information of failed implants in different placement protocol	3	Glauser et al. (2003), Glauser (2013), Ostman, Hellman, Albrektsson, and Sennerby (2007)
Insufficient information of failed implants in different loading protocol	2	Felice, Grusovin, Barausse, Grandi, and Esposito (2015), Wilson, Roccuzzo, Ucer, and Beagle (2013)
Study scope focusing on grafting techniques	3	Lang et al. (2015), Siormpas, Mitsias, Kontsiotou-Siormpa, Garber, and Kotsakis (2014), Urban, Kostopoulos, and Wenzel (2012)
Data retrieved from chart reviews	6	Al Amri et al. (2017), Bell and Bell (2014), El-Chaar (2011), Harel, Moses, Palti, and Ormianer (2013), Ormianer and Palti (2008), Pozzi, Tallarico, Marchetti, Scarfo, and Esposito (2014)
Multiple studies on the same population	9	Buser, Bornstein et al. (2008), Buser, Chappuis, Kuchler et al. (2013), Buser et al. (2009, 2011), Kan, Rungcharassaeng, and Lozada (2003), Mangano et al. (2012), Schropp, Kostopoulos, Wenzel, and Isidor (2005), Shibly, Kutkut, Patel, and Albandar (2012)
Total	39	

TABLE 2 Quality assessment and risk of bias of included CCTs

Study	Representative of the exposed cohort	Selection of the nonexposed cohort	Ascertainment of exposure	Outcome of risk not present at commencement of study	Comparability of cases and controls	Assessment of outcome	Sufficient follow-up time for outcomes to occur	Adequacy of follow-up	Total
Achilli et al. (2007)	*	*	*	*	*	*	*	*	8
De Bruyn et al. (2013)	*	*	*	*	*	*	*	*	8
Heinemann, Biffar, Schwahn, and Mundt (2013)	*	*	*	*	*	*	*		7
Meizi, Meir and Laster (2014)	*	*	*	*		*	*		6
Mertens and Steveling (2011)	*	*	*	*		*	*	*	7
Schropp and Isidor (2008)	*	*	*	*	*	*	*	*	8
Vandeweghe et al. (2013)	*		*	*	*	*	*		6

FIGURE 2 Risk of bias summary: review authors' judgements about each risk of bias item for each included RCTs

Despite the vast scientific evidence on implant placement and implant loading protocols, treatment outcomes assessing the timing of implant placement and loading as treatment co-variables have not been systematically reviewed. The aim of this systematic review is to answer the PICO question: "In partially edentulous patients with immediate or early placement and loading protocols, do the implant-prosthodontic survival and success differ when compared to conventional protocols?"

2 | MATERIAL AND METHODS

This systematic review was conducted consulting the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Liberati et al., 2009), the Standards for Developing Trustworthy Clinical Practice Guidelines published by the Institute of Medicine (IOM) (Institute of Medicine Committee on Standards for Developing Trustworthy Clinical Practice, 2011), and the Cochrane Handbook for Systematic Reviews of Interventions (Higgins and Green 2017). The review was registered with the PROSPERO database (CRD42017080776).

2.1 | Focus question

The focus PICO question (population, intervention, comparison, outcome) was formulated with partially edentulous patients as the population; immediate/early placement and loading protocols as the intervention of interest; late placement and conventional loading protocols as the intervention of comparison; and implant-prosthodontic survival and success as the primary outcome. Thus, the PICO question was formulated as follows: "In partially edentulous patients with immediate or early placement and loading protocols, do the implant-prosthodontic survival and success differ when compared to conventional protocols?"

The placement protocols were defined as follow:

- Late implant placement: Dental implants are placed after completely bone healing, more than 6 months after tooth extraction.
- Early implant placement: Dental implants are placed with soft tissue healing or with partial bone healing, 4–8 weeks or 12–16 weeks after tooth extraction.
- Immediate implant placement: Dental implants are placed in the fresh socket on the same day of tooth extraction (Chen & Buser, 2009; Chen et al., 2004; Hammerle et al., 2004).

The loading protocols were defined as follows:

TABLE 3 RCT included for analysis [In PDF format, this table is best viewed in two-page mode]

Study	Comparison	Timing of placement	Timing of restoration/loading	Mean follow-up (mo)	No. of patients	No. of patients drop-out
Bömicke, Gabbert, Koob, Krisam, and Rammelsberg (2017)	Type 4A	>6 weeks	≤1 day	36	19	0
	Type 4C	>6 weeks	3 months		19	3
Cucchi et al. (2017)	Type 1C	≤1 day	3 months	24.4	48	3
	Type 4C	>3 months	3 months		44	4
Felice et al. (2015)	Type 1A	≤1 day	≤1 day	12	16	0
	Type 1C	≤1 day	4 months		9	0
	Type 4A	4 months	≤1 day		6	2
	Type 4C	4 months	4 months		19	
Ganeles et al. (2008)	Type 4A	≥4 months	≤1 day	12	138	NR
	Type 4B	≥4 months	28–34 days		128	NR
Gjelvold, Kisch, Chrcanovic, Albrektsson, and Wennerberg (2017)	Type 4A	≥4 months	≤1 day	12	25	0
	Type 4C	≥4 months	≥4 months		25	0
Göthberg, Andre, Grondahl, Thomsen, and Slotte (2016)	Type 4A	>3 months	<2 days	12	26	0
	Type 4C	>3 months	3 months		24	0
Hall et al. (2007)	Type 4A	NR	≤1 day	12	14	0
	Type 4C	NR	6 months		14	2
Kim et al. (2015)	Type 4A	≥6 months	≤1 day	12	21	0
	Type 4C	≥6 months	20–23 weeks			0
Malchiodi, Balzani, Cucchi, Ghensi, and Nocini (2016)	Type 1C	≤1 day	3 months	12	20	0
	Type 2-3C	>12 weeks	3 months		20	0
Margossian et al. (2012)	Type 4A	≥4 months	≤1 day	24	80	0
	Type 4C	≥4 months	NR		37	0
Schincaglia, Marzola, Giovanni, Chiara, and Scotti (2008)	Type 4A	≥4 months	≤1 day	12	15	0
	Type 4C	≥4 months	3–4 months		15	0
Schropp et al. (2014)	Type 2-3C	10 days	3 months	120	22	4
	Type 4C	>3 months	3 months		22	1
	Type 4C	17 months	3 months		19	2
Shibly et al. (2010)	Type 1A	≤1 day	≤1 day	24	30	2
	Type 1C	≤1 day	3 months		30	
Slagter et al. (2016)	Type 1C	≤1 day	3 months	12	20	0
	Type 4C	>3 months	3 months		20	0
Van de Velde, Sennerby, and De Bruyn (2010)	Type 4A	≥4 months	≤1 day	18	13	1
	Type 34B	≥4 months	6 weeks		13	

BL: bone level implant; NR: not reported; RBM: resorbable blast media; SLActive: hydrophilic and chemically active sandblasted, large grit, acid etched; TL: tissue level implant.

- Conventional loading: Dental implants are allowed a healing period more than 2 months after implant placement with no connection to the prosthesis.
- Early loading: Dental implants are connected to the prosthesis between 1 week and 2 months after implant placement.
- Immediate loading: Dental implants are connected to the prosthesis within 1 week subsequent to implant placement.

This is in line with the publications of the previous ITI Consensus Conferences (Benic et al., 2014; Chiapasco, 2004; Cochran et al., 2004; Gallucci et al., 2009, 2014; Ganeles & Wismeijer, 2004; Grutter & Belser, 2009; Morton et al., 2004; Papaspyridakos et al., 2014; Roccuzzo et al., 2009; Schimmel et al., 2014; Schrott et al., 2014; Weber et al., 2009).

2.2 | Search strategy

The search strategy was developed in close collaboration with a trials search coordinator, who also serves as the Reference and Education Services Librarian at the Countway Library of Medicine of the Harvard Medical School, Boston, Massachusetts. The electronic search was performed utilizing the databases of PubMed/Medline,

TABLE 3 (additional columns)

No. of implants	Implant type	Implant surface	No. of implant failed	Implant survival rate (%)	Implant success rate (%)	Prosthetic success rate (%)
19	Nobel BL tapered	TiUnite	1	94.8	NR	84.2
16			0	100	NR	68.8
49	BTK BL tapered	Dual acid etched	2	95.5	NR	100
48			0	100	NR	100
16	Dentsply XiVE	NR	2	87.5	NR	100
9			0	100	NR	100
6			0	100	NR	100
19			0	100	NR	100
197	Straumann TL parallel	SLActive	4	98	NR	NR
186			6	97	NR	NR
25	BioHorizons tapered	NR	0	100	96	100
25			1	96	88	100
78	Nobel BL	TiUnite	4	94.9	NR	NR
72			2	97.2	NR	NR
14	Southern tapered	Roughened	1	92.9	NR	92.3
14			0	100	NR	85.7
22	Straumann TL parallel	SLActive	3	86.4	NR	NR
24			0	100	NR	NR
20	SybronPRO XRT parallel	RBM	0	100	100	NR
20			0	100	100	NR
209	Biomet 3i	Osseotite	7	96.7	96.7	NR
98			0	100	100	NR
15	Nobel	TiUnite	1	93.3	NR	NR
15	BL parallel		0	100	NR	NR
22	Biomet 3i parallel	Osseotite	2	90.9	NR	NR
22			1	95	NR	NR
19			0	100	NR	NR
30	Nobel BL parallel	TiUnite	1	96.7	NR	NR
30			2	93.3	NR	NR
20	NR	NR	0	100	NR	NR
20	NR	NR	0	100	NR	NR
36	Straumann TL tapered	SLA	1	97.3	72.2	100
34			0	100	82.35	100

TABLE 4 CCT included for analysis [In PDF format, this table is best viewed in two-page mode]

Study	Comparison	Timing of placement	Timing of restoration/loading	Mean follow-up (mo)	No. of patients	No. of patients drop-out
Achilli et al. (2007)	Type 4A	≥3 months	≤1 day	12	21	0
	Type 4B	≥3 months	6 weeks		33	0
De Bruyn et al. (2013)	Type 1A	≤1 day	≤1 day	36	55	0
	Type 4A	NR	≤1 day		58	0
Heinemann et al. (2013)	Type 1C	≤1 day	5–6 months	4–45.6	35	NR
	Type 4C	≥6 months	5–6 months		23	NR
Meizi et al. (2014)	Type 1A	≤1 day	≤3 days	12	155	NR
	Type 4A	≥3 months	≤3 days			
	Type 1C	≤1 day	Max: 6 months; mand: 3 months			
	Type 4C	≥3 months	Max: 6 months; mand: 3 months			
Mertens and Steveling (2011)	Type 1A	≤1 day	≤1 day	60	17	2
	Type 4A	NR	≤1 day			
	Type 1B	≤1 day	9.56 weeks			
	Type 4B	NR	9.56 weeks			
Schropp and Isidor (2008)	Type 2-3C	10 days	4–5 months	60	23	2
	Type 4C	>3 months	4–5 months		22	
Vandeweghe et al. (2013)	Type 1A	≤1 day	≤1 day	26	38	NR
	Type 4A	NR	≤1 day			NR

BL: bone level implant; NR: not reported; Mand: mandible; Max: maxilla.

Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL) to identify publications in English up to December 2017.

For the PubMed/MEDLINE screening, combinations of controlled terms (MeSH) and keywords were used whenever possible. The search terms used for the PubMed search were as follows: (dental implantation, endosseous[MeSH] OR dental implants[MeSH] OR implantation OR implant OR implants) AND (denture, partial, fixed[MeSH] OR dental prostheses, implant supported [MeSH] OR fixed partial denture OR FPD OR FPDs OR fixed dental prosthesis OR fixed dental prostheses OR bridge OR crown) AND (immediate implant OR immediate implantation OR immediate implant placement OR immediate placement OR immediate OR early OR placement OR time OR timing OR fresh extraction sockets OR immediate extraction sockets OR post-extraction implant placement OR post-extractive OR early implantation OR early implant placement) AND (immediate dental implant loading[MeSH] OR function OR time OR immediate OR early OR load) AND (English[Language]). The references were managed with a specific bibliographic software (EndNote X8, Version 8.1, Thomson Reuters®, New York, NY, USA).

2.3 | Selection criteria

All types of study designs were included provided they met the following criteria:

- Human studies;
- At least 10 participants;
- Partially edentulous patients receiving Implant Fixed Dental Prostheses (IFDPs);
- Implant placement and implant loading protocols were specifically reported;
- Implant success criteria were reported;
- Minimum follow-up period of 1 year;
- Root-form or cylindrical implant with a rough surface;
- Intra-osseous implant diameter between 3 and 6 mm.

The exclusion criteria were as follows:

- Animal or in vitro studies;
- Zirconia implants;
- Implants with machined surfaces or hydroxyapatite (HA) coatings;
- Implants supporting full-arch restorations or removable appliances;
- Implants placed in irradiated bone or alveolar clefts;
- Data retrieved from chart reviews or questionnaires;
- Insufficient information provided on implant placement protocol;
- Insufficient information provided on loading protocol or type of implant superstructures;
- Insufficient information provided to determine implant survival rate or success rate;

TABLE 4 (additional columns)

No. of implants	Implant type	Implant surface	No. of implant failed	Implant survival rate (%)	Implant success rate (%)	Prosthetic success rate (%)
43	Nobel BL tapered	TiUnite	0	100	100	NR
69			0	100	100	NR
55	Dentsply	OsseoSpeed	3	94.6	87	NR
58			1	98.3	92	NR
83	Dentaurum BL tapered	Rough ceramic blasted	0	100	100	NR
53			0	100	100	NR
161	Saturn	NR	7	95.65	NR	NR
23			0	100	NR	NR
54			3	98.2	NR	NR
106					NR	NR
10	Dentsply	OsseoSpeed	0	100	100	100
4			0	100	100	100
3			1	97.14	97.14	100
32						100
23	Biomet 3i parallel	Osseotite	2	91.3	NR	95.24
22			1	95.45	NR	
23	Southern tapered	Moderately rough	0	100	NR	97.7
20			0	100	NR	

- Insufficient information provided to identify success criteria.

In case of multiple publications on the same study population, only the study with the longest follow-up was included for reporting of results, whilst previous studies were consulted only to retrieve information not provided in the most recent publication.

Studies pertaining to implant rehabilitation in both completely edentulous and fully edentulous patients will only be included where success/survival data are clearly separated between these two different population groups.

2.4 | Screening of studies

Screening and data extraction were performed independently by two reviewers (WZ and AH). Disagreements were resolved by discussion between reviewers and consultation with a third reviewer (GO) where required.

2.5 | Data collection

Data on study design, timing of implant placement postextraction, timing of functional loading, mean follow-up period, number of patients, number of implants, location, implant characteristics (i.e., diameter, length, type and surface), flap design, bone graft, surgical guide, implant stability assessment, intention to treat (ITT), occlusion contact of provisional prosthesis, final prosthesis design, success criteria, time of failure, implant survival rate, implant success rate, and prosthesis success rate were extracted from the included studies and recorded on standardized forms.

Authors were contacted directly via email as needed for clarification or missing information. Authors were contacted if further clarification on the extracted data was necessary.

2.6 | Quality assessment

Two independent reviewers (WZ and AH) assessed the methodological quality of all included comparative studies. Randomized controlled trials (RCTs) were rated per their risk of bias using the Cochrane quality assessment tool for RCTs. The Newcastle–Ottawa scale (NOS) was used to assess the quality of controlled clinical trials (CCTs).

Some RCT studies which reported detailed information on timing of implant placement and loading were included but analyzed as CCTs (Cannizzaro, Torchio, Felice, Leone, & Esposito, 2010; Schropp & Isidor, 2008) or prospective cohort studies (Barone et al., 2016; Bianchi & Sanfilippo, 2004; De Angelis et al., 2011; Fung, Marzola, Scotti, Tadinada, & Schincaglia, 2011; Meloni, Jovanovic, Pisano, & Tallarico, 2016; Migliorati, Amorfini, Signori, Biavati, & Benedicenti, 2015; Prosper, Gherlone, Redaelli, & Quaranta, 2003) as the comparison was not between different placement or loading protocols. For prospective and retrospective cohort study, no quality assessment was performed.

TABLE 5 Noncomparative studies included for analysis [In PDF format, this table is best viewed in two-page mode]

Study	Study design	Placement and loading protocol	Timing of placement	Timing of restoration/loading	Mean follow-up (mo)	No. of patients	No. of patients drop-out
Becker et al. (2011)	RC	Type 1A	≤1 day	≤3 days	12	100	NR
Belser et al. (2009)	RC	Type 2-3B	4–8 weeks	6–12 weeks	31.44	45	4
Blus and Szmukler-Moncler (2010)	RC	Type 1A	≤1 day	≤1 day	12	23	NR
		Type 1B	≤1 day	1 week to 3 months	12		
		Type 1C	≤1 day	3–6 months	12		
Boronat, Penarrocha, Carrillo, and Marti (2008)	RC	Type 1B	≤1 day	8 weeks (max); 6 weeks (mand)	12	30	12
		Type 4B	NR	8 weeks (max); 6 weeks (mand)	12		
Brown and Payne (2011)	RC	Type 1A	≤1 day	≤1 day	12	25	0
Fugazzotto (2012)	RC	Type 1C	≤1 day	3–7 months	62	64	NR
Hartlev et al. (2013)	RC	Type 1A	≤1 day	≤1 day	33	55	13
Kolerman et al. (2016)	RC	Type 1A	≤1 day	≤1 day	29	34	NR
Mangano et al. (2013)	RC	Type 1A	≤1 day	≤1 day	31.09	22	0
		Type 4A	≥6 months	≤1 day	34.4	18	0
Mura (2012)	RC	Type 1A	≤1 day	≤1 day	60	48	8
Paul and Held (2013)	RC	Type 1A	≤1 day	≤1 day	40.8	26	2
Sener-Yamaner, Yamaner, Sertgoz, Canakci, and Ozcan (2017)	RC	Type 4B	≥4 months	3–8 weeks	81	55	NR
Van Nimwegen et al. (2016)	RC	Type 1A	≤1 day	≤1 day	48	51	NR
Akca, Cavusoglu, Uysal, and Cehreli (2013)	PC	Type 4B	NR	5–6 weeks	14	22	0
Barone et al. (2016)	PC	Type 4C	≥3 months	3 months	12	116	0
Bianchi and Sanfilippo (2004)	PC	Type 1C	≤1 day	3–4 months	108	116	3
Bornstein et al. (2010)	PC	Type 4B	≥4 months	3 weeks	36	39	0
Buser, Chappuis, Bornstein et al. (2013), Buser, Chappuis, Kuchler et al. (2013)	PC	Type 2-3C	4–8 weeks	8–12 weeks	84	41	8
Calandriello and Tomatis (2011)	PC	Type 4A	≥4 months	≤1 day	60	33	NR
Calvo-Guirado et al. (2015)	PC	Type 1A	≤1 day	≤1 day	36	53	NR
Chappuis et al. (2013)	PC	Type 2-3C	4–8 weeks	8–12 weeks	120	20	0
Covani et al. (2012)	PC	Type 1C	≤1 day	6 months	120	91	7
Covani, Canullo, Toti, Alfonsi, and Barone (2014)	PC	Type 1C	≤1 day	4 months	60	47	NR
Cristalli et al. (2015)	PC	Type 1A	≤1 day	≤1 day	12	24	0
Degidi et al. (2011)	PC	Type 4A	NR	≤1 day	36	24	0
Del Fabbro, Boggian, and Taschieri (2009)	PC	Type 1C	≤1 day	3–4 months	18.5	30	2 implants
De Angelis et al. (2011)	PC	Type 1C	≤1 day	3–4 months	12	80	1
De Rouck, Collys, and Cosyn (2008)	PC	Type 1A	≤1 day	≤1 day	12	30	1
Fugl et al. (2017)	PC	Type 4A	≥2 months	≤1 day	12	91	6
Fung et al. (2011)	PC	Type 4A	≥4 months	≤1 day	36	10	0

(Continues)

TABLE 5 (additional columns)

No. of implants	Implant type	Implant surface	No. of implant failed	Implant survival rate (%)	Implant success rate (%)	Prosthetic success rate (%)
100	Straumann TL parallel	SLActive	1	99	99	100
45	Straumann TL parallel	SLA	0	100	100	NR
6	NR	NR	0	100	NR	NR
24			0	100	NR	NR
10			0	100	NR	NR
16	DEFCON TSA	Avantblast	1	93.75	93.75	NR
90			2	97.78	97.78	NR
26	Co-Axis TL tapered	Roughened surfaces of Sa	0	100	NR	92.31
128	NR	NR	0	100	98.2	NR
55	Nobel BL tapered	TiUnite	1	98	NR	100
34	MIS BL	NR	0	100	88	NR
22	Leone Ortodonzia	NR	0	100	100	100
18			0	100	100	100
66	Nobel BL tapered	TiUnite	0	100	NR	98.5
31	Nobel	NR	0	100	100	NR
175	Straumann TL	SLA *n* = 48; SLActive *n* = 48	3	98.2	NR	NR
64	Biomet 3i	Osseotite	2	96.9	NR	NR
52	Straumann BL parallel	NR	0	100	100	100
112	Blossom BL tapered	NR	3	97.4	93.1	NR
116	Straumann TL parallel	TPS	0	100	100	NR
56	Straumann TL parallel	SLActive	0	100	100	NR
41	Straumann TL parallel& tapered	SLA	0	100	NR	NR
40	Nobel BL tapered	TiUnite	2	95	95	NR
71	MIS	Rough	0	100	NR	NR
20	Straumann BL	SLActive	0	100	95	NR
159	Sweden & Martina	SLA	13	91.8	91.8	98.7
47	Sweden & Martina	NR	2	95.7	NR	NR
25	Nobel BL tapered	TiUnite	2	91.67	91.67	NR
48	Ankylos Dentsply	SLA	0	100	100	100
61	BTI Biotechnology Institute	Acid etched	1	98.4	98.4	100
80	Biomet 3i BL tapered	Dual acid etched	7	91.25	NR	NR
30	Nobel BL tapered	TiUnite	1	97	NR	100
93	NR	NR	1	99	97	NR
20	Nobel BL	ADZ	0	100	100	85

(Continues)

TABLE 5 (Continued) [In PDF format, this table is best viewed in two-page mode]

Study	Study design	Placement and loading protocol	Timing of placement	Timing of restoration/loading	Mean follow-up (mo)	No. of patients	No. of patients drop-out
Grandi, Guazzi, Samarani, Maghaireh, and Grandi (2014)	PC	Type 1A	≤1 day	≤1 day	12	25	0
Kan, Rungcharassaeng, Lozada, and Zimmerman (2011)	PC	Type 1A	≤1 day	≤1 day	48	35	0
Karabuda, Abdel-Haq, and Arisan (2011)	PC	Type 4B	≥3 months	12 weeks (max); 8 weeks (mand)	15	22	0
Lang, Turkyilmaz, Edgin, Verrett, and Garcia (2014)	PC	Type 4A	NR	≤1 day	60	20	5
Luongo, Di Raimondo, Filippini, Gualini, and Paoleschi (2005)	PC	Type 4A	NR	≤1 day *n* = 10; 2–11 days *n* = 30	12	40	0
Malchiodi, Cucchi, Ghensi, and Nocini (2013)	PC	Type 1A	≤1 day	≤1 day	36	58	0
Mayer, Hawley, Gunsolley, and Feldman (2002)	PC	Type 4C	NR	6 months (max); 4 months (mand)	45.9	57	2 implants
		Type 1C	≤1 day	6 months (max); 4 months (mand)	45.9	2	
Meloni et al. (2016)	PC	Type 4C	NR	3 months	36	18	0
Migliorati et al. (2015)	PC	Type 1A	≤1 day	≤1 day	24	47	1
Montoya-Salazar et al. (2014)	PC	Type 1C	≤1 day	4.5 months	36	NR	NR
Noelken, Neffe, Kunkel, and Wagner (2014)	PC	Type 1A	≤1 day	≤1 day	27	19	1
Ostman et al. (2008)	PC	Type 4A	≥4 months	≤1 day	48	NR	0
Oyama, Kan, Rungcharassaeng, and Lozada (2012)	PC	Type 4A	≥2 months	≤1 day	12	13	NR
Prosper et al. (2003)	PC	Type 1C	≤1 day	4–6 months	48	83	0
Romeo, Chiapasco, Ghisolfi, and Vogel (2002)	PC	Type 4C	>6 months	3–6 months	84	109	6
Siddiqui et al. (2008)	PC	Type 4A	>6 months	≤1 day	12	44	NR
Valentini, Abensur, Albertini, and Rocchesani (2010)	PC	Type 1A	<1 week	<1 week	33.6	40	NR

ADZ: oxide-anodized; BL: bone level implant; FBR: fast bone regeneration; HA: hydroxyapatite; Mand: mandible; Max: maxilla; NR: not reported; PC: prospective cohort study; RC: retrospective cohort study; SLA: sandblasted, large grit, acid etched; SLActive: hydrophilic and chemically active sandblasted, large grit, acid etched; TL: tissue level implant; TPS: titanium-sprayed surface.

2.7 | Validation criteria

To formulate conclusions and propose clinical recommendations for all types of placement and loading protocols, the included studies were ranked per their design, sample size, and outcome homogeneity (OH). The outcome homogeneity was considered positive (OH+) when the variation of implant survival rates for the same treatment protocol was 10% or less, and negative (OH–) when the variation was >10% (Gallucci et al., 2009). Using these criteria, scientific and/or clinical validation was determined as follows:

Scientifically and clinically validated (SCV):

- Systematic reviews of RCTs; or
- Two or more RCTs + ≥100 patients + OH+; or
- One RCT and two or more prospective studies + ≥150 patients + OH+

Clinically well documented (CWD):

- One RCT and two or more prospective studies + ≥40 patients + OH+; or

TABLE 5 (additional columns - continued)

No. of implants	Implant type	Implant surface	No. of implant failed	Implant survival rate (%)	Implant success rate (%)	Prosthetic success rate (%)
25	JDentalCare tapered	Dual acid etched	0	100	NR	100
35	Nobel BL tapered	HA	0	100	100	NR
96	Straumann TL parallel	SLA *n* = 48; SLActive *n* = 48	1	NR	98.96	NR
20	Zimmer tapered	NR	1	95	NR	NR
82	Straumann TL parallel	SLA	1	98.8	97.5	NR
64	NR	FBR	0	100	100	NR
67	Biomet 3i	Osseotite Dual acid etched	1	98.51	98.51	NR
4			0	100	NR	NR
36	Nobel BL tapered	TiUnite	0	100	NR	100
47	Straumann BL tapered	SLActive	0	100	NR	NR
36	MIS	NR	1	97.22	NR	NR
34	NR	OsseoSpeed	0	100	100	NR
180	Nobel	TiUnite	1	99.44	NR	NR
17	Dentsply Xives	Grit-blasted thermal acid etched	0	100	100	NR
111	NR	Sand blasted	3	NR	97.3	NR
187	Straumann TL parallel	TPS	9	96.7	93.6	NR
51	Zimmer tapered	Microtextured	1	98.04	98.04	NR
43	Dentsply	TiOblast	2	95.3	NR	NR

- No RCTs but at least three prospective studies + ≥60 patients + OH+; or
- No RCTs but two or fewer prospective studies + ≥100 patients + OH+

Clinically documented (CD):

- No RCTs, at least two prospective + any retrospective studies + ≤40 patients + OH−; or
- No RCTs, retrospective studies + ≥60 patients + OH−/+

Clinically insufficiently documented (CID):

- None of the above, expert opinion only, case report only.

2.8 | Statistical analysis

Agreement between the reviewers was calculated by Cohen's kappa statistical analysis. Descriptive analysis was used to report the success and survival rates for the various implant placement protocols and loading protocols. A mean cumulative survival rate for each of the implant placement and loading protocols was calculated and weighted by the duration of patient follow-up and number

TABLE 6 Classification according to the implant placement and loading protocol [In PDF format, this table is best viewed in two-page mode]

	Loading protocol							
	Immediate restoration/loading (type A)					Early loading (type B)		
	Type	Weighted mean survival (%)	Mean follow-up (mo)	N° of included implants	N° of studies	Type	Weighted mean survival (%)	Mean follow-up (mo)
Implant placement protocol								
Immediate placement (Type 1)	1A	98.4 (87.5–100)	28.9 (12–60)	1,067	6[a] 18[b]	1B	98.2 (93.8–100)	28.0 (12–60)
Early placement (Type 2-3)	2-3A	NA	NA	NA	0[a] 0[b]	2–3B	100	31.4
Conventional placement (Type 4)	4A	97.9 (83.3–100)	24.3 (12–60)	1,356	16[a] 10[b]	4B	98.3 (97–100)	29 (12–81)

Note.. Range of results indicated in brackets.
Type 1A: Immediate Placement + Immediate Restoration/Loading; Type 1B: Immediate Placement + Early Loading; Type 1C: Immediate Placement + Conventional Loading; Type 2-3A: Early Placement + Immediate Restoration/Loading; Type 2-3B: Early placement + Early Loading; Type 2-3C: Early Placement + Conventional Loading; Type 4A: Late Placement + Immediate Restoration/Loading; Type 4B: Late Placement + Early Loading; Type 4C: Late Placement + Conventional Loading.
[a]No. of comparative studies.
[b]No. of noncomparative studies.

of implants. The weighted average of survival rate is calculated as followed:

$$\bar{x} = \frac{X_1 t_1 n_1 + X_2 t_2 n_2 + \ldots + X_k t_k n_k}{t_1 n_1 + t_2 n_2 + \ldots + t_k n_k} \times 100\%$$

X = survival rate reported in the included study; t = follow-up period; n = number of implants. All studies included in this SR were carefully selected according to their described research variables. For each study, we looked for a clear information on the placement and loading protocols to be one of the variables studied/reported.

3 | RESULTS

A total number of 5,248 titles publications were identified by the search. Following the title screening, 2,362 abstracts and 449 full-text articles were evaluated for inclusion (Figure 1). The interrater reliability Kappa score was 0.97. A total of 108 articles were included for data extraction. Thirty-nine articles had to be excluded from the final analysis for not meeting the inclusion criteria (Table 1). A total of 69 studies met the including criteria and were finally included in this systematic review, which were comprised of 15 RCTs, 7 CCTs, 34 prospective cohort studies, and 13 retrospective cohort studies. The excluded studies and the reasons for exclusion were listed in Table 1.

Several follow-up studies reporting on the same patient population previously published were each combined to one line with the most comprehensive results from each reported. Data were extracted from the most recent publications and tabulated. Any missing data were obtained from the earlier publications.

Although all included studies defined specific survival/success criteria, the definitions of survival/success varied between the studies making standardization of the criteria not possible. Furthermore, despite reporting success criteria, many of the studies still only reported survival rates as an outcome measure.

Considerable heterogeneity in study design was found, with a lack of RCTs and comparative studies which compared across the same implant placement and loading protocol combinations. Therefore, a meta-analysis of controlled studies was not possible.

3.1 | Quality assessment for including comparative studies

Table 2 demonstrated the risk of bias for included RCTs. Twelve studies were well conducted with respect to randomization by reporting the methods to generate randomized sequences. Ten studies reported the concealment of allocation. However, regarding of blinding of participants/operators (performance bias), all the studies had a high risk of bias, as the operators would know the randomized type of treatment and the patients had the right to know which treatment was used. For the CCTs, the Newcastle–Ottawa scale (NOS) results are presented in Figure 2.

3.2 | Outcome analysis of each placement and loading protocol

The data extraction is summarized in Tables 3 and 4 for comparative data (RCT and CCT studies) and Table 5 for noncomparative data (prospective and retrospective cohort studies).

TABLE 6 (additional columns)

		Conventional loading (type C)				
N° of included implants	N° of studies	Type	Weighted mean survival (%)	Mean follow-up (mo)	N° of included implants	N° of studies
43	1[a] 2[b]	1C	96.0 (91.3–100)	38.4 (12–120)	963	6[a] 10[b]
45	0[a] 1[b]	2–3C	96.3 (90.9–100)	96.0 (60–120)	106	2[a] 2[b]
789	4[a] 5[b]	4C	97.7 (95.5–100)	30.6 (12–120)	898	14[a] 4[b]

Placement and loading protocols were used to group the data set in 12 well-differentiated treatment protocols (Table 6). This resulted in a novel classification combining placement and loading protocols in oral implantology as follows:

Type 1A: Immediate Placement + Immediate Restoration/Loading
Type 1B: Immediate Placement + Early Loading
Type 1C: Immediate Placement + Conventional Loading
Type 2A: Early Placement with Soft Tissue Healing + Immediate Restoration/Loading
Type 2B: Early placement with Soft Tissue Healing + Early Loading
Type 2C: Early Placement with Soft Tissue Healing + Conventional Loading
Type 3A: Early Placement with Partial Bone Healing + Immediate Restoration/Loading
Type 3B: Early placement with Partial Bone Healing + Early Loading
Type 3C: Early Placement with Partial Bone Healing + Conventional Loading
Type 4A: Late Placement + Immediate Restoration/Loading
Type 4B: Late Placement + Early Loading
Type 4C: Late Placement + Conventional Loading.

Due to the limitations in distinct specification of the implant placement time in many clinical studies reports, the implant paced with both early loading protocols (types 2 and 3) were combined for this review.

3.2.1 | Type 1A—Immediate Placement + Immediate Restoration/Loading

Two RCTs, 4 CCTs, and 18 noncomparative studies provided the data on the outcomes of implants following Type 1A protocol. In total, 35 of 1,079 Type 1A implants failed. The weighted cumulative survival rate was of 98.4% (median 100%; range 87.5%–100%) with a mean follow-up of 28.9 (*SD* = 15.2; range 12–60) months. The success rates ranged from 87% to 100%.

3.2.2 | Type 1B—Immediate Placement + Early Loading

One CCT and two noncomparative studies reported on the outcome of implants following Type 1B protocol. One of the 43 Type 1B implants failed. The weighted cumulative survival rate was of 98.2% (median 100%; range 93.75%–100%) with a mean follow-up of 28.0 (*SD* = 27.7; range 12–60) months. Implant success rates ranged from 93.75% to 100%.

3.2.3 | Type 1C Immediate Placement + Conventional Loading

Five RCTs, 1 CCT, and 10 noncomparative studies provided data on outcomes of implants following Type 1C protocol. In total, 24 of 963 Type 1C implants failed. The weighted cumulative survival rate was 96% (median 99.2%; 91.3%–100%) with a follow-up of 38.7 (*SD* = 34.3; range 12–120) months. The success rates ranged from 91.8% to 100%.

3.2.4 | Type 2-3A—Early Placement + Immediate Restoration/Loading

None of the included study reported on this protocol.

TABLE 7 Criteria for placement and loading protocol and intention to treat (ITT) analysis

Study	Placement and loading protocol	Criteria for placement protocol (Type 1 or Type 2)	Criteria for loading protocol (immediate or early loading)	No. of patients intended to treat	No. of patients failed to treat	ITT (%)	Reason for exclusion
RCT							
Bömicke et al. (2017)	Type 4A vs. Type 4C	Bone height ≥12 mm and bone width of 6 mm; Enabling implant placement without grafting; Attached gingiva ≥4 mm	IT ≥35 Ncm	38	38	100	–
Cucchi et al. (2017)	Type 1C vs. Type 4C	Adequate bone to place a 3.7 × 10 mm or larger implant without bone augmentation procedures	NR	102	3	97.1	Three patients decided not to restore implant with a definitive crown
Felice et al. (2015)	Type 1A vs. Type 1C vs. Type 4A vs. Type 4C	<4 mm of the buccal wall missing after tooth extraction	IT ≥35 Ncm	55	5	90.9	>4 mm of buccal bone loss when compared to the palatal wall after extraction
Ganeles et al. (2008)	Type 4A vs. Type 4B	Adequate bone quality and quantity	NR	NR	NR	NR	NR
Gjelvold et al. (2017)	Type 4A vs. Type 4C	No need for bone grafting or ridge augmentation at the implant site	IT ≥30 Ncm	62	12	80.6	Four patients did not want treatment for economic reasons; three patients presented extensive osseous defects that would require a bone graft to make the insertion of an implant possible; one patient desired a tooth supported bridge instead of an implant; three patients decided to leave the study before surgery
Gothberg et al. (2016)	Type 4A vs. Type 4C	NR	Good primary stability with ≥1 mm coverage of surrounding bone	NR	NR	NR	NR
Hall et al. (2007)	Type 4A vs. Type 4C	No need for bone grafting or ridge augmentation prior to implant surgery	Primary implant stability could be achieved following placement	28	0	100	–
Kim et al. (2015)	Type 4A vs. Type 4C	Adequate bone to place 4.1/4.8 × 10/12 mm implants without bone augmentation; ≥2 mm attached (keratinized) gingiva	NR	21	0	100	–
Malchiodi et al. (2016)	Type 1C vs. Type 4C	Extraction socket with a containing alveolus (4 bone-wall defect); Bone height ≥9 mm in the maxilla and ≥11 mm in the mandible; ≥3 mm of bone beyond the root apex	NR	40	0	100	–
Margossian et al. (2012)	Type 4A vs. Type 4C	Adequate bone height to place a 10 mm or longer implant	IT ≥30 Ncm ISQ ≥60	117	0	100	–
Schincaglia et al. (2008)	Type 4A vs. Type 4C	Adequate bone to place a 5 × 8.5 mm or larger implant	IT ≥20 Ncm	NR	NR	NR	NR

(Continues)

TABLE 7 (continued)

Study	Placement and loading protocol	Criteria for placement protocol (Type 1 or Type 2)	Criteria for loading protocol (immediate or early loading)	No. of patients intended to treat	No. of patients failed to treat	ITT (%)	Reason for exclusion
Schropp et al. (2014)	Type 2-3C vs. Type 4C	NR	NR	72	9	87.5	Four patients were judged not suitable for single implant therapy; five patients withdrew during the period from tooth extraction to commencement of implant treatment
Shibly et al. (2010)	Type 1A vs. Type 1C	Extraction sockets with an open defect, lacking ≥1 bone walls	IT ≥35 Ncm	72	12	83.3	The placement of immediate implants after extraction was not possible
Slagter et al. (2016)	Type 1C vs. Type 4C	Labial bony defect of ≥5 mm after tooth removal; sufficient bone on the palatal side	NR	40	0	100	–
Van de Velde et al. (2010)	Type 4A vs. Type 4B	Adequate bone to place 2–3 4.1 × 8–12 mm implants	NR	14	2	85.7	One patient needed bone regeneration; one patient died during the course of study
CCT							
Achilli et al. (2007)	Type 4A vs. Type 4B	NR	Reverse IT of 30 Ncm	NR	NR	NR	NR
De Bruyn et al. (2013)	Type 1A vs. Type 4A	No need for bone grafting	IT 15–20 Ncm	157	44	72.0	25 implants need bone regenerative procedures; nine implants insufficiently stable for immediate loading
Heinemann et al. (2013)	Type 1C vs. Type 4C	NR	NR	NR	NR	NR	NR
Meizi et al. (2014)	Type 1A vs. Type 4A vs. Type 1C vs. Type 4C	Adequate bone height ≥8 mm; Adequate bone width to retain ≥1 mm of cortical bone on the buccal and lingual/palatal after osteotomy preparation	IT ≥30 Ncm	NR	NR	NR	NR
Mertens and Steveling (2011)	Type 1A vs. Type 4A vs. Type 1B vs. Type 4B	No signs of inflammation; adequate vertical bone height to retain an implant	Good bone quantity and quality; high primary stability could be achieved during implant placement	NR	NR	NR	NR
Schropp and Isidor (2008)	Type 2-3C vs. Type 4C	NR	NR	NR	NR	NR	NR
Vandeweghe et al. (2013)	Type 1A vs. Type 4A	No signs of peri-apical inflammation	IT ≥40 Ncm	NR	NR	NR	NR
Retrospective cohort study							
Becker et al. (2011)	Type 1A	≥3 mm of apical circumferential bone to place a 5.8 mm or longer implant; ≥1 mm inside facial plate	IT ≥15 Ncm ISQ ≥50	NR	NR	NR	NR

(Continues)

TABLE 7 (continued)

Study	Placement and loading protocol	Criteria for placement protocol (Type 1 or Type 2)	Criteria for loading protocol (immediate or early loading)	No. of patients intended to treat	No. of patients failed to treat	ITT (%)	Reason for exclusion
Belser et al. (2009)	Type 2-3B	NR	NR	NR	NR	NR	NR
Blus and Szmukler-Moncler (2010)	Type 1A vs. Type 1B vs. Type 1C	No signs of periodontal disease or infection at the apex; nonresorbed buccal wall	NR	NR	NR	NR	NR
Boronat et al. (2008)	Type 1B vs. Type 4B	NR	NR	NR	NR	NR	NR
Brown and Payne (2011)	Type 1A	Presence of 4 mm bone apical to the socket; stable socket walls postextraction with three-wall dehiscence of <4 mm; sockets allowing to place a 4 × 13 mm or larger implant; Mesial distal proximal distance ≥6 mm; adequate bone quality and quantity (Types I–III)	IT 35–40 Ncm	27	2	92.6	Low IT
Fugazzotto (2012)	Type 1C	Buccal alveolar wall was intact, or a fenestration was present that was ≥5 mm apical to the alveolar crest	NR	NR	NR	NR	NR
Hartlev et al. (2013)	Type 1A	Marginal bone loss <1 mm buccally after tooth extraction; no acute infection	IT >30 Ncm	NR	NR	NR	NR
Kolerman et al. (2016)	Type 1A	Compromised buccal plate (<1 mm, dehiscenced or fenestrated); augmentation procedure needed; ≥5 mm of apical or palatal bone	IT ≥32 Ncm	NR	NR	NR	NR
Mangano et al. (2013)	Type 1A vs. Type 4A	Intact socket walls; thick gingival biotype; no active periodontal infections; no need for hard/soft tissue grafting before implant placement	NR	NR	NR	NR	NR
Mura (2012)	Type 1 A	No signs of active periodontal disease	IT ≥45 Ncm for single implant; IT ≥35 Ncm for multiple splinted implants	NR	NR	NR	NR
Paul and Held (2013)	Type 1A	NR	NR	NR	NR	NR	NR
Sener-Yamaner et al. (2017)	Type 4B	NR	NR	NR	NR	NR	NR
Van Nimwegen et al. (2016)	Type 1A	No significant soft tissue loss; distance of the contact point to bone level at the adjacent teeth ntct; mid-buccal vertical bone loss ≤3 mm	IT >35 Ncm	NR	NR	NR	NR
Prospective cohort study							
Akca et al. (2013)	Type 4B	Adequate bone height to place a 10 mm or longer implant; reduced bone (<6 mm) width that need augmentation to place a regular diameter implant	NR	NR	NR	NR	NR

(Continues)

TABLE 7 (continued)

Study	Placement and loading protocol	Criteria for placement protocol (Type 1 or Type 2)	Criteria for loading protocol (immediate or early loading)	No. of patients intended to treat	No. of patients failed to treat	ITT (%)	Reason for exclusion
Barone et al. (2016)	Type 4C	No bone augmentation needed	NR	120	4	96.7	Two patients required bone augmentation simultaneously with placement, one patient did not accept to undergo the follow-up, one patient showed an excessive insertion torque during surgery
Bianchi and Sanfilippo (2004)	Type 1C	Adequate width and height to place an immediate implant	NR	NR	NR	NR	NR
Bornstein et al. (2010)	Type 4B	NR	Bone densities of Class I to III	56	2	96.4	Two implants rotated slightly during healing cap removal were considered to be "spinners" after the initial healing phase
Buser, Chappuis, Bornstein et al. (2013), Buser, Chappuis, Kuchler et al. (2013)	Type 2-3C	NR	NR	NR	NR	NR	NR
Calandriello and Tomatis (2011)	Type 4A	Adequate bone height to place a 8.5 mm or longer implant; implant to crown length ratio ≥1:1	IT ≥35 Ncm	NR	NR	NR	NR
Calvo-Guirado et al. (2015)	Type 1A	Adequate bone to place a 4.1 × 10 mm or larger implant; ≥3 mm width of soft tissue	ISQ <60	71	0	100	–
Chappuis et al. (2013)	Type 2-3C	NR	NR	20	0	100	–
Covani et al. (2012)	Type 1C	≥4 mm native bone apical to the root apex; adequate quality	NR	115	17	85.2	Seven patients declined to participate; postextraction socket of 10 patients did not allow for the insertion of an immediate implant.
Covani et al. (2014)	Type 1C	Extraction sites with no deficiency of buccal bone plate	NR	NR	NR	NR	NR
Cristalli et al. (2015)	Type 1A	Absence of active infection around the surgical site; adequate bone (≥4 mm beyond the root apex); keratinized tissue ≥2 mm	IT ≥35 Ncm	28	4	85.7	Presence of fenestrations or dehiscences on buccal plate of extraction socket
Degidi et al. (2011)	Type 4A	Adequate quantity of bone in the surgery site	IT ≥25 Ncm ISQ ≥60	NR	NR	NR	NR
Del Fabbro et al. (2009)	Type 1C	Adequate quality and quantity of native bone to achieve primary stability	NR	NR	NR	NR	NR

(Continues)

TABLE 7 (continued)

Study	Placement and loading protocol	Criteria for placement protocol (Type 1 or Type 2)	Criteria for loading protocol (immediate or early loading)	No. of patients intended to treat	No. of patients failed to treat	ITT (%)	Reason for exclusion
De Angelis et al. (2011)	Type 1C	Residual buccal bone-to-implant gap ≥1 mm	NR	95	15	84.2	Six patients refused to participate, five patients had an acute abscess and were treated with delayed implants; two patients would have had the implant inserted near another implant; two patients required a sinus lift procedure
De Rouck et al. (2008)	Type 1A	Ideal soft tissue contour at the facial; normal to thick-flat gingival biotype; adequate bone height apical to the alveolus of the failing tooth (≥5 mm)	IT ≥35 Ncm	32	2	93.75	Loss of the labial crest after extraction of the failing tooth
Fugl et al. (2017)	Type 4A	Adequate bone to place a 3.5 × 8 mm or larger implant; no need for major bone augmentation					
Fung et al. (2011)	Type 4A	Adequate bone height to place a 8.5 mm or longer implant; adequate bone width, no need for bone augmentation	IT ≥20 Ncm ISQ ≥60	NR	NR	NR	NR
Grandi et al. (2014)	Type 1A	Adequate bone to place a 3.7 × 11.5 mm or longer implant	IT ≥45 Ncm	28	3	89.3	Three patients had buccal wall fracture after tooth extraction
Kan et al. (2011)	Type 1A	Intact labial bony plate; adequate bone to place a 3.5 × 13.0 mm or larger implant without bone grafting; adequate and harmonious gingival architecture	Adequate primary implant stability	NR	NR	NR	NR
Karabuda et al. (2011)	Type 4B	NR	NR	22	0	100	–
Lang et al. (2014)	Type 4A	Adequate bone to place a 3.7 to 4.7 × 13 mm or larger implant without grafting; ≥2 mm attached keratinized tissue	IT ≥35 Ncm	NR	NR	NR	NR
Luongo et al. (2005)	Type 4A	Adequate bone volume	IT ≥15 Ncm	45	5	88.9	One patient withdrew from the study prior to implant surgery. 3 patients did not achieve primary stability and a torque of 15 Ncm; nine implants placed in one patient which violate the protocol.
Malchiodi et al. (2013)	Type 1A	Normal or thick soft tissue biotype; ≥2 mm attached keratinized tissue	NR	NR	NR	NR	NR
Mayer et al. (2002)	Type 1C vs. Type 4C	≥1 mm of bone available at the buccal and lingual aspects of the implant and below the apex	NR	NR	NR	NR	NR
Meloni et al. (2016)	Type 4C	Residual bone height ≥10 mm; Residual bone width ≥6 mm; ≥2 mm keratinized gingiva crestally	IT 35–45 Ncm	18	0	100	–
Migliorati et al. (2015)	Type 1A	Adequate native bone; ≥2 mm facial keratinized gingiva; Intact facial socket walls or only small dehiscence defects affecting the crestal bone <3 mm in height	Primary stability achieved	48	0	100	–

(Continues)

TABLE 7 (continued)

Study	Placement and loading protocol	Criteria for placement protocol (Type 1 or Type 2)	Criteria for loading protocol (immediate or early loading)	No. of patients intended to treat	No. of patients failed to treat	ITT (%)	Reason for exclusion
Noelken et al. (2014)	Type 1A	NR	IT ≥15 Ncm	NR	NR	NR	NR
Montoya-Salazar et al. (2014)	Type 1C	Adequate quality and quantity of native bone; adequate mesio-distal space (>7 mm)	Primary stability achieved	NR	NR	NR	NR
Ostman et al. (2008)	Type 4A	Adequate bone to place two 7-mm or longer implants or one 15-mm-long implant; no sigh of infection	IT ≥30 Ncm ISQ ≥60	91	14	84.6	Low primary stability
Oyama et al. (2012)	Type 4A	Adequate bone to place a 3.0 × 11 mm or larger implant	IT ≥25 Ncm	NR	NR	NR	NR
Prosper et al. (2003)	Type 1C	Postextraction pocket with 4 walls and minimal bone resorption; 3-5 mm of bone below the implant apex	NR	NR	NR	NR	NR
Romeo et al. (2002)	Type 4C	Adequate bone volume	No signs of peri-implant inflammation	NR	NR	NR	NR
Siddiqui et al. (2008)	Type 4A	Adequate bone to place a 3.7 mm × 10 mm or larger implant; adequate bone width to preserve ≥1.0 mm of buccal and lingual plate thickness after osteotomy preparation	IT ≥30 Ncm; Resist rotation of 30 Ncm when abutment screw tightening	73	29	60.3	Three for inadequate bone; three for personal reasons; two for previously undetected medical conditions that precluded implant placement; one patient required bone grafting; four patients failed to achieve primary implant stability (IT <30 Ncm); final restoration not performed within the required 2-week timeframe; insufficient bone remaining after implant placement; implant placement inadvertently performed using a straight rather than a tapered implant design from the same manufacture
Valentini et al. (2010)	Type 1A	NR	IT ≥40 Ncm	94	51	45.7	IT <40 Ncm

ISQ: implant stability quotient; IT: insertion torque; NR: not reported.

TABLE 8 Classification according to the implant placement and loading protocol

	Loading Protocol		
	Immediate restoration/loading (type A)	Early loading (type B)	Conventional loading (type C)
Implant placement protocol			
Immediate placement (Type 1)	Type 1A CD	Type 1B CD	Type 1C SCV
Early placement (Type 2-3)	Type 2-3A CID	Type 2-3B CID	Type 2-3C SCV
Late placement (Type 4)	Type 4A CD	Type 4B SCV	Type 4C SCV

Note. Type 1A: Immediate Placement + Immediate Restoration/Loading; Type 1B: Immediate Placement + Early Loading; Type 1C: Immediate Placement + Conventional Loading; Type 2-3A: Early Placement + Immediate Restoration/Loading; Type 2-3B: Early placement + Early Loading; Type 2-3C: Early Placement + Conventional Loading; Type 4A: Late Placement + Immediate Loading; Type 4B: Late Placement + Early Loading; Type 4C: Late Placement + Conventional Loading.
CD (yellow): clinically documented; CID (red): clinically insufficiently documented (includes loading protocols that are not documented); CWD (green): clinically well documented; SCV: scientifically and clinically validated.

3.2.5 | Type 2-3B—Early Placement + Early Loading

Only one retrospective cohort study reported the outcome of implants following Type 2-3B protocol. None of the 45 implants failed with a mean follow-up of 31.4 months. The success rate was 100%.

3.2.6 | Type 2-3C—Early Placement + Conventional Loading

One RCT, one CCT, and two noncomparative studies provided the data on the outcomes of implants following Type 2-3C protocol. In total, 5 of 106 Type 2-3C implants failed. The weighted cumulative survival rate was 96.3% (median 95.65; range 90.9%–100%) with a mean follow-up of 96.0 (*SD* = 29.4; range 60–120) months. The success rates reported by noncomparative studies were 100%.

3.2.7 | Type 4A—Late Placement + Immediate Restoration/Loading

Ten RCTs, 6 CCTs, and 10 noncomparative studies provided the data on the outcomes of implants following Type 4A protocol. In total, 42 of 1,338 Type 4A implants failed. The weighted cumulative survival rate was 97.90% (median 98.55; range 83.3%–100%) with a mean follow-up of 24.3 (*SD* = 17.0; range 12–60) month. The success rates ranged from 72.2% to 100%.

3.2.8 | Type 4B—Late Placement + Early Loading

Two RCTs, two CCTs, and five noncomparative studies reported data on the outcomes of implants following Type 4B protocol. In total, 9 of 789 Type 4B implants failed. The weighted cumulative survival rate of 98.3% (median 98.96%; 97.1%–100%) with a mean follow-up of 28.9 (*SD* = 25.3; range 12–60) months. The success rates ranged from 82.4% to 100%.

3.2.9 | Type 4C—Late Placement + Conventional Loading

Twelve RCTs, two CCTs, and four noncomparative studies provided the data on the outcomes of implants following Type 4C protocol. In total, 11 of 898 Type 4C implants failed. The weighted cumulative survival rate was 97.7% (median 100%; range 95.5%–100%) with a mean follow-up of 30.6 (*SD* = 30.2, range 12–120) months. The success rates ranged from 88% to 100%.

3.3 | Criteria for implant placement and loading protocol

Table 7 showed the criteria for selection of specific placement/loading protocols. These were generally presented separately for placement and loading protocols as follows:

3.3.1 | Anatomic criteria for implant placement protocol

An adequate bone height and width for implant placement was a requirement for inclusion in most studies; however, the specific criteria of what is considered adequate vary and are not always well reported. Bone grafting was not performed in most studies. Two studies required adequate bone volume for multiple implant placement.

Extraction sockets with an intact alveolus (four bone-wall defects) were required by 10 studies, three of which required a facial plate width ≥1 mm after the removal of tooth.

Socket wall with dehiscence or fenestration was acceptable by seven studies, but each of them gave a limitation of the defect size. For example, the range of dehiscence was limited to <4 mm (Brown & Payne, 2011) and the fenestration was required to be ≥5 mm apical to the alveolar crest (Fugazzotto, 2012).

Extraction socket with an open defect which lacks at least one bone wall was required by Shibly, Patel, Albandar, and Kutkut (2010) and Slagter, Meijer, Bakker, Vissink, and Raghoebar (2016) to evaluate the effect of bone augmentation along with immediate placement and immediate restoration/loading.

Adequate bone quality was another criterion in six studies. No signs of periodontal disease or infection at the apex were required by eight studies. Nine studies required adequate width of keratinized tissue and three studies required a thick biotype at the implant site.

3.3.2 | Procedural criteria for implant loading protocol

Adequate implant primary stability was required by most of the studies when attempting to conduct an immediate or early loading. Implant insertion torque (IT) judged by the surgeon intraoperatively was the most common evaluation indicator; however, the specific value may vary among studies. IT ≥45 Ncm was proposed by 1 study, IT ≥40 Ncm by 2 studies, IT ≥35 Ncm by 12 studies, IT ≥30 Ncm by 5 studies, IT ≥20 Ncm by 1 study, and IT ≥15 Ncm by 3 studies. Reverse torque of 30 Ncm at insertion was proposed by Achilli, Tura, and Euwe (2007).

Resonance frequency analysis (RFA) in conjunction with insertion torque was another significant evaluation indicator for immediate/early loading. IT ≥30 Ncm with ISQ ≥60 was proposed by Margossian, Mariani, Stephan, Margerit, and Jorgensen (2012) and Ostman, Hellman, and Sennerby (2008); IT ≥25 Ncm with ISQ ≥60 by Degidi, Nardi, and Piattelli (2011); IT ≥20 Ncm with ISQ ≥60 by Fung et al. (2011); and IT ≥15 Ncm with ISQ ≥50 by Becker, Wilson, and Jensen (2011). Bone density of Class I to III was required by Bornstein, Wittneben, Bragger, and Buser (2010) for an early loading.

3.3.3 | Intention to treat analysis (ITT)

Table 7 summarizes how many implants were originally intended for immediate/early placement and loading, and how many of those implants were ultimately not immediately/early placed and loaded because they did not fulfill certain criteria established by the respective authors. In addition, the calculated ITT percentage and detailed reasons for exclusion were listed in the Table 7.

A 100% ITT percentage was reported by 11 studies, which means there was no bias between the planning and treatment, and all implants achieved the required criteria for each type of placement and loading protocol. However, more than half of the studies (39/69) analyzed in this systematic review did not provide information on ITT.

Reasons for exclusion can be generalize into four categories: patient-related factors (28%), low primary stability (32%), need for bone augmentation (32%), and alteration of the study design (8%).

Using the validation tool for the 12 types of placement and loading protocols, Type 1C, Type 2-3C, Type 4B, and Type 4C were scientifically and clinically validated (SCV). Type 1A, Type 1B, and Type 4A were clinically documented (CD) and Type 2-3A and Type 2-3B were clinically insufficiently documented (CID) (Table 8).

4 | DISCUSSION

Implant placement and loading protocols have been widely presented as key elements of implant treatment planning. However, their assessment has mainly been by separating the surgical parameters pertaining to the implant placement technique from the loading aspects related to the restorative phase. Previous systematic reviews on implant placement/loading protocols only compared the various implant loading and placement protocols as entirely unrelated variables (Buser et al., 2017; Papaspyridakos et al., 2014; Schrott et al., 2014). In these reviews, the effects of the interrelated variables based on differing implant loading and implant placement protocols are not accounted for. Papaspyridakos, Chen, Singh, Weber, and Gallucci (2012) emphasized on the importance of assessing outcomes in oral implantology by considering the implant-prosthetics complex as a single variable. Hence, a broad PICO question and search strategy was used in this study, relating to all combinations of implant placement and loading protocols. Using this approach, this systematic review describes nine possible combinations of placement and loading protocols resulting in a proposed new classification and allowing for individual outcome assessment for each treatment protocol (Table 6).

Inconsistencies in outcome reporting and a lack of comparative studies which compare across the same implant placement/loading protocols combinations made meta-analysis of the results not possible. For prospective and retrospective cohort study, no quality assessment was performed. Despite these limitation, the broad search defined by this systematic review identifies the current basis of scientific evidence for the various combinations of implant placement and loading protocols (Table 8). It must be recognized that inclusion of study designs other than RCTs increases the risk of biases incorporated in this review.

The literature clearly shows that specific patient inclusion criteria have been outlined in most studies included in this systematic review (Table 7). These include specific anatomical criteria which were applied to select for suitability for immediate implant placement, as well as procedural criteria in determining suitability for immediate restoration/loading such as adequate primary stability. For instance, this indicates that survival rates may only be applicable in a select group of patients with specific anatomical conditions. It is interesting that the magnitude of individuals who have not met the inclusion criteria was generally not well reported. Thus, intention to treat analysis (ITT) seems to be a very important variable that allows for a comprehensive clinical translation of the available evidence. More than half of the studies (39/69) analyzed in this systematic review did not provide information on ITT.

Type 1A was deemed according the validation tool as presenting clinical documentation. Although there were six comparative studies and 18 noncomparative studies in this group, the validation of this protocol was influenced by a negative outcome homogeneity (OH) ranging from 87.5% to 100% survival rate. The studies that reported on the success criteria showed a range of 87% to 100%. From the studies assessing Type 1A, carefully case selection criteria were described.

Here, the presence of sufficient apical bone, intact buccal plate, and absence of infection at the extraction site was predominant. For Type 1A, the negative OH should be considered as clinical relevant particularly when careful patient selection criteria are recommended. Type 1B was deemed to be CD as only three studies reported on this group with a small cohort and a very short-term follow-up. Given the lack of evidence, the clinical indication for Type 1B compared to Type 1A needs to be carefully considered with limited potential patient benefits for the Type 1B protocol. Conversely to Type 1A and 1B, Type 1C was deemed to be SCV. Survival rates and success rates for Type 1C ranged from 91.3% to 100%. Here again, very strict case selection criteria were used. From the data pulled for Type 1—immediate placement, it appears evident that the loading protocol is the influential factor driving the variation in outcome observed for this group.

Considerable variation in surgical treatment protocols was reported with additional confounding factors being present; flapless vs. flapped, bone graft vs. no bone graft, connective tissue graft vs. no connective tissue graft. The studies on immediate implants (Type 1A, 1B, 1C) use a variation of these four interventions which make it difficult to interpret their influence on outcomes. Therefore, this systematic review is not able to make any conclusions on surgical, hard, and soft tissue grafting protocols utilized in conjunction with the loading protocols.

Type 2-3A was deemed as CID, as there were no articles reporting on this protocol. Type 2-3B presented favorable clinical documentation from only one article (Belser et al., 2009) with a large cohort of patients in a medium-term follow-up. This protocol showed the best outcome-benefit ratio for the patient in term of treatment duration and survival/success rate. It can be argued that identifying case selection criteria for Type 2-3A and 2-3B may result in potential benefits for the patient, particularly in reducing the overall treatment time and an early re-shaping of peri-implant soft tissues. Type 2-3C was scientifically and clinically validated showing excellent survival and success results in a long-term follow-up. Type 2C has been presented as the standard, in the anterior zone when predictable aesthetics outcomes are required.

Type 4A resulted in the category of CD. The validation of this protocol was influenced by a negative outcome homogeneity (OH) ranging from 83.3% to 100% survival rate. One study showed inferior results for Type 4A implants placed in the posterior maxilla. Further interpretation of this data should ideally separate the results based on implant location in the oral cavity and the type of implant reconstruction. Type 4B and Type 4C were all deemed to be SCV. In these groups, when implants were placed in healed sites, the loading protocols have not influenced the survival or success rate. Type 4C was the most documented study protocol and remains the standard of care, particularly when treatment modifiers such as bone augmentation, low insertion torque, reduced diameter implants, and patient local and systemic factors are present (Gallucci et al., 2014).

The criteria for selection of the placement protocols require attention when selecting among the 12 treatment protocols presented in this review. Although case selection criteria presented in this review have several commonalities, there are significant variations on the quantification of these criteria. More important, the implications of these case selection criteria for implant placement on long-term survival and success rate are at the present are not fully understood.

For loading protocols, primary stability, RFA in conjunction with insertion torque values was the most commonly used criterion for selecting the loading protocols. It was observed that the loading protocol was an influential outcome variable for Type 1 placement protocols. Otherwise, the loading protocol appears not having an influence on the outcome of Type 2-3 and Type 4 implant placement.

5 | CONCLUSION

Data assessed in this systematic review highlight the importance of evaluating outcomes in oral implantology by combining the placement and loading protocols variables as a single denominator for survival/success.

For Type 1 placement, the loading protocol appears influential in the treatment outcome, with Type 1C being the only approach scientifically and clinically validated. For Type 1A, Type B, and Type C, specific placement and loading criteria are required to ensure the clinical efficacy of these treatment modalities.

Type 2-3C was scientifically and clinically validated and should be considered routine when. Type 2-3B showed very promising results and more evidence is needed to validate this approach. Type 2-3A was not reported yet.

The selection among the 12 placement/loading types presented in this SR should be based on the consideration of specific procedural criteria for implant placement and loading protocol.

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CONFLICT OF INTERESTS

The authors wish to declare no conflict of interests and that no external funding was received for the completion of this systematic review.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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REVIEW ARTICLE

WILEY CLINICAL ORAL IMPLANTS RESEARCH

Performance and outcome of zirconia dental implants in clinical studies: A meta-analysis

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Abstract

Objectives: To evaluate implant survival, peri-implant marginal bone loss, technical, and biological complications as well as aesthetic outcomes of zirconia implants in clinical studies.

Material and Methods: Electronic (Medline, Embase) and hand searches were performed to identify clinical studies published between January 2004 and March 2017 investigating zirconia dental implants with a mean follow-up of at least 12 months. Primary outcomes were implant survival and peri-implant marginal bone loss. Secondary outcomes included technical and biological complications as well as aesthetic outcomes. Meta-analyses were performed to estimate implant survival and marginal bone loss.

Results: From 943 titles, 264 abstracts were selected. Subsequently, 80 full-text articles were screened, and 18 studies were included for data extraction. One- (14 studies) and 2-piece zirconia implants (4 studies) were investigated. Commercially available (CA) (510 implants, 398 patients) and not commercially available (NCA) zirconia implants (618 implants, 343 patients) were identified. For CA implants (follow-up: 12–61.20 months), technical complications (1.6%), implant fractures (0.2%) and biological complications (4.2%) were reported. Meta-analyses estimated 1- and 2-year survival rates of 98.3% (95% CI: 97.0%–99.6%) and 97.2% (95% CI: 94.7%–99.7%), respectively, and a mean 1-year marginal bone loss of 0.7 mm (95% CI: 0.4–1.0 mm).

Conclusions: Since 2004, the survival rates of CA implants significantly improved compared with NCA implants. CA 1-piece zirconia implants showed similar 1- and 2-year mean survival rates and marginal bone loss after 1 year compared with published data for titanium implants. However, more clinical long-term data are needed to confirm the presently evaluated promising short-term outcomes.

KEYWORDS

biological complications, dental implants, aesthetics, implant survival, marginal bone loss, meta-analysis, prosthetics, soft tissue, technical complications, yttria stabilized tetragonal zirconia, zirconium oxide

1 | INTRODUCTION

Currently, titanium implants with a micro-rough surface are the "gold standard" in implant dentistry based on their excellent osseous integration, clinical reliability and scientific documentation (Buser et al., 2012; Cochran et al., 1996; Roehling, Meng, & Cochran, 2015). However, the initial period of implant dentistry dates back to when clinicians and scientists were already driven by the vision to achieve a

more natural, tooth-like colored implant material. Thus, at the end of the 1960s, the first ceramic dental implants made from alumina were developed (Sandhaus, 1968), scientifically investigated and clinically used for a few decades until the early 1990s (De Wijs, Van Dongen, De Lange, & De Putter, 1994; Schlegel, Jacobs, & Leitenstorfer, 1994; Zetterqvist, Anneroth, & Nordenram, 1991). However, due to their poor biomechanical properties – alumina implants were prone to fracture when loaded extra-axially (Andreiotelli, Wenz, & Kohal, 2009) – these ceramic implants were finally removed from the market. At the beginning of the 1990s, a new material called "zirconium dioxide" (zirconia, ZrO_2) was introduced to dentistry. In comparison with other ceramics, zirconia shows superior biomechanical properties such as a high fracture toughness and bending strength (Christel, Meunier, Heller, Torre, & Peille, 1989) giving these implants the ability to withstand oral occlusal forces (Andreiotelli, Kohal, et al., 2009). Thus, zirconia is currently the material of choice for the fabrication of ceramic dental implants. As implant material, several advantages, such as its color, significantly reduced in vitro bacterial biofilm formation, and reduced numbers of inflammatory cells in the peri-implant soft tissues of healing caps and abutments have been reported for zirconia compared with titanium (Degidi et al., 2006; Roehling et al., 2017; Welander, Abrahamsson, & Berglundh, 2008). Equivalent to titanium, experimental studies have shown that increased surface roughness of zirconia implants is correlated with a higher degree of bone-to-implant contact and that micro-rough zirconia implants (Sa range 0.6–0.7 μm) show a comparable osseointegrative capacity to micro-rough titanium implants (Sa = 1.3 μm, Gahlert et al., 2007; Gahlert, Roehling, et al., 2012; Janner et al., 2018).

At the beginning of 2004, the first 1-piece zirconia dental implants were established on the market. Initially, creating micro-rough surface topographies without compromising the biomechanical stability of zirconia implants was a technical challenge. Thus, reduced survival rates and numerous zirconia implant fractures were reported for the first generation of zirconia implants (Gahlert, Burtscher, Grunert, Kniha, & Steinhauser, 2012; Gahlert et al., 2013; Osman, Swain, Atieh, Ma, & Duncan, 2014; Roehling, Woelfler, Hicklin, Kniha, & Gahlert, 2016). Since then, the industry has constantly improved manufacturing processes to gain micro-roughened zirconia implants with reliable fracture rates and fatigue strength. In addition, zirconia implants were developed not only in terms of the surface microstructure but also with regard to their macroscopic design. In contrast, the first zirconia implant systems were limited to a 1-piece design, and 2-piece zirconia implants with a cement- or screw-retained abutment and supra structures have also become available. Consequently, within the last 14 years, different zirconia implant generations with varying designs, diameters, physical properties and surface topography characteristics were introduced on the market. On the one hand, these developments have made zirconia implants a reliable treatment option with survival rates of more than 96% for an investigation period of 5 years (Grassi et al., 2015). On the other hand, the different implant generations can be confusing for the interpretation of published scientific data and for the clinical application of zirconia implants, which becomes even more relevant as most recently published systematic reviews and meta-analyses have pooled the available data on zirconia implants without considering the different physical properties and ongoing market availability of the investigated zirconia implants (Hashim, Cionca, Courvoisier, & Mombelli, 2016; Pieralli, Kohal, Jung, Vach, & Spies, 2017). Thus, the clinical relevance of the outcomes reported in the latter studies is rather controversial as only 5.3% (Hashim et al., 2016) and 55.3% (Pieralli et al., 2017) of the investigated implants were available on the market.

The objective of the present systematic review was to collect clinical data on zirconia implants with regard to survival rates, marginal bone loss, technical and biological complications as well as aesthetic outcomes. Moreover, the ongoing market availability of the investigated zirconia implants was considered for the first time to identify if significant changes regarding clinical outcomes have occurred over time.

2 | MATERIALS AND METHODS

This systematic review was conducted according to the Preferred Reporting Items for Systematic review and Meta-Analysis Protocols (PRISMA-P (Moher et al., 2015)) statement using the Population, Intervention, Comparison and Outcome (PICO) method (Schardt, Adams, Owens, Keitz, & Fontelo, 2007). The protocol for this systematic review was registered on PROSPERO (CRD42016049624).

2.1 | Focused question

For the present review, the focused (PICO) question to be addressed was as follows: "In clinical studies, what are the outcomes of zirconia dental implants with regard to implant survival, peri-implant marginal bone loss, technical and biological complications as well as aesthetic outcomes?"

2.2 | Search strategy

An electronic, systematic search of the Medline via Pubmed and Embase via Elsevier databases was performed in March 2017. Articles in the English and German languages were included. For the literature search, clinical as well as preclinical studies were included. However, the present review includes only data from clinical studies. For the Medline search, the following terms and combinations were applied:

"Dental implants" [MeSH] OR "dental implantation" [MeSH] AND "zirconium oxide" [MeSH] OR "yttria-stabilized tetragonal zirconia" [MeSH] OR "zirconia" OR "zirconia implant*" OR "ceramic implant*" AND "osseointegration" [MeSH] or "bone-implant-interface" [MeSH] or "survival rate" [MeSH] or "success rate" or "marginal bone loss" or "soft tissue".

With regard to the Embase search, the following EMTREE words and combination were used:

"tooth implant" OR "tooth implantation" AND "zirconium oxide".

In addition to the electronic search, a hand search of the reference list of all included full-texts was performed.

For the electronic Medline search, reference management software (Endnote X 7.7.1, Thomson Reuters) was used. The obtained publications from the Embase search were also imported into the reference management software and finally screened.

2.3 | Inclusion criteria

For the systematic review, the following inclusion criteria were defined:

- Human trials investigating zirconia implants published between January 2000 and March 2017
- Studies at all levels of evidence, except expert opinion
- Case reports must include at least 10 patients
- Follow-up for at least 12 months
- Reported details regarding early and late implant failures
- Language: English, German

2.4 | Exclusion criteria

Studies not meeting the inclusion criteria were excluded from the review. Moreover, clinical studies investigating individually designed zirconia implants or multiple publications on the same patient population, as well as investigations based on charts, questionnaires or interviews, were excluded.

2.5 | Selection of studies

After elimination of duplicates, the reviewers (SR, MG) independently screened titles, abstracts and full-texts meeting the selection criteria. Unclear titles were included in the abstract screening. If titles or abstracts did not provide sufficient information for selection, full texts were obtained. Any disagreement with regard to inclusion and exclusion was resolved by discussion between the reviewers. To evaluate the agreement between the reviewers, Cohen's kappa coefficient (κ) was calculated for title and abstract selection (Landis & Koch, 1977).

2.6 | Data extraction and outcome measures

Data extraction by the reviewers was independently performed for all included studies (SR, MG) using data extraction tables. Disagreement with regard to data extraction was resolved by discussion. In case of missing or unclear information, the corresponding authors of the papers were contacted via email. If the information was still not sufficient for inclusion and evaluation, the study was excluded for the present review.

The timing of implant placement was classified as defined by Hammerle, Chen and Wilson (2004):

- Type 1: Immediate implant placement following tooth extraction.
- Type 2: Early implant placement after complete soft tissue healing (4–8 weeks)
- Type 3: Early implant placement after partial bone healing (12–16 weeks)
- Type 4: Late implant placement after complete bone healing (more than 16 weeks)

Implant loading protocols were classified as follows by Weber et al. (2009):

- Immediate loading: Functional loading of implants earlier than 1 week subsequent to implant placement
- Early loading: Functional loading of implants between 1 week and 2 months subsequent to implant placement
- Conventional loading: Functional loading after more than 2 months subsequent to implant placement

Implant failures were classified as follows:

- Early implant failures: Implant loss before prosthetic loading
- Late implant failures: Implant loss after prosthetic loading
- Implant fractures: Implant fracture after prosthetic loading

Technical complications were defined as abutment fracture, fracture of the implant prosthesis, chipping of the veneering ceramic and loosening of the implant prosthesis. Implant fractures were classified as an independent implant failure category and were not included in the technical complications.

The biological complications included bone loss of more than 2 mm over the observation periods, soft tissue complications (swelling, fistulas, mucositis) and peri-implantitis.

Aesthetic outcomes were evaluated using the pink aesthetic score (PES) according to Furhauser et al. (2005) or the papilla index according to Jemt (1997).

For all included clinical studies, the ongoing market clinical availability of the investigated zirconia implants was considered. Prototype zirconia implants that have never been commercially available or zirconia implant types or surface topographies that have been removed from the market while being further developed are defined in the text as "Not Commercially Available (NCA)" implants. Zirconia implant types and surface topographies that are still commercially available as investigated in the included studies are defined as "Commercially Available (CA)" implants.

From the included clinical full-text articles, the following data were extracted: author(s), year of publication, design of study (retrospective study design (RE)/prospective study design (PR)/randomized clinical trial (RCT)), number of included patients and implants, implant material (yttria-stabilized zirconia (YTZP)/alumina-toughened zirconia (ATZ),/titanium), implant design (1-piece/2-piece), implant system, implant surface treatment, surface roughness, market availability of investigated zirconia implant surface (yes/no), type of implant placement (Type 1/2/3/4), use of bone augmentation during surgery (yes/no), use of immediate temporization directly after implant placement (yes/no), immediate loading (yes/no), time period between implant

placement and final prosthetic reconstruction (weeks), type of prosthetic restoration (single crown (SC)/fixed dental partials (FDP)/removable hybrid dentures (RHD)), retention modes prosthetics (abutments and prostheses, cement-retained (CR)/screw-retained (SR)), number of implant drop outs, number of early/late implant failures and implant fractures, mean observation period (months), implant survival (%) and mean peri-implant marginal bone loss (MBL, mm). Moreover, technical and biological complications as well as results regarding soft tissue aesthetics were recorded.

Primary outcomes were implant survival and peri-implant marginal bone loss (MBL). Secondary outcomes included technical and biological complications as well as aesthetic outcomes. In addition, the influence of the time point of implant placement, implant loading protocols, temporization, simultaneous bone augmentation during implant placement, implant bulk material (YTZP or ATZ), implant design, type of prosthetic reconstruction and market respectively clinical availability of the evaluated zirconia implants as confounding factors for implant survival and MBL were analyzed.

2.7 | Statistical analysis

For survival rates as well as for MBL after an observation period of 1 year, a random-effect meta-analysis was performed. The number of implants as well as standard errors, confidence intervals and weights depending on the final number of implants was included in the statistical analysis with regard to the estimation of survival rates. The amount of heterogeneity across studies was assessed with the I^2 measure (Higgins, Thompson, Deeks, & Altman, 2003). Unfortunately, not all studies reported confidence intervals, standard deviations or standard errors. To include these studies in the meta-analyses, standard errors where imputed by means of the reported standard errors and calculated standard errors from studies reporting either confidence intervals or standard deviations.

Forest plots were used for graphical presentations of the survival rates and MBL values in each study with confidence intervals and the weights given to each study in the meta-analyses, along with the overall pooled prevalence. In the graphs, the weight of each study included in the meta-analyses is represented by the area of a box with a center representing the size of the effect estimated from that study. The confidence intervals for the effect from each study are also shown. The summary effect is indicated by the middle of a diamond with left and right extremes representing the corresponding confidence interval.

In cases of evidence of heterogeneity in implant survival and MBL between studies, meta-regressions were used to analyze associations between survival and MBL and study characteristics. The estimated effects yielded evidence for the effects of time point of implant placement, implant loading protocols, temporization, simultaneous bone augmentation during implant placement, implant design, type of zirconia implant bulk material, type of prosthetic reconstruction and market clinical availability on survival and MBL. Both meta-analyses and meta-regressions were performed using STATA statistical software version 15.0 (StataCorp LLC, College Station, USA).

3 | RESULTS

The electronic database search resulted in 2,758 publications (Pubmed: 2304; Embase: 454, Figure 1). After removal of duplicates, 941 titles were available, and 2 additional studies were included after hand searching. Thus, the reviewers screened a total of 943 titles. The inter-examiner agreement for title selection was $\kappa = 0.9$, resulting in 264 abstracts for further evaluation. After screening the abstracts, a total of 80 publications were selected for full-text evaluation (inter-examiner agreement $\kappa = 0.8$). After analysis of the included full-text articles, a total of 18 clinical studies fulfilled the inclusion criteria and were included in the qualitative and quantitative analyses (Figure 1, Tables 1–4). Sixty-two reports had to be excluded (Table 5).

3.1 | Study characteristics

Of the 18 clinical studies that were included in the analysis (Tables 1–3), only 3 were prospective randomized clinical trials (RCT) that compared titanium ($n = 71$) and zirconia ($n = 89$, (Osman et al., 2014; Payer et al., 2015)) or immediately ($n = 20$) and conventionally ($n = 20$) loaded zirconia implants (Cannizzaro, Torchio, Felice, Leone, & Esposito, 2010). Fifteen publications reported observational studies. Of those, 11 were prospectively and 4 retrospectively designed (Table 1).

Most of the studies ($n = 14$) investigated 1-piece zirconia implants. Only 4 publications examined 2-piece zirconia implant systems (Table 1). When 2-piece implants were investigated, abutments as well as prosthetics were cement-retained (Table 2). With regard to zirconia implant diameter, the values ranged from 3.25 to 5.5 mm. Implant placement was performed immediately after tooth extraction (type 1), after soft tissue (type 2) or osseous healing (types 3 and 4, Table 2). In addition, immediate (2 studies) and conventional loading (16 studies) were applied (Table 2). Interestingly, 4 studies allowed early loading only for implants placed in the mandible, whereas conventional loading was applied for the maxilla (Jung et al., 2016; Spies, Balmer, Patzelt, Vach, & Kohal, 2015; Kohal, Knauf, Larsson, Sahlin, & Butz, 2012; Kohal, Patzelt, Butz, & Sahlin, 2013). The reported time periods between implant placement and installation of the final prosthetic reconstructions ranged between 6 and 30 weeks. Moreover, 14 studies allowed simultaneous bone regeneration during implant placement (Table 2). With regard to prosthetic reconstructions, the investigated implants were exclusively restored with SCs (10 studies, 452 implants), with SCs or FDPs (5 studies, 386 implants), exclusively with RHDs (1 study, 73 implants) or FDPs (1 study, 56 implants) and with SCs, FDPs, or RHDs (1 study, 161 implants, Table 2). Unfortunately, not every study provided detailed information regarding the implant diameter and distribution, type of implant placement and prosthetic reconstructions. Specific information in terms of the implant design was available for 17 studies investigating 890 1-piece and 117 2-piece zirconia implants (Table 1). In addition, 1 study investigated 121 1- and 2-piece zirconia implants. However, the authors did not provide detailed information regarding

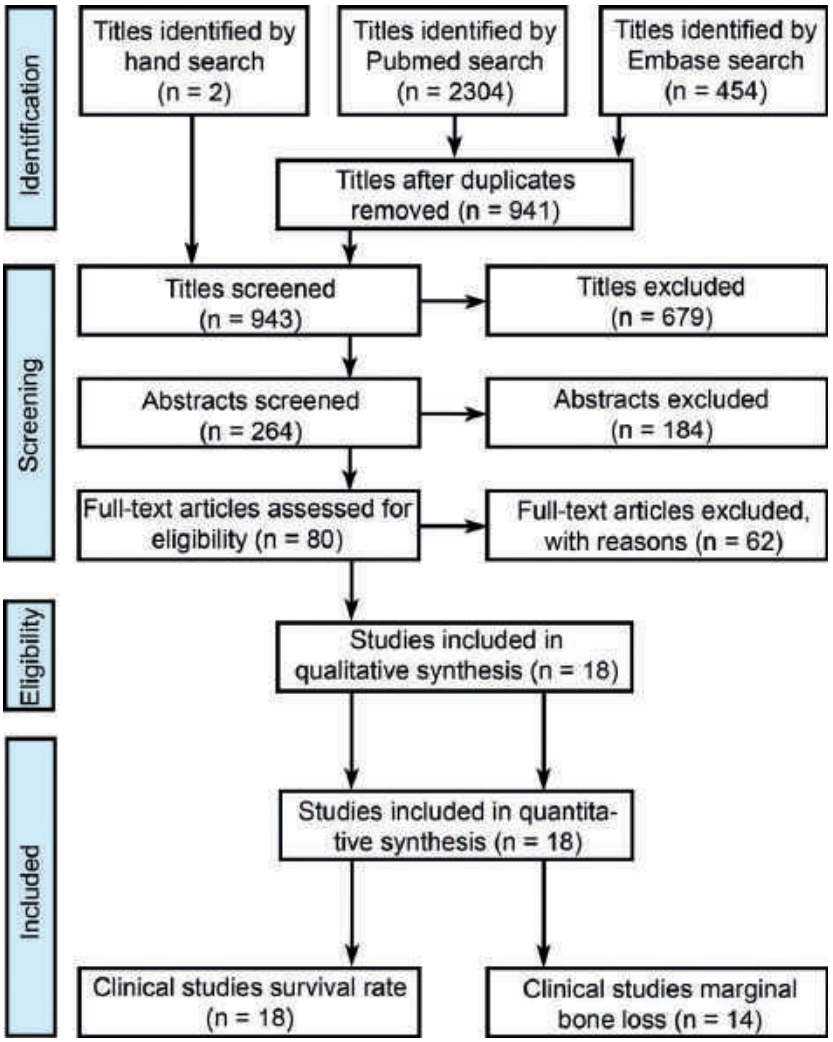

FIGURE 1 Search strategy and selection process for the included studies

the exact implant distribution (Brull, van Winkelhoff, & Cune, 2014). The evaluated zirconia implants were placed in a university setting (718 implants), in a private practice (334 implants) or in a multicenter setting consisting of university and private practice (76 implants, Table 1).

In 18 studies, 11 different zirconia implant types from 10 companies were evaluated. However, only 9 publications provided results for 5 types of CA zirconia implant surfaces: Zircon Vision: ZV 3, Straumann: PURE Ceramic Implant, Vita Zahnfabrik: Vitaclinical ceramic.implant, Bredent: Whitesky, Metoxit AG: Ziraldent (Table 1).

3.2 | Implant survival

Considering all included studies, data from 1,128 zirconia implants and 741 patients were included in the present review with regard to implant survival. A total of 21 patients (2.8%) and 55 zirconia implants (4.9%) were reported as dropouts (Table 3). Overall, 44 implants were reported as early failures (3.9%), 19 implants as late failures (1.7%) and 22 implants as fractures (2.0%). Thus, 7.5% of all investigated implants failed. Six studies provided detailed information regarding reasons for early and late implant failures. Interestingly, in the latter studies, implant mobility without any clinical signs of infection was reported as a reason for early and late failures (Brull et al., 2014; Cannizzaro et al., 2010; Cionca, Muller, & Mombelli, 2015; Kohal et al., 2012, 2013; Roehling et al., 2016).

3.2.1 | NCA zirconia implants

Nine studies reporting data on 618 implants and 343 patients were included (Table 1). The survival rates ranged between 71.2% and 100% for an overall mean observation period of 6 years (range 12–71 months, Table 3). Overall, 11.8% (73 implants) zirconia implants failed (5.8% early failures (36 implants), 2.6% late failures (16 implants), 3.4% fractures (21 implants)).

Two randomized clinical trials directly compared the clinical performance of titanium and zirconia implants. In detail, Payer et al. (2015) investigated 2-piece zirconia and 2-piece titanium implants with cement-retained SCs. Thirty months after implant placement, survival rates of 93.3% and 100% were reported, respectively. In addition to that, Osman et al. (2014) stabilized RHDs on 73 1-piece zirconia and 56 titanium implants in 24 edentulous patients.

TABLE 1 Clinical studies investigating implant survival. Impl: Implants; Impl. Design: Implant Design, 1: 1-piece implant design; 2: 2-piece implant design; Univ.: University; Priv. pract.: Private practice; Ti: Titanium; YTZP: yttria-stabilized zirconia; ATZ: alumina-toughened zirconia; PR: prospective study design; RE: retrospective study design; RCT: randomized clinical trial; NR: not reported

Author/year	Study design	Patients (n)	Impl. (n)	Material	Impl. design	Setting	Company/Implant type	Surface treatment	Surface roughness (µm)
Hollander et al. (2016)	RE	38	106	YTZP	1	Univ.	Z-Systems/Z-Look3	Sandblasting	0.5 < Ra < 3–5
Roehling et al. (2016)	RE	71	161	YTZP	1	Priv. pract.	Z-Systems/Z-Look3	Sandblasting	0.5 < Ra < 3–5
Cionca et al. (2015)	PR	32	49	ATZ	2	Univ.	Dentalpoint/Zeramex T (ZERAFIL 3)	Sandblasting, acid etching	NR
Mellinghoff et al. (2015)	RE	23	51	YTZP	1	Priv. pract.	Z-Systems/Z-Look3 Evo	Sandblasting	0.5 < Ra < 3–5
Payer et al. (2015)	RCT	22	16	YTZP	2	Univ.	Ziterion/Vario z	Sandblasting	NR
			15	Ti	2		Ziterion, Vario t	Sandblasting, Bonit® coating	NR
Osman et al. (2014)	RCT	12	73	YTZP	1	Univ.	Southern Implants	Acid etching	Ra 1–2
		12	56	Ti	1		Southern Implants	Sandblasting, acid etching	Ra 1–2
Kohal et al. (2013)	PR	28	56	YTZP	1	Univ.	Nobel Biocare/ZiUnite	Sintering with rough pore former	Sa 1.24
Kohal et al. (2012)	PR	65	66	YTZP	1	Univ.	Nobel Biocare/ZiUnite	Sintering with rough pore former	Sa 1.24
Cannizzaro et al. (2010)	RCT	20	20	YTZP	1	Priv. pract.	Z-Systems/Z-Look3	Sandblasting	0.5 < Ra < 3–5
		20	20	YTZP	1		Z-Systems/Z-Look3	Sandblasting	0.5 < Ra < 3–5
Becker et al. (2017)	PR	52	52	YTZP	2	Univ.	Zircon Vision/ZV3	Air particle abrading, sintering	Ra 7.0
Kniha et al. (2017)	PR	62	66	YTZP	1	Priv. pract.	Straumann/PURE Ceramic Implant	Sandblasting, acid etching	Sa 0.70
		16	16	YTZP	1		Straumann/PURE Ceramic Implant	Sandblasting, acid etching	Sa 0.70
Gahlert et al. (2016)	PR	44	44	YTZP	1	Priv. pract. and Univ.	Straumann/PURE Ceramic Implant	Sandblasting, acid etching	Sa 0.70
Jung et al. (2016)	PR	60	71	YTZP	1		Vita Zahnfabrik/ceramic. implant	Sandblasting, acid etching	Ra 1.2
Grassi et al. (2015);	PR	17	16	YTZP	1	Priv. pract.	Bredent/WhiteSky	Sandblasting	Sa 1.17
		17	16	YTZP	1	and Univ.	Bredent/WhiteSky	Sandblasting	Sa 1.17
Spies, Balmer, et al. (2015)	PR	40	53	ATZ	1	Univ.	Metoxit AG/Ziraldent FR 1	Sintering with pore-building polymers	Ra 1.8
Brull et al. (2014)	RE	74	121	YTZP	1, 2	Univ.	Zircon Vision/ZV 3	Air particle abrading, sintering	Ra 7.0
Borgonovo, Censi, et al. (2013)	PR	13	35	YTZP	1	Univ.	Bredent/WhiteSky	Sandblasting	Ra 0.9–1.0
Payer et al. (2013)	PR	20	20	YTZP	1	Univ.	Bredent/WhiteSky	Sandblasting	Sa 1.17

Yellow background: NCA zirconia implants.
White background: CA zirconia implants.

TABLE 2 Clinical studies investigating implant survival. Ti: Titanium; YTZP: yttria-stabilized zirconia; ATZ: alumina-toughened zirconia; SC: single crowns; FDP: fixed dental partials; RHD: removable hybrid denture; CR: cement-retained; SR: screw-retained; RM: removable

Author/year	Material	Type implant placement	Simultaneous bone augmentation	Immediate temporization	Immediate loading	Time period placement – final reconstruction (weeks)	Prosthetics	Retention modes prosthetics (abutments/prostheses)
Hollander et al. (2016)	YTZP	NR	NR	No	No	Maxilla: 24 Mandible: 16	SC, FDP	–/CR; –/CR
Roehling et al. (2016)	YTZP	2,3,4	Yes	No	No	12	SC, FDP, RHD	–/CR; –/CR; –/RM
Cionca et al. (2015)	ATZ	3,4	Yes	No	No	12	SC	CR/CR
Mellinghoff et al. (2015)	YTZP	NR	No	No	No	Maxilla: 24 Mandible: 12	SC	–/CR
Payer et al. (2015)	YTZP	4	No	No	No	Maxilla: 24 Mandible: 16	SC	CR/CR
	Ti	4	No	No	No	Maxilla: 24 Mandible: 16	SC	SR/CR
Osman et al. (2014)	YTZP	4	Yes	Yes	No	16	RHD	–/RM
	Ti	4	Yes	Yes	No	16	RHD	–/RM
Kohal et al. (2013)	YTZP	1,2,3,4	Yes	Yes	No	Maxilla: 14 Mandible: 6	FDP	–/CR
Kohal et al. (2012)	YTZP	1,2,3,4	Yes	Yes	No	Maxilla: 14 Mandible: 6	SC	–/CR
Cannizzaro et al. (2010)	YTZP	1,2,3,4	Yes	Yes	Yes	18	SC	–/CR
	YTZP	1,2,3,4	Yes	Yes	No	18	SC	–/CR
Becker et al. (2017)	YTZP	2,3,4	Yes	No	No	Maxilla: 12 Mandible: 10	SC	CR/CR
Kniha et al. (2017)	YTZP	3,4	Yes	No	No	12	SC	–/CR
	YTZP	1	Yes	Yes	No	12	SC	–/CR
Gahlert et al. (2016)	YTZP	2,3,4	Yes	No	No	26	SC	–/CR
Jung et al. (2016)	YTZP	NR	Yes	Yes	No	Maxilla:16 Mandible: 8	SC, FDP	–/CR; –/CR
Grassi et al. (2015)	YTZP	1	Yes	Yes	Yes	14	SC	–/CR
	YTZP	4	Yes	Yes	Yes	14	SC	–/CR
Spies, Balmer, et al. (2015)	ATZ	1,2,3,4	Yes	Yes	No	Maxilla: 14 Mandible: 6	SC, FDP	–/CR; –/CR
Brull et al. (2014)	YTZP	1,2,3,4	Yes	No	No	18.4	SC, FDP	CR/CR; CR/CR
Borgonovo, Censi, et al. (2013)	YTZP	NR	Yes	Yes	No	24	SC, FDP	–/CR; –/CR
Payer et al. (2013)	YTZP	3,4	No	Yes	No	16	SC	–/CR

Yellow background: NCA zirconia implants.
White background: CA zirconia implants.

TABLE 3 Clinical studies investigating implant survival. Impl: Implants; Ti: Titanium; YTZP: yttria-stabilized zirconia; ATZ: alumina-toughened zirconia; NR: not reported

Author/year	Impl. (*n*)	Material	Follow-up after placement (months)	Drop Outs Implants (*n*)	Early failures (*n*)	Late failures (*n*)	Fractures (*n*)	Survival rate (%)	Mean MBL (mm)
Hollander et al. (2016)	106	YTZP	14.25	–	0	0	0	100	NR
Roehling et al. (2016)	161	YTZP	71.28	–	14	4	18	77.3	0.97 ± 0.07
Cionca et al. (2015)	49	ATZ	19.32	2	1	5	0	87.3	≤1
Mellinghoff et al. (2015)	51	YTZP	29.08	0	0	0	0	100	0.63 ± 0.94
Payer et al. (2015)	16	YTZP	30	0	0	1	0	93.3	1.38 ± 0.86
	15	Ti	30	0	0	0	0	100	1.27 ± 0.43
Osman et al. (2014)	73	YTZP	16	7	12	6	3	71.2	0.42 ± 0.4
	56	Ti	16	27	2	8	0	82.1	0.18 ± 0.47
Kohal et al. (2013)	56	YTZP	12	0	1	0	0	98.2	1.95 ± 1.71
Kohal et al. (2012)	66	YTZP	12	1	3	0	0	95.4	1.31 ± 1.49
Cannizzaro et al. (2010);	20	YTZP	12	0	3	0	0	85	0.9 ± 0.48
	20	YTZP	12	0	2	0	0	90	0.72 ± 0.59
Becker et al. (2017)	52	YTZP	24	4	0	2	0	95.8	NR
Kniha et al. (2017)	66	YTZP	15	0	0	0	0	100	NR
	16	YTZP	15	0	0	0	0	100	NR
Gahlert et al. (2016)	44	YTZP	12	2	1	0	0	97.6	1.02 ± 0.9
Jung et al. (2016)	71	YTZP	16	3	1	0	0	98.6	0.78 ± 0.79
Grassi et al. (2015)	16	YTZP	61.2	1	1	0	0	93.3	1.29 ± 0.25
	16	YTZP	61.2	0	0	0	0	100	1.17 ± 0.33
Spies, Balmer, et al. (2015)	53	ATZ	36	1	3	0	0	94.2	0.79 ± 0.67
Brull et al. (2014)	121	YTZP	18.4	–	1	1	1	96.5	0.13 ± 0.6
Borgonovo, Censi, et al., 2013	35	YTZP	48	7	0	0	0	100	1.63
Payer et al. (2013)	20	YTZP	24	0	1	0	0	95	1.29 ± 1

Yellow background: NCA zirconia implants.
White background: CA zirconia implants.

TABLE 4 Technical and biological complications. Impl: Implants; NA: not applicable due to 1-piece implant design; NR: not reported

Author/year	Impl. (*n*)	Chipping (*n*)	Decementation (*n*)	Abutment fracture (*n*)	Bone loss >2 mm (*n*)	Soft tissue complications (*n*)	Peri-implantitis (*n*)
Hollander et al. (2016)	106	NR	NR	NA	NR	0	0
Roehling et al. (2016)	161	NR	NR	NA	0	0	0
Cionca et al. (2015)	49	0	0	2	0	0	0
Mellinghoff et al. (2015)	51	3	0	NA	0	NR	0
Payer et al. (2015)	31	NR	NR	NR	0	NR	0
Osman et al. (2014)	129	NR	NR	NA	0	NR	0
Kohal et al. (2013)	56	NR	NR	NA	22	0	0
Kohal et al. (2012)	66	NR	NR	NA	27	0	0
Cannizzaro et al. (2010)	40	1	1	NA	0	1	0
Becker et al. (2017)	52	0	0	1	NR	NR	18
Gahlert et al. (2016)	44	NR	NR	NA	0	NR	0
Jung et al. (2016)	71	0	0	NA	0	0	0
Grassi et al. (2015)	32	NR	NR	NA	0	0	0
Spies, Balmer, et al. (2015)	53	NR	NR	NA	0	0	0
Brull et al. (2014)	121	NR	NR	NR	0	0	0
Borgonovo, Censi, et al. (2013)	35	NR	NR	NA	0	0	0
Payer et al. (2013)	20	NR	NR	NA	0	NR	0

Yellow background: NCA zirconia implants.
White background: CA zirconia implants.

However, the authors used a novel, unestablished surgical protocol combining alveolar and palatal implants in the maxilla. Thus, 16 months after implant placement, survival rates 82.1% for titanium and of 71.2% for zirconia were observed. Additionally, when comparing different loading protocols for 1-piece zirconia implants restored with cement-retained SCs, decreased survival rates were reported for immediately (85%) compared to conventionally loaded (90%) implants at 12 months after placement (Cannizzaro et al., 2010).

Considering NCA zirconia implants, the meta-analysis estimated a 1-year zirconia implant survival rate of 91.2% (CI 85.7–96.6). For the included studies, a high degree of heterogeneity was evaluated (I^2 = 96.4%, p < 0.01, Figure 2).

3.2.2 | CA zirconia implants

A total of 510 zirconia implants and 398 patients were investigated in 9 studies (Table 1). The reported survival rates ranged from 93.3% to 100% for mean follow-up periods between 12 and 61.20 months (5.10 years, Table 3). Overall, 12 implants (2.4%) failed (early failures: 8 implants (1.6%), late failures: 3 implants (0.6%), fractures: 1 implant (0.2%)).

Two prospective observational studies evaluated different surgical protocols. In detail, Grassi et al., 2015 investigated the clinical performance of immediately loaded 1-piece zirconia implants restored with cement-retained SCs either placed in postextraction (type 1) or in healed sites (type 4). The authors reported 1 early failure only in the

TABLE 5 Excluded studies

Reason for exclusion	Number	Studies
Studies investigating alumina dental implants	2	Pigot, Dubruille, Dubruille, Mercier, and Cohen (1997), Stuge and Ellingsen (1991)
Review articles	19	Andreiotelli, Wenz, et al. (2009), Apratim et al. (2015), Buser, Sennerby, and De Bruyn (2017), Chen, Moussi, Drury, and Wataha (2016), Depprich et al. (2014), Elnayef et al. (2017), Hashim et al. (2016), Hisbergues, Vendeville, and Vendeville (2009), Hobkirk and Wiskott (2009), Kohal, Att, Bächle, Butz, and Author (2008), Kumar, Jain, Jayesh, Parthasaradhi, and Venkatakrishnan (2015), Ozkurt and Kazazoglu (2011), Özkurt and Kazazoğlu (2010), Pieralli et al. (2017), Prithviraj, Deeksha, Regish, and Anoop (2012), Regish, Sharma, and Prithviraj (2013), Van Dooren et al. (2012), Vohra et al. (2015), Wenz, Bartsch, Wolfart, and Kern (2008)
Case reports/case series of less than 10 patients	12	Arnetzl et al. (2010), Aydin, Yilmaz, and Ata (2010), Aydin, Yilmaz, and Bankoglu (2013), Bankoglu Gungor, Aydin, Yilmaz, and Gul (2014), Borgonovo, Boninsegna, Dolci, Ghirlanda, and Censi (2010b), Kohal and Klaus (2004), Mehra and Vahidi (2014), Oliva, Oliva, and Oliva (2008a,b, 2010b), Parmigiani-Izquierdo, Cabana-Munoz, Merino, and Sanchez-Perez (2017), Sierraalta and Razzoog (2009)
Clinical studies investigating root shaped, individually designed zirconia implants	6	Nair, Prithviraj, Regish, and Prithvi (2013), Patankar, Kshirsagar, Patankar, and Pawar (2016), Pirker and Kocher (2008, 2009, 2011), Pirker, Wiedemann, Lidauer, and Kocher (2011)
Clinical studies: Multiple publications on the same patient population	14	Borgonovo et al. (2011), Borgonovo, Arnaboldi, Censi, Dolci, and Santoro (2010), Borgonovo et al. (2015), Borgonovo, Corrocher, et al. (2013) Borgonovo, Fabbri, Vavassori, Censi, and Maiorana (2012), Borgonovo, Vavassori, et al. (2013), Gahlert, Burtscher, et al. (2012); Gahlert et al. (2013), Kniha et al. (2016), Oliva, Oliva, and Oliva (2007), Osman and Ma (2014), Osman, Payne, Duncan, and Ma (2013), Siddiqi, Kieser, De Silva, Thomson, and Duncan (2015), Spies, Sperlich, Fleiner, Stampf, and Kohal (2016b)
Clinical studies only investigating prosthetic outcomes and not zirconia implant survival	4	Spies, Kohal, Balmer, Vach, and Jung (2017), Spies, Patzelt, Vach, and Kohal (2016), Spies, Stampf, and Kohal (2015), Spies, Witkowski, Butz, Vach, and Kohal (2016)
Data not clear for evaluation	4	Blaschke and Volz (2006), Lambrich and Iglhaut (2008), Mellinghoff (2006), Oliva, Oliva, and Oliva (2010a)
Publications based on charts, questionnaires or interviews	1	Jank and Hochgatterer (2016)

postextraction group. Thus, after a mean follow-up period of more than 5 years after placement (mean 61.2 months), survival rates of 93.3% and 100% were evaluated for type 1 and type 4 implant placement, respectively (Grassi et al., 2015). In contrast, equivalent survival rates (100%) were reported 15 months after implant placement for 1-piece zirconia implants restored with cement-retained SCs when type 1 or type 3 and 4 implant placements were applied (Kniha et al., 2017).

When considering CA zirconia implants, the meta-analysis estimated a 1-year survival rate of 98.3% (CI 97.0–99.6). For the evaluated studies, a moderate degree of heterogeneity was estimated (I^2 = 52.7%, p = 0.02, Figure 2). CA zirconia implants showed statistically significantly increased implant survival rates compared with NCA zirconia implants (p = 0.028).

The meta-regression for CA zirconia implants showed that type 1 implant placement, immediate temporization, immediate loading and simultaneous bone augmentation procedures did not have any significant effect on the reported 1-year survival rates (p > 0.05, Figure 3). Moreover, studies that evaluated SCs and FDPs showed similar survival rates compared to studies exclusively investigating SCs (p > 0.05, Figure 4). Interestingly, the meta-regression estimated higher survival rates for YTZP compared with ATZ and for 1-piece compared with 2-piece zirconia implants. However, these differences were not statistically significant (p > 0.05, Figure 3).

For a reduced number of studies reporting data for 192 implants and 159 patients, a 2-year meta-analysis could be performed (Becker et al., 2017; Borgonovo, Censi, et al., 2013; Grassi et al., 2015; Payer et al., 2013; Spies, Balmer, et al., 2015). A mean 2-year survival rate of 97.2% (CI 94.7–99.7) and a moderate degree of heterogeneity (I^2 = 58.0%, p = 0.036) was estimated (Figure 4). In addition, the meta-regression showed that the confounding factors did not have any significant effect on the survival rates (p > 0.05, Figure 5).

3.3 | Peri-implant marginal bone loss

Fourteen studies investigating 839 zirconia implants and 558 patients reported detailed marginal bone loss evaluations between implant placement and follow-ups (Table 3). Two studies had to be excluded from the 1-year MBL analysis as only panoramic radiographs were evaluated (Roehling et al., 2016) or detailed MBL values were only provided after 2 years of investigation (Mellinghoff, Cacaci, & Detsch, 2015). Thus, 12 studies evaluating periapical radiographs could be included in the 1-year meta-analysis (Figure 6).

3.3.1 | NCA zirconia implants

Data from 251 implants and 273 patients were available. The meta-analysis evaluation estimated a mean 1-year marginal bone loss

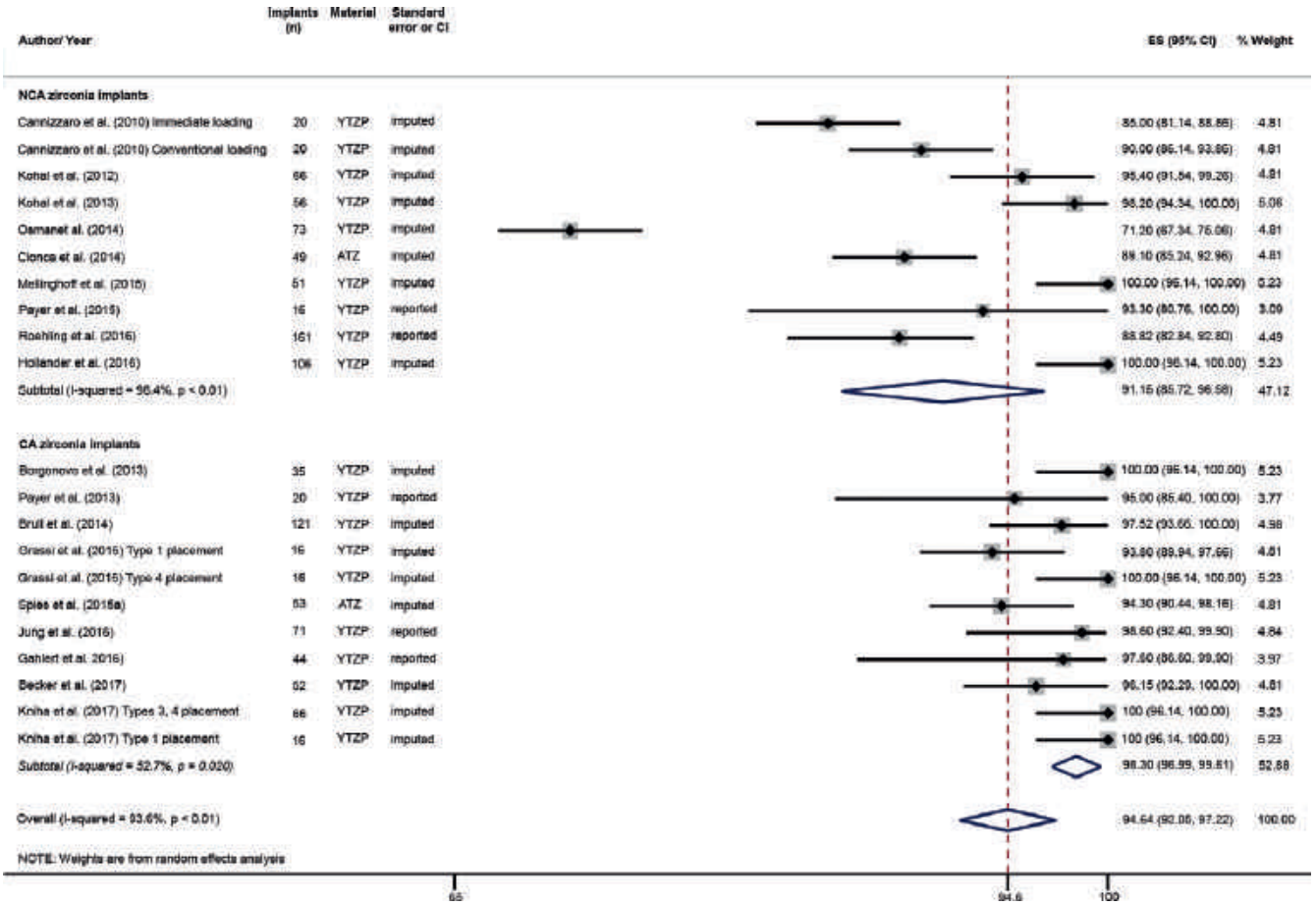

FIGURE 2 Forest plot of 1-year survival of NCA and CA zirconia implants. Significantly increased survival rates for CA compared with NCA zirconia implants ($p = 0.028$)

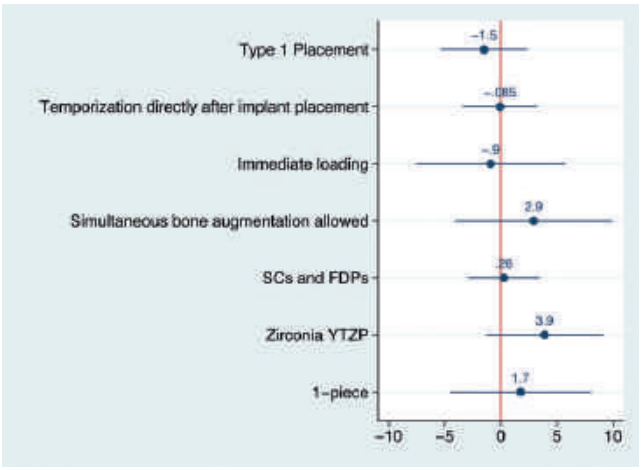

FIGURE 3 Effects of single factors on 1-year survival of CA zirconia implants. Illustrated are the estimated coefficients, including 95% confidence intervals. Coefficients >0 imply a positive effect on survival and coefficients <0 a negative effect on survival. All single 95% confidence intervals crossing the zero line imply no significant effect on implant survival

of 1.0 mm (CI 0.6–1.3). A high degree of heterogeneity was noted across the studies ($I^2 = 93.2\%$, $p < 0.01$, Figure 6).

3.3.2 | CA zirconia implants

Overall, data from 376 implants and 285 patients were available. The evaluated mean 1-year marginal bone loss was 0.7 mm (CI 0.4–1.0). Again, a high degree of heterogeneity was found between the studies ($I^2 = 95.9\%$, $p < 0.01$, Figure 6). The difference between NCA and CA zirconia implants was statistically not significant ($p = 0.28$).

The meta-regression for CA zirconia implants revealed that the type of implant placement, simultaneous bone augmentation procedures during implant placement, zirconia implant material and implant design did not have any significant effect on MBL ($p > 0.05$, Figure 5). Interestingly, temporization directly after implant placement and immediate implant loading were associated with increased MBL. However, these differences were not statistically significant ($p > 0.05$, Figure 7).

3.4 | Technical complications

Only 5 of 18 included studies investigating 263 implants (140 × NCA zirconia implants, 123 × CA zirconia implants) after follow-up periods between 12 and 24 months provided information with regard to technical complications or prosthetic outcomes, excluding implant fractures (Becker et al., 2017; Cannizzaro et al., 2010; Cionca et al., 2015; Jung et al., 2016; Mellinghoff et al., 2015). Taking both

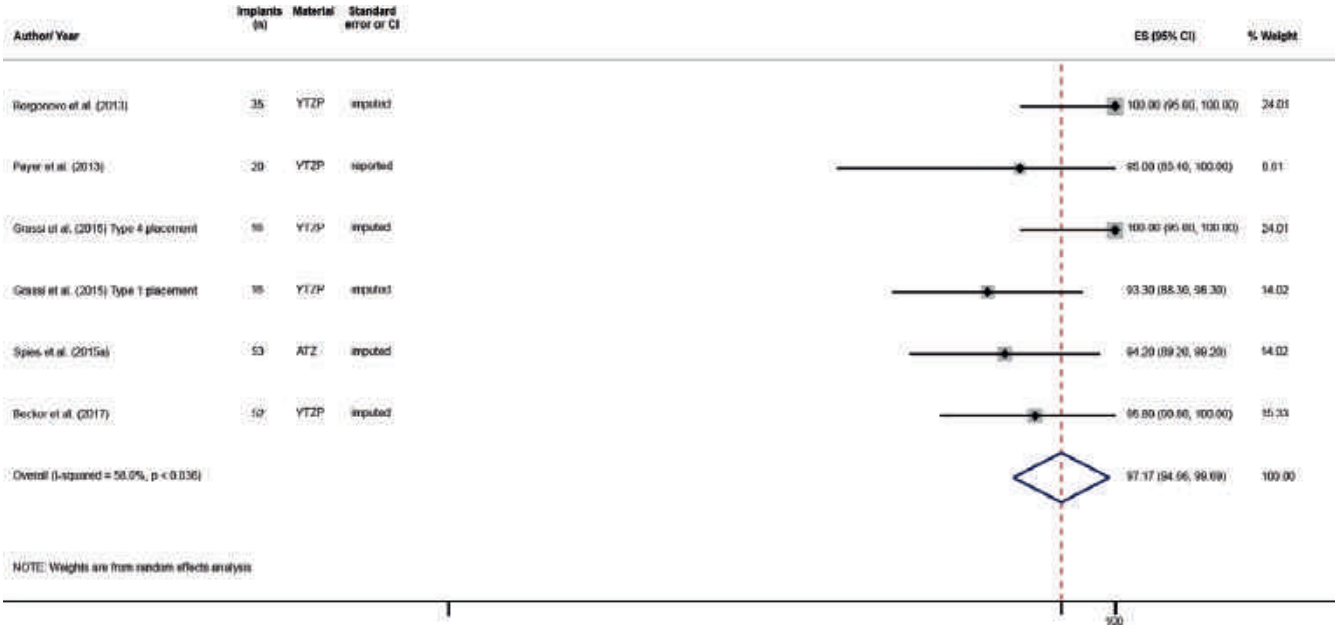

FIGURE 4 Forest plot of the 2-year survival of CA zirconia implants

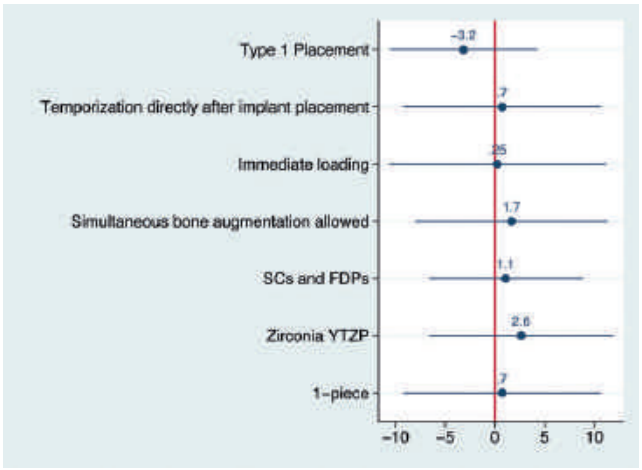

FIGURE 5 Effects of single factors on the 2-year survival of CA zirconia implants. Illustrated are the estimated coefficients, including 95% confidence intervals. Coefficients >0 imply a positive effect on survival and coefficients <0 a negative effect on survival. All single 95% confidence intervals crossing the zero line imply no significant effect on implant survival

types of implant generations together (NCA and CA zirconia implants), an overall complication rate of 3.4% was evaluated.

3.4.1 | NCA zirconia implants

When technical complications were observed for 1-piece zirconia implants restored with cement-retained SCs, the authors reported chipping of the veneering ceramic, fractures of the cemented crowns (4 SCs, 2.9%) or decementation (1 SC, 0.7% (Cannizzaro et al., 2010; Mellinghoff et al., 2015)). Moreover, when 2-piece zirconia implants were evaluated, 2 ATZ abutment fractures (1.4%) were observed during the functional loading period after cementation of the abutments and SCs. However, abutment fractures were not associated with zirconia implant fractures (Cionca et al., 2015). The overall technical complication rate for NCA zirconia implants was 5%.

3.4.2 | CA zirconia implants

Technical complications (1 SC chipping, fracture of the ceramic crown, 0.8%) were only reported for 2-piece zirconia implants restored with cement-retained SCs. In the same study, 1 fiberglass abutment fracture (0.8%) was observed during the loading period after cementation of the abutment and SC. Again, abutment fractures were not associated with implant fractures (Becker et al., 2017). Thus, an overall technical complication rate of 1.6% was evaluated for CA zirconia implants.

3.5 | Zirconia implant fractures

Three studies reported a total of 22 zirconia implant fractures (1.95%) in 16 patients (Tables 1 and 3).

3.5.1 | NCA zirconia implants

Twenty-one of 618 implants fractured (3.40%). Most of the fractures were observed in 1 study. In detail, Roehling et al. (2016) investigated 161 1-piece zirconia implants with different diameters after a mean follow-up of 5.9 years. The authors reported 18 fractures in 12 patients who occurred after a mean period of 15.3 months after placement. Of these 18 fractures, 15 implants had a diameter of 3.25 mm and only 3 implants had a diameter of 4.0 mm. Eleven implants were prosthetically restored with cement-retained SCs and 7 with cement-retained FDPs. Fourteen fractures were recorded in the maxilla and only 4 in the mandible. Moreover, Osman et al. (2014)

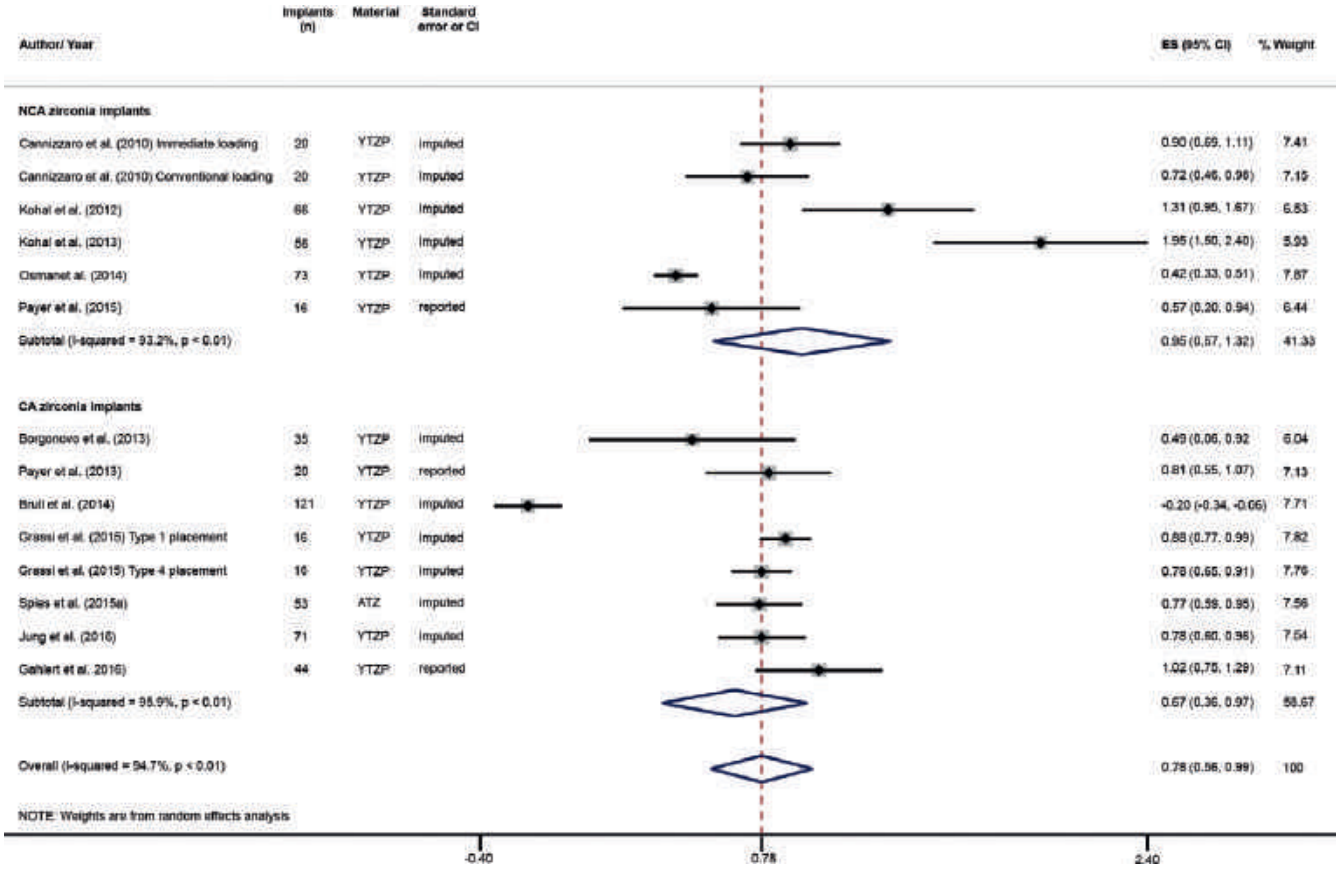

FIGURE 6 Forest plot of 1-year marginal bone loss of NCA and CA zirconia implants. No significant differences between NCA and CA zirconia implants

observed three 1-piece zirconia implant fractures in 3 patients who were restored with RHDs. Two implant fractures occurred in the maxilla and 1 in the mandible. No further information was provided with regard to the fracture details.

3.5.2 | CA zirconia implants

One of 510 zirconia implants fractured (0.20%). However, no information with regard to implant design, diameter, location and time point of implant fracture was reported (Brull et al., 2014).

3.6 | Biological complications

Overall, clinical and radiographic data from 1117 implants (689 × NCA zirconia implants, 428 × CA zirconia implants) were considered (Table 4).

3.6.1 | NCA zirconia implants

One study observed hypertrophic gingiva at 4 months after implant placement approximately 1 of 40 1-piece zirconia implants restored with cement-retained SCs (Cannizzaro et al., 2010). In addition, 2 studies investigating 1-piece zirconia implants evaluated marginal bone loss of more than 2 mm within the first year after

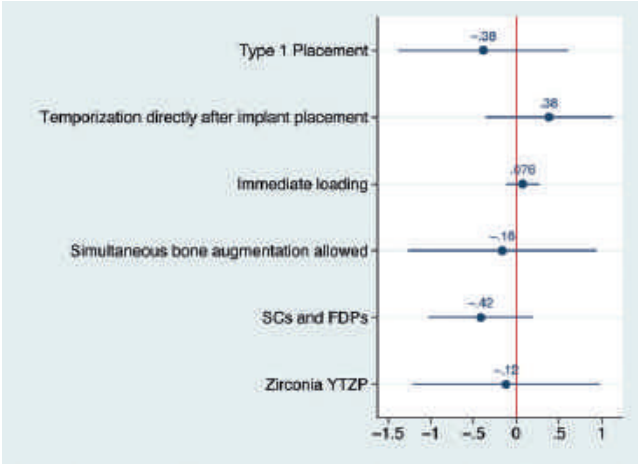

FIGURE 7 Effects of single factors on 1-year MBL of CA zirconia implants. Illustrated are the estimated coefficients, including 95% confidence intervals. Coefficients >0 imply an increase in MBL and coefficients <0 a decrease in MBL. All single 95% confidence intervals crossing the zero line imply no significant effect on MBL

implant placement for 41% and 39% of the investigated implants restored with cement-retained SCs and FDPs, respectively (Kohal et al., 2012, 2013). Overall, the incidence of biological complications was 7.3%.

3.6.2 | CA zirconia implants

One study reported "initial peri-implantitis" between 12 and 24 months after implant placement approximately 18 (37.5%) of 48 investigated 2-piece zirconia implants restored with cement-retained SCs. However, MBL analyses were not provided (Becker et al., 2017). Thus, an overall incidence of 4.2% was evaluated for biological complications.

3.7 | Aesthetic outcomes

Soft tissue outcomes were evaluated for 1- as well as for 2-piece zirconia implants restored with cement-retained SCs.

3.7.1 | NCA zirconia implants

A prospective RCT investigated 2-piece implants and directly compared titanium implants (restored with titanium abutments and ceramic crowns) to zirconia implants (restored with zirconia abutments and ceramic crowns). At baseline, after 6, 12, 18 and 24 months after crown cementation, PES scores of 2.4, 6.5, 9.0, 8.1 and 10.8, respectively, were reported for titanium. In contrast, zirconia implants showed significantly increased PES values of 6.9, 8.0, 10.3, 11.0 and 11.2 at corresponding time points (Payer et al., 2015). Another study observed that 69.8% of the placed 1-piece zirconia implants showed papilla scores of 2 and 3 according to Jemt after a mean follow-up period of 14.25 months (Hollander et al., 2016).

3.7.2 | CA zirconia implants

A prospective observational study investigated twenty 1-piece zirconia implants. PES scores of 8.1, 9.0 and 10.0 were reported at crown cementation, 12 and 24 months after implant placement. However, this increase was not statistically significant (Payer et al., 2013). When using the papilla index according to Jemt, a significant increase in papilla growth within the course of the investigation has been reported for 1-piece zirconia implants. In detail, only 17% of the papillae revealed indices of 2 and 3 at crown cementation, whereas 3 years after implant placement, this distribution significantly increased up to 56% (Spies, Balmer, et al., 2015).

4 | DISCUSSION

Implant survival was evaluated as one of the primary outcomes. Regarding NCA zirconia implants, the reported survival rates widely ranged between 71.2% and 100%, whereas the estimated mean 1-year survival rate was 91.15% (Table 4, Figure 2). Studies evaluating low overall survival rates of less than 80% observed high early implant failure and fracture rates (Osman et al., 2014; Roehling et al., 2016). CA zirconia implants showed less variation with regard to the reported survival rates (93.3%–100%) and a statistically significantly increased estimated mean 1-year survival rate (98.3%) compared with NCA zirconia implants ($p = 0.028$). In detail, more early and late failures as well as a higher implant fracture rate was evaluated for NCA (5.8% early failures, 2.6% late failures, 3.4% fractures) compared with CA implants (1.6% early failures, 0.6% late failures, 0.2% fractures). Interestingly, comparable values were reported for both generations of zirconia implants with regard to the reported quantitative surface characteristics (NCA: Ra: 0.5–5 μm; Sa: 1.24 μm; CA: Ra: 0.9–7.0 μm, Sa: 0.7–1.17 μm, Table 2). Consequently, the significantly improved survival rates might not just be attributed to increased quantitative surface roughness characteristics, but mainly to the 17 times higher fracture incidence for NCA zirconia implants compared with CA zirconia implants. However, it must be noticed that a comparison of single surface roughness parameters reported in different studies is not reasonable as standards and techniques for the used surface metrologies vary, and a successful osseointegration is not exclusively linked to one particular surface roughness feature (Jarmar et al., 2008; Wennerberg & Albrektsson, 2010). In addition to quantitative surface roughness, the morphological micro-textures and the surface treatment procedures are of high relevance for the osseous integration of zirconia implants, as experimental studies have reported that sandblasted and acid-etched zirconia implants with a surface roughness of 0.6 μm show similar bone-to-implant contact and removal torque out values compared with sandblasted and acid-etched titanium implants with a surface roughness of 1.2 μm (Bormann et al., 2012; Gahlert et al., 2009; Gahlert, Burtscher, et al., 2012; Gahlert, Roehling, et al., 2012).

When detailed information regarding early and late implant failures was provided, the authors reported that the suddenly noted implant mobility was not accompanied by any clinical signs of infection for cement-retained SCs on 2-piece implants (Cionca et al., 2015) and for cement-retained SCs and FDPs on 1-piece implants (Kohal et al., 2012, 2013; Roehling et al., 2016). Cionca et al., 2015 described these observations as "aseptic loosening", a term that was initially used in orthopedic total hip replacement surgery. The authors of the latter studies concluded that not bacterial infections but rather disintegration or premature loading may have caused the implant failures (Cionca et al., 2015; Kohal et al., 2012, 2013; Roehling et al., 2016). These findings are in contrast to results obtained for titanium implants showing that the main reasons for early implant failure were peri-implant inflammation, followed by failure of osseointegration (Han, Kim, & Han, 2014). The presently evaluated mean 1- and 2-year survival rates of 98.30% and 97.2%, respectively, for CA zirconia implants are comparable to data reported in systematic reviews on titanium implants, describing mean 1-year survival rates ranging from 96.8% to 99.5% (Benic, Mir-Mari, & Hammerle, 2014; Chambrone, Shibli, Mercurio, Cardoso, & Preshaw, 2015; Karl & Albrektsson, 2017). Previously, meta-analyses investigating zirconia implants reported 1-year survival rates of 92% (Hashim et al., 2016) and 95.6% (Pieralli et al., 2017), which are inferior compared with the presently evaluated survival rates for CA zirconia implants. However, both latter reviews evaluated overall survival rates that combined NCA and CA zirconia implants.

Based on the clinical relevance and significant impact on implant survival, the influence of confounding factors on primary outcomes using meta-regressions was evaluated only for CA zirconia implants. Immediate and conventional loading as well as early and late placement of zirconia implants showed reliable clinical outcomes within follow-up periods up to 2 years. However, immediate implant loading and type 1 implant placement tended to be associated with a non-significant decrease in implant survival (Figures 3 and 5). In addition to that, increased survival rates were calculated for 1- compared with 2-piece and for YTZP compared with ATZ zirconia implants. Again, the effects on survival rates were not statistically significant (Figures 3 and 5). It should be noted that these results also might have been influenced by the inclusion in the present review of only 2 studies investigating 2-piece zirconia implant systems and only 1 study evaluating ATZ implants (Table 1).

As an additional primary outcome, MBL was analyzed. The meta-analysis estimated a decreased mean 1-year MBL for CA (0.67 mm) compared with NCA zirconia implants (0.95 mm), but this difference was not statistically significant. Interestingly, all 2-piece zirconia implant systems that were included in the present review had a tissue level design. In this context, it must be noted that MBL is not only dependent on surface roughness or implant design (Hermann, Buser, Schenk, & Cochran, 2000; Valderrama et al., 2011) but also on surgical trauma during implant placement (Cochran et al., 1996) or the position of the rough/smooth border of 1-piece implants; in contrast, a subcrestal implant shoulder position leads to increased crestal bone loss (Hartman & Cochran, 2004; Hermann, Cochran, Nummikoski, & Buser, 1997; Hermann et al., 2011).

The mean 1-year MBL for CA zirconia implants (0.67 mm) is in agreement with previously published pooled data on NCA and CA zirconia implants after 1 year of investigation (0.79 mm, CI 0.73–0.86, (Pieralli et al., 2017)) and comparable to titanium implants after follow-up periods from 1 to 5 years (range 0.41–0.89 mm, (Karl & Albrektsson, 2017)). The meta-regression analysis for CA zirconia implants showed that none of the confounding factors had any significant effect on MBL (Figure 5). Based on the observation that only 1 publication provided pooled MBL values for 1- and 2-piece zirconia implants (Brull et al., 2014), implant design (1-piece compared with 2-piece macro design) could not be considered in the meta-regression evaluation for MBL.

In the present review, technical complications and implant fractures were considered as separate factors as only a few publications reported technical complications (Becker et al., 2017; Cannizzaro et al., 2010; Cionca et al., 2015; Jung et al., 2016; Mellinghoff et al., 2015), whereas information with regard to implant fractures was available for all included studies (Tables 3 and 4). The fracture incidence of NCA zirconia implants was clearly associated with a decreasing implant diameter (Roehling et al., 2016). Experimental investigations have shown that zirconia implants have the ability to withstand the forces of the oral cavity (Andreiotelli, Kohal, et al., 2009; Silva et al., 2009). However, uncontrolled surface treatment procedures like conventional sandblasting or uncontrolled machining or grinding processes can lead to surface micro-cracks and might reduce the fracture strength and lead to implant fractures in NCA 1-piece zirconia dental implants (Gahlert, Burtscher, et al., 2012; Osman, Ma, et al., 2013). Thus, manufacturing as well as uncontrolled grinding processes or a reduced implant diameter of NCA zirconia implants might have promoted the implant fractures reported in the present review. The presently evaluated fracture rate of 0.2% for CA zirconia implants is comparable to data reported in a systematic review on titanium implants, describing a mean titanium implant fracture rate of 0.2% after 5 years (Jung, Zembic, Pjetursson, Zwahlen, & Thoma, 2012).

With respect to biological complications, 2 studies investigating 1-piece NCA zirconia implants evaluated marginal bone loss of more than 2 mm within the first year after implant placement (Table 4). Interestingly, the authors of the latter studies reported that the increased MBL was not caused by inflammatory reactions to plaque or bacteria, but possibly were caused by the implant design or cement remnants in the peri-implant soft tissues (Kohal et al., 2012, 2013). Regarding CA zirconia implants, peri-implant infections were reported in 1 study and described as “initial peri-implantitis”, whereas longitudinal MBL data were not provided. Interestingly, the authors observed only “minor crestal bone levels not exceeding the upper 25% of the implant length” and only “moderate” probing depth values for the respective implants (Becker et al., 2017). Thus, a more pronounced physiological marginal bone level remodeling influenced by the implant design or surgical trauma during implant placement and not bacterial infection/peri-implantitis might rather be considered as a reason for the reported findings. The presently evaluated biological complication incidence of 4.2% for CA zirconia implants is comparable to data reported in systematic reviews on titanium implants for observation periods from 1 to 5 years (range 5.2%–7.1%, (Jung et al., 2012; Karl & Albrektsson, 2017; Zembic, Kim, Zwahlen, & Kelly, 2014)).

As a limiting factor of the present review, it should be noted that a wide range of quality of the reported clinical data was noted among the included studies. Thus, not every clinical relevant parameter could be extrapolated for analysis in the present review (e. g., implant diameter, implant location, type of implant placement, bone augmentation procedures, type of prosthetic reconstruction, prosthetic outcomes). In addition, the reported mean observation periods ranged from 12.00 to 71.28 months (5.94 years). Due to the wide variation regarding the follow-up periods, only 1-year meta-analyses and meta-regressions could be evaluated with regard to the primary outcomes when all included studies were considered. Thus, for the evaluation of the 2-years meta-analyses and meta-regressions, studies with observation periods of only 12 months had to be excluded. Based on the available clinical data, a statement concerning the clinical performance of zirconia compared with titanium implants is not possible as only 2 RCTs directly compared NCA zirconia to titanium implants (Osman et al., 2014; Payer et al., 2015). Moreover, the results of the present review showed that the available clinical data for zirconia implants can be confusing as different generations of zirconia implants have been scientifically investigated since the early 2000s. The market availability of zirconia implant generations should be considered when interpreting results from evidence-based investigations, a feature that becomes even more relevant since clinical

studies and even meta-analysis published between 2016 and 2017 report outcomes for NCA zirconia implants (Hashim et al., 2016; Hollander et al., 2016; Pieralli et al., 2017; Roehling et al., 2016).

5 | CONCLUSIONS

Since the beginning of the 2000s, the clinical performance of CA zirconia implants has significantly improved compared with NCA implants. Regarding CA 1-piece zirconia implants, the present meta-analysis evaluated similar 1- and 2-years mean survival rates and peri-implant marginal bone loss after 1 year compared with published data on established titanium implants. Currently, CA 1-piece zirconia implants can be considered as a reliable treatment option for follow-up periods up to 2 years. Regarding the clinical application of 2-piece zirconia implants, very little evidence-based data are available. However, further prospective clinical long-term studies providing detailed information with regard to the time point of implant placement, type of loading, implant failures, biological and technical complications and prosthetic and aesthetic outcomes are urgently needed to confirm the present promising short-term findings.

CONFLICT OF INTEREST

The authors report no conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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REVIEW ARTICLE

WILEY CLINICAL ORAL IMPLANTS RESEARCH

Number of implants placed for complete-arch fixed prostheses: A systematic review and meta-analysis

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Abstract

Objectives: The main purpose of this systematic review was to evaluate outcomes related to the number of implants utilized to support complete-arch fixed prostheses, both for the maxilla and the mandible.

Materials and methods: This review followed the reporting guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). A focused question using the PICO format was developed, questioning whether "In patients with an implant supported fixed complete dental prosthesis, do implant and prosthetic survival outcomes differ between five or more compared to fewer than five supporting implants?". A comprehensive search of the literature was formulated and performed electronically and by hand search. Two independent reviewers selected the papers and tabulated results. Primary outcomes analyzed were implant and prosthesis survival. Implant distribution, loading, and type of retention were observed as secondary outcomes, as they relate to the number of implants. A meta-analysis was performed to compare results for studies by number of implants.

Results: The search strategy identified 1,579 abstracts for initial review. Based on evaluation of the abstracts, 359 articles were identified for full-text evaluation. From these, 93 were selected and included in this review, being nine RCTs, 42 prospective and 42 retrospective. Of the 93 selected studies, 28 reported number of implants for the maxilla, 46 for the mandible, and 19 for both maxilla and mandible. The most reported number of implants for the "fewer than five" group is 4 for the maxilla, and 3 and 4 for the mandible, whereas for the "five or more" implants group, the most reported number of implants was 6 for the maxilla and 5 for the mandible. No significant differences in the primary outcomes analyzed were identified when fewer than five implants per arch were compared with five or more implants per arch ($p > 0.05$), in a follow-up time ranging from 1 to 15 years (median of 8 years).

Conclusions: Evidence from this systematic review and meta-analysis suggests that the use of fewer than five implants per arch, when compared to five or more implants per arch, to support a fixed prosthesis of the completely edentulous maxilla or mandible, present similar survival rates, with no statistical significant difference at a $p < 0.05$ and a confidence interval of 95%.

KEYWORDS
complete, complete fixed prosthesis, dental implants, edentulous, number of implants

1 | INTRODUCTION

The initial concept for clinical utilization of osseointegrated dental implants was developed and proven through the rehabilitation of edentulous patients. The number of implants utilized per arch varied significantly in early publications and was inconsistently reported on. Brånemark's configuration proposed using five implants for the mandible and six for the maxilla to support a complete-arch fixed prosthesis, with all implants distributed anteriorly, placed parallel to each other and splinted together by a passively fitted prosthesis. Implant and prosthesis survival rates were considered satisfactory, exceeding 90% after 10 years (Adell, Eriksson, Lekholm, Brånemark, & Jemt, 1990; Adell, Lekholm, Rockler, & Brånemark, 1981; Brånemark, Svensson, & van Steenberghe, 1995). Other authors reported using as many implants as possible in the maxilla (ranging from 6 to 10), and five to six implants distributed between mental foramen in the mandible, as a standard choice (Zarb & Schmitt, 1990). There have been reports documenting the use of as low as two (Cannizzaro et al., 2012) or three (Brånemark et al., 1999; De Bruyn et al., 2001) implants to support a fixed restoration in the mandible. More recently, suggestions for the use of as many as eight implants in the maxilla and six in the mandible for segmented full-arch restorations have also been proposed (Gallucci et al., 2016).

Biomechanics and more specifically implant distribution is a consideration. Efforts to reduce possible negative outcomes associated with cantilevers, on both the implants and prostheses, have seen an added focus on distribution of implants in addition to number (Lambert, Weber, Susarla, Belser, & Gallucci, 2009; Primo, Mezzari, da Fontoura Frasca, Linderman, & Rivaldo, 2018; Schley & Wolfart, 2011). Early publications (Brånemark et al., 1995; Zarb & Schmitt, 1990) proposed that dental implants be positioned parallel to each other when used to support full-arch prostheses. In the maxilla, where bone may not be available to support satisfactory distribution, grafting techniques can be used to create bone volume capable of supporting not only more implants, but also an improved biomechanical distribution (Schliephake, Neukam, & Wichmann, 1997). Although grafting techniques such as sinus floor augmentations are predictable methods of improving bone volume for long-term implant survival and success (Aghaloo & Moy, 2007; Chiapasco, Casentini, & Zaniboni, 2009), increased treatment time, cost, and morbidity are considerations, and researchers and clinicians seek alternative protocols.

Reducing invasiveness and the costs associated with grafts and a higher number of implants is often a goal that can make implant rehabilitation available to a greater number of edentulous patients. Intentionally tilted or inclined implants have been proposed as an alternative to grafting. These techniques can assist in reducing the length of cantilevers and improve the antero-posterior distribution of implants around an arch (Aparicio, Perales, & Rangert, 2001; Krekmanov, 2000). This approach may also reduce the number of implants required to support a fixed complete-arch prosthesis (Kronström et al., 2003; Maló, Rangert, & Nobre, 2003) and has become a popular clinical solution in recent years.

Lambert et al. (2009) showed that in the maxilla, the antero-posterior distribution of the implants influenced the survival rates. Implant-prosthetic protocols with an adequate anterior–posterior implant distribution resulted in statistically significant improvements in prosthodontic survival rates when compared to those with a more anterior, less well-distributed implant position. However, the same assumption cannot be made for the mandible. In a systematic review, Papaspyridakos, Mokti, et al. (2014) reported that the number of supporting implants and the implant distribution had no influence on the implant survival in the mandible. Of 2,827 implants placed, 2,501 (88.5%) were placed interforaminally. No report was made relative to whether implants included in the evaluation were positioned parallel to each other or with inclination, in order to reduce the cantilever.

A two-stage implant placement procedure was recommended as standard, and long-term follow-up studies have demonstrated high survival rates for complete-arch fixed rehabilitations supported by smooth surface implants, with the majority of reports documenting a number of implants ranging from 6 to 12 in the maxilla (Jemt & Johansson, 2006) and 4 to 8 in the mandible (Balshi, Wolfinger, Stein, & Balshi, 2015). However, immediate loading also demonstrates benefit for patients, associated with reduced overall treatment times. With the evolution and improvement in surgical techniques, implant surfaces and connections, immediate loading protocols have been more frequently used and reported on (Shigehara, Ohba, Nakashima, Takanashi, & Asahina, 2015; Strietzel, Karmon, Lorean, & Fischer, 2011; Weber et al., 2009). Papaspyridakos, Chen, Chuang, and Weber (2014) conducted a systematic review on immediate loading protocols for completely edentulous patients rehabilitated with fixed prosthesis and concluded that when selecting cases carefully, and using implants with a microroughened surface, immediate loading with fixed prostheses in edentulous patients results in similar implant and prosthesis survival and failure rates when compared to early and conventional loading.

Surgical and restorative protocols continue to evolve, with digital impression making, digital surgical and prosthetic planning and computer-aided design and manufacturing allowing for a more precise infrastructure, delivered in a shorter period of time for the patient. More rapid protocols allow for predictable early and immediate patient treatments with growing scientific support (Kapos, Ashy, Gallucci, Weber, & Wismeijer, 2009; Lee & Gallucci, 2013; Maló, Nobre, Borges, Almeida, 2012; Papaspyridakos et al., 2016; Papaspyridakos, Rajput, Kudara, & Weber, 2017).

There are, however, several variables to be considered when discussing the number of implants utilized to support a complete-arch fixed restoration (Ellis & McFadden, 2007; Mericske-Stern, & Worni, 2014; Schley & Wolfart, 2011). These include the soft and hard tissue conditions of the edentulous jaw, distribution of the implants, anatomic risks, aesthetics and facial appearance, choice of material and design of prostheses, type of retention of the prostheses and type and timing of occlusal loading. Recommendations for the number of implants, and the type of complete-arch fixed prosthesis are mostly empirical, and decisions are made as a result of clinical experience, anatomic conditions, patients' preferences and costs. Hence, the number and distribution of implants placed to support a fixed complete-arch restoration, both in the maxilla and in the mandible, remains an interesting and controversial topic. There is an increasing volume of papers describing the use of fewer implants, with varying distribution.

This review therefore focuses only on reported outcomes associated with the number of supporting implants (as the variable) utilized for fixed dental prostheses in the completely edentulous maxilla and mandible.

2 | MATERIALS AND METHODS

This review followed the reporting guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Liberati et al., 2009). The PRISMA 2009 checklist statement consists of a 27-item checklist and a four-phase flow diagram (Figure 1). The checklist provides guidelines for transparent reporting of a systematic review.

2.1 | PICO focused question

A focused question using the PICO (Population, Intervention, Comparison, Outcomes) format was developed, questioning whether "in patients with an implant supported fixed complete dental prosthesis, do implant/prosthetic outcomes differ between five or more compared to fewer than five supporting implants?".

Population was defined as edentulous arch with an implant supported fixed prosthesis; Interventions as fixed prosthesis supported by five or more implants; and comparison as fixed prosthesis supported by fewer than five implants. Primary outcomes measured were implant and restoration survival rates.

2.2 | Data sources and eligibility criteria

A comprehensive search of the literature was performed by a medical librarian (*TWE*) in Ovid MEDLINE, PubMed, EMBASE, and the full Cochrane Library. All searches were updated on March 31, 2018, and all databases were searched from inception. Bibliographies of relevant studies were also reviewed for additional references.

The complete search strategies for each database are reported in Appendix S1 and can be reproduced. Database-specific subject headings and keyword variants for each of the four major concepts—edentulism, dental prostheses, dental implant numbers and survival—were identified and combined.

2.3 | Inclusion and exclusion criteria

Studies were included if they:

1. examined rehabilitation of edentulous patients with complete-arch fixed prosthesis;
2. included at least 10 patients with a minimum follow-up period of 12 months;
3. *clearly* stated the number of implants used for each arch (maxilla or mandible);
4. described the survival rates for the prosthesis and the implants.

Tilted implants and graft cases were considered, as long as they met the previous criteria.

Randomized clinical trials, prospective and retrospective studies were considered, if the above criteria were met.

Results were limited to the English language. Animal and in vitro studies were excluded as well as single case reports. Zygomatic implants and oncologic rehabilitation publications were excluded.

2.4 | Study selection

References were identified through database searching as described in the search methodology. Duplicates were removed, and titles and abstracts were screened independently by two reviewers (WDP and TA), using the specific inclusion and exclusion criteria to accomplish the item generation and item reduction. Kappa agreement of inter-rater reliability was performed. Cohen's κ was run to determine whether there was agreement between the two authors' judgments during the item reduction. For title and abstract review, there was good agreement between the two authors' judgments, $\kappa = 0.46$ (80% agreement rate).

Full text was requested after selection and reviewed for inclusion and exclusion criteria. Two reviewers (WDP and TA) independently selected the studies to be included. During full-text review, any disagreements were resolved through direct communication, until consensus was reached.

2.5 | Data extraction

After reviewing the full paper, data were extracted and tabled in the following order: number of implants per arch, first author, year of publication, study design, total number of implants, total number of arches, position of implants per arch, type of implants (manufacturer), mean follow-up, follow-up range, survival of implants, survival of restorations, type of loading (immediate vs. delayed) and form of retention (screw vs. cemented).

Primary outcomes analyzed were the survival of implants (defined as an implant reported as stable, still fulfilling function as a support for the prosthesis, with no signs of infection), and survival

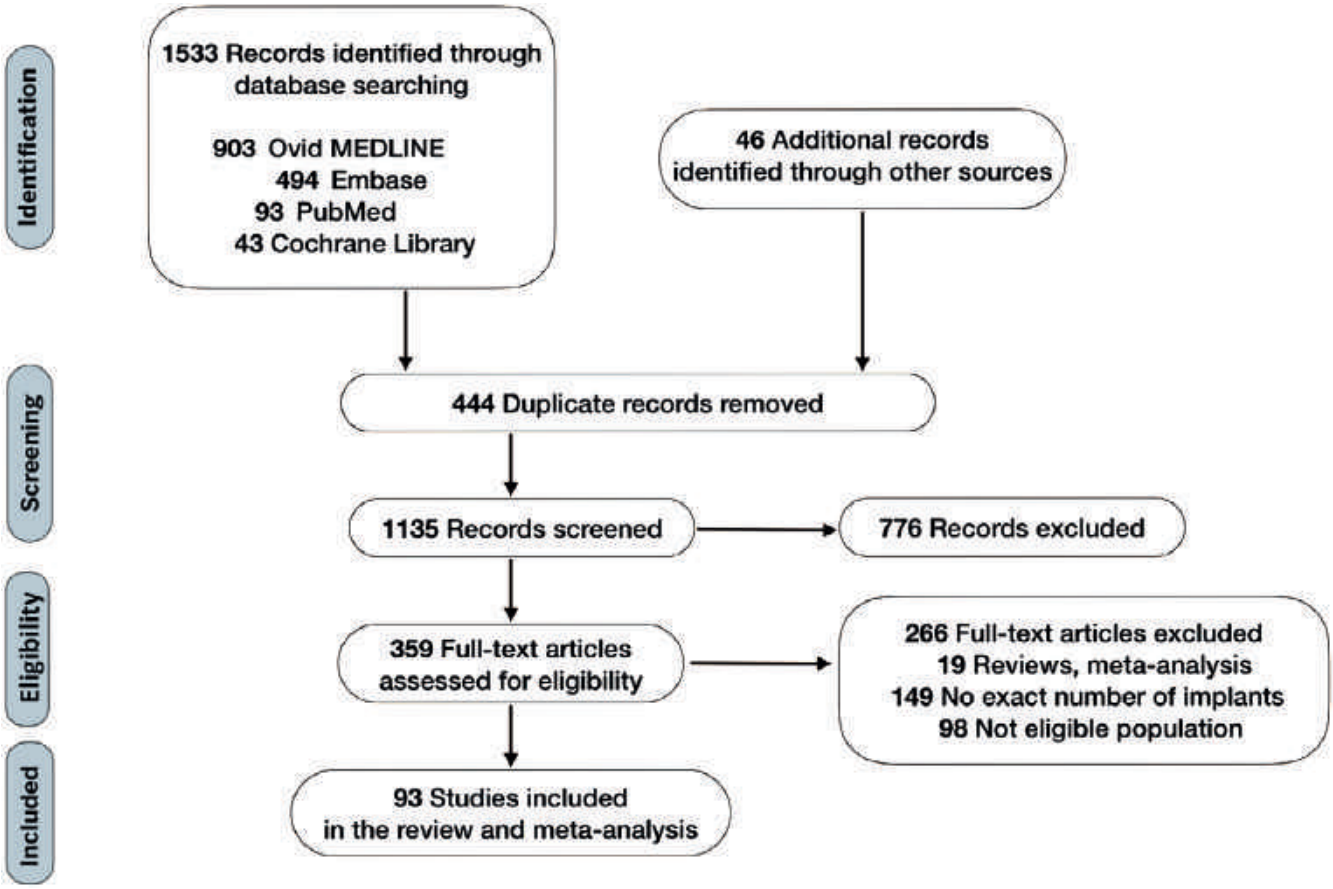

FIGURE 1 PRISMA flow diagram

of restorations (defined as a prosthesis reported to be in function, without the need for a complete replacement), per number of implants placed per arch. Secondary outcomes included distribution of implants, type of loading and form of retention.

2.6 | Risk of bias assessment

The risk of bias was assessed according to the type of study available. The nine RCTs available were assessed using the Cochrane Risk of Bias Tool (Higgins et al., 2011). The non-RCT studies of interventions included (42 prospective and 42 retrospective) were assessed for the risk of bias using the ROBINS-I tool (Risk Of Bias In Non-randomized Studies – of Intervention). It includes the risk of bias due to confounding factors, selection of participants into the study, classification of interventions, deviations from intended intervention, missing data, measurement of outcomes and selection of reported result (Sterne et al., 2016).

The reviewers ranked independently each included study and resolved any disagreement by reciprocal consulting.

2.7 | Statistical analysis

Assessment of heterogeneity was performed using Cochran's *Q*-statistic and the I^2 statistic model. Statistically significant heterogeneity between studies was observed, as indicated by the *Q* test and I^2 shown in Figures 2–5.

Due to the high heterogeneity of the selected studies, a decision was made to perform a meta-analysis using the random-effects model.

A random-effects meta-analysis was performed using R statistical software (random-effects model function from the metafor package), to compare papers reporting fewer than five implants with those reporting five or more implants for maxilla and mandible independently, as well as for implant and prosthesis survival rates. Additionally, the study type was also reported (randomized controlled trial, prospective, retrospective).

Forest plots were used to visualize the results for maxilla implants (Figure 2), maxilla prosthesis (Figure 3), mandible implants (Figure 4) and mandible prosthesis (Figure 5).

3 | RESULTS

A total of 1,533 references were identified through database searching, and an additional 46 from relevant bibliographies, for a total of 1,579 records identified (Figure 1). After removing 444 duplicates, 1,135 unique titles and abstracts were screened independently by two reviewers (*WDP* and *TA*), based on the defined inclusion and exclusion criteria.

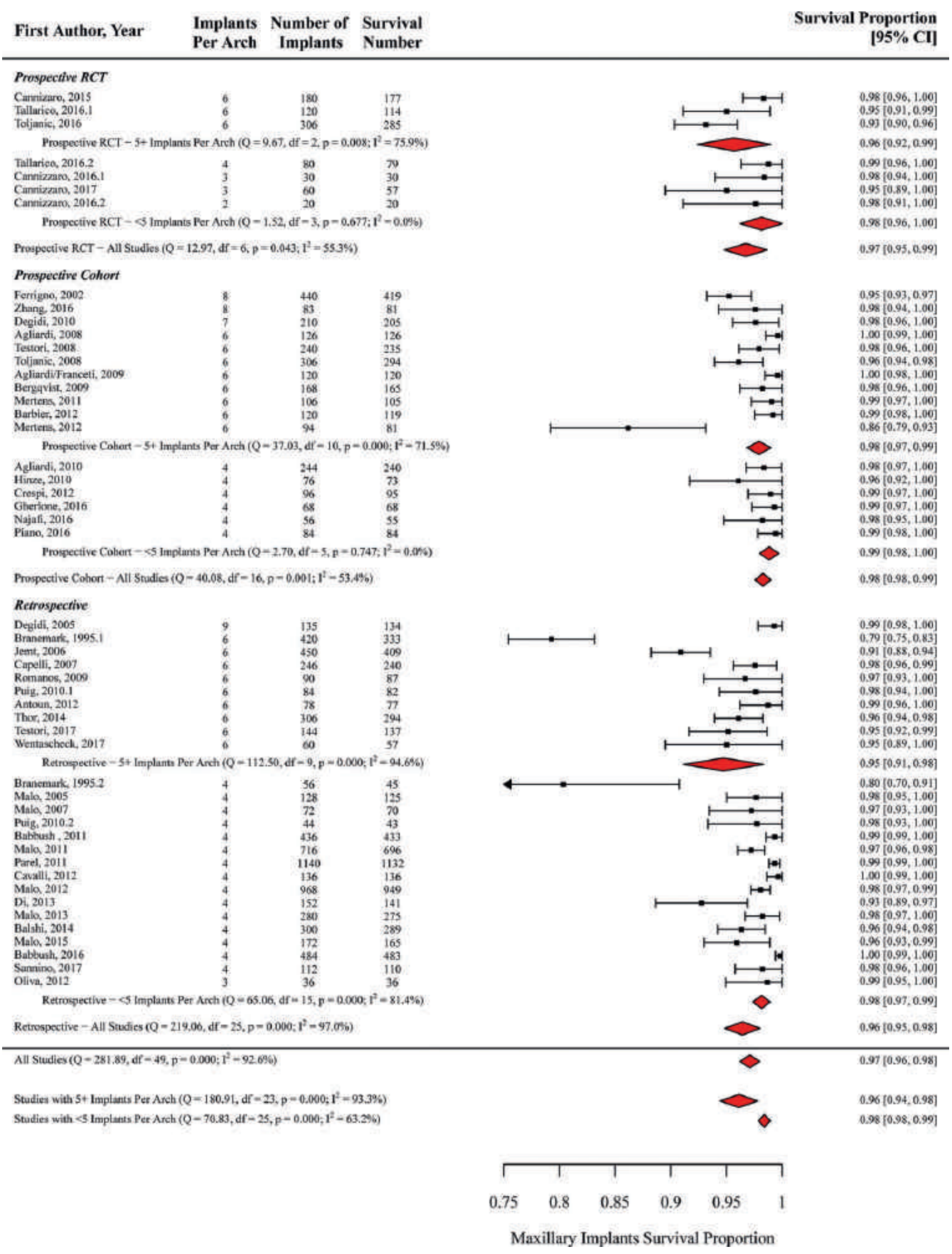

FIGURE 2 Meta-analysis forest plot—maxilla, implants

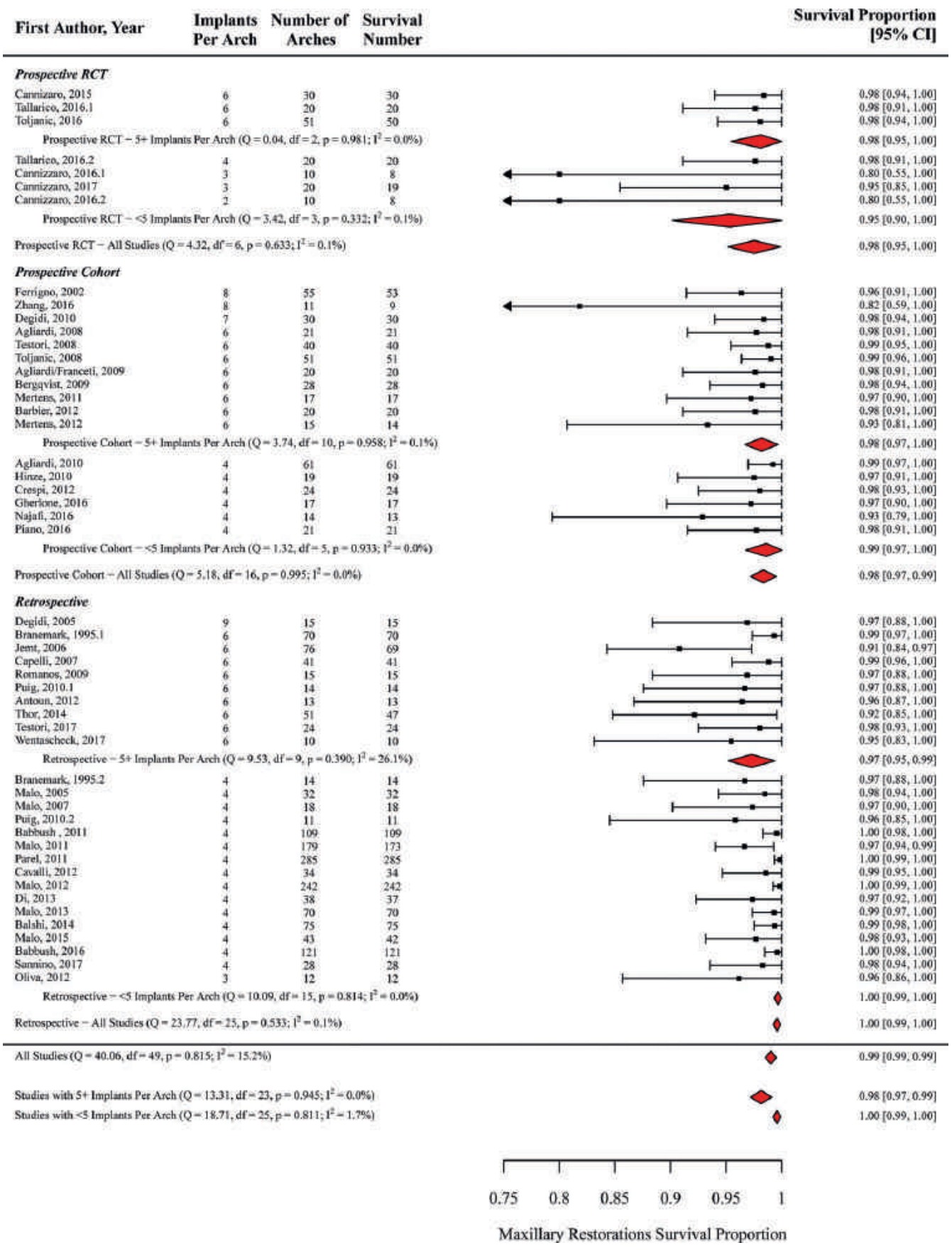

FIGURE 3 Meta-analysis forest plot—maxilla, prosthesis

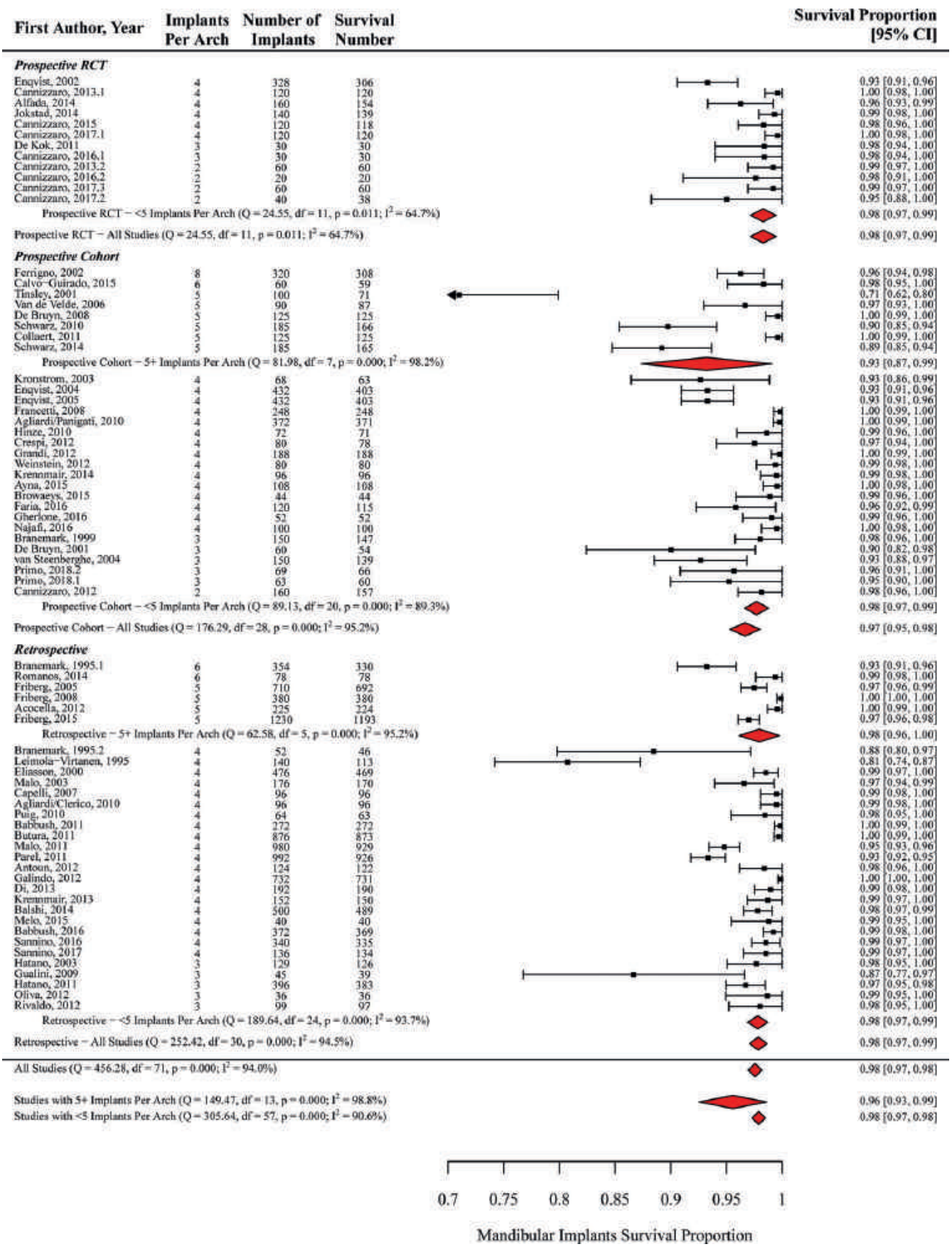

FIGURE 4 Meta-analysis forest plot—mandible, implants

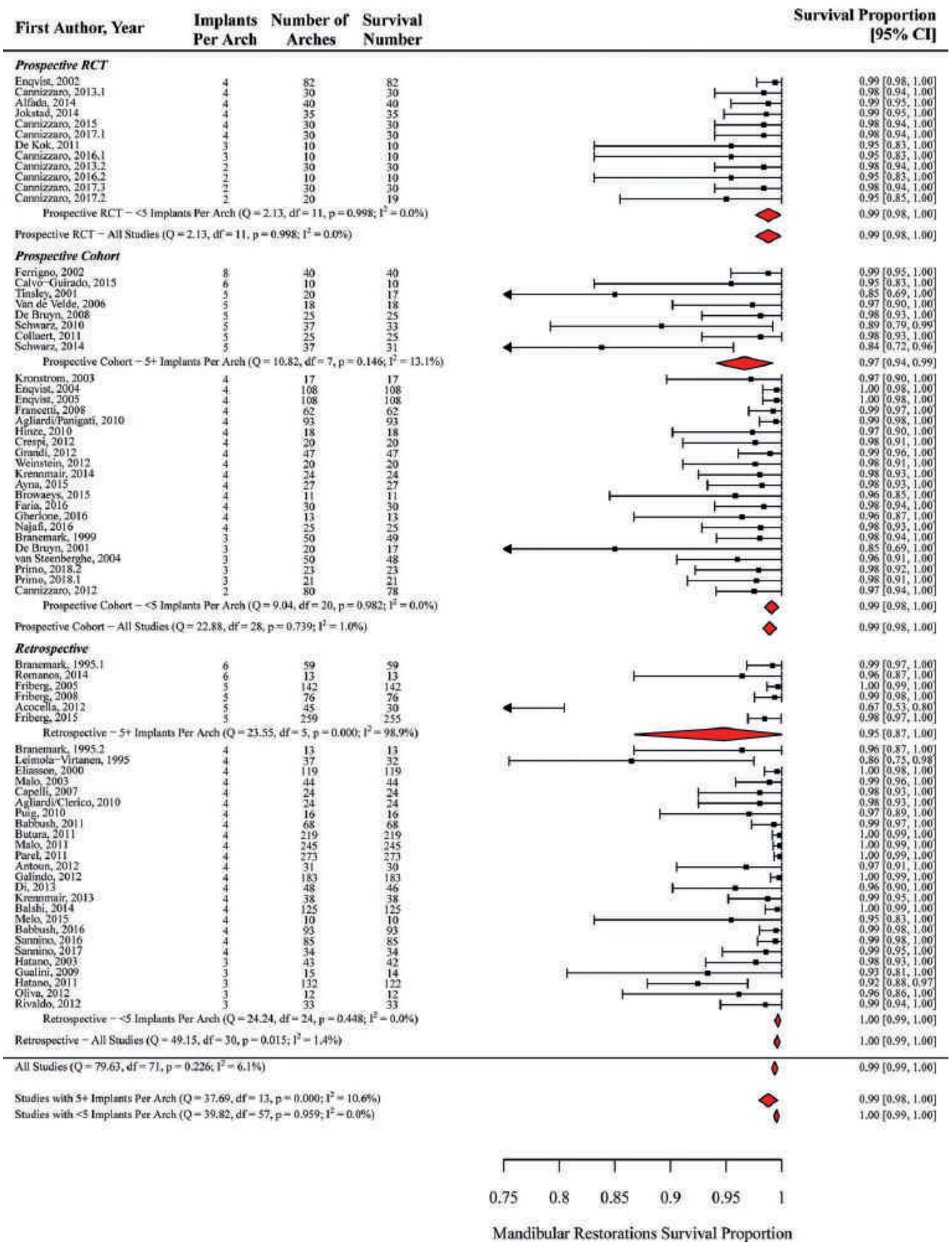

FIGURE 5 Meta-analysis forest plot—mandible, prosthesis

Full-text review was requested for 359 papers, and from those, 93 were selected and included in this review.

Main reasons for exclusion based on title/abstract review were fewer than 10 patients in the study, not exact number of implants per arch, combining survival rates for maxillary and mandibular implants, results for grafting procedures only, partial edentulism, overdentures, digital accuracy without reporting success of implants, maintenance issues and zygomatic implants. The reason for exclusion of the majority of papers after full-text review (149) was the lack of report on the exact number of implants utilized per arch, with reporting of averages only for the number of implants placed.

Of the 93 selected studies, 28 reported number of implants for the maxilla, 46 for the mandible and 19 for both maxilla and mandible, being nine RCTs, 42 prospective and 42 retrospective studies. Combining these studies for our focused analysis (exact number of implants per arch), 47 studies reported on rehabilitation for the maxilla and 65 for the mandible.

Three papers had two different groups for mandibular treatment, one had two groups for maxilla only (4 vs. 6 implants), one had three groups (two for the maxilla and one for the mandible), one had four groups (two for the maxilla and two for the mandible), and 19 had two groups (maxilla and mandible). Distributing the populations reported to both groups in the tables, led to a total

TABLE 1 Distribution of reports per number of implants—maxilla [In PDF format, this table is best viewed in two-page mode]

Number of implants per arch	First author	Year of publication	Study design	Total number of arches	Total number of implants	Position of implants per arch	Manufacturer/Type of implants
2	Cannizzaro	2016	Prospective RCT	10	20	Ant P	Prama RF Tapered
3	Oliva	2012	Retrospective	12	36	Ant P/Post DT	Straumann / Osstem
3	Cannizzaro	2016	Prospective RCT	10	30	Ant P	Prama RF Tapered
3	Cannizzaro	2017	Prospective RCT	20	60	Ant/Post P	Syra / Syra SL
4	Brånemark	1995	Retrospective	14	56	Parallel	Brånemark
4	Maló	2005	Retrospective	32	128	Ant P/Post DT	Nobel MKIII/MKIV TiUnite
4	Malo	2007	Retrospective	18	72	Ant P/Post DT	Nobel Speedy
4	Agliardi/Clerico	2010	Prospective	61	244	Ant P/Post DT	Nobel MKIV / Groovy
4	Hinze	2010	Prospective	19	76	Ant P/Post DT	Nanotite Tapered (Biomet 3i)
4	Puig	2010	Retrospective	11	44	Ant P/Post DT	Nobel Speedy Groovy/MK III Groovy
4	Malo	2011	Retrospective	179	716	Ant P/Post DT	Nobel MKIV / Groovy
4	Babbush	2011	Retrospective	109	436	Ant P/Post DT	Nobel Active
4	Parel	2011	Retrospective	285	1140	Ant P/Post DT	Nobel Active
4	Maló	2012	Retrospective	242	968	Ant P/Post DT	Brånemark / Nobel Speedy Groovy
4	Crespi	2012	Prospective	24	96	Ant P/Post DT	PAD Sweden-Martina
4	Cavalli	2012	Retrospective	34	136	Ant P/Post DT	Nobel MKIV / Groovy
4	Di	2013	Retrospective	38	152	Ant P/Post DT	Brånemark / Nobel Speedy Groovy
4	Maló	2013	Retrospective	70	280	Ant P/Post DT	Nobel
4	Balshi	2014	Retrospective	75	300	Ant P/Post DT	Nobel
4	Maló	2015	Retrospective	43	172	Ant P/Post DT	Nobel Speedy Groovy/Shorty
4	Tallarico	2016	Prospective RCT	20	80	Ant P/Post DT	Nobel Speedy
4	Babbush	2016	Retrospective	121	484	Ant P/Post DT	Nobel Active
4	Piano	2016	Prospective	21	84	Ant P/Post DT	Straumann Bone Level
4	Najafi	2016	Prospective	14	56	Ant P/Post DT	Nobel
4	Gherlone	2016	Prospective	17	68	Ant P/Post DT	IDI Evolution
4	Sannino	2017	Retrospective	28	112	Ant P/Post DT	Nobel Active/Speedy
6	Brånemark	1995	Retrospective	70	420	Parallel	Brånemark
6	Jemt	2006	Retrospective	76	450	Parallel	Brånemark
6	Capelli	2007	Retrospective	41	246	4 Ant P/2 Post DT	3i Osseotite NT
6	Testori	2008	Prospective	40	240	4 Ant P/2 Post DT	3i
6	Agliardi	2008	Prospective	21	126	Tilted V-II-V	Nobel MKIV (30)/ Groovy (96)
6	Toljanic	2009	Prospective	51	306	4 Ant P/2 Post DT	Astra Osseospeed
6	Bergqvist	2009	Prospective	28	168	Parallel	Straumann STL
6	Romanos	2009	Retrospective	15	90	Parallel	Ankylos

(Continues)

of 112 groups of patients analyzed (50 for the maxilla and 72 for the mandible).

Results for selected studies are presented in Tables 1 (maxilla) and 2 (mandible).

3.1 | Risk of bias of included studies

The risk of bias judgment for the nine RCTs is included in Table 3. Eight had a low risk of bias, and one had a high risk of bias. However, only one study (Tallarico, Meloni, Canullo, Caneva, and Polizzi (2016) was an RCT that addressed our focused question (fewer than five vs. five or more implants), comparing four vs. six implants.

The risk of bias analysis for the remaining 84 studies selected (42 prospective and 42 retrospective) was assessed using the ROBINS-I tool and is listed in Table 4. Nine studies had a low, 60 had a moderate, and 15 had a serious risk of bias.

3.2 | Maxillary outcomes (Table 1)

3.2.1 | Number of studies, implants and follow-up period

There were 50 groups of patients extracted from the 28 studies that reported numbers of implants for the maxilla (one RCT,

TABLE 1 (additional columns)

Mean follow-up years	Follow-up range	Survival implants (%)	Survival restoration (%)	Loading	Retention
1	12	100	82	Immediate provisional	Screw-retained
5	5 years	100	100	Conventional	Screw-retained
1	12	100	82	Immediate provisional	Screw-retained
1	12 months	95	95	Delayed	Screw-retained
10	10 years	80.30	100	Delayed	Screw-retained
1	12 months	97.60	100	Immediate provisional	Screw-retained
1.1	6–21 months	97	100	Immediate	Screw-retained
2.6	12–59 months	98.30	100	Immediate	Screw-retained
1	12 months	96.6	100	Immediate provisional	Screw-retained
1	12 months	98.00	100	Immediate provisional	Screw-retained
5	60 months	97.20	96.80	Immediate provisional	Screw-retained
1	12 months	99.30	100	Immediate provisional	Screw-retained
2.7	4–33 mos	99.30	100	Immediate provisional	Screw-retained
6.6	78.9–80.2 months	98	100	Immediate	Screw-retained
3	36 months	98.96	100	Immediate provisional	Screw-retained
3.2	12–73 months	100	100	Immediate provisional	Screw-retained
2.8	12–56 months	92.80	96.50	Immediate provisional	Screw-retained
3	36 months	98.10	100	Immediate provisional	Screw-retained
2.2	6–60 months	96.30	100	Immediate provisional	Screw-retained
3	4–75 months	95.70	98.20	Immediate provisional	Screw-retained
5.3	60–84 months	98.25	100	Immediate provisional	Screw-retained
1.3	12–36 months	99.80	100	Immediate provisional	Screw-retained
2	24 months	100	100	Immediate provisional	Screw-retained
3	32.5 ± 12.6	98	92	Immediate vs. delayed	Screw-retained
1	12 months	100	100	Immediate provisional	Screw-retained
2	24 months	100 (V), 98.38 (DT)	100	Immediate provisional	Screw-retained
10	10 years	79.30	100	Delayed	Screw-retained
15	15 years	90.90	90.60	Conventional	Screw-retained
1.8	6–36 months	97.59	100	Immediate provisional	Screw-retained
1	12 months	98	100	Immediate provisional	Screw-retained
1.6	4–35 Months	100	100	Immediate provisional	Screw-retained
1	12 months	96	100	Immediate provisional	Screw-retained
2.6	32 months	98.30	100	Immediate provisional	Screw-retained
3.6	22–62 months	96.66	100	Immediate provisional	Screw-retained

(Continues)

TABLE 1 (Continued) [In PDF format, this table is best viewed in two-page mode]

Number of implants per arch	First author	Year of publication	Study design	Total number of arches	Total number of implants	Position of implants per arch	Manufacturer/Type of implants
6	Agliardi	2009	Prospective	20	120	Tilted V-II-V	Nobel MKIV (30) / Groovy (90)
6	Puig	2010	Retrospective	14	84	4 Ant P/2 Post DT	Nobel Speedy Groovy/MK III Groovy
6	Mertens	2011	Prospective	17	106	Parallel	AstraTech
6	Antoun	2012	Retrospective	13	78	Parallel	Nobel
6	Barbier	2012	Prospective	20	120	Parallel	Astra Osseospeed
6	Mertens	2012	Prospective	15	94	Parallel	AstraTech
6	Thor	2014	Retrospective	51	306	Parallel	Astra Osseospeed
6	Cannizaro	2015	Prospective RCT	30	180	Parallel	3i
6	Tallarico	2016	Prospective RCT	20	120	Parallel	Nobel Speedy
6	Toljanic	2016	Prospective	51	306	4 Ant P/2 Post DT	Astra Osseospeed
6	Wentascheck	2017	Retrospective	10	60	4 Ant P/2 Post DT	Bredent BlueSky
6	Testori	2017	Retrospective	24	144	4 Ant P/2 Post DT	Biomet/3i
7	Degidi	2010	Prospective	30	210	Tilted V-III-V	Xive Plus Friadent
8	Ferrigno	2002	Prospective	55	440	Parallel	Straumann STL
8	Zhang	2016	Prospective	11	83	Parallel	Straumann
9	Degidi	2005	Retrospective	15	135	Parallel	Several

Ant, anterior; DT, distally tilted; P, parallel; Post, posterior; RCT, randomized controlled trial; V pos, position of the implants in the posterior maxilla, where the most distal implant is tilted mesially, and the implant just medial to it is tilted distally (in a 'V' shaped configuration); V-III-V, seven implants, two distal implants tilted, one mesially and one distally, and the three anterior parallel implants; V-II-V, six implants, two distal implants tilted, one mesially and one distally, and the two anterior parallel implants.

13 prospective and 14 retrospective), and from the 19 papers that reported for both groups (three RCTs, seven prospective and nine retrospective), for a total of 10,678 implants, followed for a median follow-up period of 8 years (1–15 years). Distribution of papers per number of implants for the maxilla is presented in Table 1.

Twenty-six groups had fewer than five implants, with a median follow-up time of 5.5 years (1–10 years), reported in 25 papers. One study reported on two and three implants, two reported on three implants, and 22 reported on four implants. Looking only at studies with four implants, the median follow-up time was 5.5 years (1–10 years).

Twenty-four groups had five or more implants per arch, with a median follow-up time of 8 years (1–15 years), being 20 studies reporting on six implants, and four studies reporting on more than six implants.

3.2.2 | Implant and restoration survival rates

Overall mean implant survival rate was 96%, and restoration survival rate was 99%, for a follow-up range from 1 to 15 years, with median follow-up of 8 years. For reports with fewer than five implants (26 studies), mean reported implant survival rate was 97%, and restoration survival rate was 98%, with a median follow-up time of 5.5 years (1–10 years). Looking only at the 22 studies with four implants, the mean implant survival rate was 97%, with a restoration survival rate of 99%, in a median follow-up of 5.5 years (range 1–10 years).

For the 24 reports with five or more implants, implant survival rate had a mean of 95%, and restoration survival rate was 98.5%, in a median follow-up of 8 years (1–15 years). Looking only at the 20 studies that reported on six implants per maxillary arch, mean implant survival rate was 95%, and restoration survival rate was 98.5%, in a follow-up range of 1–15 years (median of 8 years).

3.2.3 | Implant distribution

Overall, the configuration of "anterior parallel and posterior distally tilted" was used in 32 groups, whereas the "parallel" position was used in 18 reports.

When looking at the group with fewer than five implants, 22 of 26 reported on "anterior parallel and posterior distally tilted," and four were "parallel." Of the 22 papers reporting on four implants for edentulous maxillae, only one had the four implants placed in a "parallel" fashion (Brånemark et al., 1995), with a mean survival rate of 80.3% for the smooth surface implants. The other 18 papers reported the implant position as being "two anterior parallel and two posterior intentionally distally tilted," with a mean implant survival rate of 97.8% and prosthesis survival rate of 99% (follow-up 1–6.6 years, median of 3.8 years).

Analyzing the reports with five or more implants in the maxilla, the use of "anterior parallel and posterior distally tilted" was indicated in 10 reports, and the "parallel" implants were used in 18 reports. When six implants were placed, distribution varied between "parallel" (11 papers), "four anterior parallel and two posterior distally tilted" (seven papers), and two papers reported a position with "two anterior implants parallel, two anteriorly tilted mesially and two posteriorly tilted distally" configuration (V-II-V). The average

TABLE 1 (additional columns - continued)

Mean follow-up years	Follow-up range	Survival implants (%)	Survival restoration (%)	Loading	Retention
2.3	17–42 months	100	100	Immediate provisional	Screw-retained
1	12 months	98	100	Immediate provisional	Screw-retained
8	8 years	99	100	Conventional	Screw-retained
1.5	3–56 months	98.50	97.70	Immediate	Screw-retained
1	6–18 months	99.30	100	Immediate provisional	Screw-retained
11.3	10.42–12.25 years	86.70	93.30	Conventional	Screw-retained
3	36 months	96	92.50	Immediate provisional	Screw-retained
1	12	98.50	100	Immediate provisional	Screw-retained
5.3	60–84 months	95	100	Immediate provisional	Screw-retained
5	5 years	93	97.50	Immediate provisional	Screw-retained
5.3	42–84 months	95	100	Immediate provisional	Screw-retained
10	10 years	95	100	Immediate provisional	Screw-retained
3	36 months	97.8 (ax) 99.2 (tilt)	100	Immediate	Screw-retained
10	5–10 years	95.30	96.40	Early	Screw-retained
10	1, 3, 5, 10 years	97.60	79 (segmented)	Delayed	Cemented
5	60 months	99.20	100	Immediate provisional	Screw-retained

survival rate reported for six parallel placed implants to support a fixed prosthesis was of 95% and survival rate of the prosthesis of 95%, with a median follow-up time of 8 years (1–15 years). Looking only at the seven papers that reported the distribution of being "four anterior parallel and two posterior distally tilted," the median follow-up time was 5.5 years (1–10 years), and a survival rate was 96% for both the implants and prosthesis. Papers reporting more than six implants had all implants parallel to each other. There was no significant difference in implant and prosthesis survival between the different implant distributions, although it was clear that when four implants are placed, the preferred configuration is the "anterior parallel, posterior distally tilted," and when six implants were placed, there was a slight preference to use the "parallel" configuration, with a trend on more recent papers to use the "four anterior parallel and two posterior distally tilted" configuration. The influence of tilted or inclined implants is the focus of a separate systematic review of this Supplement (Lin & Eckert, 2018).

3.2.4 | Loading protocols

Immediate loading was performed in 41 reports in the maxilla (nine with conventional loading). Overall, the immediate loading had a survival rate of 96% for both implants and prosthesis, with a follow-up range of 1–10 years (median of 5.5 years). All the reports with fewer than five implants except one (Brånemark et al., 1995) reported immediate loading with a screw-retained immediate provisional prosthesis, meaning that 21 reports on the use of four implants used immediate loading, showing a mean implant survival rate of 97.8% and prosthesis survival rate of 99% (follow-up 1–6.6 years, median of 3.8 years). Of the papers reporting on five or more implants, only six reported using delayed or conventional loading, whereas 18 reported on immediate loading. All reported screw-retention for the prostheses. For the group with six implants, 16 reported immediate loading, and four conventional or early loading. There was no significant difference between outcomes of loading protocols when comparing the main two groups (four vs. six implants), with a clear preference for the "immediate loading" protocol.

3.3 | Mandibular outcomes (Table 2)

3.3.1 | Number of studies, implants and follow-up period

There were 72 groups that reported numbers of implants for the mandible, in data extracted from 46 papers that reported only cases for the mandible (five RCTs, 22 prospective and 19 retrospective), and 19 that reported for both maxilla and mandible (three RCTs, seven prospective and nine retrospective studies), for a total of 12,697 implants. The follow-up reported ranged from 1 to 10 years, with a median of 5.5 years. Distribution of papers per number of implants for the mandible is presented in Table 2.

Fifty-four groups were included in the fewer than five implants analysis, including five reports on two implants, 12 reported on three implants, and 41 reported on four implants per arch. Follow-up range was from 1 to 10 years (median of 5.5 years). One study had a

TABLE 2 Distribution of reports per number of implants—mandible [In PDF format, this table is best viewed in two-page mode]

Number of implants per arch	First author	Year of publication	Study design	Total number of arches	Total number of implants	Position of implants per arch	Manufacturer/Type of implants
2	Cannizzaro	2012	Prospective	80	160	BMF P	3i Osseotite
2	Cannizzaro	2013	Prospective RCT	30	60	BMF P	3i Osseotite/Osteogen
2	Cannizzaro	2016	Prospective RCT	10	20	BMF P	Prama RF Tapered
2	Cannizzaro	2017	Prospective RCT	20	40	BMF P	Syra / Syra SL
2	Cannizzaro	2017	Prospective RCT	30	60	BMF P and DT	Zimmer/Biomet–Megagen
3	Brånemark	1999	Prospective	50	150	BMF P	Nobel Novum
3	De Bruyn	2001	Prospective	20	60	BMF P	Brånemark
3	Hatano	2003	Retrospective	43	129	BMF P and DT	Brånemark
3	van Steenberghe	2004	Prospective	50	150	BMF P	Brånemark Novum
3	Gualini	2009	Retrospective	15	45	BMF P	Brånemark Novum
3	De Kok	2011	Prospective RCT	10	30	BMF P	Astra Osseospeed
3	Hatano	2011	Retrospective	132	396	BMF P	Brånemark
3	Rivaldo	2012	Retrospective	33	99	BMF P	Brånemark
3	Oliva	2012	Retrospective	12	36	BMF P	Straumann / Osstem
3	Cannizzaro	2016	Prospective RCT	10	30	BMF P	Prama RF Tapered
3	Primo	2018	Prospective	21	63	BMF P and DT	Brånemark
3	Primo	2018	Prospective	23	69	BMF P and DT	Brånemark
4	Leimola-Virtanen	1995	Retrospective	37	140	BMF P	ITI TPS
4	Brånemark	1995	Retrospective	13	52	BMF P	Brånemark
4	Eliasson	2000	Retrospective	119	476	BMF P	Brånemark
4	Engquist	2002	Prospective	82	328	BMF P	Brånemark
4	Maló	2003	Retrospective	44	176	BMF DT	Brånemark
4	Kronström	2003	Prospective	17	68	BMF DT	Brånemark MK IV
4	Engquist	2004	Prospective	108	432	BMF P	Brånemark
4	Engquist	2005	Prospective	108	432	BMF P	Brånemark
4	Capelli	2007	Retrospective	24	96	BMF DT	3i Osseotite NT
4	Francetti	2008	Prospective	62	248	BMF DT	Nobel MK IV/Nobel Speedy Groovy
4	Hinze	2010	Prospective	18	72	BMF DT	Nanotite Tapered (Biomet 3i)
4	Agliardi/Panigati	2010	Prospective	93	372	BMF DT	Nobel MK IV/Nobel Groovy
4	Puig	2010	Retrospective	16	64	BMF DT	Nobel Speedy Groovy/MK III Groovy
4	Agliardi/Clerico	2010	Retrospective	24	96	BMF DT	Nobel MK IV/Nobel Groovy
4	Babbush	2011	Retrospective	68	272	BMF DT	Nobel Active
4	Parel	2011	Retrospective	273	992	BMF DT	Nobel Active
4	Butura	2011	Retrospective	219	876	BMF DT	Brånemark
4	Malo	2011	Retrospective	245	980	BMF DT	Brånemark MK II, III, IV
4	Weinstein	2012	Prospective	20	80	BMF DT	Brånemark MKIV/Nobel Groovy
4	Crespi	2012	Prospective	20	80	BMF DT	PAD Sweden-Martina
4	Grandi	2012	Prospective	47	188	BMF DT	JD Evolution
4	Galindo	2012	Retrospective	183	732	BMF DT	Nobel Active/Groovy Speedy
4	Antoun	2012	Retrospective	31	124	BMF DT	Nobel
4	Cannizzaro	2013	Prospective RCT	30	120	BMF P	3i Osseotite/Osteogen
4	Di	2013	Retrospective	48	192	BMF DT	Brånemark / Nobel Speedy Groovy
4	Krennmair	2013	Retrospective	38	152	BMF DT	Screwline, Camlog
4	Krennmair	2014	Prospective	24	96	BMF DT	Screwline, Camlog
4	Alfadda	2014	Prospective RCT	40	160	BMF P	Nobel TiUnite

(Continues)

TABLE 2 (additional columns)

Mean follow-up Years	Follow-up range	Survival implants (%)	Survival restoration (%)	Loading	Retention
1	12 months	98	98	Immediate provisional	Screw-retained
1	12 months	100	100	Immediate provisional	Screw-retained
1	12 months	100	100	Immediate provisional	Screw-retained
1	12 months	95	95	Delayed	Screw-retained
3	36 months	100	100	Immediate provisional	Screw-retained
1.8	6–36 months	98	98	Immediate	Screw-retained
3	36 months	90	85	Delayed	Screw-retained
2.2	3–49 months	97.30	97	Immediate	Screw-retained
1	12 months	92.70	95	Immediate	Screw-retained
5	42–62 months	87	91	Immediate	Screw-retained
1	12 months	100	100	Delayed	Screw-retained
5	12–132 months	96.70	92.40	Immediate	Screw-retained
1.5	18 months	97.80	100	Immediate	Screw-retained
5	5 years	100	100	Delayed	Screw-retained
1	12	100	100	Immediate provisional	Screw-retained
1.5	18 months	95	100	Immediate provisional	Screw-retained
1.5	18 months	96	100	Delayed	Screw-retained
5.6	3–10 years	80.80	86.80	Delayed	Screw-retained
10	10 years	88.40	100	Delayed	Screw-retained
6	3 years	98.60	100	Delayed	Screw-retained
1	12 months	93.2 to 97.5	100	Different groups	Screw-retained
1.2	6–36 months	96.70	100	Immediate provisional	Screw-retained
1	12 months	93	100	Delayed	Screw-retained
1	12 months	93.2 to 97.5	100	Different groups	Screw-retained
3	36 months	93.2 to 93.3	100	Different groups	Screw-retained
2.4	6–36 months	100	100	Immediate provisional	Screw-retained
1.9	6–43 months	100	100	Immediate provisional	Screw-retained
1	12 months	98.70	100	Immediate provisional	Screw-retained
2.2	12–55 months	99.73	100	Immediate	Screw-retained
1	12 months	98.00	100	Immediate provisional	Screw-retained
2.7	19–47 months	100	100	Immediate	Screw-retained
1	12 months	100	100	Immediate provisional	Screw-retained
2.7	4–33 mos	93.30	100	Immediate	Screw-retained
3	36 months	99.66	100	Immediate	Screw-retained
10	5 and 10 years	94.80	100	Immediate	Screw-retained
2.5	20–48 months	100	100	Immediate provisional	Screw-retained
3	36 months	97.50	100	Immediate provisional	Screw-retained
1.5	18 months	100	100	Immediate provisional	Screw-retained
1	12 m,onths	99.86	100	Immediate provisional	Screw-retained
1.5	3–56 months	98.50	97.70	Immediate	Screw-retained
1	12 months	100	100	Immediate provisional	Screw-retained
2.8	12–56 months	99	96.50	Immediate provisional	Screw-retained
5.5	5–7 years	98.60	100	Conventional	Screw-retained
2	24 months	100	100	Immediate provisional	Screw-retained
1	12 months	96	100	Different groups	Screw-retained

(Continues)

TABLE 2 (Continued) [In PDF format, this table is best viewed in two-page mode]

Number of implants per arch	First author	Year of publication	Study design	Total number of arches	Total number of implants	Position of implants per arch	Manufacturer/Type of implants
4	Jokstad	2014	Prospective RCT	35	140	BMF P	Nobel MK III/MK IV TiUnite
4	Balshi	2014	Retrospective	125	500	BMF DT	Nobel
4	Ayna	2015	Prospective	27	108	BMF DT	Nobel Speedy
4	Cannizzaro	2015	Prospective RCT	30	120	BMF P/D	3i Osseotite
4	Browaeys	2015	Prospective	11	44	BMF P and DT	Nobel MKIII Groovy
4	Melo	2015	Retrospective	10	40	BMF P	Neodent
4	Gherlone	2016	Prospective	13	52	BMF DT	IDI Evolution
4	Faria	2016	Prospective	30	120	BMF P	Astra TiOblast
4	Najafi	2016	Prospective	25	100	BMF DT	Nobel
4	Babbush	2016	Retrospective	93	372	BMF DT	Nobel Active
4	Sannino	2016	Retrospective	85	340	BMF DT	Nobel Active/Speedy
4	Cannizzaro	2017	Prospective RCT	30	120	BMF DT	Zimmer/Biomet—Megagen
4	Sannino	2017	Retrospective	34	136	BMF DT	Nobel Active/Speedy
5	Tinsley	2001	Prospective	20	100	BMF P	Calcitek
5	Friberg	2005	Retrospective	142	710	BMF P	Brånemark Smooth
5	Van de Velde	2007	Prospective	18	90	BMF P	Brånemark MKIII/MK IV
5	Friberg	2008	Retrospective	76	380	BMF P	Nobel MK III TiUnite
5	De Bruyn	2008	Prospective	25	125	BMF P	Astra TiOblast
5	Schwarz	2010	Prospective	37	185	BMF P	Frialoc
5	Collaert	2011	Prospective	25	125	BMF P	Astra Osseospeed
5	Acocella	2012	Retrospective	45	225	BMF DT	Astra
5	Schwarz	2014	Prospective	37	185	BMF P	Frialoc
5	Friberg	2015	Retrospective	259	1230	BMF P	Brånemark/TiUnite
6	Brånemark	1995	Retrospective	59	354	Parallel	Brånemark
6	Romanos	2014	Retrospective	13	78	Parallel	Ankylos
6	Calvo-Guirado	2016	Prospective	10	60	BMF P + DS	Straumann
8	Ferrigno	2002	Prospective	40	320	Parallel	Straumann STL

BMF, between mental foramen; D, distal; DT, distally tilted; P, parallel; V, position of the maxillary implants in the posterior maxilla, where the most distal implant is tilted mesially, and the implant just medial to it is tilted distally (in a 'V' shaped configuration).

comparison between two and four implants, and another compared two and three implants.

Fourteen groups with five or more implants per arch were included, with 10 groups reporting on five implants, three studies on six implants, and one study on eight implants per arch. Follow-up range was from 1 to 10 years (median of 5.5 years).

3.3.2 | Implant and restoration survival rates

Overall mean implant survival rate was 97%, and restoration survival rate was 99%, for a median follow-up period of 5.5 years (range 1–10 years). For the 58 groups with fewer than five implants, mean reported implant survival rate was 97% and restoration survival rate was 99%. The majority of the studies (41) reported on four implants, with a mean implant survival rate of 98%, and restoration survival rate of 99%, with a median follow-up time of 5.5 years (range 1–10 years). Twelve reports on the use of three implants to support a fixed prosthesis were identified, with a survival rate of 96.3% for implants and 97% for the prosthesis, with a follow-up period of 1–5 years (median of 3 years).

For reports with five or more implants (14 studies), mean implant survival rate was 95%, and restoration survival rate was 98%. Looking at the 10 studies that reported on five implants per mandibular arch, mean implant survival rate was 93%, and restoration survival rate was 95%, with an observation period of 1–10 years (median of 4.1 years).

There was no significant difference for implant and prosthesis survival rates between less than five compared to five or more implants, but there is a clear preference for the use of four implants to support a complete-arch fixed prosthesis in the mandible, with a trend to use only three implants in more recent papers.

3.3.3 | Implant distribution

Analyzing the 58 identified reports on fewer than five implants for edentulous mandibles, 27 reported on implants positioned parallel to each other, between the mental foramen, with the mean implant survival rate of 95.9% and restoration survival of 98%. The remaining 31 had the two implants positioned closer to the midline, parallel

TABLE 2 (additional columns - continued)

Mean follow-up Years	Follow-up range	Survival implants (%)	Survival restoration (%)	Loading	Retention
5	60 months	99	100	Different groups	Screw-retained
2.2	6–60 months	97.80	100	Immediate provisional	Screw-retained
5	60 months	100	100	Immediate provisional	Screw-retained
1	12 Months	98.50	100	Immediate provisional	Screw-retained
3	36	100	100	Immediate provisional	Screw-retained
7	7 years	100	100	Immediate	Screw-retained
1	12 months	100	100	Immediate provisional	Screw-retained
2	24 months	95.83	100	Immediate provisional	Screw-retained
3	32.5 ± 12.6	100	100	Different groups	Screw-retained
1.3	12–36 months	99.30	100	Immediate provisional	Screw-retained
3	36 months	98.60	100	Immediate provisional	Screw-retained
3	36 months	100	100	Immediate provisional	Screw-retained
2	24 months	100 (V), 98.38 (DT)	100	Immediate provisional	Screw-retained
5	48–72 months	71	85	Conventional	Screw-retained
1	12 months	97.50	100	Delayed	Screw-retained
3.7	26–57 months	96.70	100	Immediate provisional	Screw-retained
1	12 months	100	100	Delayed	Screw-retained
3	36 months	100	100	Immediate provisional	Screw-retained
7.2	1–8 years	89.70	89.20	Immediate provisional	Screw-retained
2	24 months	100	100	Immediate provisional	Screw-retained
4	48 months	99.50	97.80	Immediate	Screw-retained
7.2	2–14 years	89.20	83.80	Immediate provisional	Screw-retained
5	60 months	97/99.7	98.50	Different groups	Screw-retained
10		93.20	100	Delayed	Screw-retained
6.3	6.3–134 months	100	100	Immediate provisional	Screw-retained
1	12 months	100 (P)/99(Short)	100	Delayed	Screw-retained
5	5–10 years	96.40	100	Early	Screw-retained

to each other, and the two distal implants tilted posteriorly. The mean survival rates for tilted implants in a four implant configuration were 98.6%, and the restoration survival rate was 100%. When three implants were placed (12 reports), the configuration was not always clearly reported for all papers. It varied between "parallel" and "posterior distally tilted" implants, even within the same groups, as well as one in the midline and the two distal ones as posterior as bone allowed.

When more than five implants were placed (14 studies), implant positions were parallel for 12 studies, with a reported mean survival rate of 98% for implants and 100% for prosthesis, with a median follow-up of 5.5 years (1–10 years). Only two groups with five or more implants had the distal implants tilted. One study (Calvo-Guirado et al., 2016) presented the use of six implants per arch, with two extra-short implants placed in each posterior quadrant of each edentulous mandible. These were splinted with two longer anterior implants positioned between mental foramens. Survival rates were 97.5% for the short implants and 100% for the 10-mm-long implants, with a restoration survival rate of 100% after 1 year.

3.3.4 | Loading considerations

Immediate loading was performed in 51 of the 72 groups reporting mandibular implants. Forty-eight of the 51 reports were on the group with fewer than five implants, with a mean implant survival rate of 98% and prosthesis survival rate of 99%, with a median follow-up reported of 5.5 years (range 1–10 years). Fifteen reports had conventional loading (10 in fewer than five and five in five or more), with an average implant survival rate of 94%, and average prosthesis survival rate of 96%, with reported follow-up of 1–10 years (median 5.5 years). Six papers reported a comparison between immediate and conventional (delayed) loading, and they reported no significant difference between the two loading protocols. There was no significant difference between loading protocols used for <5 when compared to 5 or more implants.

3.3.5 | Meta-analysis

Statistically significant heterogeneity between studies was observed, as indicated by the Cochran's Q test and I^2 shown in the Figures 2–5.

TABLE 3 Risk of bias assessment for RCTs—COCHRANE Tool

First author	Year of publication	Study design	Random sequence generation (Selection bias)	Blinding of participants and personnel (Performance bias)	Blinding of outcome assessment (Detection bias)	Incomplete outcome data (Attrition bias)	Selective reporting (Reporting bias)	Other sources of bias	Overall risk of bias	Comments
Alfadda	2014	Prospective RCT	Low risk	Low risk	Unclear risk	Low risk	Low risk	None	Low risk	Mand 4—Immediate vs. Delayed loading
Cannizzaro	2013	Prospective RCT	Low risk	Low risk	Low risk	Low risk	Low risk	None	Low risk	Mand Ao2 vs. Ao4—1 year
Cannizzaro	2015	Prospective RCT	Low risk	Low risk	Unclear risk	Unclear risk	Low risk	None	Low risk	Mand (4) and Max (6) / Short vs. Long
Cannizzaro/ Felice	2017	Prospective RCT	Low risk	Low risk	Low risk	Low risk	Low risk	None	Low risk	Mand Ao2 vs. Ao4—3 years
Cannizzaro/ Gastaldi	2017	Prospective RCT	Low risk	Low risk	Low risk	Low risk	Low risk	None	Low risk	Max 3 / Mand 4—Rough vs. Smooth
Cannizzaro/ Loi	2016	Prospective RCT	High risk	High risk	Low risk	Unclear risk	Low risk	None	High risk	Mand & Max—2 vs. 3 Imm Load
De Kok	2011	Prospective RCT	Low risk	Unclear risk	Unclear risk	Low risk	Low risk	None	Unclear risk	Mand 3 - vs. Overd 2
Jokstad	2014	Prospective RCT	Low risk	Low risk	Unclear risk	Low risk	Low risk	None	Low risk	Mand 4—Immediate vs. Delayed
Tallarico	2016	Prospective RCT	Low risk	Low risk	Low risk	Low risk	Low risk	None	Low risk	Max—4 vs. 6

Hence, a decision was made to perform a meta-analysis using the random-effects model.

All outcomes were dichotomous. The total number of implants and the number of implants without observed failure were used in the calculation of the survival proportion/survival rate for the implants. The survival of the implants/prosthesis refers to the presence or absence of implant/ prosthesis survival or the proportion surviving. The number of arches and the number of prosthesis without observed failure were used in the calculation of the survival proportion and survival rate for the prosthesis.

The proportions of survival along with 95% confidence intervals were estimated for all studies, by study type (randomized controlled trial, prospective, retrospective), by number of implants placed per arch, and by both factors. *p*-values <0.05 were considered statistically significant.

Overall implant and prosthesis survival was high, at 95% CI. No significant differences were found between the study types (prospective, RCT, retrospective) or when comparing studies with fewer than five implants per arch with five or more implants per arch ($p > 0.05$), for both maxillary and mandibular rehabilitations. Forest plots are presented in Figure 2 (maxilla, implants), Figure 3 (maxilla, restorations), Figure 4 (mandible, implants) and Figure 5 (mandible, restorations).

4 | DISCUSSION

4.1 | Initial considerations

The number of implants utilized to support a complete-arch prosthesis is one of the first topics discussed since the beginning of implant dentistry and still remains of interest, due to the several implications derived from the influence on the outcomes regarding the decision to place less or more implants. Initial observation from papers included in our review shows that there is a trend to use less implants, distributed with an adequate antero-posterior spread in the arch.

However, this systematic review found a lack of high-quality evidence publications dealing with the number of implants to be placed to support a complete-arch fixed prosthesis. Only nine randomized clinical trials were included, but more importantly, just one was a RCT that addressed our focused question (less than five vs. five or more implants).

It was clear that evidence from randomized trials was not sufficient to answer questions of interest to patients and healthcare providers, related to the number of implants to support a complete-arch prosthesis. Hence, we needed to include nonrandomized studies (prospective and retrospective), due to the lack of sufficient number of randomized controlled trials examining the outcomes for different number of implants. A larger number of studies were included, and the quality of evidence and the risk of bias was assessed using the ROBINS-I assessment tool.

The ROBINS-I is based on the Cochrane Risk of Bias tool for randomized trials and uses the domain-based assessment, explained in a comprehensive manual in which users can interpret the results in a similar way, thus reducing the risk of subjective evaluation (Sterne et al., 2016).

As stated by Black (1996), nonrandomized studies can provide evidence additional to that available from randomized trials about long-term outcomes, rare events, adverse effects and populations that are typical of real world practice. Using the ROBINS-I tool, the risk of bias of nonrandomized studies of interventions was assessed to be from moderate to serious, and caution has to be taken when analyzing the findings of the studies included in this systematic review of the literature (Table 4). With the above in mind, we present the summary of our findings as follows.

4.2 | Summary of main findings

This review demonstrates similar outcomes (implant and prosthesis survival) when comparing less than five to five or more supporting implants, for both the maxilla and the mandible. The results also demonstrate a larger number of studies reporting on high survival rates for the use of four (22 papers, mean implant survival rate of 97%, with a prosthesis survival rate of 99%, median follow-up of 5.5 years, range 1–10 years), and six implants (20 papers, mean implant survival rate of 95%, prosthesis survival rate of 98.5%, follow-up range of 1–15 years, median of 8 years), to support a one-piece complete-arch fixed prosthesis on the maxilla, and four implants (41 papers, implant rate survival of 97%, restoration survival of 99%, average follow-up time of 2.8 years) to support a one-piece full-arch fixed mandibular prosthesis.

Nonetheless, the authors recognize that the antero-posterior distribution of the implants is also of importance and ideally should be correlated with the number of implants, as it has a direct impact on the survival of implants and on technical complications (Heydecke et al., 2012; Papaspyridakos, Chen, Chuang, Weber, & Gallucci, 2012).

When looking at studies that report on fewer than five implants per maxillary arch, one paper reported a fixed rehabilitation using only two implants (Cannizzaro et al., 2016), and the same publication also reported on three implants per maxillary arch. Survival rates reported were of 82%, lower than the average reported for papers using four implants. Oliva, Oliva, and Oliva (2012) discussed the use of three implants in a maxillary arch, reporting 100% success after 5 years of follow-up. Although these papers report a relatively high survival rate, this approach remains controversial as the loss of one implant leads to failure of the prosthesis, with significant compromise of the outcome. Moreover, the paper with the two implants has very short follow-up and uses a prosthetic concept of a shortened dental arch, having a potential high risk of bias. Hence, one cannot assume that the use of only two implants to support a complete-arch fixed prosthesis is a valid treatment approach.

Twenty-two studies reported on the use of four implants to provide a fixed rehabilitation to the maxilla. Only one study with four implants used parallel placement (Brånemark et al., 1995). This study had a longer follow-up (10 years), used smooth surface implants and

TABLE 4 Risk of bias assessment for non-RCTs—ROBINS-I Tool [In PDF format, this table is best viewed in two-page mode]

First author	Year	Type of study	Confounding	Selection of participans	Classification of interventions
Maló	2005	Retrospective	Moderate	Moderate	Moderate
Degidi	2005	Retrospective	Serious	Serious	Serious
Jemt	2006	Retrospective	Serious	Serious	Serious
Malo	2007	Prospective	Moderate	Moderate	Moderate
Agliardi	2008	Prospective SCoHort	Moderate	Moderate	Moderate
Testori	2008	Prospective	Moderate	Moderate	Moderate
Toljanic	2009	Prospective	Moderate	Moderate	Moderate
Bergqvist	2009	Prospective	Moderate	Moderate	Low
Agliardi	2009	Prospective SCoHort	Moderate	Moderate	Low
Romanos	2009	Retrospective	Moderate	Moderate	Moderate
Degidi	2010	Prospective	Moderate	Moderate	Moderate
Babbush	2011	Retrospective	Moderate	Moderate	Moderate
Malo/de Araújo Nobre	2011	Retrospective	Moderate	Moderate	Moderate
Mertens	2011	Prospective	Moderate	Moderate	Moderate
Cavalli	2012	Retrospective	Moderate	Moderate	Moderate
Maló	2012	Retrospective	Moderate	Moderate	Moderate
Antoun	2012	Retrospective	Moderate	Moderate	Low
Barbier	2012	Prospective	Moderate	Moderate	Low
Mertens	2012	Prospective	Moderate	Moderate	Moderate
Maló	2013	Retrospective	Moderate	Moderate	Moderate
Thor	2014	Retrospective	Moderate	Moderate	Moderate
Maló	2015	Retrospective	Moderate	Moderate	Moderate
Piano	2016	Prospective CoHort	Moderate	Moderate	Moderate
Toljanic	2016	Prospective	Moderate	Moderate	Moderate
Zhang	2016	Prospective	Serious	Moderate	Moderate
Testori	2017	Retrospective	Moderate	Moderate	Moderate
Wentascheck	2017	Retrospective	Moderate	Moderate	Moderate
Brånemark	1995	Retrospective	Moderate	Serious	Moderate
Ferrigno	2002	Prospective	Moderate	Moderate	Moderate
Capelli	2007	Retrospective	Moderate	Moderate	Moderate
Agliardi/Panigati	2010	Prospective CoHort	Moderate	Moderate	Low
Hinze	2010	Prospective CoHort	Moderate	Moderate	Moderate
Puig	2010	Retrospective	Moderate	Moderate	Moderate
Parel	2011	Retrospective	Moderate	Moderate	Moderate
Oliva	2012	Retrospective	Serious	Serious	Moderate
Crespi	2012	Prospective	Moderate	Serious	Moderate
Di	2013	Retrospective	Moderate	Moderate	Moderate
Balshi	2014	Retrospective	Moderate	Moderate	Moderate
Browaeys	2015	Prospective	Moderate	Moderate	Moderate
Babbush	2016	Retrospective	Moderate	Moderate	Moderate
Gherlone	2016	Prospective	Serious	Moderate	Moderate
Najafi	2016	Prospective	Moderate	Moderate	Serious
Sannino	2017	Retrospective	Moderate	Moderate	Moderate
Leimola-Virtanen	1995	Retrospective	Moderate	Moderate	Moderate
Brånemark	1999	Prospective	Moderate	Moderate	Moderate
Eliasson	2000	Retrospective	Moderate	Serious	Moderate
De Bruyn	2001	Prospective	Moderate	Low	Low
Tinsley	2001	Prospective	Serious	Serious	Moderate
Engquist	2002	Prospective	Moderate	Low	Low

(Continues)

TABLE 4 (additional columns)

Deviation from intended interventions	Missing data	Measurements of outcomes	Selection of reported results	Overall	Arch	Number of implants
Moderate	Moderate	Moderate	Moderate	Moderate	Maxilla	4
Serious	Serious	Serious	Serious	Serious	Maxilla	9
Moderate	Serious	Moderate	Moderate	Serious	Maxilla	6
Moderate	Moderate	Moderate	Moderate	Moderate	Maxilla	4
Low	Low	Moderate	Moderate	Moderate	Maxilla	6
Moderate	Moderate	Moderate	Moderate	Moderate	Maxilla	6
Moderate	Moderate	Moderate	Moderate	Moderate	Maxilla	6
Low	Moderate	Low	Low	Low	Maxilla	6
Low	Moderate	Moderate	Low	Moderate	Maxilla	6
Moderate	Moderate	Moderate	Serious	Moderate	Maxilla	6
Moderate	Moderate	Moderate	Moderate	Moderate	Maxilla	7
Moderate	Moderate	Moderate	Moderate	Moderate	Maxilla	4
Moderate	Moderate	Moderate	Moderate	Moderate	Maxilla	4
Moderate	Moderate	Moderate	Moderate	Moderate	Maxilla	6
Moderate	Moderate	Moderate	Moderate	Moderate	Maxilla	4
Moderate	Moderate	Moderate	Moderate	Moderate	Maxilla	4
Low	Low	Moderate	Moderate	Low	Maxilla	6
Moderate	Moderate	Moderate	Moderate	Moderate	Maxilla	6
Moderate	Moderate	Moderate	Moderate	Moderate	Maxilla	6
Moderate	Moderate	Moderate	Moderate	Moderate	Maxilla	4
Moderate	Moderate	Moderate	Moderate	Moderate	Maxilla	6
Moderate	Moderate	Moderate	Moderate	Moderate	Maxilla	4
Moderate	Moderate	Moderate	Moderate	Moderate	Maxilla	4
Moderate	Moderate	Moderate	Moderate	Moderate	Maxilla	6
Moderate	Moderate	Serious	Serious	Serious	Maxilla	8
Moderate	Moderate	Moderate	Moderate	Moderate	Maxilla	6
Moderate	Moderate	Moderate	Moderate	Moderate	Maxilla	6
Moderate	Moderate	Moderate	Serious	Moderate	Max/Mand	4–6 mx/4–6 md
Moderate	Moderate	Moderate	Moderate	Moderate	Max/Mand	8mx/8md
Serious	Moderate	Moderate	Moderate	Serious	Max/Mand	6mx/4md
Low	Low	Low	Moderate	Low	Max/Mand	4mx/4md
Moderate	Moderate	Moderate	Moderate	Moderate	Max/Mand	4mx/4md
Moderate	Moderate	Moderate	Moderate	Moderate	Max/Mand	4mx/6mx/4md
Moderate	Moderate	Moderate	Moderate	Moderate	Max/Mand	4mx/4md
Moderate	Serious	Serious	Serious	Serious	Max/Mand	3mx/3md
Moderate	Serious	Serious	Serious	Serious	Max/Mand	4mx/4md
Moderate	Moderate	Moderate	Moderate	Moderate	Max/Mand	4mx/4md
Moderate	Moderate	Moderate	Moderate	Moderate	Max/Mand	4mx/4md
Moderate	Moderate	Moderate	Moderate	Moderate	Max/Mand	4mx/4md
Low	Low	Moderate	Moderate	Moderate	Max/Mand	4mx/4md
Moderate	Moderate	Serious	Serious	Serious	Max/Mand	4mx/4md
Moderate	Serious	Serious	Serious	Serious	Max/Mand	4mx/4md
Moderate	Moderate	Moderate	Moderate	Moderate	Max/Mand	4mx/4md
Moderate	Moderate	Moderate	Serious	Serious	Mandible	4
Moderate	Moderate	Moderate	Moderate	Moderate	Mandible	3
Moderate	Moderate	Moderate	Serious	Serious	Mandible	4
Low	Low	Low	Low	Low	Mandible	3
Moderate	Moderate	Moderate	Serious	Serious	Mandible	5
Moderate	Low	Low	Low	Low	Mandible	4

(Continues)

TABLE 4 (Continued) [In PDF format, this table is best viewed in two-page mode]

First author	Year	Type of study	Confounding	Selection of participans	Classification of interventions
Hatano	2003	Retrospective	Serious	Serious	Moderate
Kronström	2003	Prospective	Moderate	Moderate	Moderate
Maló	2003	Retrospective	Moderate	Moderate	Moderate
van Steenberghe	2004	Prospective	Moderate	Moderate	Moderate
Engquist	2004	Prospective	Moderate	Low	Low
Engquist	2005	Prospective	Moderate	Low	Low
Friberg	2005	Retrospective	Moderate	Moderate	Moderate
Van de Velde	2007	Prospective	Moderate	Moderate	Moderate
Francetti	2008	Prospective	Moderate	Moderate	Moderate
De Bruyn	2008	Prospective	Moderate	Moderate	Moderate
Friberg	2008	Retrospective	Moderate	Moderate	Moderate
Gualini	2009	Retrospective	Moderate	Moderate	Moderate
Agliardi/Clerico	2010	Retrospective	Moderate	Moderate	Low
Schwarz	2010	Prospective	Moderate	Moderate	Moderate
Hatano	2011	Retrospective	Moderate	Moderate	Moderate
Malo/Nobre	2011	Retrospective	Moderate	Moderate	Moderate
Butura	2011	Retrospective	Moderate	Moderate	Moderate
Collaert	2011	Prospective	Moderate	Moderate	Moderate
Cannizzaro	2012	Prospective	Moderate	Moderate	Moderate
Rivaldo	2012	Retrospective	Moderate	Moderate	Moderate
Grandi	2012	Prospective CoHort	Moderate	Moderate	Moderate
Weinstein	2012	Prospective	Moderate	Moderate	Moderate
Galindo	2012	Retrospective	Moderate	Moderate	Moderate
Acocella	2012	Retrospective	Moderate	Moderate	Low
Krennmair	2013	Retrospective	Moderate	Moderate	Moderate
Krennmair	2014	Prospective	Moderate	Moderate	Moderate
Schwarz	2014	Prospective	Moderate	Moderate	Moderate
Romanos	2014	Retrospective	Moderate	Moderate	Moderate
Ayna	2015	Prospective	Moderate	Moderate	Moderate
Meló	2015	Retrospective	Serious	Serious	Moderate
Friberg	2015	Retrospective	Moderate	Moderate	Moderate
Faria	2016	Prospective	Moderate	Moderate	Moderate
Sannino	2016	Retrospective	Moderate	Moderate	Moderate
Calvo-Guirado	2016	Prospective	Low	Moderate	Low
Primo	2018	Prospective	Moderate	Moderate	Moderate

reported a survival rate for the implants of 80.30%, but a restoration survival rate of 100%. This would seem contrary to general opinion that suggests prosthesis failure would result from the loss of even one implant. Recent studies have frequently reported that the loss of one implant in a type of prosthesis supported by four implants does not necessarily mean that the prosthesis is lost. The prosthesis is lost if one of the most distal implants is lost. If one of the anterior implants is lost, then the prosthesis may survive on the remaining three implants, after relining in the area (Maló, de Araújo Nobre, Lopes, Francischone, & Rigolizzo, 2012).

All other 21 papers reported the same implant position configuration that being two anterior implants parallel to each other and the two posterior implants intentionally distally tilted or inclined. This concept has become increasingly popular, with medium to long-term studies being published in recent years (Table 1). This approach seems especially applicable to the edentulous maxilla, due to resorption on the posterior region. Inclining the distal implants reduces the prosthesis cantilever, and the need for grafting. This approach also utilizes a reduced number of implants, which may have advantages and disadvantages. It is not possible, however, to extrapolate from the reviewed literature that the reported survival rates are the result of only the reduction in cantilever dimension. The influence of additional variables cannot be excluded. The inclination of the anterior wall of the maxillary sinus, for example, plays a significant role in defining the implant inclination and therefore the length of cantilever reduction that is achievable (Bedrossian, 2011). In situations where the patient presents with teeth that are planned to be extracted, and a one-piece fixed prosthesis is planned, there

TABLE 4 (additional columns - continued)

Deviation from intended interventions	Missing data	Measurements of outcomes	Selection of reported results	Overall	Arch	Number of implants
Moderate	Serious	Serious	Serious	Serious	Mandible	3
Moderate	Moderate	Moderate	Moderate	Moderate	Mandible	4
Moderate	Moderate	Moderate	Moderate	Moderate	Mandible	4
Moderate	Moderate	Moderate	Moderate	Moderate	Mandible	3
Moderate	Low	Low	Low	Low	Mandible	4
Low	Low	Low	Low	Low	Mandible	4
Moderate	Moderate	Moderate	Moderate	Moderate	Mandible	5
Moderate	Moderate	Moderate	Moderate	Moderate	Mandible	5
Moderate	Moderate	Moderate	Moderate	Moderate	Mandible	4
Moderate	Moderate	Moderate	Moderate	Moderate	Mandible	5
Moderate	Moderate	Moderate	Moderate	Moderate	Mandible	5
Moderate	Moderate	Moderate	Moderate	Moderate	Mandible	3
Low	Moderate	Moderate	Moderate	Moderate	Mandible	4
Moderate	Moderate	Moderate	Moderate	Moderate	Mandible	5
Moderate	Moderate	Moderate	Moderate	Moderate	Mandible	3
Moderate	Moderate	Moderate	Moderate	Moderate	Mandible	4
Moderate	Serious	Serious	Serious	Serious	Mandible	4
Moderate	Moderate	Moderate	Moderate	Moderate	Mandible	5
Moderate	Moderate	Moderate	Low	Moderate	Mandible	2
Moderate	Moderate	Moderate	Moderate	Moderate	Mandible	3
Moderate	Moderate	Moderate	Moderate	Moderate	Mandible	4
Moderate	Moderate	Moderate	Moderate	Moderate	Mandible	4
Moderate	Serious	Serious	Serious	Serious	Mandible	4
Low	Low	Low	Low	Low	Mandible	5
Moderate	Moderate	Moderate	Moderate	Moderate	Mandible	4
Moderate	Moderate	Moderate	Moderate	Moderate	Mandible	4
Moderate	Moderate	Moderate	Moderate	Moderate	Mandible	5
Moderate	Moderate	Moderate	Serious	Moderate	Mandible	6
Moderate	Moderate	Moderate	Moderate	Moderate	Mandible	4
Moderate	Serious	Serious	Serious	Serious	Mandible	4
Moderate	Moderate	Moderate	Moderate	Moderate	Mandible	5
Moderate	Moderate	Moderate	Moderate	Moderate	Mandible	4
Moderate	Moderate	Moderate	Moderate	Moderate	Mandible	4
Low	Low	Low	Low	Low	Mandible	6
Moderate	Moderate	Moderate	Moderate	Moderate	Mandible	3

may be need to reduce vertically the alveolar bone, in order to create space for the restorative components. Such anatomically sound decisions are made during planning of the procedure and therefore influence outcomes. Adding an angled prosthetic component may also influence the mechanical outcome of a one-piece fixed prosthesis.

The use of digital planning can greatly assist in choosing the most appropriate and beneficial implant inclination and therefore defining indications for the use of a tilted implant as opposed to a short implant or a sinus floor elevation graft. Additionally, digital impressions and the use of computer-aided designed and manufactured infrastructures are rapidly growing, allowing for more accurate fit, with an intent to reduce surgical burden, expedite prosthetic delivery and improve long-term results. This approach is being frequently reported in recent publications (Gherlone et al., 2016; Kapos et al., 2009; Papaspyridakos et al., 2017).

One paper (Tallarico et al., 2016) compared use of four and six implants, with 20 patients followed an average of 63.8 months. The implant survival rate was similar, although slightly lower for the group of six implants (95%) than the group with four implants (98.3%). These findings were similar to those reported in a 15-year analysis of fixed rehabilitations for the edentulous maxilla, published by Lambert et al. (2009). These authors concluded that protocols with more than six implants demonstrated a higher survival rate than those with fewer than six implants, although with no statistically significant difference.

For the mandible, although five papers report 98% survival rates on the use of only two implants to support a fixed restoration, they

are all from the same author, with a high risk of bias. In contrast, there are a significant number of reports on the use of three implants for a fixed mandibular restoration. The usually higher bone density of the anterior mandible may allow for improved results with this configuration. A recent report by Primo et al. (2018) used three implants to support a fixed prosthesis in edentulous patients, obtaining survival rates for the implants and the prosthesis of 95%. They compared on the same paper immediate vs. conventional loading and had no significant difference. Of interest was that they positioned the distal implants with a DT (distally tilted) configuration, in an attempt to reduce the cantilever, in a few cases. This approach is also used in a previous study by the same group (Rivaldo, Montagner, Nary, da Fontoura Frasca & Brånemark 2012), that proposed it to facilitate the protocols once defined as the "Brånemark Novum" technique (Brånemark et al., 1999), that used parallel placed implants. The distribution of the implants is also emphasized by Oliva et al. (2012), that state that the anterior–posterior distribution of the implants was such as to significantly reduce cantilevers. In the study by Primo et al. (2018), there was no statistically significant association of peri-implant bone loss with the effort arm/resistance arm ratio. Their findings confirm those of Gallucci, Doughtie, Hwang, Fiorellini, and Weber (2009), who did not find a linear correlation between the cantilever length and the number or type of prosthesis-related complications at 5 years of function (Gallucci et al., 2009).

The use of four implants to support a complete mandibular arch fixed prosthesis was by far the most reported on treatment approach, with 41 papers clearly stating the use of four implants with anterior–posterior spread and a screw-retained restoration. Analyzing the results compared to the 10 papers that reported the use of five implants, there was no statistically significant difference. However, most of the papers reporting on five implants utilized smooth surface implants and reported a slightly lower survival rate. The majority of papers discussing on the use of four implants reported utilization of more modern roughened implant surfaces, illustrating an increase in survival rates. A large number of papers reported on use of four implants with immediate loading, beginning in 2003 (Maló et al., 2003) and reviewed in 2014 (Patzelt, Bahat, Reynolds, & Strub, 2014). Anatomic observations and considerations cannot be overlooked when determining clinical applicability of distally tilted or inclined posterior implants.

Immediate loading was reported as the preferred loading approach in the majority of the studies (92 groups of 112 analyzed utilized immediate loading, being 41 in the maxilla, and 52 in the mandible). The majority of the immediate loaded prosthesis were provisional, with acrylic material and screw-retained. There was a clear preference for the use of immediate loading in both maxilla and the mandible, irrespective of the number of implants.

4.3 | Strengths and limitations

This is a comprehensive review and meta-analysis of controlled interventions aimed at rehabilitation of fully edentulous patients with fixed restorations. The strength of this study is the comparison of reports that are clear on the description of the number of implants per arch used. The methodology facilitates comparison of available data where the number of implants was among the main purposes of the studies. Many publications that report on bone grafts and reconstructions have several variable factors in addition to the number of implants. That same issue is found in early publications about osseointegration, where up to 10 implants were placed but not all loaded or utilized, with additional implants placed to cover for failures should they occur. As confidence in osseointegration developed, and microroughened surfaces showed improved results, less implants were placed.

The greatest limitations to this report are the low level of evidence of the majority of the reports (84 non-RCT studies of 93 selected), as well as the relatively short observational period of the majority of the studies with fewer than five implants (median observation period of 5.5 years). The reduced number of descriptive results regarding technical (restoration) and biological complications is also a limitation, as they are expected to increase as time of using the prosthesis progresses. Further, the results reported cannot be evaluated beyond the implant number, to include additional variables, such as the use of angled abutments, surgical and restorative difficulty, one-piece vs. multiple segmented restorations and cantilever lengths. These factors can result from implant position and distribution in addition to implant number and influence outcomes. Based on the parameters of our search, there is inadequate data to compare the marginal bone loss around parallel and distally tilted implants, both for the maxilla as well as for the mandible. However, survival of both implants and prosthesis reported are in excess of 95%. Moreover, our review focused on implant and prosthesis survival, which is not the most challenging method to evaluate implant and patient outcomes.

Regarding the meta-analysis using a random-effects model, and comparing different types of studies, statistical tests of heterogeneity are included in this review, depicted in Figures 2–4. Most show statistically significant heterogeneity, which was anticipated. All meta-analyses with heterogeneity require the same underlying assumption that combining the results is acceptable to obtain an overall interpretation. Moreover, our purpose was not to compare among the treatments tested within each of the published studies. Studies directly comparing fewer than five with five or more implants per arch are not available, so we pulled single arms from the individual studies. Results from the meta-analysis can be interpreted analyzing the figures and are of value to assess the focused question.

4.4 | Comparison with previous systematic reviews

Early publications focusing on fixed rehabilitation of complete edentulous arches report on the mean number of implants per edentulous arch and an overall survival rate. These studies do not report on an exact number of implants per arch. Recent systematic reviews also report on a mean number of implants per arch. Our methodology involved selecting only papers that made clear the

exact number of implants placed per arch, as this was our focused question.

The majority of the populations reported (63 out of 112) dealt with four implants per arch. For both the maxilla and the mandible, the most used configuration was two parallel implants placed in the anterior region, where there is usually more bone available, and two distal implants (right and left) with the head of the implant distally tilted, in order to reduce the cantilever and engage adequate available bone. A one-piece complete-arch prosthesis was used with this configuration. This is in accordance with previous systematic reviews (Del Fabbro, Bellini, Romeo, & Francetti, 2012), Patzelt et al., 2014).

As there is usually less bone in the posterior region of the jaws, that configuration also reduces the need for a bone graft and staged implant placement. This allows more patients to be rehabilitated, as it is a less invasive and less expensive procedure, when compared to the grafting alternatives. Although it requires adequate surgical skills to be able to place an inclined implant in the correct 3D position and with good primary stability, it still requires less expertise than a staged bone graft procedure, being much less demanding for the patient regarding overall treatment invasiveness, time and cost. Additionally, a tilted implant approach requires also an advanced prosthodontic expertise and it is more challenging than having to restore parallel placed implants.

Bone remodeling around angled abutments positioned on top of distally tilted implants seems not to be higher, according to Monje, Chan, Suarez, Galindo-Moreno, and Wang (2012). These authors reported in a meta-analysis that marginal bone loss around tilted implants that were splinted to support fixed prostheses was not significantly different from straight implants for the short- or medium-term reviews. However, tilted implants had slightly more marginal bone loss at the medium-term review. There was no evidence that tilted implants are associated with a higher incidence of biomechanic complications. Recent findings related to this approach are being discussed in detail by another systematic review part of this conference (Lin & Eckert, 2018).

Passoni et al. (2014) reported on the relationship between the number of implants and peri-implant disease for full fixed restorations. These authors evaluated 32 patients and 132 implants divided into two groups, five or less and more than five for each arch. Several parameters related to peri-implant disease were observed, and their conclusion was that the use of more than five implants per arch to support a full fixed rehabilitation may increase bone loss and consequently the prevalence of perimplantitis. These findings are in agreement with Corbella, Del Fabbro, Taschieri, De Siena, and Francetti (2011), suggesting that the reduced number of implants, together with motivation of the patient to perform correct hygiene, correct positioning of implants and integrated planning are factors that favor the manufacturing of a suitable prosthesis and increase the chance of maintaining peri-implant health.

Lambert et al. (2009) suggest that six implants are a critical number with respect to the prosthetic survival rate. Our review also shows a high survival rate for studies that use five or more implants, both for the maxilla and the mandible. For the maxilla, the use of six implants seems to be a common protocol, whereas in the mandible, four or five implants were also used frequently.

Gallucci et al. (2016) present the treatment planning variables for maxillary fixed prosthesis, discussing on the utilization of a one-piece vs. a segmented prosthesis. The vast majority of the papers in our review reported on the use of a one-piece prosthesis, splinting all the implants. That approach is required when fewer than five implants are performed. When planning a two, three or four piece segmented restoration for an edentulous arch, the clinician must consider the need to place six to eight implants. Segmented restorations using six to eight implants for support and retention may allow for a better precision on fitting the prosthesis, more accurate laboratory work, and fewer restorative maintenance visits. However, these protocols require optimal bone support and may not be suitable for the majority of the patients, due to lack of adequate bone and/or an increased financial expense. If grafting procedures are indicated, cost and number of interventions for the patient may increase.

Analyzing the data of articles selected for this review, there is a similar use of four and six implants to support a one-piece fixed prosthesis in the maxilla, with immediate loading. In the mandible, there is clear preference to the use of four implants, with immediate loading. The indication of three implants to rehabilitate the mandible with an implant supported complete-arch prosthesis is being reported on with more frequency, with more articles than the classic use of five implants (12 for three implants and 10 for five implants), although with a shorter median follow-up period (3 years for three implants and 4.1 years for five implants), but with similar survival rates (96% and 95%). These results are consistent with the findings of the systematic review performed by Heydecke et al. (2012), and we agree with their conclusions that there is a lack of evidence to determine the optimal number and distribution of implants to support a complete-arch fixed prosthesis, even that our review shows a clear trend to the use of four to six implants. Our findings also are in agreement that there is unclear evidence that the use of more than six implants to support a fixed prosthesis is beneficial to the patients.

4.5 | Implications for researchers and clinicians

As our review included studies that clearly reported the exact number of implants per arch, with at least ten patients and 12 months of follow-up, clinicians can conclude that, at least in the short term, implant survival is high with these treatment protocols. However, many of the studies included in this review, as well as recent publications (Niedermaier et al., 2017), report on patients presenting with compromised dentition, where the treatment planning decision was to extract all teeth and place a one-piece fixed complete prosthesis (hybrid), supported by less than five implants. This modality of treatment is being increasingly performed, and there is a need to prove the long-term outcomes of this approach.

For researchers, this review may identify areas of future interest, as most of the included publications are retrospective or case series studies, with a low level of evidence.

New technologies are being developed and incorporated daily in clinical practices. The use of digital impressions, digital planning, guided surgery and digital printing or milling should provide more accurate and less invasive surgeries, better fitting of prostheses, and hopefully improved patient outcomes.

Recent implant designs, materials and surfaces may further provide higher survival rates, reducing the number of potential complications, for all number of implants used to manage edentulous arches. The use of reduced diameter implants in the anterior region, combined with short and extra-short implants placed in the posterior region, may provide to the clinicians a safer solution as far as reduced cantilever and a minimally invasive surgery, utilizing six implants to support a complete fixed restoration.

Considering that the higher level of evidence is the randomized controlled clinical trial, future research should be focused on this study design so that comparison with early and current less rigorous publications can be more meaningful.

5 | CONCLUSIONS AND RELEVANCE

Evidence from this systematic review and meta-analysis shows that the most reported number of implants for the "fewer than five" group is four for the maxilla, and three and four for the mandible, whereas for the "five or more" implants group, the most reported number of implants was six for the maxilla and five for the mandible. Data analyzed from the included papers suggest that the use of fewer than five implants for rehabilitation of the edentulous maxilla or mandible with a one-piece fixed prosthesis has survival rates (implant and prostheses) similar to those observed using five or more implants per arch, with no statistical significant difference at a $p > 0.005$ and a confidence interval of 95%, with a median follow-up time of 8 years, ranging from 1 to 15 years.

Immediate loading of implants placed in both the maxilla and mandible also provided high survival rates, and most reports utilized immediately positioned screw-retained provisional restorations, substituted by a definitive one-piece rehabilitation after the healing period.

For both maxillary and mandibular rehabilitations, the use of the distal implants with posterior inclination did not seem to affect the overall survival rate for implants and restorations. This was the most reported configuration when using fewer than five implants. When five or more implants were used, the more classic use of parallel implants was reported. Survival rates were similar for both configurations.

It is clear from this review that the placement of fewer than five implants to support a complete-arch fixed restoration allows for high survival rates, for both the maxilla and the mandible. However, additional key variables should ultimately be considered by clinicians when planning treatment for edentulous arches (Gallucci et al., 2016). The number of implants is only one of these variables. The final prosthetic plan should be considered when developing the surgical plan for implant treatment of edentulous arches. Factors to be considered include prosthesis material, one-piece or segmented prostheses, aesthetic factors (lip support, smile line), opposing dentition, available prosthetic space, anatomy of the edentulous ridge (maxilla, mandible, bone volume and quality, anatomic limitations), distribution of implants in the arch, cantilever length, hygiene space, patient preference and compliance.

It should be recognized that a "one-fits-all" approach cannot be identified, and the risks and benefits of choosing the adequate number of implants for each treatment should be evaluated considering all the mentioned variables, to obtain predictable and long-lasting results.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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REVIEW ARTICLE

WILEY CLINICAL ORAL IMPLANTS RESEARCH

A systematic review of the survival and complication rates of zirconia-ceramic and metal-ceramic multiple-unit fixed dental prostheses

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Abstract

Objectives: The aim of the present review was to compare the outcomes, that is, survival and complication rates of zirconia-ceramic and/or monolithic zirconia implant-supported fixed dental prostheses (FDPs) with metal-ceramic FDPs.

Materials and Methods: An electronic MEDLINE search complemented by manual searching was conducted to identify randomized controlled clinical trials, prospective cohort studies and retrospective case series on implant-supported FDPs with a mean follow-up of at least 3 years. Patients had to have been examined clinically at the follow-up visit. Assessment of the identified studies and data extraction was performed independently by two reviewers. Failure and complication rates were analyzed using robust *Poisson* regression models to obtain summary estimates of 5-year proportions.

Results: The search provided 5,263 titles and 455 abstracts. Full-text analysis was performed for 240 articles resulting in 19 studies on implant FDPs that met the inclusion criteria. The studies reported on 932 metal-ceramic and 175 zirconia-ceramic FDPs. Meta-analysis revealed an estimated 5-year survival rate of 98.7% (95% CI: 96.8%–99.5%) for metal-ceramic implant-supported FDPs, and of 93.0% (95% CI: 90.6%–94.8%) for zirconia-ceramic implant-supported FDPs ($p < 0.001$). Thirteen studies including 781 metal-ceramic implant-supported FDPs estimated a 5-year rate of ceramic fractures and chippings to be 11.6% compared with a significantly higher ($p < 0.001$) complication rate for zirconia implant-supported FDPs of 50%, reported in a small study with 13 zirconia implant-supported FDPs. Significantly ($p = 0.001$) more, that is, 4.1%, of the zirconia-ceramic implant-supported FDPs were lost due to ceramic fractures compared to only 0.2% of the metal-ceramic implant-supported FDPs. Detailed analysis of factors like number of units of the FDPs or location in the jaws was not possible due to heterogeneity of reporting. No studies on monolithic zirconia implant-supported FDPs fulfilled the inclusion criteria of the present review. Furthermore, no conclusive results were found for the aesthetic outcomes of both FDP-types.

Conclusion: For implant-supported FDPs, conventionally veneered zirconia should not be considered as material selection of first priority, as pronounced risk for

framework fractures and chipping of the zirconia veneering ceramic was observed. Monolithic zirconia may be an interesting alternative, but its clinical medium- to long-term outcomes have not been evaluated yet. Hence, metal ceramics seems to stay the golden standard for implant-supported multiple-unit FDPs.

KEYWORDS
biological, complications, fixed dental prostheses, implant bridge, meta-analysis, metal-ceramics, survival, systematic review, technical, zirconia framework

1 | INTRODUCTION

In recent years, the variety of restorative materials for implant-supported reconstructions has significantly increased (Fehmer, Muhlemann, Hammerle, & Sailer, 2014). While metal ceramics were the golden standard for the fabrication of implant-supported reconstructions in the past, CAD/CAM technology allows for the use of less expensive materials and faster manufacturing procedures aiming to increase the general efficiency of the treatments nowadays (Benic, Muhlemann, Fehmer, Hammerle, & Sailer, 2016; Joda, Zarone, & Ferrari, 2017). As a consequence, the application of all-ceramics in general, and specifically zirconia as restorative material for implant-supported single crowns (SCs) and fixed dental prostheses (FDPs), has increased (Guess, Att, & Strub, 2012).

One advantage of the recent CAD/CAM ceramics such as zirconia is reduced treatment costs and treatment time (Joda et al., 2017). Another advantage is the improved aesthetics with the all-ceramic implant reconstructions as compared to metal-ceramic reconstructions. As an example, studies have shown that zirconia abutments supporting all-ceramic implant reconstructions exhibited superior soft tissue color outcomes compared with metal abutment supporting metal-ceramic reconstructions (Jung et al., 2008).

Yet, despite the large selection of materials available on the market today, the selection of the best possible restorative solution remains to be difficult for the clinicians. Up to date, the most investigated restorative material in the prosthodontic literature remains to be metal ceramics. Clinicians, however, increasingly tend to use zirconia for the fabrication of implant-supported SC and FDPs in their daily practices. The long-term behavior of more recent restorative materials such as zirconia, and their impact on the survival and complication rates of implant-supported reconstructions, still remains an open question. Hence, the long-term outcomes have to be elucidated in more detail and compared to the golden standard before considered a standard of care.

Two systematic reviews from 2012 reported on the survival and complication rates of implant-supported SCs and FDPs in general, yet not focusing on the type of material used for restoration (Jung, Zembic, Pjetursson, Zwahlen, & Thoma, 2012; Pjetursson, Thoma, Jung, Zwahlen, & Zembic, 2012). The systematic review of Pjetursson et al. reported an estimated 5-year survival rate of implant-supported FDPs of 95.4% (95% CI: 93.1%–96.9%). Regarding technical complications, fractures of the veneering material occurred in 13.5% (95% CI: 8.5%–20.8%), abutment or screw loosening occurred in 5.3% (95% CI: 3.6%–7.7%), and loss of retention occurred in 4.7% (95% CI: 2.6%–8.5%). The authors concluded that implant-supported FDPs are a valid and predictable treatment option and dentists should decide upon reliable materials for the implant-supported reconstructions.

For this reason, it was the aim of the present review to analyze the outcomes, that is, survival rates and technical, biologic and aesthetic complication rates of the zirconia-ceramic and/or monolithic zirconia implant-supported multiple-unit FDPs, as compared to the golden-standard, the metal-ceramic implant-supported multiple-unit FDPs.

2 | MATERIAL AND METHODS

This systematic review was registered at the National Institute for Health Research PROSPERO, International Prospective Register of Systematic Reviews (registration number CRD42017079072).

2.1 | Focused question

The focused question was determined according to the PICO strategy (Population, Intervention, Comparison, and Outcome) (Akobeng, 2005; Sackett, Richardson, Rosenberg, & Haynes, 2000).

- Population: Partially edentulous patients
- Intervention: Implant-supported fixed dental prostheses (FDPs) with veneered zirconia framework or monolithic zirconia as restoration material
- Comparison: FDPs with metal ceramic as restoration material
- Outcome: Survival and complication rates of the reconstructions

The focused question of the present review was: "In partially edentulous patients with implant-supported fixed dental prostheses (FDPs), do zirconia-ceramic and/or monolithic zirconia FDPs exhibit different prosthetic outcomes compared to metal-ceramic FDPs?"

2.2 | Search strategy

Electronic Medline (PubMed) search was performed for studies published until and including November 2016. The extracted data

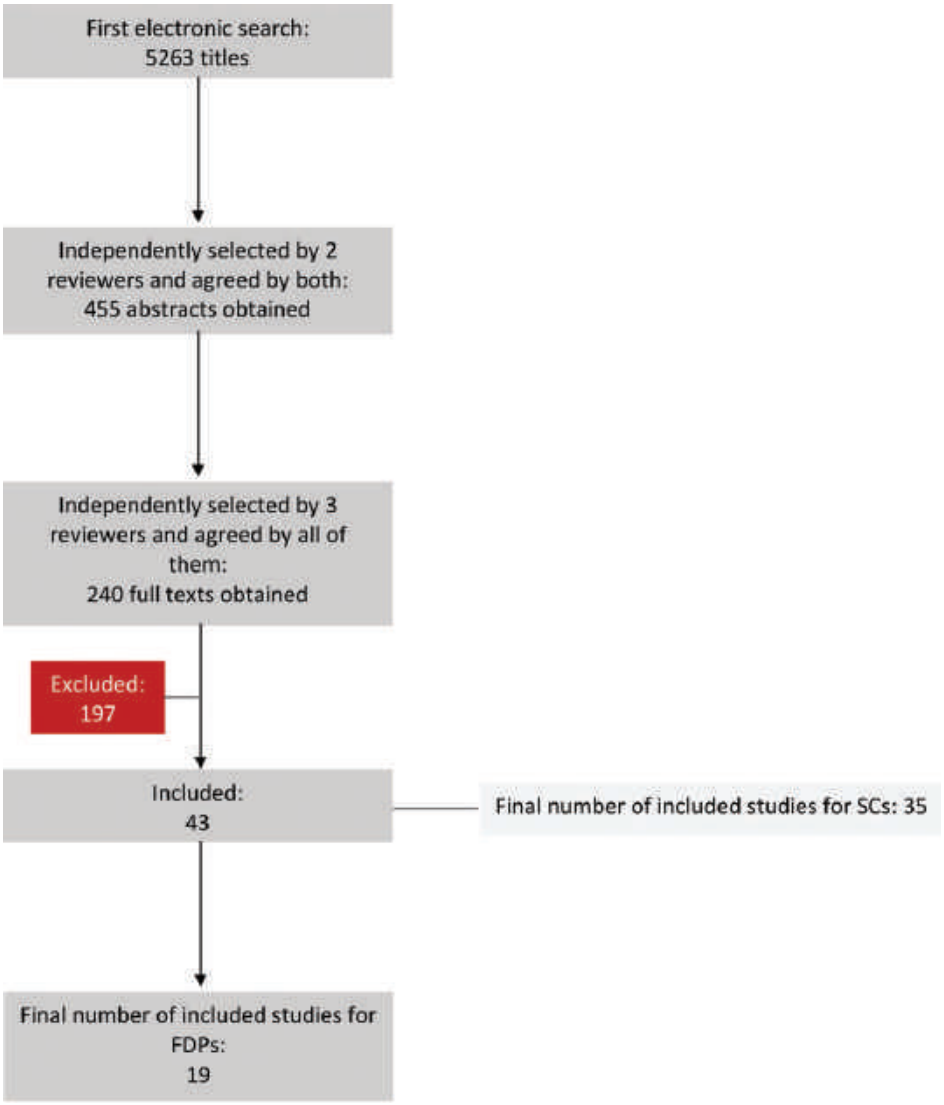

FIGURE 1 Search strategy

were used for conducting two systematic reviews and meta-analyses, one focusing on zirconia- and metal-ceramic implant-supported single crowns (SCs) and the second one focusing on zirconia- and metal-ceramic multiple-unit FDPs. The data were divided into the separate groups for SCs and FDPs during data extraction. Furthermore, a hand search was performed, taking into consideration all the reference lists of the included literature, and of the two relevant systematic reviews on implant-supported fixed reconstructions (Jung et al., 2012; Pjetursson et al., 2012), comprising publications from August 2006 up to August 2011 (Jung et al., 2012) and publications from 2004 up to August 2011 (Pjetursson et al., 2012).

2.3 | Search terms

The following search strategy was applied for the Pubmed search:

(((((jaw, edentulous, partially, dental implants, Dental Prosthesis, Implant-Supported[mesh]) OR (partially edentulous) OR (partial edentulism) OR (fixed implant prosthesis))) AND/OR ((Implant-Supported Dental Prosthesis, Crown* AND/OR Bridge* AND/OR fixed partial denture* AND/OR fixed dental prosthesis, zirconium, zirconia, zirconium oxide[mesh]) OR (dental implants, dental prostheses[mesh]) OR (zirconia framework) OR (monolithic zirconia))) AND/OR ((Implant-Supported Dental Prosthesis, Crown*, Bridge*, fixed partial denture*, fixed dental prosthesis, metal*, metal ceramic* [mesh]) OR (dental implants, dental prostheses[mesh]) OR (metal framework))) AND/OR (Outcome Assessment, Treatment Outcome, dental implants, dental prostheses[mesh] OR dental prostheses outcomes OR dental implant prosthetic outcomes OR dental implant prosthetic failure)

The search was limited to "clinical trial" and "review," "abstract," "free full text" and "full text" and to "humans."

2.4 | Inclusion criteria

No language restrictions were applied; consequently, studies in all languages were included. This systematic review aimed to include

primarily RCTs, but also prospective cohort studies and case series and retrospective case series.

Studies were included if they met the following inclusion criteria:

- Human
- Clinical studies: that is, randomized controlled clinical trials, controlled trials, prospective cohort studies, prospective case series, retrospective studies
- patients were clinically examined
- At least 10 patients treated
- A mean follow-up time of at least 3 years
- Restoration type, SCs or multiple-unit FDPs, clearly reported
- Restorative materials described in detail
- Restorative materials metal ceramic or zirconia ceramic
- All-ceramic restorations with zirconia frameworks subsequently veneered, or monolithic zirconia restorations
- Studies that pooled the outcomes of different materials were included if more than 90% of reconstructions belonged to the same material group that is zirconia or metal-ceramic groups.

2.5 | Exclusion criteria

The following studies were excluded:

- Studies that did not report on the restorative material in detail
- Studies with pooled results of different restorative materials
- Studies with pooled results for SCs and FDPs that did not allow a distinction between the results of SCs and FDPs
- Studies including implant-supported full arch reconstructions in a higher proportion than 15%
- Studies on removable implant-supported reconstructions
- In vitro studies
- Animal trials
- Preclinical studies
- Studies with less than 10 patients treated
- Less than 3 years of mean follow-up time
- Studies that did not meet the above inclusion criteria

2.6 | Selection of studies

For the selection of the abstracts, two of the authors (NAV, SL) screened the titles independently. Whenever there was disagreement, it was solved by discussion. After having agreed on the abstracts to be included, the abstracts were screened by three of the authors (MS, NAV, SL) independently. Again, whenever there was a dissent the authors agreed by discussion. In case an abstract was not available in Pubmed, the abstract was extracted out of the printed article. The same three investigators (MS, NAV, SL) continued with the selection of the full-text articles, based on the agreed inclusion criteria on abstract level. Finally, the selected full-text articles were double-checked independently by the two senior authors of the present review (IS, BEP).

Additionally, the reference lists of all included studies and the references lists of the previously mentioned reviews (Jung et al., 2012; Pjetursson et al., 2012) were hand searched.

2.7 | Excluded studies

A total of 240 full-text articles were screened by the authors, out of which 197 articles were excluded (Figure 1). The detailed references and individual reasons for exclusion are given in the reference list of excluded literature. Main reasons for exclusion were lacking information on the type of material, no details or differentiation of the restoration type, and pooled results for either different material or different restoration types. Other reasons for exclusion were restoration material other than zirconia ceramic and metal ceramic, insufficient follow-up time, and <10 patients treated.

2.8 | Data extraction

After the extensive search of the literature, and after the additional hand search, in total, 43 studies could be included in the present systematic review (Figure 1). For the extraction of the data, a table was designed, containing 58 parameters that were to be extracted out of the studies.

The data extraction was performed by four reviewers (BEP, IS, MS, NAV). In order to follow a standardized method, in the beginning, every author extracted the data of three articles and these results were then discussed within the group. This way the same approach for data extraction by all reviewers could be guaranteed. It was distinguished between data for implant-supported SCs and multiple-unit FDPs and for the present meta-analysis, only data for the multiple-unit FDPs were included. Whenever a clear distinction of reconstruction types and/or materials was not possible, either the corresponding author was contacted for clarification, or the study was excluded due to the pooled data.

Data were extracted on follow-up period, the type/s of reconstruction material, the way of fixation of the reconstruction, the cement type, the region of the reconstruction in the oral cavity, the number of failure of the reconstructions as well as the number of biological, mechanical, and aesthetic complications. As mechanical complications, restoration fractures, abutment fractures, screw fractures and screw loosening, ceramic fractures, ceramic chippings, and loss of retention were included. The biological complications contained soft tissue complications and reported number of implants with significant bone loss. Besides aesthetic complications, aesthetic failures, as well as mucosal discolorations were extracted.

Of each included study, the available data were extracted. Studies that reported on the survival of the FDPs were used for the extraction of the survival rates. Studies that reported on the complications but not in detail on the survival were used for the extraction

TABLE 1 Study and patient characteristics of the reviewed studies on metal-ceramic FDP

Metal-ceramic fixed dental prostheses												
Study (Year)	**Study Design**	**Planned no of patients**	**Number of patients at end of study**	**Sex M/F**	**Drop out %**	**Mean age**	**Age range**	**Setting**	**Implant system**	**Ant.**	**Post.**	**Max.**	**Mand.**
Mangano, Iaculli, Piattelli, and Mangano (2015)	Retrospective	49	49	26/23	0	54.5 ± 3.1	22–70	Private practices	Mac System	n.r.	n.r.	n.r.	n.r.
Wittneben et al. (2014)	Retrospective	358	303	143/160	15	n.r.	n.r.	University	Straumann	n.r.	n.r.	n.r.	n.r.
Francetti, Azzola, Corbella, Taschieri, and Del Fabbro (2014)	Prospective case series study	22	19	10/12	14	n.r.	n.r.	Private clinic	Nobel Replace	n.r.	n.r.	5	13
Romeo, Storelli, Casano, Scanferla, and Botticelli (2014)	Prospective (RCT)	24	18	12/12	25	54.3 ± 11.3	32–75	University	Straumann	0	24	n.r.	n.r.
Mangano et al. (2014)	Prospective	642	606	356/286	6	n.r.	20–82	Private practice	Leone Implant System	n.r.	n.r.	n.r.	n.r.
Vanlioglu, Ozkan, and Kulak-Ozkan (2013)	Retrospective	95	95	46/49	0	41.2	n.r.	University	Straumann	0	n.r.	0	0
Perelli, Abundo, Corrente, and Saccone (2012)	Prospective	87	87	52/35	0	n.r.	n.r.	Private Practice	n.r.	n.r.	n.r.	n.r.	n.r.
Palmer, Howe, Palmer and, Wilson (2012)	Prospective	31	27	9/22	7	50 ± 15.8	18–70	University	MT Osseospeed Astra Tech AB	0	28	20	8
Nissan, Narobai, Gross, Ghelfan, and Chaushu (2011)	Retrospective on prospective cohort	38	38	16/22	0	58 ± 16	38–70	University	Biomet 3i internal hex	0	76	n.r.	n.r.
Wahlstrom, Sagulin, and Jansson (2010)	Retrospective	50	46	13/33	8	n.r.	n.r.	Public dental service	Astra Tech, Nobel Biocare	n.r.	n.r.	34	0
Romeo, Tomasi, Finini, Casentini, and Lops (2009)	Prospective	59	32	25/34	46	63	42–100	University + private practice	straumann	n.r.	n.r.	33	26
Ozkan, Ozcan, Akoglu, Ucankale, and Kulak-Ozkan (2007)	Prospective cohort	63	63	25/38	0	46.9	18–63	University setting	Straumann Camlog, Frialit	0	70	32	38
Romeo et al. (2006)	RCT	188	161	83/105	14	55.8	21–74	University setting	Straumann	n.r.	n.r.	n.r.	n.r.
Jemt et al. (2003)	Prospective	42	35	n.r.	17	53 ± 11.5	25–74	Multicenter	Brånemark	n.r.	n.r.	10	49
Bambini, Lo Muzio, and Procaccini (2001)	Retrospective	59	59	35/24	0	56.5	38–65	Private practice	Calcitek	n.r.	n.r.	n.r.	n.r.
Aparicio, Perales, and Rangert (2001)	Retrospective	25	25	10/15	0	54	n.r.	University	Nobel Biocare Brånemark	0	22	n.r.	n.r.

Note. n.r. stands for not reported.

TABLE 2 Study and patient characteristics of the reviewed studies on implant-supported zirconia-ceramic FDPs

Zirconia-ceramic fixed dental prostheses													
Study (Year)	Study Design	Planned no of patients	Number of patients at end of study	Sex	Drop out %	Drop-out number	Mean age	Age range	Setting	Implant system	Ant.	Post.	Max.	Mand.
Worni, Kolgeci, Rentsch-Kollar, Katsoulis, and Mericske-Stern (2015)	retrospective	95	90	52/43	5.3	5	59.1 ± 11.7	n.r.	University	Nobel Biocare	n.r.	n.r.	45	28
Kolgeci et al. (2014)	prospective	137	127	51/76	7.3	10	62.5 ± 13.4	n.r.	private practice	Nobel Replace	n.r.	n.r.	n.r.	n.r.
Larsson and Vult von Steyern (2010)	prospective	18	18	n.r.	0	0	n.r.	37–70	university	Astra Tech standard / ST Astra Tech	n.r.	n.r.	n.r.	n.r.

Note.. n.r. stands for not reported.

of the complication rates, meanwhile no data on the survival were gained from these studies. From studies reporting in detail on implant single crowns and multiple-unit FDPs in the same cohort, solely the data on the FDPs were extracted for the present review. Hence, the numbers of patients and/or reconstructions may differ in the present data as compared to the originally included patients/reconstructions.

After the individual data extractions, the extracted data weres compared and in case of differing outcomes, corrections were discussed and made in consensus.

2.9 | Statistical analysis

In the present systematic review, like in previous reviews (Jung et al., 2012; Pjetursson et al., 2012), *survival* was defined as the FDP remaining in situ with or without modification for the entire observation period.

In addition, failure and complication rates were calculated by dividing the number of events (failures or complications) in the numerator by the total FDP exposure time in the denominator.

The numerator could usually be extracted directly from the publication. The total exposure time was calculated by taking the sum of:

- Exposure time of FDPs that could be followed for the whole observation time.
- Exposure time up to a failure of the FDPs that were lost due to failure during the observation time.
- Exposure time up to the end of observation time for FDPs that did not complete the observation period due to reasons such as death, change of address, refusal to participate, nonresponse, chronic illnesses, missed appointments, and work commitments.

For each study, event rates for the FDPs were calculated by dividing the total number of events by the total FDP exposure time in years. For further analysis, the total number of events was considered to be Poisson distributed for a given sum of FDP exposure years and Poisson regression were used with a logarithmic link function and total exposure time per study as an offset variable (Kirkwood & Sterne, 2003a).

Robust standard errors were calculated to obtain 95% confidence intervals of the summary estimates of the event rates. To assess heterogeneity of the study-specific event rates, the Spearman goodness-of-fit statistics and associated *p*-value were calculated. The five-year survival proportions were calculated via the relationship between event rate and survival function *S*, $S(T) = \exp(-T * \text{event rate})$, by assuming constant event rates (Kirkwood & Sterne, 2003b). The 95% confidence intervals for the survival proportions were calculated by using the 95% confidence limits of the event rates. Multivariable Poisson regression was used to investigate formally whether event rates varied by material utilized and study design. For the present systematic review, the literature review and evidence synthesis were conducted following the PRISMA guidelines from 2009 with the exception of a formal quality assessment of the

included studies as all the included studies were case series and cohorts for which no appropriate tools have been developed and the main issue is completeness of follow-up. All analyses were performed using Stata®, version 12.1 (Stata Corp., College Station, TX, USA).

3 | RESULTS

3.1 | Study characteristics

3.1.1 | Included Studies

A total of 19 studies were included in the systematic review. Sixteen of them reported on implant-supported metal-ceramic FDPs and three reported on implant-supported FDPs with zirconia framework. No randomized controlled clinical trials, comparing metal-ceramic, and zirconia-ceramic FDPs were available. Furthermore, no studies reporting on monolithic zirconia FDPs fulfilled the inclusion criteria of the present systematic review.

Sixteen of the included studies reported on metal-ceramic FDPs, while only three studies could be included on zirconia-ceramic FDPs. A larger amount of metal-ceramic FDPs were, hence, analyzed in this review.

Eleven of the included studies were prospective cohort studies and the remaining eight studies were retrospective in design (Tables 1 and 2). One of the included studies, furthermore, randomized the implant sites comparing 6-mm-long implants with 10-mm implants (Romeo et al., 2006). The studies reporting on implant-supported metal-ceramic FDPs were published between 2001 and 2015 with a median publication year of 2012. Two of the studies on zirconia implant-supported FDPs were published in 2014 and the remaining one in 2010.

The studies included patients between 18 and 100 years old. The information on number of patients who could not be followed for the entire study period was available for all included studies and was on average 8.8%. Only one of the included studies had a drop-out proportion exceeding 25% (Table 1).

The 16 included studies, analyzing the outcome of metal-ceramic implant-supported multiple-unit FDPs, included a total of 993 reconstructions supported by 2,289 implant abutments, from which 73% were cement-retained and only 27% screw-retained (Tables 3 and 4). The three included studies reporting on implant-supported multiple-unit FDPs with zirconia framework included a total of 175 reconstructions, from which only 15% were cement-retained and 85% screw-retained.

The studies on metal-ceramic FDPs reported on 2- to 6-unit FDPs, the studies on the zirconia-ceramic FDPs reported on 3- to 5-unit FDPs (Tables 1–4). One study on zirconia-ceramic FDPs included up to 12-unit FDPs (Kolgeci et al., 2014). The data in these studies were not in detail reported in correlation to the different number of units.

The studies were conducted both in an institutional environment, such as university or specialized implant clinics and in private practice setting.

3.1.2 | Survival

Survival was defined as the FDPs remaining in situ with or without modification for the entire observation period. Fourteen of the included studies provided data on the survival of metal-ceramic implant-supported FDPs and three studies provided data on survival of zirconia implant-supported FDPs (Table 5). The first group consisted of 932 metal-ceramic FDPs with a mean follow-up of 6.3 years and the second group of 175 zirconia FDPs and a mean follow-up time of 5.1 years (Table 5).

Meta-analysis revealed that 15 out of the 932 metal-ceramic implant-supported FDPs originally inserted were lost. The annual failure rate was estimated at 0.26 (95% CI: 0.10 – 0.64) (Figure 2), translating into a 5-year survival rate for metal-ceramic implant-supported FDPs of 98.7% (95% CI: 96.8%–99.5%) (Table 5). From the 175 zirconia implant-supported FDPs, nine were known to be lost. For this group, the annual failure rate was estimated at 1.45 (95% CI: 1.06 – 1.98) (Figure 3), translating into a 5-year survival rate for zirconia implant-supported FDPs of 93.0% (95% CI: 90.6%–94.8%) (Table 5). The difference in survival rates between metal-ceramic and zirconia FDPs reached statistical significance ($p < 0.001$).

The reported survival rate was also analyzed according to study design. The 11 included prospective studies with 710 FDPs and the six retrospective studies with 397 FDPs (Tables 1–4) were analyzed separately. For the prospective studies, the estimated 5-year survival was 97.9% (95% CI: 94.0%–99.3%) and for the retrospective studies the estimated 5-year survival was 98.5% (95% CI: 94.8%–99.5%). The difference between the study designs did not reach statistical significance ($p = 0.714$).

3.1.3 | Success

Success was defined as an implant-supported FDP being free of all complications over the entire observation period.

Three studies including 371 metal-ceramic implant-supported FDPs reported on the total number of FDPs with biological or technical complications. The estimated 5-year complication rate for metal-ceramic FDPs was 15.1% (95% CI: 11.2%–20.4%) (Table 6). Hence, 84.9% of the metal-ceramic implant-supported FDPs were free of all complications over the entire observation period. None of the included studies on zirconia implant-supported FDPs reported on the total number of complications or the number of FDPs free of all complications.

3.2 | Technical complications

The total number of complications found at the metal-ceramic FDPs was 15.1% (95% CI: 11.2%–20.4%). None of the studies on the zirconia-ceramic FDPs reported the total number of complications.

Twelve studies reporting on metal-ceramic implant-supported FDPs and one study (Kolgeci et al., 2014) on zirconia implant-supported FDPs analyzed the incidence of fracture of abutments, abutment screws or occlusal screws. Not one single incidence

TABLE 3 Information on materials and procedures of metal-ceramic FDPs

Metal-ceramic fixed dental prostheses								
Study (Year)	**Material framework**	**Monolithic yes/no**	**Material veneering ceramic**	**Cemented**	**Screw retained**	**Total number of included FDPs**	**Examined FDPs in situ at end of observation**	**No. of units (if multiple unit)**
Mangano et al. (2015)	Metal-ceramic	No	n.r.	n.r.	n.r.	29	29	20: 2-units, 5: 3-units, 4: >3-units
Wittneben et al. (2014)	Metal-ceramic	No	Feldspathic porcelain	n.r.	n.r.	129	128	47: 2-units, 57: 3-units, 21: 4-units, 2: 5-units, 1: 6-units
Francetti et al. (2014)	Metal-ceramic	No	Ceramic	18	0	18	18	n.r.
Romeo et al. (2014)	Metal-ceramic	No	n.r.	n.r.	0	24	18	2 or 3-units (number not reported)
Mangano et al. (2014)	Metal-ceramic	No	n.r.	242	0	242	244	n.r.
Vanlioglu et al. (2013)	Metal-ceramic	No	Feldspathic porcelain	52	0	52	52	Only 3-unit
Perelli et al. (2012)	Metal-ceramic	No	n.r.	n.r.	n.r.	47	n.r.	n.r.
Palmer et al. (2012)	Metal-ceramic	No	n.r.	0	28	28	23	n.r.
Nissan et al. (2011)	Metal-ceramic	No	Noritake EX-3	38	38	76	76	2 or 3-units (number not reported)
Wahlstrom et al. (2010)	Metal-ceramic	No	Ceramic	n.r.	n.r.	34	n.r.	13: 2-units, 23: 3-units, 6: 4-units, 3: 5-units, 1: 6-units
Romeo et al. (2009)	Gold alloy	No	Ceramic	46	13	59	n.r.	n.r.
Ozkan et al. (2007)	Metal-ceramic	No	Feldspatic porcelain	n.r.	n.r.	70	70	14: 2-units, 47: 3-units, 9: 4-units
Romeo et al. (2006)	Metal-ceramic	No	n.r.	83	32	115	114	n.r.
Jemt et al. (2003)	Metal-ceramic gold	No	Feldspathic porcelain	0	21	21	18	n.r.
Bambini et al. (2001)	Metal-ceramic	No	Feldspathic porcelain	0	27	27	27	17: 2-units, 10: 3-unit
Aparicio et al. (2001)	Metal-ceramic	No	Ceramic	0	22	22	22	n.r.

Note. n.r. stands for not reported.

of such complications was reported for the material analyzed (Table 6). Abutment or occlusal screw loosening was, on the other hand, reported for 4.1% of the implant abutments supporting metal-ceramic FDPs. None of the included studies on zirconia implant-supported FDPs reported on abutment or occlusal screw loosening (Table 6).

The incidence of ceramic fractures or chippings was not reported in a standardized way and changed significantly depending on the definition utilized. Thirteen studies with 781 metal-ceramic implant-supported FDPs estimated a 5-year rate of pronounced ceramic fractures and chippings to be 11.6% compared with a significantly higher ($p < 0.001$) rate for extensive fracture and chipping for zirconia implant-supported FDPs of 50%, reported in a small study with only 13 zirconia implant-supported FDPs (Table 6). No difference was found regarding the rates for repairable fractures or chippings at the two types of FDPs (metal ceramics: 4.7% (0.9%–22.4%); zirconia ceramics: 2.5% (1.3%–4.9%)) (Table 6).

When analyzing only the FDPs that needed a repair because of ceramic fractures the complication rate dropped down to 4.7% for metal-ceramic implant-supported FDPs and 2.5% for zirconia implant-supported FDPs. The difference between the material groups did not reach statistical significance ($p = 0.481$) (Table 6). However, significantly ($p = 0.001$) more, that is 4.1%, of the zirconia implant-supported FDPs were lost due to ceramic or framework fractures compared to metal-ceramic implant-supported FDPs were only 0.2% of the restorations were lost due to material fractures (Table 6). For six studies, with 476 cemented metal-ceramic implant-supported FDPs the estimated a 5-year rate for loss of retention was 1.9%. The two studies including cemented zirconia implant-supported FDPs did not report on this complication.

3.3 | Biological complications

Peri-implant mucosal lesions were reported in various ways in different publications. The 5-year rate of peri-implantitis or soft tissue complications was estimated to be 3.1% for metal-ceramic implant-supported FDPs and based on one study (Kolgeci et al., 2014) reporting on 73 FDPs this complication was estimated to be significantly ($p = 0.030$) higher for zirconia implant-supported FDPs that is 10.1% (Table 6).

Furthermore, 1.0% of the implants supporting metal-ceramic FDPs experienced substantial bone loss, defined as marginal bone levels more than 2 mm below what can be expected as normal bone remodeling. None of the included studies on zirconia implant-supported FDPs reported on marginal bone loss (Table 6).

3.4 | Aesthetic complications

Two studies including 94 metal-ceramic implant-supported FDPs and one study (Kolgeci et al., 2014), with 73 zirconia implant-supported FDPs reported on aesthetic issues. The authors reported that none of included reconstructions had to be remade due to aesthetic reasons over the 5 years observation period (Table 6).

TABLE 4 Information on materials and procedures of zirconia-ceramic FDPs

Zirconia-ceramic fixed dental prostheses							
Study (Year)	Material framework	Monolithic yes/no	Material veneering ceramic	Cemented	Screw retained	Total number of included FDPs	Examined FDPs in situ at end of observation	No. of units (if multiple unit)
Worni et al. (2015)	Zirconia	No	Feldspathic porcelain	0	89	89	91	60: 3-units, 18: ≥4-units
Kolgeci et al. (2014)	Zirconia	No	Nobel Rondo, Cerabien, Creation	13	60	73	73	55: 3/4-units, 18: 5/12 units
Larsson and Vult von Steyern (2010)	Zirconia	No	Espident Triceram (Dentaurum)	13	0	13	13	11: 2-units, 11: 3-units, 1: 4-units, 1: 5-units

Note. n.r. stands for not reported.

TABLE 5 Annual failure rates and survival of FPDs divided according to material utilized

Study (Year)	Total no. of FDPs	Mean follow-up time (years)	No. of failures	Total exposure time (years)	Estimatedannual failure rate[a] (per 100 FDP years)	Estimated survival after 5 years[a] (in percent)
Metal ceramic						
Mangano et al. (2015)	29	16	0	464	0	100
Wittneben et al. (2014)	129	10.8	2	1,365	0.15	99.3
Francetti et al. (2014)	18	6.8	0	123	0	100
Romeo et al. (2014)	24	4.3	1	99	1.01	95.1
Mangano et al. (2014)	242	5	2	1,210	0.17	99.2
Vanlioglu et al. (2013)	52	5	2	260	0.77	96.2
Perelli et al. (2012)	47	5	0	235	0	100
Palmer et al. (2012)	28	2.8	6	77	7.79	67.7
Nissan et al. (2011)	76	5.3	0	402	0	100
Romeo et al. (2009)	59	10	0	590	0	100
Ozkan et al. (2007)	70	2	0	210	0	100
Romeo et al. (2006)	115	5.5	1	637	0.16	99.2
Jemt et al. (2003)	21	4.8	1	102	0.98	95.2
Aparicio et al. (2001)	22	3	0	68	0	100
Total	**932**	**6.3**	**15**	5,842		
Summary estimate (95 % CI) [a]					**0.26 (0.10–0.64)**	**98.7** (96.8–99.5)
Zirconia ceramic						
Kolgeci et al. (2014)	73	3.2	4	234	1.71	91.8
Worni et al. (2015)	89	3.6	5	322	1.55	92.5
Larsson and Vult von Steyern (2010)	13	5	0	65	0	100
Total	**175**	**5.1**	**9**	**621**		
Summary estimate (95 % CI) [a]					**1.45 (1.06–1.98)**	**93.0 (90.6–94.8)**

Note. [a]Based on robust Poisson regression.

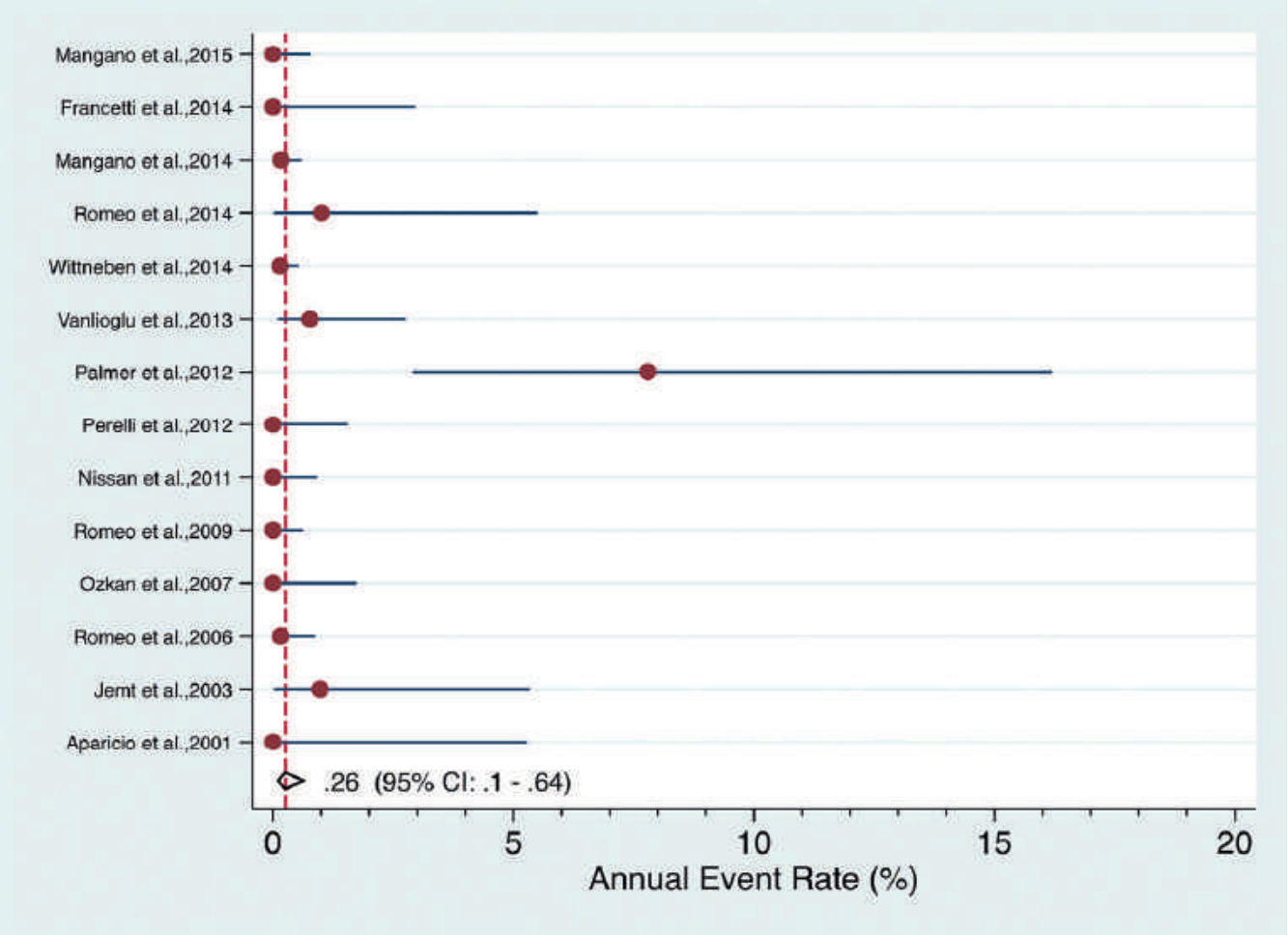

FIGURE 2 Annual failure rates (per 100 years) of implant-supported metal-ceramic FDPs

4 | DISCUSSION

The present systematic review showed that, in general, implant-supported FDPs exhibited very high 5-year survival rates. It was observed, however, that the 5-year survival rates of the zirconia-ceramic implant FDPs were significantly lower than the ones of the metal-ceramic implant FDPs. Catastrophic fracture of the FDP occurred significantly more often at the zirconia-ceramic FDPs than at metal-ceramic FDPs. The predominant technical complication at both types of FDPs was chipping and/or fracture of the veneering ceramic. This complication was more often observed at the zirconia-ceramic FDPs and, in addition, significantly more often led to loss of the FDP in the zirconia-ceramic group than in the metal-ceramic group.

Until today, metal-ceramics is the "golden standard" material of choice for the fabrication of multiple-unit implant- or tooth-borne FDPs (Creugers, Käyser, & van't Hof, 1994; Scurria, Bader, & Shuggars, 1998; Walton, 2002, 2003, 2015). More recently, zirconia-based reconstructions have increasingly been used instead, in an attempt to provide patients with metal-free reconstructions of higher aesthetics and lower price (Heintze & Rousson, 2010).

Yet, both teeth- and implant-supported zirconia-ceramic FDPs showed lower 5-year survival rates than the metal-ceramic FDPs (Pjetursson, Sailer, Makarov, Zwahlen, & Thoma, 2015, 2017), the difference reaching statistical significance in the present review. Frequent reason for failure was a catastrophic fracture of the zirconia framework itself. Another often observed reason for failure was extended chipping of the veneering ceramic (Sailer et al., 2017).

Chipping of the zirconia veneering ceramic has been a frequently reported problem since the introduction of the zirconia-based reconstructions (Heintze & Rousson, 2010). The frequency of zirconia veneering ceramic chipping in a systematic review has been reported to be 54% at tooth-supported reconstructions (Heintze & Rousson, 2010). Studies on implant-supported zirconia FDPs reported on rates up to 50% (Larsson & Vult von Steyern, 2016). Further developments of the zirconia veneering ceramics and of the veneering procedures have helped lower the initially high incidences of chipping, still, the problem remains to be the predominant technical complication.

In general, bilayer materials are prone to delamination or chipping as the material scientific research has shown (Zhang, Sailer, & Lawn, 2013). One possible, interesting alternative to bilayers is the application of monolithic types of reconstructions (Zhang et al., 2013). A few years ago, this was not possible with zirconia materials, as the aesthetics of the yttria-stabilized zirconia used for FDP framework fabrication was too poor.

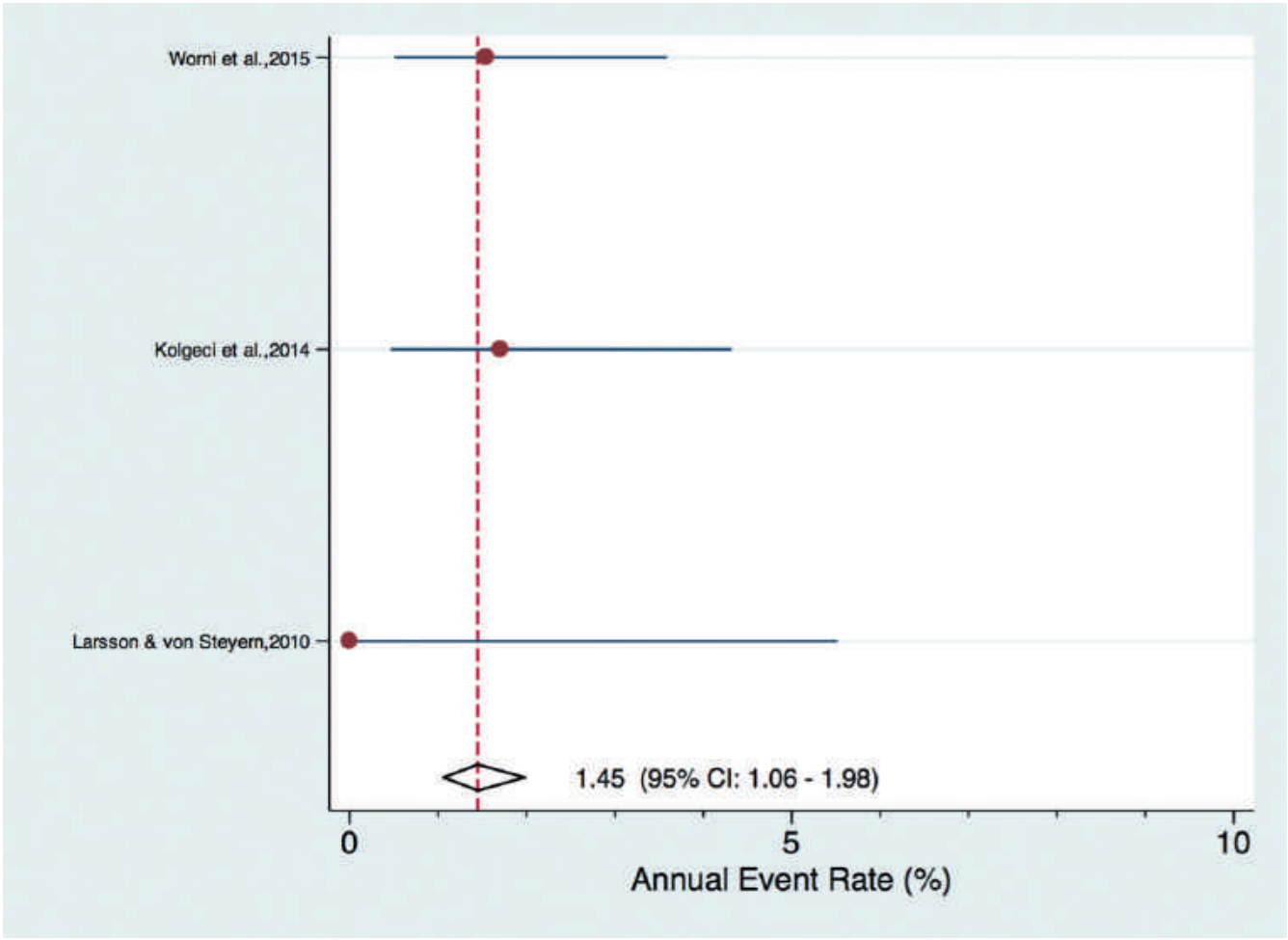

FIGURE 3 Annual failure rates (per 100 years) of implant-supported zirconia-ceramic FDPs

More recently, however, new more translucent and/or colored new types of zirconia ceramics were introduced reducing the need for veneering ceramic. Monolithic zirconia reconstructions may be a promising alternative to the zirconia-ceramic reconstructions and may exhibit lower rates of chipping of the ceramic. The literature on this topic is still scarce. Unfortunately, no studies on monolithic zirconia implant-supported reconstructions were available for the present review with follow-up periods of 3 years or more. For this reason, the present systematic review failed to analyze the above assumption, and the meta-analysis has to be repeated in a few years when more information is available.

Numerous preclinical and clinical studies on zirconia implants have proved its biocompatibility and indicated excellent soft tissue integration (Pieralli, Kohal, Jung, Vach, & Spies, 2017).

Future studies on monolithic zirconia are needed to analyze and document the biologic integration of the zirconia-based reconstructions in more detail, besides the general clinical outcomes.

The present systematic displayed exhibited some limitations of the available literature and the present results need to be interpreted with this in mind. First, and most importantly, the numbers of metal-ceramic and zirconia-ceramic FDPs included in this meta-analysis were highly differing. More information was available on metal-ceramic FDPs. Zirconia-ceramic FDPs seemed to suffer from more technical problems, yet, this result came from few studies and will need further observation. Furthermore, no RCTs comparing the two treatment options were available for this review. Finally, no studies on monolithic zirconia could be included at this point; hence, the interpretation of the results is limited to veneered zirconia. Reviews on tooth-supported FDPs made out of veneered zirconia, however, demonstrated similar outcomes (Heintze & Rousson, 2010; Schley et al., 2010). Therefore, the results obtained by the present meta-analysis are in accordance with previously published outcomes of the zirconia-ceramic FDPs. Future research should focus on the more recent monolithic zirconia reconstructions to evaluate their outcomes as compared to metal-ceramics.

Finally, it may be questioned why only one data base, that is, Medline was used for the literature search. In almost all previous reviews of the present team of reviewers, a very focussed literature search was firstly performed in Medline, followed by searches of additional sources like Embase, or the Cochrane Library. Yet, the number of additional studies, solely included through these additional sources and not identified before, was zero. Most studies not previously found through the main search in Medline resulted from hand searching the reference lists of significant publications, however. Therefore, the strategy at the present review was to focus on a rather

TABLE 6 Comparing annual failure and complication rates of metal-ceramic FDPs and zirconia-ceramic FDPs

Complication	Number of FDPs	Estimated annual complication rates (95 % CI)	Cumulative 5 year complication rates (95 % CI)	Number of FDPs	Estimated annual complication rates (95 % CI)	Cumulative 5 year complication rates (95 % CI)	p-value
	Metal-ceramic			Zirconia-ceramic			
Total number of FDPs with complications	371	3.28[a] (2.37–4.55)	15.1%[a] (11.2%–20.4%)	0	n.r.	n.r.	n.a.
Abutment fracture	1,641	0[a]	0%[a]	169	0[a]	0%[a]	n.a.
Abutment or occlusal screw fracture	1,571	0[a]	0%[a]	169	0[a]	0%[a]	n.a.
Abutment or occlusal screw loosening	1,359	0.84[a] (0.22–3.13)	4.1%[a] (1.1%–14.5%)	0	n.r.	n.r.	n.a.
Ceramic fracture or chipping	781	2.48[a] (1.40–4.39)	11.6%[a] (6.7%–19.7%)	13	13.85[a] (6.53–24.66)	50.0%[a] (29.1%–72.1%)	<0.001
Ceramic chipping with repair	427	0.95[a] (0.18–5.07)	4.7%[a] (0.9%–22.4%)	102	0.52[a] (0.27–1.00)	2.5%[a] (1.3%–4.9%)	0.481
Restoration lost due to ceramic fracture	966	0.05[a] (0.01–0.23)	0.2%[a] (0.05%–1.1%)	175	0.97[a] (0.38–2.48)	4.7%[a] (1.9%–11.7%)	0.001
Loss of retention of cemented FDPs	476	0.39[a] (0.21–0.72)	1.9%[a] (1.0%–3.6%)	0	n.r.	n.r.	n.a.
Soft tissue complications	445	0.64[a] (0.21–1.92)	3.1%[a] (1.0%–9.2%)	73	2.14[a] (0.70–4.92)	10.1%[a] (3.4%–21.8%)	0.030
Significant marginal bone loss	1,138	0.21[a] (0.06–1.41)	1.0%[a] (0.3%–3.3%)	0	n.r.	n.r.	n.a.
Aesthetic failures	94	0[a]	0%[a]	73	0[a]	0%[a]	n.a.

Notes. n.r. stands for not reported; n.a. stands for not analyzed.
[a]Based on robust Poisson regression.

open and rather unrestricted title search, avoiding limitations and filters during in order to be as inclusive as possible on the title level. The subsequent thorough screening of the titles, abstracts, and full-text articles, and the additional meticulous hand searching of all reference lists of previous reviews helped identify the included studies of the present and a second review (Pjetursson et al., 2018; ITI CC SR).

5 | CONCLUSIONS

For implant-supported FDPs conventionally veneered zirconia shall not be considered the material of first priority, due to persisting pronounced risk for fractures of the framework and chipping of the zirconia veneering ceramic. Monolithic zirconia may be an interesting alternative, but its clinical medium- to long-term outcomes have not been analyzed yet. Hence, until today, metal-ceramics appear to stay the golden standard for the implant-supported FDPs.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

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SUPPORTING INFORMATION

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REVIEW ARTICLE

WILEY CLINICAL ORAL IMPLANTS RESEARCH

A systematic review of the survival and complication rates of zirconia-ceramic and metal-ceramic single crowns

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Abstract

Objectives: The aim of the present systematic review was to analyze the survival and complication rates of zirconia-based and metal-ceramic implant-supported single crowns (SCs).

Materials and Methods: An electronic MEDLINE search complemented by manual searching was conducted to identify randomized controlled clinical trials, prospective cohort and retrospective case series on implant-supported SCs with a mean follow-up time of at least 3 years. Patients had to have been clinically examined at the follow-up visit. Assessment of the identified studies and data extraction was performed independently by two reviewers. Failure and complication rates were analyzed using robust *Poisson's* regression models to obtain summary estimates of 5-year proportions.

Results: The search provided 5,263 titles and 455 abstracts, full-text analysis was performed for 240 articles, resulting in 35 included studies on implant-supported crowns. Meta-analysis revealed an estimated 5-year survival rate of 98.3% (95% CI: 96.8–99.1) for metal-ceramic implant supported SCs (n = 4,363) compared to 97.6% (95% CI: 94.3–99.0) for zirconia implant supported SCs (n = 912). About 86.7% (95% CI: 80.7–91.0) of the metal-ceramic SCs (n = 1,300) experienced no biological/technical complications over the entire observation period. The corresponding rate for zirconia SCs (n = 76) was 83.8% (95% CI: 61.6–93.8). The biologic outcomes of the two types of crowns were similar; yet, zirconia SCs exhibited less aesthetic complications than metal-ceramics. The 5-year incidence of chipping of the veneering ceramic was similar between the material groups (2.9% metal-ceramic, 2.8% zirconia-ceramic). Significantly (p = 0.001), more zirconia-ceramic implant SCs failed due to material fractures (2.1% vs. 0.2% metal-ceramic implant SCs). No studies on newer types of monolithic zirconia SCs fulfilled the simple inclusion criteria of 3 years follow-up time and clinical examination of the present systematic review.

Conclusion: Zirconia-ceramic implant-supported SCs are a valid treatment alternative to metal-ceramic SCs, with similar incidence of biological complications and less aesthetic problems. The amount of ceramic chipping was similar between the material groups; yet, significantly more zirconia crowns failed due to material fractures.

KEYWORDS

biological, complications, fixed dental prostheses, implant crown, meta-analysis, metal-ceramics, success, survival, systematic review, technical, zirconia framework

1 | INTRODUCTION

The continuous pursuit for aesthetic perfection has led to a constant search for materials that could best serve this purpose, that is, the aesthetic improvement of tooth- and implant-supported reconstructions. The desire for materials that closest approached the appearance of natural dental tissues led to the development and use of zirconia ceramic as reconstructive material (Filser et al., 2001). Over the years, this material has been introduced into common everyday clinical practice, thanks in particular to the promising outcomes of many studies on the properties of zirconia (Guazzato, Albakry, Ringer, & Swain, 2004; Guazzato, Proos, Quach, & Swain, 2004; Guazzato, Quach, Albakry, & Swain, 2005; Studart, Filser, Kocher, & Gauckler, 2007a,2007b; Studart, Filser, Kocher, Luthy, & Gauckler, 2007). Today, it is also widely utilized in implant prosthodontics, in both the realization of single crowns (SCs) and fixed dental prostheses (FDPs).

Even though the data coming from the basic research on zirconia have reassured the clinicians that the mechanical characteristics of zirconia are promising and its clinical use is save (Pjetursson, Sailer, Makarov, Zwahlen, & Thoma, 2015; Sailer, Makarov, Thoma, Zwahlen, & Pjetursson, 2015), it is still uncertain whether or not the zirconia-ceramic reconstructions are a valid alternative to classic metal-ceramics today.

Two recent systematic reviews have investigated the outcomes of implant supported SCs and FDPs without focusing on the difference between all-ceramics and metal-ceramics but rather on the survival and frequency of complications in general (Jung, Zembic, Pjetursson, Zwahlen, & Thoma, 2012; Pjetursson, Thoma, Jung, Zwahlen, & Zembic, 2012).

The systematic review of Jung et al., 2012 reported a 5-year survival rate of implant-supported SCs of 96.3% (95% CI: 94.2–97.6). The 5-year rate of different technical complications reached 8.8% for screw loosening, 4.1% for loss of retention and 3.5% for fracture of the veneering material. The aesthetic complication rate was 7.1% over the 5-year observation period (Jung et al., 2012).

Zirconia implant abutments have been well-documented in the last decade, and their outcomes were shown to be equal to the ones of metal abutments (Sailer et al., 2009). Yet, until today it is not yet fully elucidated whether or not the prognosis of zirconia implant-supported reconstructions is similar to that of metal-ceramic implant reconstructions or not.

For this reason, the aim of the present systematic review was to analyze the outcomes, that is survival rates and technical, biologic and aesthetic complication rates of veneered zirconia and/or monolithic zirconia implant-supported SCs compared to the golden standard, the metal-ceramic implant reconstructions.

2 | MATERIALS AND METHODS

This review was registered at the National Institute for Health Research PROSPERO, International Prospective Register of Systematic Reviews (CRD42017079002).

2.1 | General search strategy

The focused question for this review was determined according to the well-established PICO strategy (Population, Intervention, Comparison, and Outcome) (Sackett 2000, Akobeng 2005).

1. Population: Partially edentulous patients,
2. Intervention: Implant-supported SCs with zirconia framework or monolithic zirconia as restoration material,
3. Comparison: Implant-supported SCs with metal-ceramic as restoration material,
4. Outcome: Survival and complication rates of the reconstructions.

2.2 | Focused question

The focused question of the present review was: "In partially edentulous patients with implant-supported single crowns (SCs) do veneered zirconia and/or monolithic zirconia SCs exhibit differences in prosthetic outcomes compared with metal-ceramic implant-supported SCs?"

2.3 | Literature search strategy

The literature search for this systematic review concentrated on the outcomes of single-unit and multiple-unit implant reconstructions, all relevant literature was included. In the final article selection phase, data were divided into implant-supported SCs, for the present systematic review and fixed dental prostheses (FDPs) for the review by Sailer et al. (2018). Both reviews were prepared in the context of the ITI Consensus Conference 2018.

An extensive search for clinical trials was conducted, through PubMed, until and including November 2016, without time limits. No language limits were applied. An additional manual search was executed to identify relevant articles among the reference lists of all included full-text articles and among the references of the above-mentioned systematic review on implant-supported SCs (Jung et al., 2012).

2.4 | Search terms

The terms of the research were as follows: (((((jaw, edentulous, partially, dental implants, Dental Prosthesis, Implant-Supported[mesh]) OR (partially edentulous) OR (partial edentulism) OR (fixed implant prosthesis))) AND/OR ((Implant-Supported Dental Prosthesis, Crown* AND/OR Bridge* AND/OR fixed partial denture* AND/OR fixed dental prosthesis, zirconium, zirconia, zirconium oxide[mesh]) OR (dental implants, dental prostheses[mesh]) OR (zirconia framework) OR (monolithic zirconia))) AND/OR ((Implant-Supported Dental Prosthesis, Crown*, Bridge*, fixed partial denture*, fixed dental prosthesis, metal*, metal ceramic* [mesh]) OR (dental implants, dental prostheses[mesh]) OR (metal framework))) AND/

OR (Outcome Assessment, Treatment Outcome, dental implants, dental prostheses[mesh] OR dental prostheses outcomes OR dental implant prosthetic outcomes OR dental implant prosthetic failure).

2.5 | Inclusion criteria

Clinical studies were considered for inclusion if all of the following inclusion criteria were met:

1. Human studies.
2. At least 10 patients treated.
3. A follow-up time of at least 3 years.
4. Detailed information on the restoration material utilized.
5. Restoration type clearly described and data from SC and FDP reported separately.
6. If multiple publication on the same patient cohort, only the publication with the longest follow-up time is included.
7. Zirconia-based all-ceramic crowns.
8. Gold-alloy-based metal-ceramic crowns, other metals such as titanium, cobalt-chromium, etc. were excluded.
9. In studies mixing data on different restoration materials, data were only included if less than 10% of the reconstructions were of the second material.

2.6 | Exclusion criteria

Studies not meeting all inclusion criteria were excluded. Also reports based on questionnaires, interviews, and case reports were excluded from the present review.

2.7 | Selection of studies

Two authors (SL and NAV) independently screened the titles derived from the initial search in consideration for inclusion. Disagreements were resolved by discussion. After title screening, the abstracts obtained were screened for inclusion by SL, MS, and NAV. Whenever an abstract was not available electronically, it was extracted from the printed article. Based on the selection of abstracts, articles were then obtained in full text. Again, disagreements were resolved by discussion. Finally, the selection based on inclusion/exclusion criteria was made for the full-text articles by the authors SL, MS, and NAV. For this purpose, materials and methods, results, and discussions of these studies were screened. The selected articles were then double checked by the senior authors IS and BEP. Any issues regarding the selection that came up during the screening were discussed within the group to reach a consensus.

2.8 | Data extraction and method of analysis

Four reviewers (IS, MS, BEP, and NAV) independently extracted the data of the selected articles using data extraction tables. For standardization purposes, every author extracted the data of the same three articles in the beginning of the literature analysis, and the results were then compared within the group and any disagreements were discussed aiming at a consensus to standardize the subsequent analyses.

In some case, when a publication did not provide sufficient information but was judged worthy to be included, the authors were contacted by e-mail or telephone.

All extracted data were double checked, and any questions that came up during the screening and the data extraction were discussed within the group.

Information on the following parameters was extracted: author(s), year of publication, study design, number of patients, number of patients at the end of the study, number of crowns, dropouts, mean age of patients, age range, implant type, restoration type, framework material, brand name for framework material, whether the restoration was monolithic or not, material veneering ceramic, manufacturing procedure, brand name for manufacturing procedure, abutment material, type of fixation, number of crown in-situ at the end of the observation, location in the oral cavity, follow-up time (range, mean), published crown survival rate, location of lost crowns, number of complications (technical, biological), and aesthetic outcomes, reported number of crowns free of complications.

2.9 | Statistical analysis

In the present systematic review, like in previous work, s*urvival* was defined as the SCs remaining in situ with or without modification for the observation period.

In addition, failure and complication rates were calculated by dividing the number of events (failures or complications) in the numerator by the total SC exposure time in the denominator.

The numerator could usually be extracted directly from the publication. The total exposure time was calculated by taking the sum of:

1. Exposure time of SCs that could be followed for the whole observation time.
2. Exposure time up to a failure of the SCs that were lost due to failure during the observation time.
3. Exposure time up to the end of observation time for SCs in patients that were lost to follow-up due to reasons such as death, change of address, refusal to participate, non-response, chronic illnesses, missed appointments, and work commitments.

For each study, event rates for the SCs were calculated by dividing the total number of events by the total SC exposure time in years. For further analysis, the total number of events was considered to be Poisson's distributed for a given sum of FDP exposure years and Poisson's regression was used with a logarithmic link-function and total exposure time per study as an offset variable (Kirkwood & Sterne, 2003).

Robust standard errors were calculated to obtain 95% confidence intervals of the summary estimates of the event rates (White, 1980, 1982).

To assess heterogeneity of the study specific event rates, the Spearman goodness-of-fit statistics and associated p-value were calculated. The five year survival proportions were calculated via the relationship between event rate and survival function S, $S(T) = \exp(-T^*\text{event rate})$, by assuming constant event rates (Kirkwood & Sterne, 2003). The 95% confidence intervals for the survival proportions were calculated using the 95% confidence limits of the event rates. Multivariable Poisson's regression was used to investigate formally whether event rates varied by material utilized, location in the oral cavity, and study design. For the present systematic review, the literature review and evidence synthesis was conducted following the PRISMA guidelines from 2009 with the exception of a formal quality assessment of the included studies as all the included studies were case series and cohorts for which no appropriate tools have been developed and the main issue is completeness of follow-up. All analyses were performed using Stata®, version 12.1 (Stata Corp., College Station, TX, USA).

3 | RESULTS

3.1 | Included studies

A total of 36 studies were included in the present systematic review (Figure 1). Thirty of the 36 studies reported on implant-supported metal or metal-ceramic SCs, eight reported on zirconia-based implant-supported SCs, and two included material consisting of both metal-ceramic and zirconia-ceramic implant-supported SCs. The included zirconia-based SCs all consisted of zirconia core with veneering ceramic and no monolithic zirconia crowns. Two of the included studies were randomized controlled clinical trials (RCTs) comparing flapless implant placement and immediate loading with conventional placement (Cannizzaro, Leone, Consolo, Ferri, & Esposito, 2008) and comparing early implant placement with delayed placement (Schropp & Isidor, 2008a,2008b) 20 studies were prospective cohort studies and the remaining 14 studies were retrospective in design (Table 1).

The studies reporting on implant-supported metal-ceramic SCs were published between 1998 and 2017 with a median publication year of 2012. The studies on zirconia-ceramic implant-supported SCs were on average younger, all published 2013 or later.

The studies included patients between 15 and 81 years old. The proportion of patients who could not be followed for the entire study period was available for majority of the studies and ranged from 0% to 52%. However, only three of the included studies had a drop-out proportion of more than 25% (Table 1).

The 30 included studies, analyzing the outcome of metal-ceramic implant-supported SCs, included a total of 4,542 crowns, from which 83% were cement-retained and only 17% screw-retained. The 8 included studies reporting on zirconia-based implant-supported SCs included a total of 912 crowns, from which 51% were cement-retained and 49% screw-retained (Table 2).

The studies were conducted both in an institutional environment, such as university or specialized implant clinics and in private practice setting.

3.2 | Survival

SC survival was defined as the SCs remaining in situ, with or without modification, for the entire observation period. Twenty-eight studies provided data on survival of metal-ceramic implant-supported SCs and eight studies provided data on survival of zirconia-based implant-supported SCs (Table 3). The first group consisted of 4,363 metal-ceramic SCs, with a mean follow-up of 5.7 years and the second group with a total of 912 zirconia-ceramic SCs and a mean follow-up time of 5.1 years (Table 3).

Meta-analysis revealed that of the originally 4,363 metal-ceramic implant-supported SCs inserted, 87 were lost. The annual failure rate was estimated at 0.35% (95% CI: 0.19–0.66) (Figure 2), translating into a 5-year survival rate for metal-ceramic implant-supported SCs of 98.3% (95% CI: 96.8–99.1) (Table 3). From the 912 zirconia implant-supported SCs, 23 were known to be lost. For this group, the annual failure rate was estimated at 0.49% (95% CI: 0.21–1.18) (Figure 3), translating into a 5-year survival rate for zirconia implant-supported SCs of 97.6% (95% CI: 94.3–99.0) (Table 3). The difference in survival rates between metal-ceramic and zirconia-ceramic SCs did not reach statistical significance ($p = 0.514$).

Moreover, the survival rate of implant-supported SCs was analyzed regarding the location in the dental arch. The 5-year survival rates for both metal-ceramic and zirconia-ceramic SCs were slightly higher in the posterior compared with the anterior area. For metal-ceramic implant-supported SCs, the difference was 97.3% vs. 99.0% and for zirconia-ceramic implant-supported SCs, and the difference was 97.9% vs. 98.6%. The difference, however, did not reach statistical significance ($p = 0.201$ and $p = 0.511$) (Table 4).

The reported survival rate was also analyzed according to study design. The 22 RCTs and prospective studies and the 14 retrospective studies were analyzed separately. For the prospective studies, with 1,873 implant-supported SCs, the estimated 5-year survival was 97.5% (95% CI: 95.3–98.7) and for the retrospective studies, based on 3,402 implant-supported SCs, the estimated 5-year survival was 98.4% (95% CI: 96.8–99.2). The difference between the two groups did not reach statistical significance ($p = 0.373$).

3.3 | Success

Success was defined as an implant-supported SC being free of all complications over the entire observation period.

Nine studies, including 1,300 metal-ceramic implant-supported SCs and two studies with 76 zirconia implant-supported SCs, reported on the total number of implant-supported SCs with experiencing biological or technical complications during the observation period. The estimated 5-year complication rate for metal-ceramic SCs was 13.3% (95% CI: 9.0–19.3) and for zirconia SCs 16.2% (95% CI: 6.2–38.4). The difference between the material groups did not reach statistical significance ($p = 0.622$) (Table 4). Hence, 86.7% of the metal-ceramic implant-supported SCs and 83.8% of the zirconia implant-supported SCs were free of all complications over the entire observation period.

3.4 | Biological complications

Peri-implant mucosal lesions were reported in various ways by the different authors. The 5-year rate of peri-implantitis or soft tissue complications was estimated to by 5.1% for metal-ceramic implant-supported SCs and 5.3% for zirconia implant-supported SCs. Moreover, 3.3% of the implants supporting metal-ceramic SCs and 4.3% of the implants supporting zirconia-based SCs experienced significant bone loss, defined as marginal bone levels more the 2 mm below what can be expected as normal bone remodeling. The difference between the two material groups did, however, not reach statistical significance ($p = 0.946$ and 0.481) (Table 5).

3.5 | Aesthetic complications

From seven studies including 627 metal-ceramic implant-supported SCs, 1.7% of the reconstructions were redone due to aesthetic reasons over the 5-year observation period. Four of the included studies on zirconia implant-supported crowns reported on this issue, and none of the zirconia based crowns had to be redone due to aesthetic reasons. The difference between the material groups reached in this respect statistical significance ($p < 0.001$).

3.6 | Technical complications

Fracture of abutments, abutment screws, or occlusal screws were rare complications with only 0.2% of the metal-ceramic and 0.4% of the zirconia implant-supported SCs experiencing abutment fractures and 0.05% of the metal-ceramic and 0.1% of the zirconia SCs having abutment or occlusal fractures during a 5-year observation period. Abutment or occlusal screw loosening was, however, significantly ($p = 0.015$) more frequent by metal-ceramic implant-supported SCs compared with the zirconia implant-supported SC with a 5-year complication rate of 3.6% and 1.0%, respectively (Table 5).

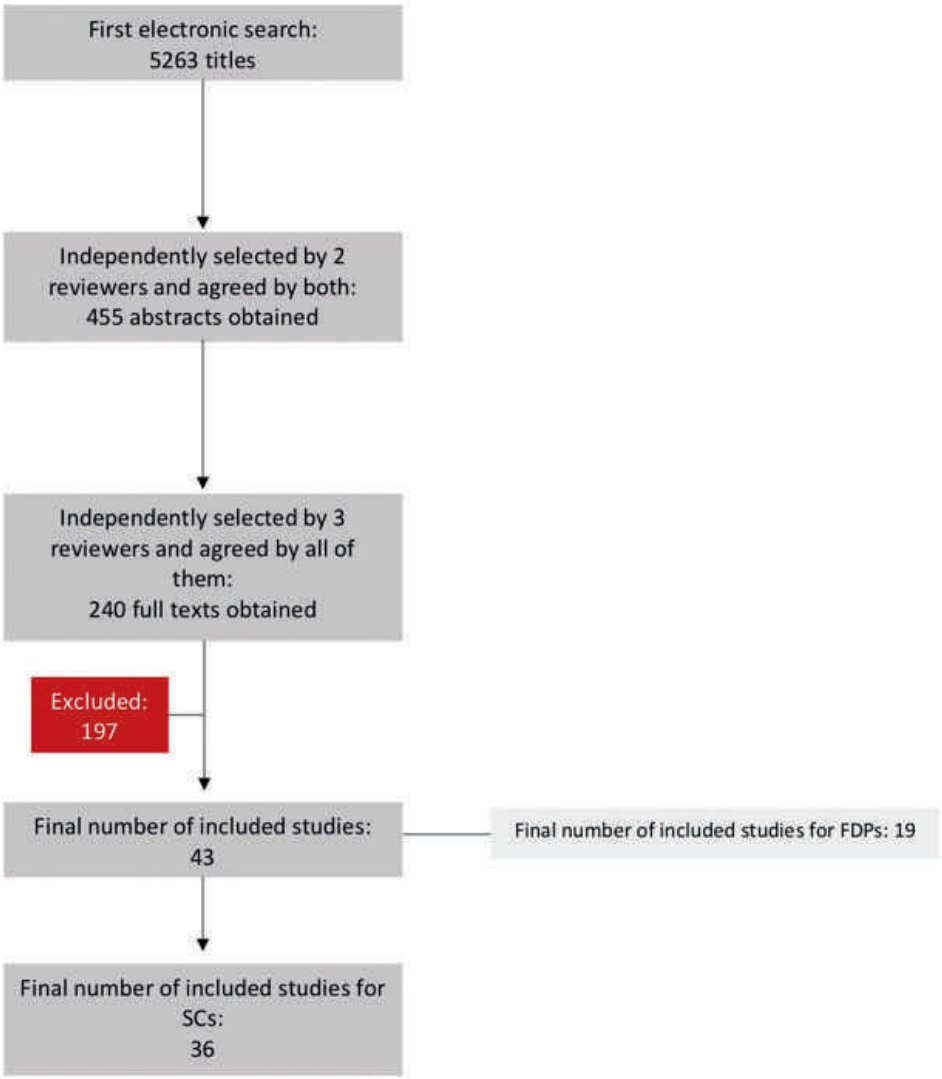

FIGURE 1 Search strategy

TABLE 1 Study and patient characteristics of the reviewed studies

Author (year)	Study design	Planned no. of patients	No. of patients at the end	Drop-out (%)	Mean age (years)	Age range (years)	Setting	Implant system
(a) Metal-ceramic single crowns								
Tey, Phillips and Tan (2017)	Retrospective	781	194	n.r.	57	24–80	Specialist practice	Straumann, Nobel Biocare, Biomet 3i
Mangano et al. (2017)	Retrospective	103	103	0	41.1	24–65	Multicentric private practice	n.r.
Vigolo, Gracis, Carboncini and Mutinelli (2016)	Retrospective	1,159	934	19	49.6	n.r.	Private practices	Various brands with internal and external connections
Donati, Ekestubbe, Lindhe and Wennstrom (2016)	Prospective	40	31	23	40.9	20–71	University	Astra
Walton (2015)	Retrospective	174	174	0	42.3	15–79	Private practice	Nobel Biocare
Mangano, Iaculli, Piattelli and Mangano (2015)	Retrospective	49	49	0	54.5	22–70	Private practice	Mac System
Pozzi, Tallarico and Moy (2014)	Prospective	34	34	0	52.2	39–59	University	Nobel Biocare, Groovy, Speedy
Francetti, Azzola, Corbella, Taschieri and Del Fabbro (2014)	Prospective	22	19	14	n.r.	n.r.	Private clinic	Nobel Replace
Mangano, Shibli, et al. (2014)	Prospective	194	189	3	49.1	24–74	Private practice	Leone Implant System
Mangano, Macchi, et al. (2014)	Prospective	642	606	6	n.r.	20–82	Private practice	Leone Implant System
Wittneben et al. (2014)	Retrospective	358	303	15	n.r.	n.r.	University	Straumann
Vanlioglu, Ozkan and Kulak-Ozkan (2013)	Retrospective	95	95	0	41.2	n.r.	University	Straumann
Lops, Bressan, Chiapasco, Rossi and Romeo (2013)	Prospective	85	81	5	54	36–67	University	Astra
Lai et al. (2013)	Retrospective	168	168	0	45.9	23–72	Hospital	Straumann SLA implants
Perelli, Abundo, Corrente and Saccone (2012)	Prospective	87	87	0	n.r.	n.r.	Private Practice	n.r.
Gotfredsen (2012)	Prospective	20	20	0	33	18–59	University	Astra Tech ST
Schmidlin et al. (2010)	Retrospective	64	41	51	47	24–66	University	n.r.
Cannizzaro et al. (2008)	RCT	40	40	0	n.r.	n.r.	Private practice	Tapered swiss plus (zimmer dental)
Jemt (2008)	Retrospective	38	27	29	25.4	n.r.	Specialist clinic	Brånemark
Schropp and Isidor (2008a,2008b)	Randomized study	45	34	24	48	20–74	University	Osseotite implant (Biomet 3i)

(Continues)

TABLE 1 (Continued)

Author (year)	Study design	Planned no. of patients	No. of patients at the end	Drop-out (%)	Mean age (years)	Age range (years)	Setting	Implant system
(a) Metal-ceramic single crowns								
Ozkan, Ozcan, Akoglu, Ucankale and Kulak-Ozkan (2007)	Prospective	63	63	0	46.9	18–63	University	Straumann, Camlog, Frialit
Turkyilmaz (2006)	Prospective	19	19	0	39	20–55	University	Nobel Mk III
Romeo et al. (2006)	RCT	188	161	14	55.8	21–74	University	Straumann
Dhanrajani and Al-Rafee (2005)	Prospective	101	101	0	35.4	17–69	Private practice	Nobel, 3i, Calcitek, Steri-Oss
Covani, Crespi, Cornelini and Barone (2004)	Prospective	95	n.r.	n.r.	n.r.	20–68	University	Sweden and Martina
Norton (2001)	Retrospective	23	11	52	49	23–77	Private practice	Astra
Bambini, Lo Muzio and Procaccini (2001)	Retrospective	59	59	0	57	38–65	Private practice	Calcitek
Mericske-Stern, Grutter, Rosch and Mericske (2001)	Prospective	72	70	3	50	19–82	University, private practice	Straumann
Polizzi, Fabbro, Furri, Herrmann and Squarzoni (1999)	Prospective	21	21	0	30	13–58	Private center	Nobel Biocare, Brånemark
Scheller et al. (1998)	Prospective	82	66	20	35	14–73	Multicenter	Nobel
		4,921	≈ 3,895					
(b) Zirconia ceramic single crowns								
Vigolo et al. (2016)	Retrospective	1,159	934	19	49.6	n.r.	Private practices	Various brands with internal and external connections
Guncu, Cakan, Aktas, Guncu and Canay (2016)	Prospective	24	24	0	44.1	30-64	University, private practice	Astra
Branzen, Eliasson, Arnrup and Bazargani (2015)	Retrospective	46	36	22	20.5	16–37	University	Nobel Biocare- Brånemark
Worni, Kolgeci, Rentsch-Kollar, Katsoulis and Mericske-Stern (2015)	Retrospective	95	90	5	59.1	n.r.	University	Nobel Biocare
Kolgeci et al. (2014)	Prospective	137	127	7	62.5	n.r.	Private practice	Nobel Replace
Nothdurft, Nonhoff and Pospiech (2014)	Prospective	24	23	4	n.r.	n.r.	University	Xive, Dentsply
Lops et al. (2013)	Prospective	85	81	6	54	36–67	University	Astra
Hosseini, Worsaae, Schiodt and Gotfredsen (2013)	Prospective	59	59	0	27.9	18–50	University	Astra
		1,629	1,374					

Note. n.r.: not reported; RCT: randomized controlled clinical trial.

TABLE 2 Information on materials and procedures of single crowns

Author (year)	Material framework	Monolithic (yes/no)	Veneering material	No. of cemented crowns	No. of screw-retained crowns	No. of crowns anterior	No. of crowns posterior	Total no. of crowns	No. of crowns at the end of observation
Tey et al. (2017)	Metal-ceramic	No	n.r.	263	3	38	228	103	103
Mangano et al. (2017)	Metal-ceramic	No	n.r.	103	0	103	0	45	35
Vigolo et al. (2016)	Metal-ceramic	No	n.r.	1,174	253	169	1,210	1,428	1,428
Donati et al. (2016)	Metal-ceramic	No	n.r.	45	0	21	24	220	220
Walton (2015)	Metal-ceramic	No	n.r.	13	207	139	81	15	15
Mangano et al. (2015)	Metal-ceramic	No	n.r.	n.r.	n.r.	n.r.	n.r.	88	88
Pozzi et al. (2014)	Metal-ceramic	No	n.r.	88	0	0	88	15	14
Francetti et al. (2014)	Metal-ceramic	No	Ceramic	15	0	3	14	215	215
Mangano, Shibli, et al. (2014)	Metal-ceramic	No	Feldspathic porcelain	215	0	0	215	482	478
Mangano, Macchi, et al. (2014)	Metal-ceramic	No	n.r.	478	0	n.r.	n.r.	268	261
Wittneben et al. (2014)	Metal-ceramic	No	Feldspathic porcelain	n.r.	n.r.	n.r.	n.r.	125	125
Vanlioglu et al. (2013)	Metal-ceramic	No	Feldspathic porcelain	125	0	n.r.	n.r.	47	44
Lops et al. (2013)	Metal-ceramic	No	n.r.	47	0	n.r.	44	229	218
Lai et al. (2013)	Metal-ceramic	No	Ceramic	229	0	0	229	63	nr
Perelli et al. (2012)	Metal-ceramic	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	20	20
Gotfredsen (2012)	Metal	No	Ceramic	20	0	n.r.	n.r.	39	39
Schmidlin et al. (2010)	Metal	No	Ceramic	35	4	n.r.	n.r.	108	108
Cannizzaro et al. (2008)	Metal	No	n.r.	108	0	35	73	47	47
Jemt (2008)	Metal	No	Ceramic (n.r.)	0	47	47	0	42	34
Schropp and Isidor (2008a,2008b)	Metal	No	n.r.	40	2	24	21	50	50
Ozkan et al. (2007)	Metal-ceramic	No	Feldspathic porcelain	n.r.	n.r.	0	50	34	33
Turkyilmaz (2006)	Metal-ceramic	No	Ceramco	36	0	14	20	73	72
Romeo et al. (2006)	Metal-ceramic	No	n.r.	58	15	n.r.	n.r.	147	138
Dhanrajani and Al-Rafee (2005)	Metal-ceramic	No	n.r.	n.r.	n.r.	74	73	163	158
Covani et al. (2004)	metal-ceramic	No	n.r.	n.r.	n.r.	n.r.	n.r.	23	12
Norton (2001)	Metal-ceramic	No	Feldspathic porcelain	14	0	12	2	32	32
Bambini et al. (2001)	Metal-ceramic	No	Feldspathic porcelain	0	32	n.r.	n.r.	109	109
Mericske-Stern et al. (2001)	Metal-ceramic	No	Feldspathic porcelain	7	102	n.r.	n.r.	30	30
Polizzi et al. (1999)	Metal-ceramic	No	Feldspathic porcelain	30	0	30	0	16	16

(Continues)

TABLE 2 (Continued)

Author (year)	Material framework	Monolithic (yes/no)	Veneering material	No. of cemented crowns	No. of screw-retained crowns	No. of crowns anterior	No. of crowns posterior	Total no. of crowns	No. of crowns at the end of observation
Scheller et al. (1998)	Metal-ceramic	n.r.	n.r.	16	0	n.r.	n.r.	n.r.	n.r.
Vigolo et al. (2016)	Zirconia-ceramic	No	n.r.	283	257	84	457	541	541
Guncu et al. (2016)	Zirconia-ceramic	No	Feldspathic porcelain	24	0	0	24	24	24
Branzen et al. (2015)	Zirconia-ceramic	n.r.	n.r.	n.r.	n.r.	28	0	28	28
Worni et al. (2015)	Zirconia-ceramic	No	Feldspathic porcelain	0	70	n.r.	n.r.	70	65
Kolgeci et al. (2014)	Zirconia-ceramic	No	Nobel Rondo, Cerabien, Creation	12	108	n.r.	n.r.	120	120
Nothdurft et al. (2014)	Zirconia-ceramic	No	System specific veneering ceramic	39	0	0	39	39	37
Lops et al. (2013)	Zirconia-ceramic	No	n.r.	38	0	0	37	38	37
Hosseini et al. (2013)	Zirconia-ceramic	No	IPS Empress, IPS e.maxceram	61	0	41	11	52	n.r.

Note. n.r.: not reported.

The incidence of ceramic fractures or chippings was reported in majority of the studies. The incidence was similar between the material groups, with 2.9% of the metal-ceramic and 2.8% of the zirconia implant-supported SCs experiencing this complication over the 5-year observation period. Significantly more zirconia implant-supported SCs than metal-ceramic implant-supported SCs, however, failed due to material fractures, with a failure rate of 2.1% compared with 0.2% for metal-ceramic ($p = 0.001$) (Table 5).

Eighteen studies, with 2,211 cemented metal-ceramic implant-supported SCs reported an estimated 5-year complication rate of 2.0% for loss of retention compared with no loss of retention reported for the 115 cemented zirconia implant-supported SCs included in the analysis. The difference between the material groups reaches statistical significance in this aspect ($p < 0.001$).

4 | DISCUSSION

The present meta-analysis showed excellent estimated 5-year survival rates for both zirconia and metal-ceramic implant-supported single crowns with no significant differences between the two material types. Both types of crowns performed equally from a biologic point of view, but the zirconia crowns performed better from an aesthetic point of view.

With respect to technical complications, the incidence of ceramic chipping was similar between the material groups. The zirconia crowns, however, had more frequently to be redone due to fracture of the core or the veneering ceramic than metal-ceramic crowns.

Zirconia-ceramic crowns are well-established as all-ceramic alternative to metal-ceramics on both implants and teeth in clinical practice today. At both indications, the zirconia crowns showed very good 5-year survival rates (Sailer, Makarov, Thoma, Zwahlen, & Pjetursson, 2016; Sailer et al., 2015). Supported by teeth zirconia SCs reached an estimated 5-year survival rate of 91.2% (82.8%–95.6%), (Sailer et al., 2015, 2016) and supported by implants in the present systematic review the zirconia implant-supported SCs even reached a higher estimated 5-year survival rate of 97.6% (94.3%–99%). No statistically significant differences were found between zirconia-based and metal-ceramic crowns in both reviews (Sailer et al., 2015, 2016).

Hence, from this perspective, zirconia is a feasible all-ceramic restorative option for single implants in anterior and posterior regions. It has to be considered that survival rates do not take into consideration that problems might have occurred at the reconstructions over time.

One frequently reported problem of zirconia-ceramic reconstructions in the literature is chipping of the veneering ceramic (Heintze & Rousson, 2010). In the initial applications of zirconia as framework material, this complication was due to the fact that prototype veneering ceramics were used (Sailer et al., 2007).

Later, low fusing veneering ceramics specifically adapted to the biomechanical properties of zirconia were introduced and the technical procedure of veneering the zirconia framework was modified (Aboushelib, Kleverlaan, & Feilzer, 2006). The problem of chipping of the zirconia veneering ceramic still persisted in the more recent

TABLE 3 Annual failure rates and survival of single crowns (SCs) divided according to material utilized

Study (year of publication)	Total no. of SCs	Mean follow-up time (years)	No. of failures	Total exposure time (years)	Estimated annual failure rate[a] (per 100 SC years)	Estimated survival after 5 years[a] (in %)
Metal ceramic						
Tey et al. (2017)	266	5.2	5	1,383	0.36	98.2
Mangano et al. (2017)	103	3	2	309	0.65	96.8
Vigolo et al. (2016)	1,428	5.7	6	8,180	0.07	99.6
Donati et al. (2016)	45	11	1	483	0.21	99.0
Walton (2015)	220	5	3	1,110	0.27	98.7
Mangano et al. (2015)	15	14.3	0	214	0	100
Pozzi et al. (2014)	88	3	0	264	0	100
Francetti et al. (2014)	15	6.8	1	102	0.98	95.2
Mangano, Shibli, et al. (2014)	215	5.6	1	1,204	0.08	99.6
Mangano, Macchi, et al. (2014)	482	5	1	2,410	0.04	99.8
Wittneben et al. (2014)	268	10.8	13	2,806	0.46	97.7
Vanlioglu et al. (2013)	125	5	2	625	0.32	98.4
Lops et al. (2013)	47	4.9	0	230	0	100
Lai et al. (2013)	229	7.2	11	1,653	0.67	96.7
Perelli et al. (2012)	63	4.8	6	300	2.00	90.5
Gotfredsen (2012)	20	10	2	200	1.00	95.1
Schmidlin et al. (2010)	39	6.2	2	243	0.82	96.0
Cannizzaro et al. (2008)	108	3	3	324	0.93	95.5
Jemt (2008)	47	12.3	11	576	1.91	90.9
Schropp and Isidor (2008a,2008b)	42	4.7	2	210	0.95	95.3
Ozkan et al. (2007)	50	3	1	150	0.67	96.7
Turkyilmaz (2006)	34	3	1	101	0.99	95.2
Romeo et al. (2006)	73	5.5	5	404	1.24	94.0
Covani et al. (2004)	163	3.9	3	636	0.47	97.7
Norton (2001)	23	5.3	0	74	0	100
Mericske-Stern et al. (2001)	109	4.3	3	469	0.64	96.9
Polizzi et al. (1999)	30	5.3	2	158	1.27	93.9
Scheller et al. (1998)	16	4.2	0	66	0	100
Total	4,363	5.7	87	24,884		
Summary estimate (95% CI) [a]					0.35 (0.19–0.66)	98.3 (96.8–99.1)

(Continues)

TABLE 3 (Continued)

Study (year of publication)	Total no. of SCs	Mean follow-up time (years)	No. of failures	Total exposure time (years)	Estimated annual failure rate[a] (per 100 SC years)	Estimated survival after 5 years[a] (in %)
Zirconia ceramic						
Vigolo et al. (2016)	541	6.1	8	3,276	0.24	98.8
Guncu et al. (2016)	24	3.9	2	94	2.13	89.9
Branzen et al. (2015)	28	6.8	0	190	0	100
Worni et al. (2015)	70	3.6	4	253	2.44	92.4
Kolgeci et al. (2014)	120	3.2	5	385	1.30	93.7
Nothdurft et al. (2014)	39	2.9	2	116	1.72	91.7
Lops et al. (2013)	38	4.9	0	185	0	100
Hosseini et al. (2013)	52	3.1	2	161	1.24	94.0
Total	912	5.1	23	4,660		
Summary estimate (95% CI) [a]					0.49 (0.21–1.18)	97.6 (94.3–99.0)

Note. [a]Based on robust Poisson's regression.

studies as predominant technical complication. Yet chipping of the veneering material is also the predominant technical complication at metal-ceramic implant reconstructions (Pjetursson et al., 2012).

Besides the material-specific factors, numerous clinical factors contribute to the risk of chipping of the veneered, that is, bi-layer materials at implant-supported reconstructions. It has been shown that the tactile sensitivity is 8.7 times lower at implants than at teeth (Hammerle et al., 1995). Furthermore, a combination of intra-oral conditions like temperature and pH changes (Scherrer, Denry, Wiskott, & Belser, 2001) and material defects due to the veneering procedures could also increase the risk (Kelly, 1995).

A promising new alternative to the bi-layer reconstructions are monolithic reconstructions, for example, out of zirconia (Hamza & Sherif, 2017). A pronounced increase in application of the monolithic zirconia implant-supported reconstructions can already be noted. One of the aims of the present systematic review was to analyze the outcomes of monolithic zirconia reconstructions after an observation period of at least 3 years. Unfortunately, no clinical studies on monolithic zirconia reconstructions fulfilled the relatively simple inclusion criteria of the present systematic review. Clinical medium- to long-term studies have, hence, to be awaited before clinical recommendations can be made in this respect.

One main reason for the use of all-ceramics instead of metal-ceramics was and still is aesthetics. Indeed, the zirconia-ceramic SCs exhibited better aesthetic outcomes than the metal-ceramic crowns in the present systematic review.

Zirconia has been reported to have a low plaque accumulation rate, (Cionca, Hashim, & Mombelli, 2017; Roehling et al., 2017) and an excellent hard and soft tissue integration (Thoma et al., 2015) equivalent to the one of titanium. In the present review, no differences of the biologic outcomes of the zirconia and metal-ceramic implant-supported SCs were found. Low incidence of soft tissue complication and marginal bone loss was found for both types of reconstructions.

The main limitation of the present systematic review was that no RTCs were available addressing the present focused question, and that the overall conclusions were based on pooled data of different types of implants placed in different positions in the jaws (maxilla, mandible; anterior, posterior) and different genders. Furthermore, there was a lack of standardized approaches to report biological and technical complications in the available studies. Furthermore, the included studies often clustered data from patients with different observation periods instead of following patients for a well-defined time period. Finally, it may be questioned whether searching only one literature database, that is, Medline, involves a risk that important studies that fulfill the inclusion criteria of the present systematic review go un-noticed. In several systematic reviews published by our research team, the primary literature search was performed in Medline, followed by additional searches of different databases such as Embase and the Cochrane Library. However, the number of additional studies, included through these additional sources, was limited. Therefore, the search strategy of our group has changed

to apply a very open and unrestricted title search, avoiding limitations and filters in order to be as inclusive as possible on the title level. Additionally, meticulous hand-searching of all reference lists of previous reviews and all included full-text papers of the present systematic review helped locating the included studies of the present and a parallel review addressing multiunit implant supported fixed dental prostheses (Sailer et al., 2018; ITI CC SR).

5 | CONCLUSIONS

In conclusion, the zirconia-ceramics can be recommended as valid alternative to metal-ceramics for implant-supported SCs. Although bi-layered, veneered zirconia has been dominantly associated with the technical complication such as "chipping of the veneering ceramic" in the literature, this problem was also frequently found for metal-ceramic implant reconstructions. Newer types

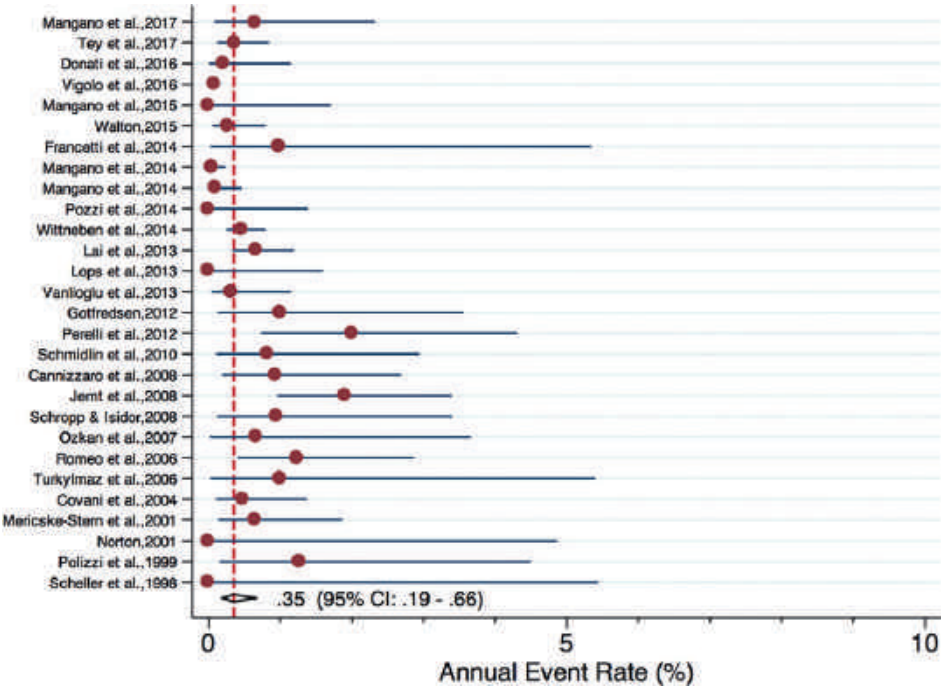

FIGURE 2 Annual failure rates (per 100 years) of implant-supported metal-ceramic single crowns.

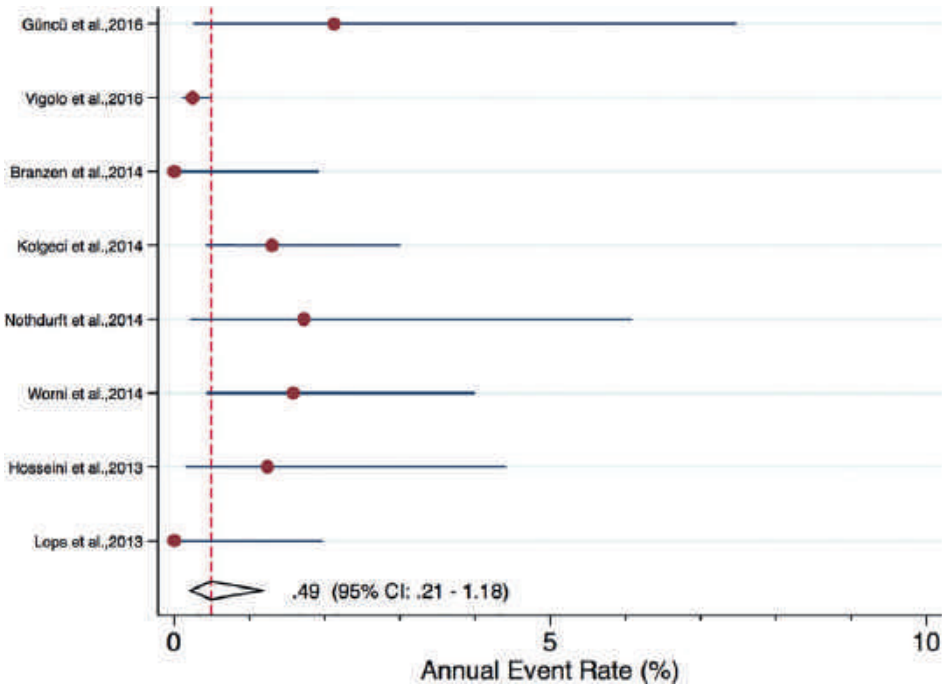

FIGURE 3 Annual failure rates (per 100 years) of implant-supported zirconia single crowns.

TABLE 4 Annual failure rates and estimated 5-year survival according to position in the mouth. Based on robust Poisson's regression

	Total number of single crowns (SCs)	Estimated annual failure rate (95% CI)	5-year summary estimate, % (95% CI)	Total number of SCs	Estimated annual failure rate (95% CI)	5-year summary estimate, % (95% CI)	*p*-Value*
	Anterior			Posterior			
Metal-ceramic	520	0.55* (0.14–2.06)	97.3* (90.2–99.3)	2,078	0.19* (0.07–0.53)	99.0* (97.4–99.6)	0.201
Zirconia-ceramic	112	0.43* (0.15–1.25)	97.9* (94.0–99.3)	557	0.28* (0.11–0.74)	98.6* (96.4–99.5)	0.511

*Based on robust Poisson's regression.

TABLE 5 Comparing annual failure and complication rates of metal-ceramic single crowns (SCs) and zirconia-ceramic SCs. Based on robust Poisson's regression

Complication	Number of SCs	Estimated annual complication rates (95% CI)	Cumulative 5 year complication rates, % (95% CI)	Number of SCs	Estimated annual complication rates (95% CI)	Cumulative 5 year complication rates, % (95% CI)	*p*-Value
	Metal-ceramic			Zirconia-ceramic			
Total number of SCs with complications	1,300	2.85* (1.89–4.29)	13.3* (9.0–19.3)	76	3.53* (1.29–9.69)	16.2* (6.2–38.4)	0.622
Soft tissue complications	2,118	1.05* (0.47–2.34)	5.1* (2.3–11.0)	234	1.09* (0.40–2.95)	5.3* (2.0–13.7)	0.946
Significant marginal bone loss	3,254	0.67* (0.32–1.41)	3.3* (1.6–6.8)	670	0.88* (0.69–1.13)	4.3* (3.4–5.5)	0.481
Aesthetic failures	627	0.34* (0.10–1.15)	1.7* (0.5–5.6)	224	0 (0–0.44)	0* (0–2.2)	<0.001
Abutment fracture	3,998	0.03* (0.01–0.09)	0.2* (0.06–0.5)	790	0.07* (0.04–0.12)	0.4* (0.2–0.6)	0.199
Abutment or occlusal screw fracture	3,788	0.01* (0.003–0.3)	0.05* (0.01–0.2)	814	0.02* (0.01–0.04)	0.1* (0.07–0.2)	0.204
Abutment or occlusal screw loosening	3,954	0.7* (0.34–1.56)	3.6* (1.7–7.5)	694	0.21* (0.10–0.43)	1.0* (0.5–2.1)	0.015
Ceramic fracture or chipping	4,090	0.58* (0.35–0.97)	2.9* (1.7–4.7)	694	0.57* (0.13–2.60)	2.8* (0.6–12.2)	0.986
Failure due to fracture of the restoration	2,592	0.04* (0.01–0.14)	0.2* (0.07–0.67)	371	0.43* (0.18–1.06)	2.1* (0.9–5.1)	0.001
Loss of retention of cemented SCs	2,211	0.40* (0.25–0.64)	2.0* (1.3–3.1)	115	0 (0–0.99)	0* (0–4.8)	<0.001

*Based on robust Poisson's regression.

of monolithic zirconia reconstructions seem interesting with this respect; yet, clinical studies reporting on medium-to long-term outcomes of monolithic zirconia restorations are still lacking. Hence, more research is needed until conclusions on their indications and limitations can be drawn.

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CONFLICT OF INTEREST

The authors have no specific conflict of interest related to the present systematic review.

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SUPPORTING INFORMATION

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CONSENSUS REPORT

WILEY CLINICAL ORAL IMPLANTS RESEARCH

Group 2 ITI Consensus Report: Prosthodontics and implant dentistry

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Abstract

Objectives: Working Group 2 was convened to address topics relevant to prosthodontics and dental implants. Systematic reviews were developed according to focused questions addressing (a) the number of implants required to support fixed full-arch restorations, (b) the influence of intentionally tilted implants compared to axial positioned implants when supporting fixed dental prostheses (FDPs), (c) implant placement and loading protocols, (d) zirconia dental implants, (e) zirconia and metal ceramic implant supported single crowns and (f) zirconia and metal ceramic implant supported FDPs.

Materials and methods: Group 2 considered and discussed information gathered in six systematic reviews. Group participants discussed statements developed by the authors and developed consensus. The group developed and found consensus for clinical recommendations based on both the statements and the experience of the group. The consensus statements and clinical recommendations were presented to the plenary (gathering of all conference attendees) and discussed. Final versions were developed after consensus was reached.

Results: A total of 27 consensus statements were developed from the systematic reviews. Additionally, the group developed 24 clinical recommendations based on the combined expertise of the participants and the developed consensus statements.

Conclusions: The literature supports the use of various implant numbers to support full-arch fixed prostheses. The use of intentionally tilted dental implants is indicated when appropriate conditions exist. Implant placement and loading protocols should be considered together when planning and treating patients. One-piece zirconia dental implants can be recommended when appropriate clinical conditions exist although two-piece zirconia implants should be used with caution as a result of insufficient data. Clinical performance of zirconia and metal ceramic single implant supported crowns is similar and each demonstrates significant, though different, complications. Zirconia ceramic FDPs are less reliable than metal ceramic. Implant supported monolithic zirconia prostheses may be a future option with more supporting evidence.

KEYWORDS
ceramic crown, ceramic fixed dental prosthesis, full-arch prosthesis, implant loading, implant number, implant placement, implant survival, patient outcomes, tilted implants, zirconia implants

1 | INTRODUCTION

Prosthodontic treatment assisted by dental implants has continued to evolve and is a routine option for clinicians and patients. There are, however, questions that remain for newer treatment protocols.

For treatment of edentulous arches, the appropriate number of implants required to support a prosthesis and the influence of implant inclination remain controversial. Systematic reviews conducted by Polido et al. and by Lin and Eckert analysed and compared the implant number and inclination, respectively. For partially dentate (or edentate) arches, placement and loading protocols continue to develop. Subsequent to a systematic review of the existing literature on this topic, Gallucci et al. consider the state of the science, and propose a comprehensive classification and treatment philosophy that considers placement and loading as a singular planning and treatment decision.

Material options continue to expand for fabrication of both dental implants and prostheses. A systematic review conducted by Roehling et al. investigated the state of the science associated with dental implants fabricated from zirconia and compared the performance of zirconia implants with those fabricated from titanium. Systematic reviews by Pjetursson et al., and Sailer et al. analysed the performance of zirconia ceramic when compared to metal ceramic restorative materials for the restoration of implants in single tooth sites and extended edentulous spans, respectively.

When developing consensus statements, the group chose to include the number and type of citations from which conclusions were drawn for the benefit of the reader.

The six systematic reviews undertaken by this group include:

1 Clinical performance of intentionally tilted implants versus axially positioned implants: A systematic review.
Wei-Shao Lin and Steven E. Eckert.

2 Implant placement and loading protocols in partially edentulous patients: A systematic review.
German O. Gallucci, Adam Hamilton, Wenjie Zhou, Daniel Buser and Stephen Chen.

3 Performance and outcomes of zirconia dental implants in clinical studies: A meta-analysis.
Stefan Roehling, Karl A. Schlegel, Henriette Woelfler and Michael Gahlert.

4 Number of implants placed for complete arch fixed prostheses: A systematic review and meta-analysis.
Waldemar Daudt Polido, Tara Aghaloo, Thomas W. Emmett, Thomas D. Taylor and Dean Morton.

5 A systematic review of the survival and complication rates of zirconia-ceramic and metal-ceramic multiple-unit fixed dental prostheses.
Irena Sailer, Malin Strasding, Nicola Alberto Valente, Marcel Zwahlen, Shiming Liu and Bjarni Elvar Pjetursson.

6 A systematic review of the survival and complication rates of zirconia-ceramic and metal-ceramic single crowns.
Bjarni E. Pjetursson, Nicola A. Valente, Malin Strasding, Marcel Zwahlen, Shiming Liu and Irena Sailer.

1.1 | Disclosures

All participants were asked to disclose any possible conflicts of interest that could potentially influence the direction of the consensus deliberations. No conflicts of interest were identified.

2 | NUMBER OF IMPLANTS PLACED FOR COMPLETE ARCH FIXED PROSTHESES: A SYSTEMATIC REVIEW AND META-ANALYSIS

2.1 | Preamble

Varying numbers of implants have been reported in the literature as being used to supported fixed full-arch prostheses for completely edentulous arches. Many factors are reported to influence the decision regarding the number if implants chosen. This systematic review was designed to evaluate surgical and prosthetic outcomes associated with five or more implants, and compare these with using less than five implants, when providing full-arch fixed prostheses for completely edentulous arches. Primary outcomes investigated were implant and prosthesis survival. Secondary outcomes included distribution of implants, implant inclination, loading protocol and mode of prosthesis retention.

2.2 | Consensus statements

1. There is no statistically significant difference in implant survival rates associated with the use of fewer than five implants when compared to five or more implants when supporting a fixed dental prosthesis. This statement is based on outcomes reported in 93 studies (9 RCTs, 42 Prospective and 42 Retrospective) with a median follow-up of 8 years (range: 1–15 years).
2. There is no statistically significant difference in outcomes (implant and prosthesis survival) for full-arch FDPs in the maxilla supported by fewer than five implants (median follow-up of 5.5 years) when compared to five or more implants (median follow-up of 8 years). This statement is based on the analysis of data from 50 groups of patients, extracted from the 28 studies that reported numbers of implants for the maxilla (1 RCT, 13 Prospective and 14 retrospective), and from the 19 papers that reported for both groups (3 RCT, 7 Prospective and 9 Retrospective), among which 26 reported on fewer than five implants, and 24 reported on five or more implants. In all, 47 publications reported outcomes for the maxilla (4 RCTs, 20 Prospective and 23 Retrospective). Of the 26 studies documenting outcomes for fewer than five implants, the majority reported on the use of four implants incorporating distally tilted posterior implants and an immediate loading protocol (23 reports with a median follow-up of 5.5 years). A majority of the 24 studies documenting outcomes for five or more implants reported use of six implants positioned in a parallel configuration and utilizing an immediate loading protocol (20 reports with a median follow-up of 8 years).
3. There is no statistically significant difference ($p < 0.05$) in outcomes (implant and prosthesis survival) for full-arch FDPs in the mandible supported by less than five implants (median follow-up of 5.5 years) when compared to five or more implants (median follow-up of 5.5 years). This statement is based on the analysis of data from 72 groups, among which 58 reported on fewer than five implants and 14 reported on five or more. Data were extracted from 65 publications that reported on the mandible (8 RCT, 29 Prospective and 28 Retrospective). Of the 14 studies documenting use of five or more implants to support a complete arch prosthesis in the mandible, a majority used five implants (10 reports with a median follow-up of 4 years) in a parallel configuration (12 reports) and with an immediate loading protocol (8 reports). Of the 58 studies documenting use of fewer than five implants, a majority used four implants (41 studies with a median follow-up of 5.5 years and a range of 1–10 years). A parallel configuration was reported in 27 papers and use of posterior distally inclined implants reported in 31. An immediate loading protocol was reported as being used in 48 of the 58 articles.

2.3 | Clinical recommendations

1. The final prosthetic plan should be considered when developing a surgical plan for implant treatment of edentulous arches. Factors to be considered include:
   a. Prosthesis material
   b. One-piece or segmented prostheses
   c. Aesthetic factors (e.g., lip support, smile line)
   d. Condition of the opposing dentition
   e. Available space for the prosthesis
   f. Anatomy of the edentulous ridge (maxilla, mandible, bone volume and quality, anatomic limitations)
   g. Planned implant distribution (AP distribution) and cantilever length
   h. Space available for hygiene and maintenance
   i. Patient preference and compliance
2. When patients present with teeth in place, all treatment options should be considered as part of the informed consent process and appropriate consideration should be given to preservation of teeth. When the decision is made to rehabilitate the patient with a full-arch prosthesis, and tooth extraction is required, planning consideration must be given to the space required for the prosthesis in all dimensions.
3. A minimum number of four appropriately distributed implants are recommended to support a one-piece full-arch fixed prosthesis. However, the impact of future implant loss/complications on prosthesis support should be considered when choosing implant number. Additional implants can provide options for fixed full-arch segmented prostheses.
4. When selecting the placement and loading protocol, the following conditions should be considered:
   a. Systemic conditions
   b. Implant stability (insertion torque/ISQ)
   c. The need for bone grafting at the time of placement
   d. Implant size and shape
   e. Experience and skill of the clinician
   These modifiers should be considered for each site where an implant is planned.
5. As part of a comprehensive plan, and when clinician skill and oral environment are favourable, the invasiveness of surgery can be reduced through utilization of improved implant materials, surfaces and designs (short, narrow, tapered), prosthetic connections and placement options (tilted implants).
6. Bone augmentation is recommended when there is a need to increase implant distribution or number in response to the prosthetic plan. These procedures are more invasive and challenging, increasing the level of clinician skill and experience required.

2.4 | Recommendations for future research

1. There is a need for additional randomized clinical trials comparing use of four and six implants for support of fixed full-arch prostheses.
2. Studies comparing one-piece and segmented prostheses for the rehabilitation of edentulous arches are required.
3. Studies evaluating the influence of digital planning and guided surgical options on treatment predictability and patient outcomes are required.
4. Studies evaluating the influence of intraoral optical scanning and the use of CAD-CAM technology on full-arch prosthesis fit and patient outcomes are required.
5. There is a need for research evaluating the use of reduced diameter, short and extra-short implants when planning and treatment edentulous arches with full-arch prostheses. Randomized clinical trials comparing outcomes for these with four implants including tilted options are needed.

3 | CLINICAL PERFORMANCE OF INTENTIONALLY TILTED IMPLANTS VERSUS AXIALLY POSITIONED IMPLANTS

3.1 | Preamble

A treatment approach using intentionally tilted implants has been recommended to both reduce prosthetic cantilevers and additional surgical interventions. This review was undertaken to determine the clinical performance of dental implants that are intentionally tilted when compared to implants that are placed following the long axis of the residual alveolar ridge, when used to support full-arch fixed prostheses. Primary outcomes evaluated were implant and prosthesis survival rates. Secondary outcomes included peri-implant marginal bone loss, soft and hard tissue complications, prosthetic complications and subjective patient-centred outcomes.

3.2 | Consensus statements

1. There is no statistically significant difference in primary outcomes (survival rates for implant and prosthesis) or secondary outcomes (peri-implant marginal bone loss, soft and hard tissue complications, prosthetic complications and patient-centred outcomes) for implants placed in an axial or in a tilted configuration when used to support full-arch FDPs. This statement is based on 20 studies (2 RCTs, 1 CT and 17 Prospective Cohort).
2. The most common complications associated with an interim full-arch fixed acrylic resin prosthesis were prosthesis fracture, screw loosening and fracture of the veneering material. This statement is based on 20 studies (2 RCTs, 1 CT and 17 Prospective Cohort).
3. For definitive prostheses, metal framework fracture was uncommon. More commonly encountered complications included wear or fracture of the veneering material or artificial teeth, need for re-adaptation of prostheses to tissue to compensate for continuing resorption, abutment or prosthetic screw

loosening, prosthetic screw fracture and loss of screw access restoration. This statement is based on 21 studies (2 RCTs, 1 CT and 18 Prospective Cohort).

4. The studies report satisfactory patient-reported outcomes measures. These include aesthetics, phonetics, ease of maintenance and functional efficiency. This statement is based on nine studies (1 RCT, 8 Prospective Cohort).

3.3 | Clinical recommendations

1. The anterior posterior implant distribution should be maximized for full-arch FDPs. When conditions allow implants should be positioned axially. If anatomic limitations or prosthetic indications exist, the posterior implants can be intentionally tilted.

3.4 | Recommendations for future research

1. Direct randomized controlled clinical trials or non-randomized comparative cohort studies with longer follow-up periods and larger study populations should be designed to specifically address the questions of implant and prosthesis performance when using intentionally tilted or axially placed implants to support full-arch FDPs.

4 | IMPLANT PLACEMENT AND LOADING PROTOCOLS. A SYSTEMATIC REVIEW

4.1 | Preamble

This systematic review evaluated the scientific evidence relating to post-extraction implant placement and timing and loading protocols combined. A validation tool was used to determine the level of scientific and clinical documentation for each combination of implant placement and loading protocols (Gallucci et al., 2009). Furthermore, patient- and site-specific criteria for selecting the placement and loading protocols were tabulated to formulate clinical recommendations. Due to the heterogenicity of the data, meta-analysis was not possible; however, descriptive analysis was completed.

4.2 | Definition of terms as described in: Implant placement and loading protocols. A systematic review

German Gallucci, Adam Hamilton, Wenjie Zhou, Daniel Buser and Stephen Chen.

Type 1A: Immediate placement plus immediate restoration/loading
Type 1B: Immediate placement plus early loading
Type 1C: Immediate placement plus conventional loading
Type 2A: Early placement with soft tissue healing plus immediate restoration/loading
Type 2B: Early placement with soft tissue healing plus early loading
Type 2C: Early placement with soft tissue healing plus conventional loading
Type 3A: Early placement with partial bone healing plus immediate restoration/loading
Type 3B: Early placement with partial bone healing plus early loading
Type 3C: Early placement with partial bone healing plus conventional loading
Type 4A: Late placement plus immediate restoration/loading
Type 4B: Late placement plus early loading
Type 4C: Late placement plus conventional loading

Due to the limitations in distinct specification of the implant placement time in many clinical studies reported, the early implant placement groups (types 2 and 3) were combined for each loading protocol (Type 2/3A, Type 2/3B and Type 2/3C).

Implant Placement protocols were defined as follows:

a. Immediate implant placement: Dental implants are placed in the socket on the same day as tooth extraction.
b. Early implant placement: Dental implants are placed with soft tissue healing (4–8 weeks) or with partial bone healing (12–16 weeks) after tooth extraction.
c. Late implant placement: Dental implants are placed after complete bone healing, more than 6 months after tooth extraction.

Implant loading protocols were defined as follows:

a. Immediate loading: Dental implants are connected to a prosthesis in occlusion with the opposing arch within 1 week subsequent to implant placement.
b. Immediate restoration: Dental implants are connected to a prosthesis held out of occlusion with the opposing arch within 1 week subsequent to implant placement.
c. Early loading: Dental implants are connected to the prosthesis between 1 week and 2 months after implant placement.
d. Conventional loading: Dental implants are allowed a healing period of more than 2 months after implant placement with no connection of the prosthesis.

4.3 | Consensus statements

1. The newly proposed classification assessing both the timing of implant placement and loading combinations allows for comprehensive treatment selection.
2. a. Type 1A (immediate placement plus immediate restoration/loading) is a clinically documented protocol. The survival rate was 98% (median 100, range 87%–100%).
   b. Type 1B (immediate placement plus early loading) is a clinically documented protocol. The survival rate was 98% (median 100, range 93%–100%).

c. Type 1C (immediate placement plus conventional loading) is a scientifically and clinically valid protocol. The survival rate was 96% (median 99, range 91%–100%).

3. a. Type 2-3A (early placement plus immediate restoration/loading) presents clinically insufficient documentation.
   b. Type 2-3B (early placement plus early loading) presents clinically insufficient documentation.
   c. Type 2-3C (early placement plus conventional loading) is a scientifically and clinically valid protocol. The survival rate was 96% (median 96, range 91%–100%).
4. a. Type 4A (late placement plus immediate restoration/loading) is a clinically documented protocol. The survival rate was 98% (median 99, range 83%–100%).
   b. Type 4B (late placement plus early loading) is a scientifically and clinically valid protocol. The survival rate was 98% (median 99, range 97%–100%).
   c. Type 4C (late placement plus conventional loading) is a scientifically and clinically valid protocol. [Correction added August 2019, after publication: 'immediate placement' changed to 'late placement'] The survival rate was 98% (median 100, range 95%–100%).
5. When considering placement/loading protocols, there are factors that can prevent the accomplishing of the intended treatment. These factors include:
   a. Patient-related factors.
   b. Lack of primary stability.
   c. The need for bone augmentation.

4.4 | Clinical recommendations

1. Treatment planning for implant therapy should commence once the indication for tooth extraction has been confirmed. Both the implant placement and loading protocol should be planned prior to tooth extraction. The selection of the implant placement and restoration/loading protocol should be based on achieving predictable outcomes:
   a. Long-term hard and soft tissue stability.
   b. Optimal aesthetics.
   c. Reduced risk for complications.
   d. Meet patient-specific and site-related criteria.
2. As part of the planning and consent process, alternative treatment modalities should be in place, in the event that specific intra-operative procedural criteria are not met. Implant placement and restoration/loading protocols present with different levels of clinical difficulty and overall treatment risk. When selecting treatment modalities, clinician skill and experience should match the challenges associated with the selected protocol.
3. The implant placement and loading protocol can have a negative impact on survival and success of specific selection criteria are not met, and/or execution of the clinical procedure is of insufficient quality. Careful consideration of patient-centred benefits of the different implant placement and loading protocols and the associated risks should be taken into consideration.
4. Immediate placement and immediate restoration/loading (type 1A) is a complex surgical and prosthodontic procedure and should only be performed by clinicians with a high level of clinical skill and experience. Type 1A protocol should only be considered when there are patient-centred advantages (e.g., aesthetic requirements, reduced morbidity), and when the following clinical conditions are met:
   a. Intact socket walls.
   b. Facial bone wall at least 1 mm in thickness.
   c. Thick soft tissue.
   d. No acute infection at the site.
   e. The availability of bone apical and lingual to the socket to provide primary stability.
   f. Insertion torque 25–40 Ncm and/or ISQ value >70.
   g. An occlusal scheme which allows for protection of the provisional restoration during function.
   h. Patient compliance.
5. Early implant placement may be considered in most clinical situations, such as sites with thin facial walls and defects, often requiring simultaneous bone augmentation procedures. Conventional loading (type 2-3C) is well documented and is recommended with early implant placement. Immediate (type 2-3A) and early (type 2-3B) loading protocols combined with early implant placement are not sufficiently well documented to be recommended as routine procedures.
6. As a planned procedure, late implant placement is the least desirable of the placement time options, due to the risk of alveolar ridge resorption and reduction in bone volume, as well as extended treatment time. When late placement is indication for patient- or site-related reasons, an alveolar ridge preservation procedure is recommended.
7. In the case of late implant placement, early loading (type 4B) and conventional loading (type 4C) are well-documented protocols and may be considered routine. Late implant placement with immediate loading (type 4A) may be considered when patient-centred advantages are present, and the criteria for immediate restoration/loading are met.

4.5 | Recommendations for future research

1. For future research in placement/loading protocols, it is recommended that "Intention to treat" analyses are conducted and intention to treat considered as a primary outcome measure.
2. Due to the possible negative influence of the implant placement/loading protocols on the treatment outcomes, in the absence of meeting specific criteria, randomization at the level of the chosen treatment is not recommended.
3. Future research on implant placement/loading protocols is required with well-designed prospective case series with at least 5-year follow-up, which should report on both the placement and loading protocols. The specific indications, locations, selection criteria and aesthetic parameters for the different types of implant placement and loading should also be reported.

5 | PERFORMANCE AND OUTCOMES OF ZIRCONIA DENTAL IMPLANTS

5.1 | Preamble

In recent history (since 2000s), numerous zirconia implant types exhibiting different physical properties and designs have been introduced to the dental market. This systematic review was undertaken to evaluate the performance of these implants. Primary outcomes investigated included implant survival and peri-implant marginal bone loss. Secondary outcomes included implant fractures, technical complications, biologic complications and aesthetic outcomes. Upon review of the literature, it became apparent that the data should be classified into two separate groups, those currently commercially available (CA), and those no longer commercially available (NCA).

5.2 | Consensus statements

1. The published data for CA zirconia implants only allow valid statements for one-piece designs. This statement is based on nine clinical studies (8 Prospective and 1 Retrospective) including 510 implants followed for 1-year, and five clinical studies (5 Prospective) including 192 implants followed for 2 years.
2. Comparing survival rates of CA one-piece zirconia implants with published data on titanium implants, 1-year (98%) and 2-year (97%) results showed similar outcomes. This statement is based on nine clinical studies (8 Prospective and 1 Retrospective) including 510 implants followed for 1 year, and five clinical studies (5 Prospective) including 192 implants followed for 2 years.
3. The survival rates of CA one-piece zirconia implants are statistically significantly higher than NCA implants. This statement is based on 18 clinical studies (14 Prospective and 4 Retrospective) including 1,128 implants.
4. CA zirconia implants show a mean peri-implant marginal bone loss on 0.67 mm (range: 0.20–1.02 mm) after 1 year. This statement is based on seven clinical studies (6 Prospective and 1 Retrospective) including 376 implants.
5. Comparing NCA and CA zirconia implants, marginal bone loss is not statistically significantly different. This statement is based on 14 clinical studies (11 Prospective and 3 Retrospective) including 839 implants.
6. Comparing NCA and CA zirconia implants, the fracture rate of one-piece designs has reduced from 3.4% to 0.2%. This statement is based on 18 clinical studies (14 Prospective and 4 Retrospective) including 1,128 implants.

5.3 | Clinical recommendations

1. Based on available data (up to 2 years), the use of one-piece CA zirconia implants can be recommended in cases where a one-piece soft tissue level implant with a cemented prosthesis in indicated and if requested by the patient.
2. Placement of one-piece zirconia implants should be prosthetically driven according to established guidelines for the implant design.
3. When using one-piece CA zirconia implants, the difficulties relating to a submucosal prosthodontic margin, removal of cement excess and difficulty with explantation have to be considered.
4. Two-piece CA zirconia implants can only be recommended with caution due to insufficient supporting data.

5.4 | Recommendations for future research

1. More data and clinical studies are needed regarding the clinical mid- and long-term performance of CA (2nd generation) one-piece zirconia implants.
2. More clinical studies focusing on CA (2nd generation) two-piece zirconia implants are needed to provide support for use as an alternative to the limited indications given for the one-piece implant design.

6 | SURVIVAL AND COMPLICATION RATES OF ZIRCONIA CERAMIC AND METAL CERAMIC SINGLE IMPLANT SUPPORTED CROWNS

6.1 | Preamble

The aim of this systematic review was to evaluate the available scientific evidence on the survival and complication rates of veneered zirconia ceramic crowns when compared to metal ceramic implant supported crowns. The primary outcome of this review was the comparison of the survival rates of the veneered zirconia and metal ceramic crowns. Secondary outcomes reviewed were biological complication rates, technical complication rates and aesthetic failure rates.

6.2 | Consensus statements

1. Zirconia ceramic and metal ceramic implants supported SCs exhibit similar 5-year survival rates. This applies to both anterior and posterior regions. This statement is based on 36 clinical trials (22 Prospective, 14 Retrospective), reporting on 4,363 implant supported metal ceramic SCs, and 912 veneered zirconia implant-supported SCs.
2. The overall incidence of biological and technical complication is substantial (13%–16% or 1 SC out of 6) for implant supported SCs. This statement is based on 11 of the included trials (6 Prospective and 5 Retrospective).
3. There is no statistically significant difference between the 5-year biological outcomes of zirconia ceramic and metal ceramic implant supported SCs, that is, peri-implant mucosal lesions and

marginal bone loss >2 mm. This statement is based on 36 clinical trials (22 Prospective and 14 Retrospective).

4. There is no statistically significant difference in veneering ceramic chipping between the two types of implant supported SCs at 5 years. There is also no difference in other technical complications such as the incidences of fracture of the abutment, abutment screw or occlusal screw and loss of retention (cemented SCs). However, catastrophic core fractures occur significantly more often with zirconia ceramic implant supported SCs. Furthermore, abutment screw or occlusal screw loosening occurs more frequently with metal ceramic implant supported SCs. This statement is based on 36 clinical trials (22 Prospective and 14 Retrospective).
5. The risk of aesthetic failure is lower for zirconia ceramic SCs when compared to metal ceramic SCs. This statement is based on 12 clinical trials (8 Prospective and 4 Retrospective).

6.3 | Clinical recommendations

1. For anterior and posterior implant supported SCs, both metal ceramic and zirconia ceramic can be recommended.
2. The selection of the prosthetic material should be based on the aesthetic expectations and general demands of the patients.
3. Patients should be informed about the likelihood and incidence of biological and technical complications for both types of crowns, as a substantial amount of time and effort may be needed for maintenance. Patient recall visits are highly recommended to reduce the risk of failure as a consequence of complications.

6.4 | Recommendations for future research

1. Monolithic ceramic crowns or micro-veneered ceramic crowns (facial veneering not including occlusal/functional areas) may be a promising alternative; however, scientific documentation is lacking. Future randomized controlled clinical trials should address the survival and complication rates of these more recent types of ceramic SCs, giving medium- to long-term follow-up results.
2. Randomized comparative studies of different types of monolithic ceramic SCs (lithium disilicate, zirconia, hybrid materials) need to be performed giving medium to long-term follow-up results.
3. Complications should be reported in a standardized way, using established indices and ratings.
4. Fractures of ceramic SCs should exclusively refer to catastrophic factures leading to the loss of the entire prosthesis.
5. Chipping of the ceramic should clearly be described as either:
   a. Minor chipping—polishable
   b. Major chipping—repairable
   c. Catastrophic chipping—not repairable that is, failure of the prosthesis.

7 | SURVIVAL AND COMPLICATION RATES OF ZIRCONIA CERAMIC AND METAL CERAMIC MULTIPLE UNIT FDPS

7.1 | Preamble

The aim of this systematic review was evaluation of available scientific evidence on the survival and complication rates of veneered zirconia ceramic FDPs when compared to metal ceramic implant supported FDPs. The primary outcome evaluated was comparison of the survival rates of the veneered zirconia and metal ceramic FDPs. Secondary outcomes reviewed were biological complication rates, technical complication rates and aesthetic failure rates.

7.2 | Consensus statements

1. Zirconia ceramic (veneered) implant supported FDPs exhibit significantly lower 5-year survival rates than metal ceramic implant supported FDPs. This statement is based on 14 studies reporting on 932 implant-supported metal ceramic FDPs (9 Prospective, 5 Retrospective) and three studies (2 Prospective and 1 Retrospective) reporting on 175 veneered zirconia implant-supported FDPs.
2. There is a lack of detailed information in the current literature to provide a statement on the biological and technical outcomes of the zirconia ceramic and metal ceramic implant supported FDPs. This statement is based on the systematic review scrutinizing the available literature on implant supported multiple unit FDPs.
3. Significantly more zirconia ceramic implant supported FDPs fail due to material fracture than metal ceramic implant supported FDPs. This statement is based on 18 clinical trials (11 Prospective and 7 Retrospective).
4. Chipping of the veneering ceramic is a common technical complication for both types of FDPs and may lead to a need for repair or replacement of the FDP. This statement is based on 14 clinical trials (8 Prospective and 6 Retrospective).

7.3 | Clinical recommendations

1. Zirconia ceramic (i.e., veneered) implant supported FDPs cannot be recommended as a first treatment option. If utilized, the patients need to be informed about the risks for fractures of the framework and chipping of the veneering ceramic.
2. Metal ceramic, using high noble (noble metal content > or =60% and gold > or =40%) or noble (noble metal content > or =25%) alloys, should still be considered as the first option for implant supported FDPs.
3. Due to the high costs of conventional metal ceramic FDPs and frequent technical problems associated with the veneered FDPs, monolithic zirconia may be an interesting alternative. However, clinical medium- to long-term outcomes have yet to be sufficiently analysed.

7.4 | Recommendations for future research

1. Monolithic zirconia implant supported FDPs may be a promising alternative; however, the scientific documentation is lacking. Future prospective clinical trials with a medium- to long-term follow-up should address the survival and complication rates of the monolithic zirconia FDPs in general.
2. Comparative clinical studies of monolithic zirconia and metal ceramic implant supported FDPs need to be performed before clinical recommendations can be made.
3. New material combinations including alternative metal or alloys (e.g., cobalt chromium) or polymer-based implant supported FDPs should be considered in future studies.
4. Complications should be reported in a standardized way, using established indices and ratings.
5. Fractures of ceramic prostheses should exclusively refer to catastrophic fracture leading to loss of the entire prosthesis.
6. Chipping of the ceramic should be clearly described as either minor chipping (polishable), major chipping (repairable) or catastrophic chipping (not repairable) leading to failure of the prosthesis.

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REVIEW ARTICLE

WILEY CLINICAL ORAL IMPLANTS RESEARCH

Patient-reported outcome measures focusing on aesthetics of implant- and tooth-supported fixed dental prostheses: A systematic review and meta-analysis

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Abstract

Objectives: The aim of this systematic review and meta-analysis was to summarize the existing evidence on patient-reported aesthetic outcome measures (PROMs) of implant-supported, relative to tooth-supported fixed dental prostheses.

Material and Methods: In April 2017, two reviewers independently searched the Medline (PubMed), EMBASE, and Cochrane electronic databases, focusing on studies including patient-reported aesthetic outcomes of implant- and tooth-supported fixed dental prostheses (FDPs). Human studies with a mean follow-up period of at least 1 year, a minimum of ten patients, and English, German, or French publication were included. For the comparison of subgroups, random-effects meta-regression for aggregate-level data was used.

Results: The systematic search for implant-supported prostheses focusing on patient-reported outcomes identified 2,675 titles, which were screened by two independent authors. Fifty full-text articles were analyzed, and finally, 16 publications (including 19 relevant study cohorts) were included. For tooth-supported prostheses, no studies could be included. A total of 816 implant-supported reconstructions were analyzed by patients. Overall aesthetic evaluation by the patients' visual analogue scale (VAS) rating was high in implant-supported FDPs (median: 90.3; min–max: 80.0–94.0) and the surrounding mucosa (median: 84.7; min–max: 73.0–92.0). Individual restorative materials, implant neck design (i.e., tissue or bone level type implants), and the use of a fixed provisional had no effect on patients' ratings of the definitive implant-supported FDPs.

Conclusions: Aesthetics is an important patient-reported measure, which lacks in standardized methods; however, patients' satisfaction was high for implant-supported FDPs and the surrounding mucosa.

KEYWORDS

esthetic, FDP, implant, implant-supported crown, Mucosa, patient-centered outcomes, patient-reported outcomes, PROM, PROMS, VAS

1 | INTRODUCTION

In the field of fixed prosthodontics, various assessment methods have been used to evaluate the aesthetic outcome. A distinction is made between objective and subjective criteria. Objective criteria are said to be neutral and free of any value by the evaluating person, resulting in reproducible measurements regardless of the person performing the evaluation, whereas subjective criteria

always include an influence by the judging person (De Bruyn, Raes, Matthys, & Cosyn, 2015).

Objective indices are particularly suitable for the comparison of treatment outcomes in clinical studies (Meijer, Stellingsma, Meijndert, & Raghoebar, 2005) or their application for clinical dental education (Lang, Zitzmann, Working Group 3 of the VIII European Workshop on Periodontology, 2012). Various indices have been introduced for aesthetic assessments (Belser et al., 2009; Fürhauser et al., 2005; Jemt, 1997; Meijer et al., 2005). However, even with those objective criteria, 100% exact reproducibility is rare. This even applies to the pink aesthetic score/white aesthetic score (PES/WES) (Belser et al., 2009), an objective index demonstrating the highest repeatability among all objective aesthetic indices (Tettamanti et al., 2016). However, the results vary with different examiners (den Hartog, Raghoebar, Stellingsma, Vissink, & Meijer, 2011). Even the same person reevaluating a situation at a second-time point might report a non-identical result (Schropp & Isidor, 2007).

As the influence of individual grading may vary among examiners, comparing the results of subjective evaluations is a very difficult task. The amount of grading depends on several factors, for example on the level of clinical training of each examiner (Gehrke, Degidi, Lulay-Saad, & Dhom, 2009; Meijer et al., 2005). Comparing the judgment of the aesthetic treatment outcome of lay persons and dental professionals, the ratings of lay persons are higher (Belser et al., 2009; Chang, Odman, Wennström, & Andersson, 1999; Meijndert, Meijer, Stellingsma, Stegenga, & Raghoebar, 2007). But, there are many more factors influencing the individual perception of aesthetics, such as social environment, education, or cultural background.

Patient-reported outcome measures (PROMs) are among the most frequently used subjective assessments in clinical investigations. Compared to earlier studies, the use of PROMs in general medicine has emerged, leading to a paradigm shift to "patient-centered care" (Marshall, Haywood, & Fitzpatrick, 2006). This trend can also be observed in dental medicine (Buck & Newton, 2001; Derks, Håkansson, Wennström, Klinge, & Berglundh, 2015; McGrath, Lam, & Lang, 2012). Taking into account that patient satisfaction is one of the major goals in every medical discipline, this evolution seems logical (De Bruyn et al., 2015).

One such PROM, which has moved to the forefront of dental medicine, is patients' estimation of the aesthetic outcome after prosthodontic treatment. Pleasing aesthetics in reconstructive dentistry is defined by the harmonic appearance of natural and adjacent restored teeth and soft tissue (Belser, Buser, & Higginbottom, 2004; Belser, Schmid, Higginbottom, & Buser, 2004). The scientific literature reflects this phenomenon, as the majority of studies treating aesthetic aspects of implant dentistry have been published in the last decade (Cosyn, Thoma, Hämmerle, & De Bruyn, 2017).

In partially edentulous patients demanding a fixed rehabilitation, the choice between tooth- or implant-supported fixed dental prostheses (FDPs) needs to be made. To obtain an overview with respect to the most aesthetic treatment preference according to patients, the aim of the performed literature screening was to extract PROM data from clinical studies by means of a systematic review protocol.

Today, various assessment methods exist in the form of scales or questionnaires used to acquire these data (Buck & Newton, 2001; McGrath et al., 2012). However, a standardized approach for the evaluation of PROMs is still lacking. Therefore, the results of studies using different assessment methods are hardly comparable. One of the most widely used assessment methods for PROMs in dentistry are visual analogue scales (VAS), but their application has also been criticized (Schabel, McNamara, Franchi, & Baccetti, 2009; Torrance, Feeny, & Furlong, 2001). But at least a high number of studies using VAS for PROM evaluation can be expected. Therefore, the aim of this systematic review and meta-analysis was to analyze the aesthetic results of implant-supported relative to tooth-supported FDPs according to patient-reported outcomes assessed by VAS. The results should improve understanding of patient demands in aesthetic treatment and patient satisfaction with treatment outcomes. Furthermore, the influence of restoration material, implant type, and provisional phase on PROMs, focusing on implant- and tooth-supported FDPs was analyzed.

2 | MATERIAL AND METHODS

2.1 | Definition of terms

2.1.1 | Patient-reported outcome measures (PROMs)

In dental medicine, the term "patient reported outcome measures" (PROMs) was introduced in the 8th European Workshop on Periodontology. These essentially include "subjective" reports of patients' perceptions of their oral health status and its impact on their daily life or quality of life, reports of satisfaction with oral health status, and/or oral health care and other nonclinical assessments (Cosyn et al., 2017; Lang et al., 2012; McGrath, Lam, & Lang, 2012).

2.1.2 | Visual analogue scale (VAS)

A visual analogue scale (VAS) is an instrument used to quantify a subjective experience (e.g., treatment outcome). Commonly used VAS are lines of 10 cm, labeled with worst experience (worst treatment outcome) at one end, and best experience (best treatment outcome) on the other end, without any further markings. Patients are instructed to mark the line according to their actual feeling. The clinician measures the distance of the mark from the beginning of the line and calculates a percent value according to the position of the marking.

2.2 | Study protocol

The study protocol for this systematic review was registered in the PROSPERO database. It was set in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement (Moher, Liberati, Tetzlaff, & Altman, 2009) (for PRISMA checklist, see Supporting Information). The focused leading question was set according to the P.I.C.O. model for clinical questions. The four criteria according to the P.I.C.O. model were as follows:

Population: Partially edentulous patients
Intervention: Implant-supported FDPs
Comparison: Tooth-supported FDPs
Outcome: Patient-reported outcomes (PROMs), measured with VAS

The resulting P.I.C.O. question was: "In partially edentulous patients, what are the aesthetic results of implant-supported compared to tooth-supported fixed dental prostheses using patient-reported outcomes."

2.3 | Eligibility criteria

For the systematic literature searches, an overview of the inclusion and exclusion criteria was provided in Tables 1 and 2.

Inclusion and exclusion criteria were as follows:

2.3.1 | Inclusion

- Human clinical studies (randomized controlled trials, controlled trials, prospective studies, retrospective studies, case series)
- Partially edentulous patients
- Tooth- or implant-supported FDPs
- Documentation of PROMs by VAS
- Number of patients per study arm or cohort ≥10
- Mean follow-up period ≥1 years
- Publication in English, German, or French

2.3.2 | Exclusion

- In vitro or animal studies
- Removable partial dentures
- Edentulous patients
- Fully dentate patients
- Insufficient documentation PROMs
- Fewer than 10 patients in relevant study arm/cohort
- Mean follow-up period <1 year
- Combined tooth-implant-supported restorations
- Studies not written in English, German, or French

TABLE 1 Systematic search strategy- implant-supported reconstruction

Focused question (PICO)	**In partially edentulous patients, what are the aesthetic results of implant-supported compared to tooth-supported fixed dental prostheses using patient-reported outcomes**	
Search Strategy	Population	#1 "partially edentulous" OR edentulous OR jaw OR "partially edentulous" OR "partial edentulism" OR edentulous [Mesh Term]
	Intervention or exposure	#2 implant OR crown OR reconstruct* OR FPD OR implant crown* OR Implant bridge* OR "implant supported prosthesis" OR "implant supported crown"
	Comparison	#3 "tooth supported prosthesis" OR tooth-supported OR bridge* OR fixed partial denture* OR FPD* OR crown
	Outcome	#4 aesthetic OR evaluation OR aesthetic* OR VAS OR questionnaire* OR "patient related" OR "patient reported outcome" OR "patient opinion" OR "patient perception" OR "patient report"
	Search combination	#1 AND #2 AND #3 AND # 4
Database search	Electronic	PubMed, Cochrane Central Register of Controlled Trials (CENTRAL)
	Journals	Clinical Oral Implants Research, International Journal of Oral Maxillofacial Implants, Clinical Implant Dentistry and Related Research, Implant Dentistry, Journal of Implantology, Journal of Periodontology, Journal of Clinical Periodontology
Selection criteria	Inclusion criteria	• Human clinical studies (randomized controlled trials, controlled trials, prospective studies, retrospective studies, case series) • Partially edentulous patients • Tooth or implant-supported FDPs • Documentation of PROMs • Number of patients/study arm or cohort ≥ 10 • Mean follow-up period ≥ 1 years • Publication in English, German or French
	Exclusion criteria	• In vitro or animal studies • Removable partial dentures • Edentulous patients • Fully dentate patients • Insufficient documentation PROMs • Fewer than 10 patients in relevant study arm/cohort • Mean follow-up period less than 1 year • Publications not written in English • Combined tooth-implant-supported restorations • Studies not written in English, German or French

TABLE 2 Systematic search strategy, exclusively looking for tooth-supported restorations

Focused question (PICO)	In partially edentulous patients, what are the aesthetic results of implant-supported compared to tooth-supported fixed dental prostheses using patient-reported outcomes'	
Search strategy	Population	#1 "partially edentulous" OR edentulous OR jaw OR "partially edentulous" OR "partial edentulism" OR edentulous [Mesh Term]
	Intervention or exposure	#2 "tooth-supported prosthesis" OR bridge* OR fixed partial denture* OR FPD OR SC OR crown OR crown [Mesh Term] OR fixed partial denture [Mesh Term]
	Comparison	
	Outcome	#3 aesthetic OR evaluation OR aesthetic* OR VAS OR questionnaire* OR "patient related" OR "patient reported outcome" OR "patient opinion' OR "patient perception" OR "patient report"
	Search combination	#1 AND #2 AND #3
Database search	Electronic	PubMed
	Journals	Clinical Oral Implants Research, International Journal of Oral Maxillofacial Implants, Clinical Implant Dentistry and Related Research, Implant Dentistry, Journal of Implantology, Journal of Periodontology, Journal of Clinical Periodontology
Selection criteria	Inclusion criteria	• Human clinical studies (randomized controlled trials, controlled trials, prospective studies, retrospective studies, case series) • Partially edentulous patients • Tooth-supported FDPs • Documentation of PROMs • Number of patients/study arm or cohort ≥10 • Mean follow-up period ≥1 years • Publication in English, German or French
	Exclusion criteria	• In vitro or animal studies • Removable partial dentures • Edentulous patients • Fully dentate patients • Insufficient documentation PROMs • Fewer than 10 patients in relevant study arm/cohort • Mean follow-up period less than 1 year • Publications not written in English • Combined tooth-implant-supported restorations • Studies not written in English, German or French

2.4 | Search strategy and study selection

For the initial electronic search in the MEDLINE (via PubMed), EMBASE, and COCHRANE libraries, a systematic search term for an initial search was developed (Table 1). All libraries were scanned for related literature without using any filters. Furthermore, reference lists of related articles with similar topics were systematically screened, and potentially relevant articles were added to the results of the electronic search. After eliminating duplicates, the titles of the remaining articles were checked for adequacy, according to the inclusion criteria. Irrelevant titles (e.g., in vitro studies) were excluded. If the relevance of a study was indecisive according to the title, it was included for abstract screening. If the abstract was also inconclusive, the study was included for full-text screening, resulting in a selection of eligible full texts. After reviewing the full texts, irrelevant articles were excluded, and data from the remaining articles were extracted whenever possible. Study selection and data extraction were performed independently for each step by two reviewers (JW, SA). Disagreement regarding the inclusion of specific articles was solved by discussion. If multiple relevant study arms or cohorts were identified in the same study, data from each group were recorded separately (e.g., different restoration materials). This resulted in a higher number of study populations than indicated by the number of included studies.

After data extraction, no study for the comparison group (tooth-supported FDPs) could be identified. Therefore, a second systematic search of the literature was carried out, exclusively looking for articles on tooth-supported FDPs. It was performed as outlined above. The applied systematic search strategies can be seen in Tables 1 and 2.

For data extraction, the study form included the following parameters: authors, year of publication, study design, type of support (tooth/implant), type of retention (screw/cement), mean follow-up, type of FDP, planned number of patients, actual number of patients, mean age, age range, setting, total failure of FDPs, PROMs mucosa, PROMs restoration, restoration material, implant type, implant brand, abutment material, abutment type, and provisional restoration.

2.5 | Risk of bias analysis

Quality assessment was performed by both authors according to the Cochrane risk of bias tool (Higgins & Green, 2011) for included

randomized controlled trials (RCTs) and the Newcastle-Ottawa-Scale (NOS) (Wells et al., 2013) for included observational studies.

The Cochrane risk of bias tool is a domain-based evaluation, in which critical assessments are performed independently for each domain. These domains are "selection bias," "performance bias," "detection bias," "attrition bias," "reporting bias," and "other biases." The assigned judgment for each domain can be "high risk," "low risk," or "unclear risk" of bias.

The NOS is a quality assessment tool for nonrandomized trials, for their inclusion in a systematic review and meta-analysis. The quality of included studies was assessed according to three major domains: selection of the study groups, comparability of the study groups and ascertainment of either exposure or outcome of interest. Each domain can be awarded with a certain number of stars, resulting in a maximum number of nine stars. The final judgment of the included studies according to the NOS can be "Good," "Fair," or "Poor" quality.

2.6 | Statistical analysis

Means, standard errors and the 95%-confidence intervals of PROMs of study combinations were estimated by random-effects meta-regression for aggregate-level data. The same method was used to compare the mean outcome of groups of studies. The statistical analysis was performed using Stata 14.2 and significance level set at 0.05.

2.7 | Synthesis of results

Study data were extracted whenever the study met the inclusion criteria, and PROMs regarding aesthetic results assessed by VAS were reported. It was carefully controlled that data was only extracted, if 0 represented the worst treatment outcome (poor aesthetics) and 100 the best treatment outcome (perfect aesthetics) according to the VAS. PROMs were subdivided into two domains whenever possible: mucosa and FDP. Data were extracted separately for those two domains. When studies described more than one result for any of the two domains, only the most general one was extracted. For example, when a study reported both PROMs according to the general aesthetics of the restoration, and according to the color of the restoration, only data according to general aesthetics were extracted. Whenever PROMs were not reported according to VAS or a comparable rating system, studies were not included for data extraction.

The primary outcome of the meta-analysis was to compare the aesthetic results of implant- vs. tooth-supported fixed dental prostheses (FDPs) according to patients. Secondary outcomes were the influence of restoration material, implant type, and provisional phase on PROMs. As described above, additional data were acquired during the data extraction process; however, these data could not be analyzed due to reporting heterogeneity, incomplete data (pooled results), or missing data.

3 | RESULTS

Two systematic literature searches were performed. Part one represented studies reporting on patient-related outcomes regarding implant-supported FDPs. Through this search, 2,675 titles were retrieved (initial search) which were screened independently by two authors (SA, JW) to assess their suitability for inclusion (Figure 1). A consensus was obtained following discussion for the abstract search (329 abstracts). A total of 50 full-text articles were evaluated according to the inclusion and exclusion criteria. A total of 37 were found to qualify for inclusion in the data extraction, and finally, 16 studies including 19 relevant study cohorts were eligible for inclusion in the review (Figure 1).

The same systematic review process was performed for part two—patient-reported outcomes on tooth-supported FDPs (Figure 2). Here 5,915 titles were obtained from the initial search, the abstract search included 188 studies, and from these, 17 full-text articles were selected. Eight studies qualified for inclusion for data extraction. At the end, no study reporting on tooth-supported FDPs could be included. Therefore, it was not possible to perform a meta-analysis for the primary outcome, that is, the aesthetic outcome of tooth- vs. implant-supported FDPs according to PROMs. Nevertheless, sufficient data were available for implant-supported FDPs to perform meta-analyses for the secondary outcomes.

3.1 | Description of included studies

An overview of the excluded and included studies is given in Tables 3 and 4. Means and standard deviations of the outcome of the individual studies formed the basis for the statistical analysis. Results of the quality assessment are presented in Tables 5 and 6.

The study designs of the included studies were: two randomized clinical trials, eight prospective cohort studies, four retrospective and two cross-sectional studies (Table 7). Most studies were carried out in a university setting. In two studies reporting on implant-supported FDPs, multiple (a total of five) relevant study cohorts could be identified, the data of which were recorded separately. Various restorative materials (porcelain-fused-to-metal vs. all-ceramic),(Gallucci, Grütter, Nedir, Bischof, & Belser, 2011) and various implant designs (machined neck vs. rough neck vs. scalloped neck)(den Hartog et al., 2013) were examined in these cohorts.

A total of 816 implant-supported FDPs were evaluated by the patients by means of VAS. Of these FDPs 745 (91.3%) were single crowns, 12 (1.5%) were bridges and 2 studies pooled results from bridges and single crowns (n = 59 [7.2%]). The FDPs were supported by bone level or soft tissue level type implants, 48.4% and 39.5%, respectively. In 12.1%, the implant type was not reported (Table 7).

Only 20 FDPs were screw-retained (2.5%), 532 (65.2%) cement-retained, and in 6 studies, both retention types were used (23.7%). Porcelain-fused-to-metal (PFM) was used in 131 (16.1%), veneered zirconium dioxide in 232 (28.4%) and lithium disilicate in 24 FDPs (2.9%). In 212 restorations, the type of material was not reported (Table 7).

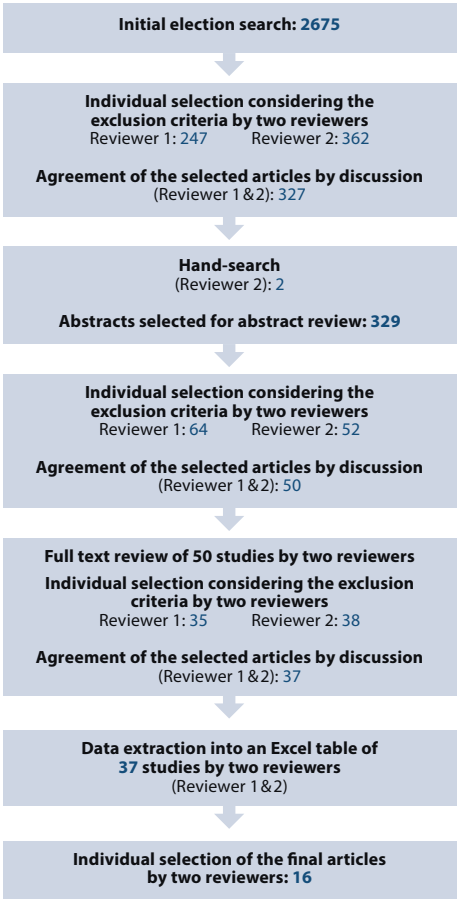

FIGURE 1 Flow diagram describing the search design implant supported group

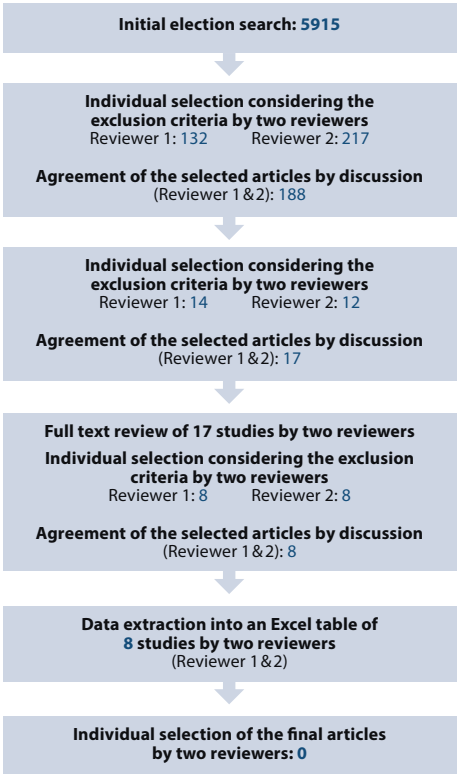

FIGURE 2 Flow diagram describing the search design tooth supported group

The implant abutments used in these included studies were predominantly made of titanium (*n* = 365 [44.7%]), titanium and zirconium dioxide (*n* = 133 [16.3%]), aluminum oxide (*n* = 10 [1.2%]), gold (*n* = 10 [1.2%]) and all-ceramic not further described (*n* = 67 [8.2%]). For 185 FDPs, the abutment material was not reported (Table 7).

In the cohorts included in this review, 385 (47.2%) FDPs were made with standardized abutments, 160 with customized abutments, both types were used in 86 restorations, and the abutment type was not reported in 185 FDPs (Table 7).

A total of 324 (39.7%) FDPs had a fixed provisional prior to insertion of the final crown or bridge and 200 (24.5%) did not. Implants documented in these studies were placed in the anterior and posterior region. In three cohorts (292 FDPs), it was not reported whether a provisional phase was performed within the prosthetic workflow (Table 7). Details on the individual VAS scores and the descriptive data are given in Table 7.

3.2 | Patient-reported VAS

3.2.1 | VAS mucosa score

Data extracted from 19 cohorts focusing on implant-supported FDPs showed that only 7 reported on the aesthetic outcome of the peri-implant soft tissue surrounding the reported FDP(s), as evaluated by the patients using VAS ratings. In 12 cohorts, this information was missing. The mean result of the "VAS mucosa score" was 84.7 (median: 86.7; min–max: 73.0–92.0) (unweighted data) (Table 8).

3.2.2 | VAS FDP score

A total of 16 studies (19 cohorts) reported on the patient evaluations focusing on the final aesthetic outcome of the implant-supported FDPs. The mean VAS was 88.9 (median: 90.3; min–max: 80.0–94.0; Table 8). The mean VAS values extracted by descriptive data are listed in detail in Table 7. For inclusion of the retrieved data into the statistical analysis (random-effects meta-analysis), only studies that reported the standard deviation of the VAS could be considered. Standard deviation of the VAS was reported only for few studies on implant-supported FDPs. An overview of the study cohorts, that were included into the meta-analysis is presented in Table 9. The VAS values of the individual study cohorts, their weight and their estimated treatment effect are given in Figures 3 and 4.

3.3 | Influence of restorative material/implant type/provisional phase on the outcome of VAS FDP

Only studies reporting the standard deviation could be considered for inclusion of the retrieved data into the statistical analysis (Table 10).

TABLE 3 Excluded studies during data extraction

Author (year)	Reason for exclusion
Implant supported (*n* = 21)	
Andersson, Bergenblock, Fürst and Jemt (2013)	Insufficient data
Andersson, Emami-Kristiansen and Högström (2003)	Follow-up <1 year
Avivi-Arber and Zarb (1997)	Insufficient data
Baracat, Teixeira, Dos Santos, de Da Cunha and Marchini (2011)	Insufficient data, no report on the amount or type of fixed reconstruction
Batisse, Bessadet, Decerle, Veyrune and Nicolas (2014)	Insufficient data
Bianchi and Sanfilippo (2004)	Insufficient data
Carollo (2003)	Insufficient data
Chang et al. (1999)	Repeated study
Gibbard and Zarb (2002)	Insufficient data
Kourkouta, Dedi, Paquette and Mol (2009)	Insufficient data
Meijndert et al. (2007)	Insufficient data
Moghadam et al. (2012)	No report on the amount or type of fixed reconstruction
Santing et al. (2013)	Not especially asked for aesthetic outcome
Schropp, Isidor, Kostopoulos and Wenzel (2004)	Insufficient data
Schropp and Isidor (2007)	Insufficient data
Sherif, Susarla, Hwang, Weber and Wright (2011)	Insufficient data
Tymstra et al. (2011)	Insufficient data
Tymstra, Meijer, Stellingsma, Raghoebar and Vissink (2010)	Insufficient data
Vanlıoğlu, Kahramanoğlu, Yıldız, Ozkan and Kulak-Özkan (2014)	PROMs not reported (email written to author-no response)
Vermylen, Collaert, Lindén, Björn and De Bruyn (1999)	Insufficient data
Vilhjálmsson, Klock, Størksen and Bårdsen (2011)	Insufficient data
Tooth supported (n = 8)	
Nicolaisen, Bahrami, Schropp and Isidor (2016)	Insufficient data
Ohlmann et al. (2014)	Insufficient data
Rimmer and Mellor (1996)	Insufficient data
Vanoorbeek, Vandamme, Lijnen and Naert (2010)	Insufficient data
Shi, Li, Ni and Zhu(2016)	Insufficient data
Alshiddi, BinSaleh and Alhawas (2015)	Insufficient data
Bömicke, Rammelsberg, Stober and Schmitter (2017)	Fully dentate patients
Nejatidanesh, Moradpoor and Savabi (2016)	Fully dentate patients

In implant-supported FDPs, mean patient ratings varied between 93.3 (95% CI = 78.8–100) (veneered zirconium dioxide) and 85.2 (95% CI = 70.5–99.9) (PFM + gold). The differences according to the applied restorative materials were not statistically significant ($p = 0.616$) (Table 10). Patients reported slightly higher VAS ratings in FDPs supported by tissue level type implants (mean = 92.5; 95% CI = 88.8–96.2) compared to bone level type implants (mean = 89.2; 95% CI = 86.1–92.4). However, the difference was not statistically significant ($p = 0.128$) (Table 10). Presence of a provisional phase did not improve the aesthetic outcome according to patients' VAS ratings (90.3 vs. 90.0; $p = 0.909$; Table 10).

4 | DISCUSSION

Within the limitations of this systematic review, patients' satisfaction was high for implant- supported FDPs and the surrounding mucosa.

No influence on the PROMs results was identified among the used dental materials for FDPs, the presence of a provisional phase within the implant-prosthetic workflow or the type of dental implant used.

The primary goal of any prosthodontic procedure is to satisfy the patient receiving a dental treatment. Although the assessment of the patient is subjective and difficult to quantify, it has gained interest in recent years, a fact also observed in clinical studies. De Bruyn stated in his systematic review about the current use of patient-centered/

TABLE 4 Included studies/cohorts (*n* = 19 cohorts, *n* = 16 studies)

Author (year)	Total *N* of FDPs	Total *N* of patients	mean follow-up (years)	Outcome Mucosa	Outcome FDP	*SD* FDP
Implant supported (*n* = 19)						
Bonde, Stokholm, Schou and Isidor (2013)	46	42	10.0	82.0	91.0	15.0
Boronat-Lopez, Carrillo, Peñarrocha and Peñarrocha-Diago (2009)	12	12	1.0	NA	83.0	
Chang et al. (1999)	21	20	3.0	NA	94.0	7.0
Chang and Wennström (2013)	32	32	7.5	NA	91.8	14.8
Cosyn et al. (2012)	46	44	2.5	92.0	94.0	6.0
Covani, Canullo, Toti, Alfonsi and Barone (2014)	47	47	5.0	73.0	80.5	11.3
De Rouck, Collys and Cosyn (2008)	30	30	1.0	NA	93.0	
den Hartog et al. (2013) (1)	31	31	1.5	86.7	88.0	11.0
den Hartog et al. (2013) (2)	31	31	1.5	87.1	89.0	10.0
den Hartog et al. (2013) (3)	31	31	1.5	83.9	91.0	8.0
Ekfeldt, Fürst and Carlsson (2011)	40	25	3.0	NA	90.0	
Gallucci et al. (2011) (1)	10	10	2.0	NA	91.8	5.9
Gallucci et al. (2011) (2)	10	10	2.0	NA	91.8	10.0
Hartlev et al. (2014)	54	54	2.8	88.0	83.0	
Hof et al. (2014)	60	60	4.1	NA	80.0	
Kolinski et al. (2014)	59	37	3.0	NA	89.2	9.4
Spies, Patzelt, Vach and Kohal (2016)	24	24	2.6	NA	90.3	13.0
Tey, Phillips and Tan (2016)	NA	206	5.2	NA	85.2	14.5
Nejatidanesh et al. (2016)	232	121	5.9	NA	93.3	5.2
Total (*n* = 19)	816	867	4.3	-	-	-

Note. [a]Number of ratings.

TABLE 5 Quality assessment of included studies according to NOS

Author (year)	Selection	Comparibility	Outcome	Quality
Bonde et al. (2013)	4	2	2	Good
Boronat-Lopez et al. (2009)	3	1	1	Fair
Chang et al. (1999)	4	2	3	Good
Chang and Wennström (2013)	4	1	3	Good
Cosyn et al. (2012)	4	2	2	Good
Covani et al. (2014)	4	2	3	Good
De Rouck et al. (2008)	4	1	2	Good
Ekfeldt et al. (2011)	4	1	3	Good
Hartlev et al. (2014)	4	2	1	Fair
Hof et al. (2014)	4	1	3	Good
Kolinski et al. (2014)	4	1	1	Fair
Spies et al. (2016)	4	1	1	Fair
Tey et al. (2016)	4	1	2	Good
Nejatidanesh et al. (2016)	4	1	3	Good

TABLE 6 Quality assessment for included randomized clinical trials, according to Cochrane risk of bias tool

Author (year)	Random sequence	Allocation concealment	Blinding	Blinding (outcome)	Outcome data	Selective reporting	Other biases
den Hartog et al. (2013)	+	+	0	+	+	+	+
Gallucci et al. (2011)	+	+	+	+	+	+	+

reported outcomes that half of the relevant literature (300 of 635) were studies published in the last 6 years. His study, therefore, concluded a growing interest in PROMs by the scientific community (De Bruyn et al., 2015).

Various terminology has been used in scientific studies, such as patient satisfaction, patient-centered outcomes, patient-reported outcomes, and patient-reported outcome measures (Cosyn et al., 2017; Lang et al., 2012; McGrath et al., 2012).

Patients' expectations are increasing and with respect to rehabilitation with fixed implant- or tooth-supported FDPs, treatments result in proportionally higher costs compared to removable prostheses. In the era of modern implantology, many surgical and prosthetic workflows are possible today with the goal of achieving the best possible aesthetic outcome. These advances substantially increase costs, resulting in even more critical patients from an aesthetic point of view (Cosyn et al., 2017). However, it has been shown that patients are less critical than clinicians when judging aesthetics (Cosyn, Eghbali, De Bruyn, Dierens, & De Rouck, 2012; Cosyn et al., 2013; Hartlev et al., 2014; Meijndert et al., 2007). In an early study by Chang et al., 1999; a total of 41 implant-supported crowns were evaluated by patients and prosthodontists (Chang et al., 1999). Patients were highly satisfied with their implant-supported crowns with mean VAS values of 100; however, the assessment by prosthodontists revealed a significantly lower degree of satisfaction. This finding was confirmed in a study from Tettamanti et al., 2016; in which patients assessed their reconstruction with respect to pink aesthetics, white aesthetics, and overall aesthetics using visual analogue scales. The same procedure was performed using a new "peri-implant and crown index (PICI)." Orthodontists, Prosthodontists, general dentists, and lay people evaluated pink and white characteristics using visual analogue scales (100 mm length) in comparison with the contralateral tooth. The patients were asked the same questions; a comparison of the patient-related outcomes and PICI was obtained. The overall aesthetic assessments of patients were 94.17%, followed by prosthodontists 68.57%, lay people (66.69%) and general dentists (65.22%), with orthodontists being the most critical (57.16%; Tettamanti et al., 2016).

In this systematic review, the patient-reported outcome of 816 FDPs evaluated by patients in the implant-supported group revealed a mean VAS value of 90 (Table 7).

Dueled, Gotfredsen, Trab Damsgaard, & Hede, 2009 performed a clinical study reporting on 129 patients with tooth agenesis rehabilitated with implant or tooth-supported FDPs. Improved aesthetic outcomes were obtained for the implant-supported group and a positive but not significant correlation was observed between the professional and patient perception of the aesthetic outcome (Dueled et al., 2009). The patients were more satisfied with the overall outcome than the professional clinician (Dueled et al., 2009).

4.1 | Influence of restoration material

In a prospective study with a 3-year follow-up, implants were restored either with all- ceramic or metal-ceramic crowns (Hosseini,

TABLE 7 Characteristics of study cohorts related to implant-supported FDPs and patient-reported outcomes (PROMS) (n = 19 cohorts, n = 16 studies)

	No. of studies (%)	Total *N* of reconstruction (%)	Total *N* of patients (%)	Outcome mean	Outcome min-max	PROMS mean unweighted	PROMS mean weighted
All study cohorts	19 (100)	816 (100)	867 (100)	88.9	80.0–94.0	88.9	88.0
Studydesign							
RCT	5 (26.3)	113 (13.8)	113 (13.0)	90.3	88.0–91.8	90.3	89.8
Prospective	8 (42.1)	293 (35.9)	266 (30.7)	88.0	80.5–94.0	88.0	87.3
Retrospective	4 (21.1)	332 (40.7)	412 (47.5)	87.1	80.0–93.3	87.1	87.1
Cross-sectional	2 (10.5)	78 (9.6)	76 (8.8)	92.9	91.8–94.0	92.9	93.1
Setting							
Private practice	3 (15.8)	286 (35.0)	381 (43.9)	87.2	83.0–93.3	87.2	87.5
University	13 (68.4)	410 (50.2)	404 (46.6)	88.9	80.0–94.0	88.9	88.1
Multicenter	1 (5.3)	59 (7.2)	37 (4.3)	89.2	-	89.2	89.2
Specialist clinic	2 (10.5)	61 (7.5)	45 (5.2)	92.0	90.0–94.0	92.0	91.8
Type of Implant							
Bone Level Implant	11 (57.9)	395 (48.4)	390 (45.0)	87.7	80.0–94.0	87.7	86.7
Soft Tissue Level Implant	5 (26.3)	322 (39.5)	209 (24.1)	92.2	90.3–94.0	92.2	93.0
NA	3 (15.8)	99 (12.1)	268 (30.9)	88.1	85.2–90.0	88.1	86.2
Brand							
Straumann	3 (15.8)	252 (30.9)	141 (16.3)	92.3	91.8–93.3	92.3	93.1
Nobel	9 (47.4)	350 (42.9)	343 (39.6)	89.2	80.0–94.0	89.2	88.1
Astra	1 (5.3)	32 (3.9)	32 (3.7)	91.8	–	91.8	91.8
Defcon Avantblast TSA	1 (5.3)	12 (1.5)	12 (1.4)	83.0	–	83.0	83.0
Sweden Martina	1 (5.3)	47 (5.8)	47 (5.4)	80.5	–	80.5	80.5
Ziraldent	1 (5.3)	24 (2.9)	24 (2.8)	90.3	–	90.3	90.3
Straumann, Nobel, Biomet 3i	1 (5.3)	0 (0.0)	206 (23.8)	85.2	–	85.2	85.2
NA	2 (10.5)	99 (12.1)	62 (7.2)	89.6	89.2–90.0	89.6	89.5
Screw/cement retention							
Screw	2 (10.5)	20 (2.5)	20 (2.3)	91.8	91.8–91.8	91.8	91.8
Cement	9 (47.4)	532 (65.2)	414 (47.8)	90.1	80.5–94.0	90.1	90.1
Both	6 (31.6)	193 (23.7)	384 (44.3)	87.2	80.0–91.0	87.2	85.7
NA	2 (10.5)	71 (8.7)	49 (5.7)	86.1	83.0–89.2	86.1	87.7
Type of reconstruction							

(Continues)

TABLE 7 (continued)

	No. of studies (%)	Total *N* of reconstruction (%)	Total *N* of patients (%)	Outcome mean	Outcome min-max	PROMS mean unweighted	PROMS mean weighted
SC	16 (84.2)	745 (91.3)	612 (70.6)	89.5	80.0–94.0	89.5	89.0
FPD	1 (5.3)	12 (1.5)	12 (1.4)	83.0	–	83.0	83.0
Both	2 (10.5)	59 (7.2)	243 (28.0)	87.2	85.2–89.2	87.2	85.8
Restoration material							
PFM	5 (26.3)	131 (16.1)	131 (15.1)	88.0	80.5–93.0	88.0	87.2
PFM+all-ceramic	2 (10.5)	100 (12.3)	98 (11.3)	88.5	83.0–94.0	88.5	87.9
PFM+Gold	1 (5.3)	–	206 (23.8)	85.2	–	85.2	85.2
All-ceramic+acrylic	4 (21.1)	117 (14.3)	97 (11.2)	91.7	90.0–94.0	91.7	91.4
Veneered Zirconia and monolithic Zirconia	1 (5.3)	232 (28.4)	121 (14.0)	93.3	–	93.3	93.3
Lithium disilicate (emax)	1 (5.3)	24 (2.9)	24 (2.8)	90.3	–	90.3	90.3
NA	5 (26.3)	212 (26.0)	190 (21.9)	87.4	80.0–91.0	87.4	86.4
Abutment							
Standardized/prefabricated	6 (31.6)	385 (47.2)	269 (31.0)	92.2	90.3–94.0	92.2	92.5
Individualized	6 (31.6)	160 (19.6)	160 (18.5)	88.7	80.5–91.8	88.7	87.0
Both	2 (10.5)	86 (10.5)	69 (8.0)	92.0	90.0–94.0	92.0	92.6
NA	5 (26.3)	185 (22.7)	369 (42.6)	84.1	80.0–89.2	84.1	84.4
Abutment material							
Titanium	5 (26.3)	365 (44.7)	254 (29.3)	89.8	80.5–93.3	89.8	90.4
Titanium + Zirconium dioxide	4 (21.1)	133 (16.3)	118 (13.6)	89.5	88.0–91.0	89.5	89.5
Titanium + ceramic	1 (5.3)	46 (5.6)	44 (5.1)	94.0	–	94.0	94.0
Gold	1 (5.3)	10 (1.2)	10 (1.2)	91.8	–	91.8	91.8
Aluminum oxide	1 (5.3)	10 (1.2)	10 (1.2)	91.8	–	91.8	91.8
ceramic—no further spec	2 (10.5)	67 (8.2)	62 (7.2)	92.5	91.0–94.0	92.5	92.0
NA	5 (26.3)	185 (22.7)	369 (42.6)	84.1	80.0–89.2	84.1	84.4
Provisional Phase loaded on implants							
Yes	11 (57.9)	324 (39.7)	302 (34.8)	89.3	83.0-93.0	89.3	88.8
No	5 (26.3)	200 (24.5)	178 (20.5)	89.9	80.5–94.0	89.9	89.2
NA	3 (15.8)	292 (35.8)	387 (44.6)	86.2	80.0–93.3	86.2	86.9

TABLE 8 No. of reconstructions, patients, mean follow-up, patient-reported outcome, studies on implant-supported FDPs (*n* = 19 cohorts, *n* = 16 studies)

	Data reported in *n* cohorts	Data missing	Mean	*SD*	Median	Min-max
N of reconstructions	19	0	45.3	49.1	31.5	10–232
Actual *N* of pts	19	0	45.6	46.0	31.0	10–206
Mean follow-up (years)	19	0	3.4	2.4	2.8	1.0–10.0
VAS mucosa	7	12	84.7	6.0	86.7	73.0–92.0
VAS crown/bridge	19	0	88.9	4.5	90.3	80.0–94.0

TABLE 9 Patient-reported outcomes for cohorts of implant FDPs including standard deviation (*SD*)—*n* = 14

	Total *N* of pats. (%)	mean VAS crown/bridge	*SD*	95%-CI
Bonde et al. (2013)	42 (6.1)	91	15	86.3–95.7
Chang et al. (1999)	20 (2.9)	94	7	90.7–97.3
Chang and Wennström(2013)	32 (4.7)	91.8	14.8	86.5–97.1
Cosyn et al. (2012)	44 (6.4)	94	6	92.2–95.8
Covani et al. (2014)	47 (6.9)	80.5	11.3	77.2–83.8
den Hartog et al. (2013) (1)	31 (4.5)	88	11	84–92
den Hartog et al. (2013) (2)	31 (4.5)	89	10	85.3–92.7
den Hartog et al. (2013) (3)	31 (4.5)	91	8	88.1–93.9
Gallucci et al. (2011) (1)	10 (1.5)	91.81	5.94	87.6–96.1
Gallucci et al. (2011) (2)	10 (1.5)	91.8	10.04	84.6–99
Kolinski et al. (2014)	37 (5.4)	89.2	9.4	86.1–92.3
Spies et al. (2016)	24 (3.5)	90.3	13	84.8–95.8
Tey et al. (2016)	206 (30.0)	85.2	14.5	83.2–87.2
Nejatidanesh et al. (2016)	121 (17.6)	93.3	5.2	92.4–94.2
Total[a]	686 (100)	90.0	1.00[b]	87.9–92.2

Notes. [a]Estimation by random-effects meta-regression. [b]Estimated standard error.

Worsaae, Schiodt, & Gotfredsen, 2013). Patient-reported outcomes and aesthetic evaluations by clinicians were assessed and no correlation could be identified between the professional and patient-reported aesthetic outcome. Patient`s evaluations regarding the aesthetic outcome showed no statistically difference of all-ceramic and metal- ceramic restorations (Hosseini et al., 2013). In the present review, the same findings were obtained. VAS ratings of the patients showed no influence of the material choice of the reconstructions.

4.2 | Influence of implant type

Implants featuring the abutment connection at the crestal bone level to replace single edentulous spaces are preferably indicated in the aesthetic zone. With a bone level implant design, the clinician has more prosthetic freedom to determine the location of the final mucosal zenith position and to individualize the emergence profile and, therefore, the peri-implant mucosa. Clinical studies have presented acceptable aesthetic outcomes (Buser et al., 2011, 2013; Santing, Raghoebar, Vissink, den Hartog, & Meijer, 2013; Wittneben et al., 2017). Consequently, an enhancement of the overall aesthetic outcome would be hypothesized. However, in this review, the patient-reported outcomes regarding VAS FDP scores were higher for patients with soft tissue level implants compared to those with bone level type implants however this was not statistically significant (Table 7).

4.3 | Influence of provisional phase implementation

The implementation of a distinct provisional phase is a commonly used treatment concept for implants placed in the aesthetic zone (Cho, Shetty, Froum, Elian, & Tarnow, 2007; Furze, Byrne, Alam, & Wittneben, 2016; Parpaiola, Sbricoli, Guazzo, Bressan, & Lops, 2013; Priest, 2005; Wittneben, Buser, Belser, & Brägger, 2013). The aim of a provisional phase is to condition and shape the peri-implant soft tissue, including the individualization of the mucosa and emergence profile, the papillae, the cervical soft tissue margin, and the finalization of the position of the gingival zenith. A randomized clinical trial by Furze et al. showed that this provisional phase with soft tissue conditioning does improve the final aesthetic result (Furze et al., 2016). 20 patients

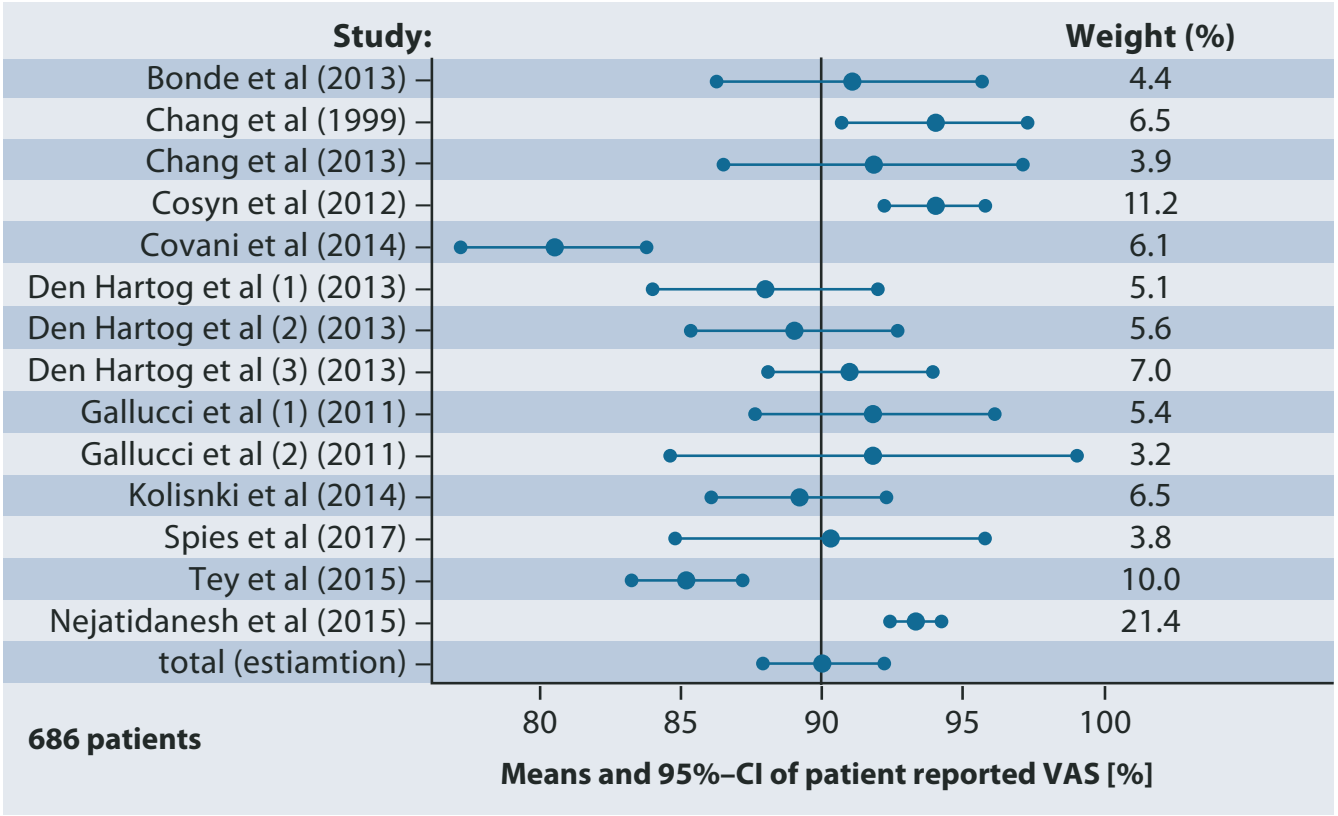

FIGURE 3 Patient-reported outcomes, implant supported group (only data with standard deviation)

received bone level implants in the aesthetic zone and after reopening, using a randomization process to assign each to either cohort group 1 (provisional phase present) or cohort group 2 (without provisional phase). Implants were finally restored with an all-ceramic crown. The mean values of combined modPES and WES were 16.7 for group 1 and 10.5 for Group 2, which concluded a statistically significant difference.

In the present study, there was no statistically significant difference with the use of provisional restorations on implant-supported FDPs according to PROMs. From the limited available data, implant-supported provisional restorations were located in both- posterior and anterior sites and therefore a conclusion cannot be stated focusing on aesthetic sites.

4.4 | Limitations of the study

In general, systematic reviews lack in homogeneity among materials used for FDPs across clinical studies, regardless of the type of support. Unfortunately, in the present review, no studies could be identified to be included focusing on tooth-supported FDP in partially edentulous patients.

The perception of a patient might be influenced by their expectations and experience but represents the value of a reconstruction evaluated by the patient him- or herself.

Aesthetics is an important PROM and, therefore, it is commonly included in clinical studies. However, the limitation of the information given by the patients is that non-standardized questions are frequently used with varying scoring methods. This lack of standardization method in the assessment of PROMs (McGrath et al., 2012) was the reason why only studies using VAS ratings were included here. Another limitation in performing the assessment is the validity and reliability of the "ad-hoc" approach.(Cosyn et al., 2017) For the use of future investigations, standardized questions related to the final aesthetic outcome should be used and patient responses collected without the clinician performing the treatment being present to minimize influencing factors.

5 | CONCLUSION

Within the limitations of this systematic review, it can be concluded that:

- The aesthetics of implant-supported FDPs are highly rated by patients (VAS = 90.0; 87.9–92.2).
- No studies were found that reported on PROMS focusing on tooth-supported FDPs in partially edentulous patients.
- The appearance of the mucosa surrounding the implant-supported FDPs was highly rated (VAS = 84.7; min. 73.0–max. 92.0) by PROMs.
- Implant neck design, that is, tissue or bone level has no influence on aesthetic ratings by the patients: 92.5 vs. 89.2.
- PROMs ratings were higher with patients having soft tissue level implants compared to the ones with bone level type implants however without being statistically significant (p = 0.128).

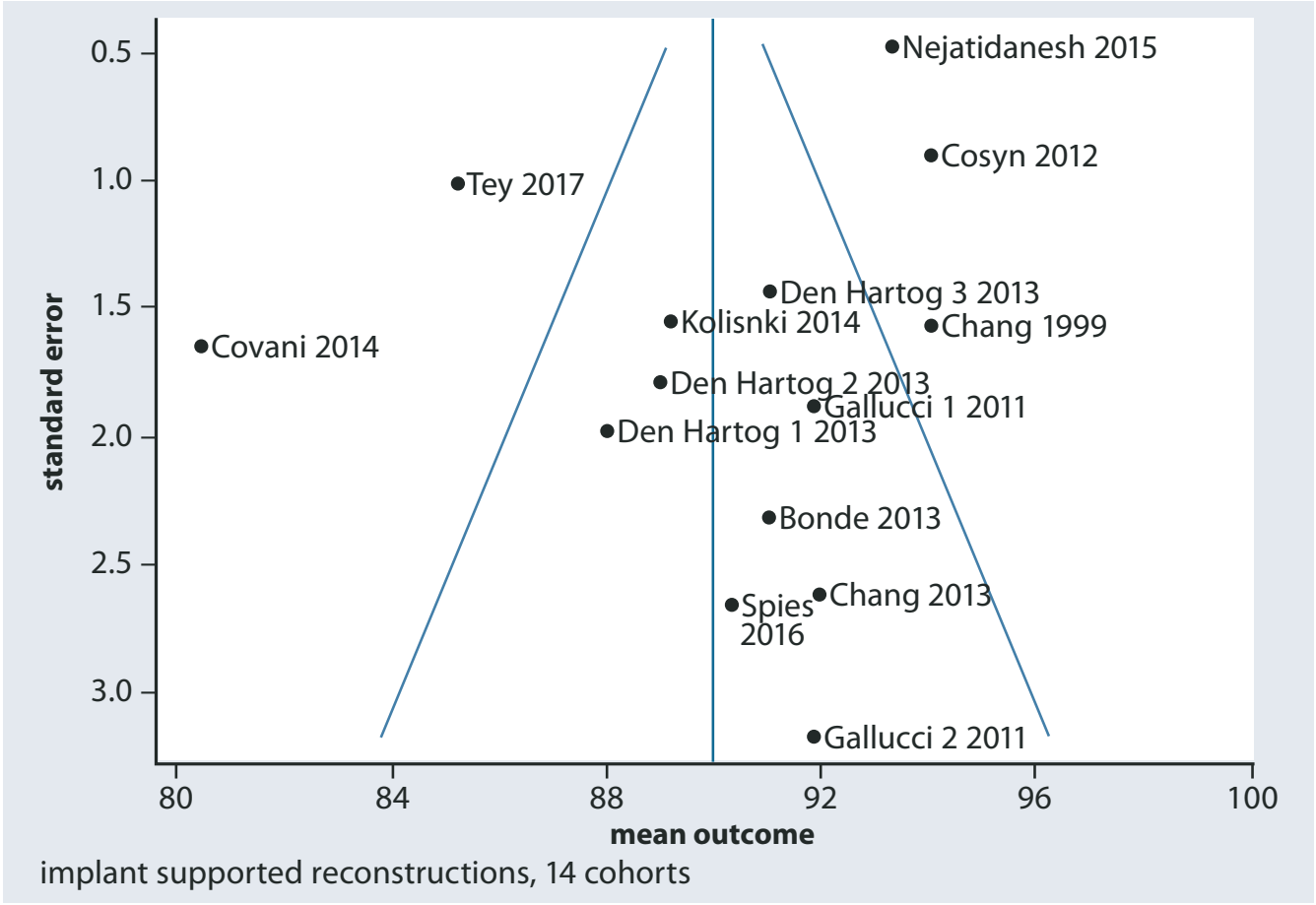

FIGURE 4 Funnel plot of included study cohorts, reporting on implant-supported reconstructions (n = 14)

TABLE 10 Patient-reported outcomes—implant-supported study cohorts—comparison of groups (estimation by random-effects meta-regression)

	Studies	Patients	Mean VAS	Standard error	95%-CI	p-value
Restoration material						
PFM	3	89	87.8	2.87	78.7–96.9	0.616
All-ceramic	3	72	92.4	2.95	83.0–100	
Veneered Zirconiumdioxide	1	121	93.3	4.54	78.8–100	
Lithiumdisilicate (emax)	1	24	90.3	5.24	73.6–100	
PFM + ceramic	1	44	94.0	4.61	79.3–100	
PFM + gold	1	206	85.2	4.63	70.5–99.9	
Implant type						
Bone level implant	7	234	89.2	1.39	86.1–92.4	0.128
Soft tissue level implant	5	209	92.5	1.63	88.8–96.2	
Provisional phase						
Yes	8	206	90.3	1.46	87.0–93.6	0.909
No	4	153	90.0	1.95	85.6–94.4	

- Individual restorative materials had no influence on ratings of PROMS focusing on the aesthetics of implant-supported FDPs.
- The use of a provisional restoration had no effect on aesthetic ratings of the definitive restorations on implant-supported FDPs evaluated by PROMs.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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REVIEW ARTICLE

WILEY CLINICAL ORAL IMPLANTS RESEARCH

Patient-reported outcome measures of edentulous patients restored with implant-supported removable and fixed prostheses: A systematic review

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Abstract

Objective: The aim of this systematic review was to compare patient-reported outcomes measures (PROMs) of implant-supported fixed complete dentures (IFCDs) and overdentures (IODs).

Material and methods: PubMed, Cochrane Library, EMBASE, Scopus and Web of Science were searched, complemented by manual search. Studies published in English up to November 2016 comparing removable with fixed implant-supported prosthesis on fully edentulous patients were included. The review focused on impact on patients' oral health-related quality of life (OHRQoL), satisfaction or other patient-reported outcomes measures.

Results: Of 1,563 initially screened articles, 13 studies including 8 prospective and 5 retrospective studies fulfilled the inclusion criteria. OHRQoL and patient satisfaction were the most common PROMs. When evaluating the levels of evidence, five of thirteen studies were graded as level III and seven reached level II. The only randomized control trial was rated as Ib. The methods used to evaluate PROMs were heterogeneous among studies, and there was a lack of standardization in the measurements employed. In general, IFCD and IOD showed no significant differences when compared for PROMs, with a slight trend of IFCD being superior to IOD in most included studies. However, conflicting results were observed in many aspects such as chewing function, phonetics-related function, overall satisfaction and aesthetics.

Conclusions: Inconsistent results were observed in PROMs when comparing IFCD and IOD for fully edentulous patients. A guideline for standardizing the assessment of PROMs in clinical research is needed in order to produce more meaningful evidence-based information.

KEYWORDS

dental prosthesis, edentulous, implant-supported, outcome assessment (Health Care), patient satisfaction, patient-reported outcomes measures, personal satisfaction, quality of life

1 | INTRODUCTION

There is currently an emerging consensus on the value of patient-reported outcomes measures (PROMs), as dental therapeutic activities should be guided by patients' needs and desires. In 2012, the VIII European Workshop on Periodontology defined PROMs as essentially "subjective" reports of patients' own perceptions of their oral health status and its impact on their daily life or quality of life (oral health-related quality of life, OHRQoL). Such reported outcomes include satisfaction with oral health status and/or oral health care and other nonclinical assessments (Lang & Zitzmann, 2012; McGrath, Lam, & Lang, 2012). Nevertheless, PROMs implementation in clinical research is still relatively limited. Many clinicians might be not familiar with the psychometric properties of PROMs and their potential to supplement and enrich the outcomes of clinical research. Consequently, a well-designed instrument that could help implement PROMs in clinical research and practice would be extremely important.

As implant dentistry is primarily a rehabilitation discipline, it is becoming evident that assessments of clinical parameters alone cannot provide the complete understanding of the benefits to patients' quality of life and well-being. Furthermore, as different treatment modalities within implant dentistry might incur substantially different levels of invasiveness, costs and time commitment, it becomes imperative to be able to assess the impact that each modality can have on patients' reported well-being, so as to better support clinical decision making.

Implants enhance the support, retention and stability of prosthesis for edentulous patients (Awad & Feine, 1998). A significant body of evidence has demonstrated that implant-supported overdentures (IODs) in mandibular fully edentulous patients can lead to improved satisfaction, improved OHRQoL or other surrogate PROMs compared with traditional complete dentures (CDs) (De Bruyn, Raes, Matthys, & Cosyn, 2015). Consequently, a two-implant-retained overdenture has been regarded as the first choice of treatment for the fully edentulous mandible (Feine et al., 2002). In contrast, studies concerning how implants serve the edentulous maxilla are scarce. This can be attributed partly to the anatomic difference of maxilla and mandible. Even without the help of implants, maxillary prostheses are usually well tolerated by patients (Thomason, Heydecke, Feine, & Ellis, 2007). A systematic review pointed out that a maxillary IOD actually failed to improve function, comfort and stability in patients who did not complain about their CD (Andreiotelli, Att, & Strub, 2009).

Furthermore, the impact on PROMs of a fixed versus a removable implant-supported prosthesis is not conclusively addressed in the literature (Emami, Michaud, Sallaleh, & Feine, 2014). Implant-supported fixed complete dentures (IFCDs) have less volume compared than removable IODs. Elimination of the palatal coverage might help reduce the uncomfortable feeling for some patients and might improve taste in individuals with palatal taste buds (Albuquerque et al., 2000; Misch, 2014). However, the anatomic conditions required for IFCDs imply that patients often need to go through bone augmentations, which are more invasive and traumatic procedures with higher treatment costs and longer duration (Sadowsky, 1997). Patients also appear to do better in performing oral hygiene with an IOD (Heydecke et al., 2003). In terms of aesthetics, IODs could better serve patients in need of more lip support through a denture flange. In general, the absolute advantage of either IFCD or IOD is not evident from patient-reported outcomes, while factors such as patients' preferences and their expectations might play a significant role.

The purpose of this systematic review was to assess the existing evidence from edentulous patients' PROMs of their fixed or removable implant-supported prostheses. Furthermore, this study aimed to identify measurement instruments and best practices towards producing a set of guidelines for the implementation of PROMs in clinical research and patient care involving rehabilitation with dental implants.

2 | METHODS

2.1 | Search strategy

A systematic literature review was performed to identify clinical studies published in English presenting patients reported outcome measures (PROMs) from patients with at least one fully edentulous jaw restored with dental implants. The PICO (Patient or population, Intervention, Control or Comparison, Outcome and study types) search strategy was followed, using MeSH keywords specific to the focus question. The review was registered online with NHS PROSPERO database (https://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42016049600).

Five electronic databases were included in the search: PubMed; Cochrane Library; EMBASE; Scopus and Web of Science. The search was run on 29th November of 2016 and included papers published from 1983 to that date. Literature search updates were performed by setting up automatic searches on each database and requesting new record alerts to be sent by email.

A general search strategy was developed as: (a) *Population:* #1 = (edentulous jaw*) OR edentulous; (b) *Intervention:* #2 = (dental prosthesis implant-supported) OR dental implant?; (c) *Comparison:* #3 = (fixed prosthesis) OR fixed denture*, #4 = (((complete denture*) OR overdenture) OR removable denture*) OR removable prosthesis; (d) *Outcome:* #5 = (((((quality of life) OR patient* centered care) OR patient* centered outcome*) OR patient* satisfaction) OR patient* preference*) OR patient* outcome*; (e) Search combination: #1 AND #2 AND (#3 OR #4) AND #5. The search algorithm was modified according to the specific guidelines of each database (Appendix I).

The initial eligibility assessment was carried out independently by 2 authors (CY and CC) based on the title of the study. As the definition of PROMs was inconsistent among studies, the group agreed to adopt broad inclusion criteria at this stage. After thorough consideration, a list of inclusion and exclusion criteria was developed by the authors (Appendix II). Reasons for exclusion were listed and the Kappa value of the final full-text screening was calculated.

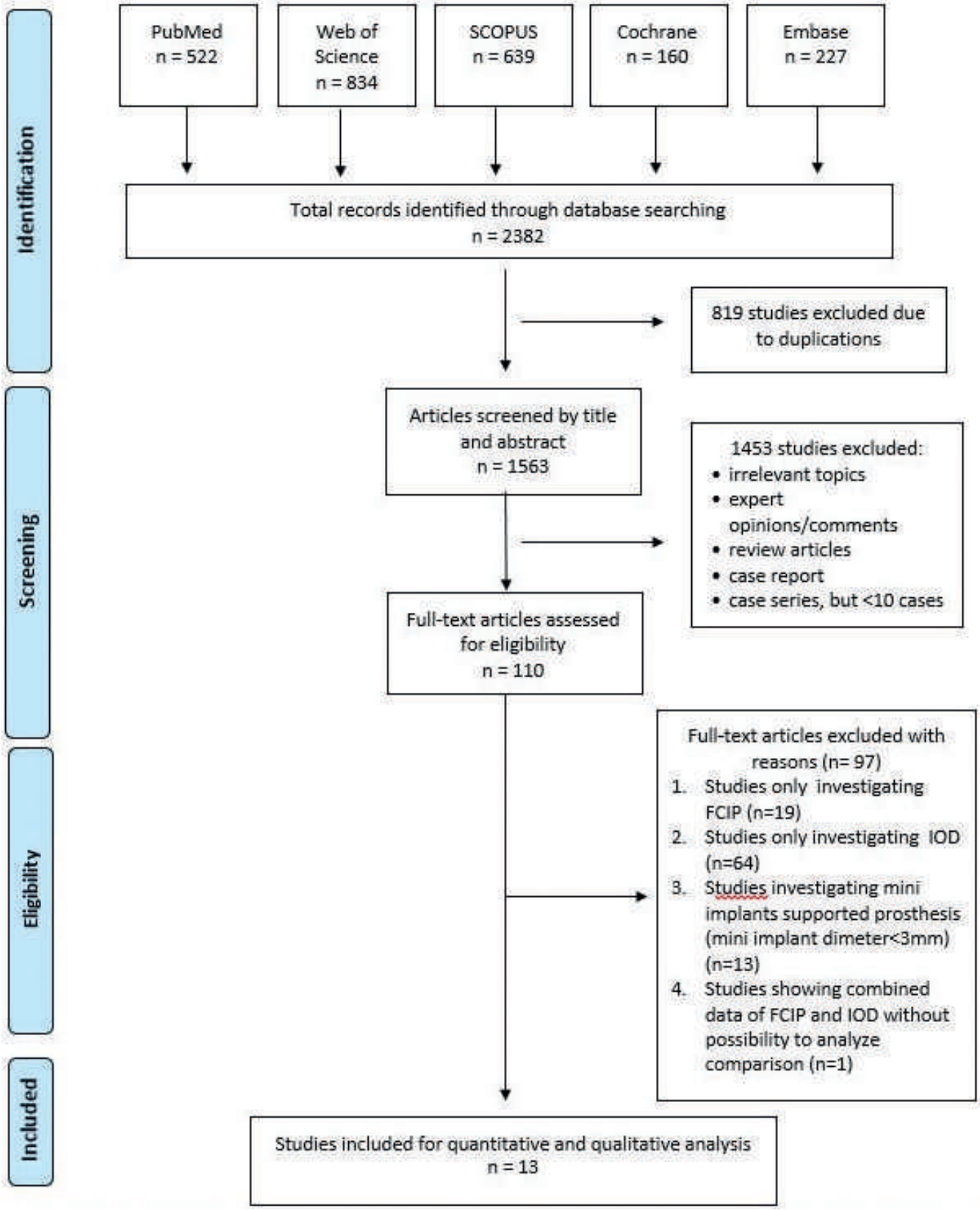

FIGURE 1 Flow chart of publication selection for inclusion

TABLE 1 Number of studies with patient-reported outcome measures (PROMs) in implant dentistry according to year of publication

Time frame	Studies found through searching electronic databases	Final inclusion
1983–1999	170	2
2000–2009	540	4
2010–2016	853	7

2.2 | Data extraction

A data extraction sheet was drafted after reaching consensus within the research group with regards to the important information to be collected. Two authors (CY and CC) independently screened the articles selected and extracted data from included studies. Another two authors (MB and NM) checked the extracted data. Disagreements were resolved by discussion among the four authors.

From each study, data were collected as follows: (a) author information (journal and publish year); (b) study design (retrospective/prospective; nature of investigating PROMs); (c) sample (age; prosthesis distribution; the antagonist type); (d) intervention (implant number; prosthesis type); (e) measurement/timeframe (time point; follow-up time); (f) type of PROMs (OHRQoL; satisfaction, etc.); (g) evaluation method (standard questionnaire; visual analogue scale; Likert-type scale); (h) level of evidence and bias assessment following the guidelines of the US Agency for Health Care Policy and Research (AHCPR, 2012) (Appendix III); (i) results (comparison between IFCD and IOD; comparison of pre- and post-treatment).

3 | RESULTS

After removing duplications, 1,563 articles were identified from 5 different databases (Figure 1). As shown in Table 1, almost 2/3rds of these articles were published during the last 6 years. After excluding the nonrelevant studies at the title stage, the abstracts were screened by two authors, independently (CY and CC). Based on the exclusion criteria presented in the methodology, 1,453 studies were removed. The Kappa value was 0.79. Full texts of the remaining 110 articles were then analysed. Of these, 97 studies were excluded. Reasons for exclusion are presented in Figure 1. Finally, 13 studies met the inclusion criteria and were further analysed, allowing for a comparison of PROMs reported by edentulous patients with fixed (IFCDs) and removable (IODs) implant-supported prostheses.

3.1 | Study characteristics and level of evidence

Details of each study and related PROMs are shown in Table 2. Not all studies reported the treatment protocol followed during the implant surgery and restoration. It was also apparent that the included studies adopted different restoring protocols for implants. Among the 13 publications, 5 studies included patients with fully edentulous maxillae and mandibles; 5 reported prostheses only in the mandible, and 3 investigated prostheses in the maxilla. Not every study stated clearly, if at all, which type of prosthesis was provided in the opposing jaw.

Oral health-related quality of life (OHRQoL) and *Satisfaction* were the most common PROMs in the reviewed papers. All included studies reported either the term "OHRQoL", "Satisfaction" or both. In terms of study design, analysed publications included 8 prospective and 5 retrospective studies. However, in reality many of the studies are cross sectional with regards to the assessment of PROMs, as they only assess PROMs at one time point, even if the design is a prospective cohort with regards to other parameters, for example, incidence of technical complications (Katsoulis, Brunner, & Mericske-Stern, 2011). Determining the actual study design with regards to the investigation of PROMs is therefore not simple and the overall study design might be misleading. Sample sizes ranged from 13 to 150 patients. The assessment time varied from 2 months to 10 years. Among the prospective studies, only 3 (De Kok, Chang, Lu, & Cooper, 2011; Martínez-González, Martín-Ares, Cortés-Bretón Brinkmann, Calvo-Guirado, & Barona-Dorado, 2013; Zitzmann & Marinello, 2000) provided the baseline PROMs, which allowed for prospective assessment pre- and post-treatment. Four publications from the same research group (Feine et al., 1994, 2002), adopted a quasi-randomized cross-over design (De Grandmont et al., 1994; Feine et al., 1994; Heydecke, McFarland, Feine, & Lund, 2004; Heydecke et al., 2003). In addition, one retrospective study by Oh et al. (2016) attempted to investigate PROMs before and after treatment through a one-time face-to-face interview assisted by a questionnaire. The majority of publications did not reach the highest levels of evidence (Table 2). Only one study was graded as level Ib, which also was the only randomized controlled trial (RCT) identified in the present systematic review (De Kok et al., 2011). Five of thirteen studies were graded as level III and seven reached level II.

3.2 | Methodologies of studies

The methods used to evaluate PROMs were heterogeneous among studies. Measurements varied considerably in terms of type of scale and scores calculated. Nine studies utilized a Likert-type scale, seven studies used visual analogue scale (VAS), and two adopted a dichotomous coding system (Table 2). The number of items in the questionnaires ranged from 5 (Feine et al., 1994) to 49 (De Kok et al., 2011). Generally, the Oral Health Impact Profile (OHIP) was widely employed. One study measured the complete OHIP-49 (De Kok et al., 2011), while the short version OHIP-14 was adopted in five studies (Brennan, Houston, O'Sullivan, & O'Connell, 2010; Katsoulis et al. (2011); Martínez-González et al. (2013); Martín-Ares, Barona-dorado, Guisado-moya, Martínez-rodríguez, & Martínez-gonzález, 2016; Oh et al., 2016). However, two of them took items from OHIP-14 in order to create a modified questionnaire. Therefore, wording of the items was inconsistent (Martín-Ares

TABLE 2 Characteristics of included studies

Author	Study design	Sample	Interventions studied	Measurements/ Timeframe	Type of PROMs	PROMs evaluation method	Level of evidence	Results
Oh et al. (2016)	Retrospective Cross-sectional[a] Interview post-treatment	• 86 patients; • Maxilla or Mandible or both • Mean age: o IOD 54.7 o IFCD 54.4 o CD 56.1	29 IFCD; 27 CD; 30 IOD	At least 6 months in function, 69.8% of subjects were examined 1–3 years after receiving new prostheses	• OHRQoL • Satisfaction • Oral health and dental management	• 14 items measuring satisfaction, ad hoc (code = 0–4) • OHIP-14 (code = 0–4)	III	• OHRQoL improved significantly after treatment in both groups • No significant difference of satisfaction or OHRQoL was found between IFCD and IOD
De Souza et al. (2016)	Retrospective	• 75 patients • Mandible	23 IOD: 52 IFCD • Mandible: o 23 IOD 2 implants (bar clip) o 52 IFCD (Brånemark protocol: 4–6 implants) • Maxilla: CD	At least 6 months in function	Satisfaction OHRQoL	9-items survey measuring dichotomous responses (YES/NO) (ad hoc)	III	IFCD was rated higher, but no significant difference of any items was found between IFCD and IOD
Martín-Ares et al. (2016)	Retrospective	• 150 patients • Maxilla and Mandible • Age 60–80	50 IFCD; 50 IOD; 50 CD • Maxilla o IOD 4 implant o IFCD 8 implants; • Mandible: o IOD 4 implants o IFCD 6 implants • Most antagonistic jaw CD	At least 5 years in function	Satisfaction with function and hygiene maintenance	9 items from OHIP-14 and 2 items from the Dental Impact Profile (code = 0–4)	III	• Overall compete satisfaction rate: CD14% significantly lower than IOD 36% and IFCD 46% • No significant difference between IFCD and IOD, apart from IFCD showed significantly lowest satisfaction in self oral hygiene, but better sense of taste
Martínez-González et al. (2013)	Prospective Cohort	• 40 patients • Maxilla and Mandible • Mean age: o IOD 62 o IFCD 61.1	20 IFCD; 20 IOD • Maxilla: o IOD 4 implants o IFCD 8 implants • Mandible: o IOD 2 implants o IFCD 6 implants	• Pretreatment, • Follow-up 1, 3, 5 years	• Impact of prosthetic type on quality of life • Satisfaction	14 items from OHIP-14 and 5 items created by authors (code = 0–4) (ad hoc)	IIb	• For both groups, satisfaction improved significantly over the 1st year, but no significant difference between follow-up 3 or 5 years was found • Generally, no statistically significant differences were found in each item when comparing between IOD and IFCD regardless of study time, but IFCD showed a higher level of overall satisfaction ($p = 0.03$) • Oral hygiene ability was statistically better in IOD after 1 year
De Kok et al. (2011)	Prospective Randomized controlled trail	• 20 patients • Mandible • Mean age: o IOD 62.6 o IFCD 62.4	10 IOD; 10 IFCD (randomized) • Mandible: o IOD 2 implants (ball attachment) o IFCD 3 implants (CAD/CAM) • Early loading protocol • New maxilla CD	• Pretreatment, • 12 months in function	• OHRQoL; • Satisfaction	• 9 items VAS (ad hoc) • OHIP-49 items (code = 0–4)	Ib	• OHRQoL improved after treatment in both groups; • No significant difference of OHRQoL (7 domains) or satisfaction • Patients' reported better capacity of conducting oral hygiene with IOD
Katsoulis et al. (2011)	Prospective[a] Cross sectional[a]	• 41 patients • Maxilla • Mandible partially edentulous • Mean age: 63.3 (52–78)	28 IOD; 13 IFCD • Maxilla: IOD 4,5, or 6 implants: o IOD Gold bar ($n = 16$), o IOD Ti bar ($n = 12$), o IFCD CAD/CAM ($n = 13$) • 8 patients (2 IFCD and 6 IOD treated with flapless procedure	2-years in function	OHRQoL	• OHIP-14 items (code = 0–4)	IIb	• The mean OHIP values were 1.7 (IFCD), 6.7 (gold IOD), and 7.3 (Ti IOD); • Ratings in the IFCD group were significantly better

(Continues)

TABLE 2 (Continued)

Author	Study design	Sample	Interventions studied	Measurements/ Timeframe	Type of PROMs	PROMs evaluation method	Level of evidence	Results
Brennan et al. (2010)	Retrospective	• 62 patients • Maxilla and Mandible • Mean age o IOD 57.5 o IFCD 56	25 IOD; 37 IFCD • Maxilla: o 9 IFCD o 22 IOD • Mandible: o 28 IFCD o 3 IOD Each patient got at least 4 implants	• IOD average follow-up 25.5 months (3–66 months); • IFCD average 24 months (3–80 months)	• OHRQoL; • Satisfaction	• OHIP-14 • 14 items survey (ad hoc) (code = 1–5)	III	• IFCD generally showed better patient satisfaction than IOD, especially in aesthetics; chewing capacity and overall satisfaction • OHRQoL scores for IFCD were marginally better in all 7 domains, but significance was only achieved in psychological disability
Quirynen et al. (2005)	Retrospective	• 37 patients • Mandible • Mean age: o IOD 63.7 o IFCD 54.9	• Mandible: o 25 IOD: 2 implants bar/ magnet/ball attachments o 12 IFCD: No information • Maxilla CD	At least 10-years in function	Satisfaction	• Likert-type scale-5 items (code = 1–9); • YES/NO type-4 items • 14 items VAS (ad hoc)	III	IFCD group presented with significantly higher scores for general satisfaction and chewing comfort
Heydecke et al. (2004)	Prospective[a] Cross-over Cross sectional[a]	• 30 patients, • Maxilla • Age 30–60	Trail 1: mandible IOD • LBO1[b]: maxilla 5 IOD without palate (6 implants) • Maxilla 8 IFCD Trail 2: mandible IFCD • LBO2[b]: maxilla 6 IOD without palate (4 implants) • LBOP[c]: maxilla 7 IOD with palate coverage	2 months after each treatment	Speech	• VAS (ad hoc)	IIa	Statistically significant difference in the ability to speak was only found in Trial 1: subjects with LBO (IOD) perceived their ability to speak was better than the subjects with IFCD.
Heydecke et al. (2003)	Prospective Cross-over	• 13 patients • Maxilla • Mean age 45.1	• Maxilla: o 4–6 implant-supported prostheses o 5 LBO[b]: IOD without palate (bar) o 8 IFCD no information • Mandible: IOD	• Pretreatment • 2 months after each treatment	• Satisfaction • Choice of prosthesis	• VAS • Likert-type scale (ad hoc)	IIa	• IOD significantly higher in general satisfaction (e.g., general satisfaction as compared to the natural teeth;ability to speak and ease of cleaning) • No difference was found for comfort, stability, aesthetics, occlusion or ability to chew • In assessing embarrassment at work and avoiding conversation, IFCD scored inferior to LBO [b] IOD • Among 13 subjects, 4 preferred IFCD compared to 9 IOD
Zitzmann and Marinello (2000)	Prospective	• 20 patients • Maxilla • Age: 35–79	• Maxilla: o 10 IOD (bar) o 10 IFCD no information • Mandible: No information	• Pretreatment; • 6 months post-treatment	• Oral health psychological impact	• VAS (ad hoc)	IIb	• There was no significant difference between IOD and IFCD group • Both groups significantly improved comparing pre- and post-treatment
De Grandmont et al. (1994)	Prospective Cross-over	• 15 patients • Mandible • Mean Age: o IFCD 49.5 o IOD: 58.1	• Mandible o 7 IOD; o 8 IFCD • Maxilla CD	• Pretreatment; • 2 months after each treatment	• General satisfaction • Aesthetics; • Ability to speak • Chewing ability • Fit and retention • Function • Quality of life	• VAS • Likert-type (ad hoc)	IIa	• There was no significant difference between IFCD and IOD in general satisfaction; ability to speak and aesthetics; • Significant differences were found in reported chewing ability for harder foods, for example, carrot, apple and sausage. IFCD was rated higher than IOD

(Continues)

TABLE 2 (Continued)

Author	Study design	Sample	Interventions studied	Measurements/ Timeframe	Type of PROMs	PROMs evaluation method	Level of evidence	Results
Feine et al. (1994)	Prospective Cross-over Cross sectional[a]	• 15 patients • Mandible • Mean Age: ○ IFCD 49.5 ○ IOD 58.1	• Mandible ○ 7 IOD; ○ 8 IFCD • Maxilla CD	2 months after each treatment	• Stability • Ability to chew • Ability to clean • Ability to speak • Aesthetics • Choice of prosthesis	• VAS (ad hoc)	IIa	• Stability and ability to chew were significantly higher with IFCD; • Ability to clean was significantly higher with IOD • There was no significant difference in patients' choice of IFCD or IOD, • For IFCD patients mostly valued stability, ability to chew, and ease of cleaning • For IOD, patients mostly valued ease of cleaning, aesthetics and stability

Note. CD, complete denture; IFCD, implant-supported fixed complete denture; IOD, implant-supported overdenture; OHIP, oral health impact profile; OHRQoL, oral health–related quality of life; VAS, visual analogue scale.

"ad hoc" indicates scale without evidence of validity and reliability for measurement of psychometric properties in terms.

[a]Oh et al. (2016); Feine et al. (1994); Heydecke et al. (2004); Katsoulis et al. (2011): Prospective observation of complications or other parameters, but collection of PROMS only conducted at one time point as a cross sectional study. [b]Long bar overdenture without palatal coverage. [c]Long bar overdenture with palatal coverage

et al., 2016; Martínez-González et al., 2013). Regarding evaluation of patient satisfaction, no standard questionnaire was found in the included studies. There was also a lack of consistency in definition of patient satisfaction.

3.3 | Synthesis of reported outcomes

The most common parameters employed in PROMs measurements were listed in Table 3 in the order of frequency in which they were reported. The most frequently reported outcomes involved chewing function (11 studies), phonetic function (10 studies), overall satisfaction (9 studies), aesthetics (7 studies); comfort (5 studies); retention/stability (5 studies), and capacity to conduct oral hygiene (5 studies).

Generally, apart from one study by Heydecke et al. (2003), the trend of IFCD overriding IOD was found in the majority of included studies but not always reaching statistical significance (De Kok et al., 2011; De Souza et al., 2016; Martín-Ares et al., 2016; Martínez-González et al., 2013; Oh et al., 2016; Quirynen et al., 2005). For *chewing function*, the majority of studies (8/11) revealed no significant differences between IFCD and IOD, apart from Feine et al. (1994), Quirynen et al. (2005) and Brennan et al. (2010). When assessing *phonetics*, only Heydecke et al. (2004) reported that patients with IOD had better experiences with speaking compared with IFCD, while other studies did not find significant differences (9/10). With regard to *overall satisfaction*, four studies claimed that patients rated IFCD significantly higher than IOD (4/9) while another four studies found no differences (4/9). Only Heydecke et al. (2003) reported the reverse, that is, IOD achieved better overall satisfaction than IFCD. In terms of *aesthetics*, Brennan et al. (2010) concluded that IFCDs were rated significantly higher than IODs; however, the residual 5 studies were not statistically different. Five studies reached a similar conclusion in patients' *capacity of maintaining oral hygiene* for their new prostheses: patients considered IOD as easier to clean (De Grandmont et al., 1994; De Kok et al., 2011; Feine et al., 1994; Martín-Ares et al., 2016; Martínez-González et al., 2013). In terms of the *retention or stability of dentures*, only Feine et al. (1994) reported higher scores for the IFCD group (1/5), while the remaining four studies found no significant differences. Two studies evaluated the *sense of taste* as an item of PROMs. Only Martín-Ares et al. (2016) found that IOD was reported by patients as negatively affecting the sense of taste. Meanwhile, Feine et al. (1994) and Heydecke et al. (2003) measured patients' preferences for *choice of the prosthesis* in the mandible and maxilla respectively, but no statistical significance was reached.

When comparing assessment before and after treatment, Zitzmann and Marinello, (2000), Oh et al. (2016) and De Kok et al. (2011) agreed that OHRQoL and patient satisfaction were significantly improved in all domains after completion of the treatment with both IOD and IFCD. This was confirmed in studies by Martínez-González et al. (2013) and Quirynen et al. (2005) with long-term follow-up data. In these studies, patients wearing implant-supported prostheses were interviewed retrospectively at 5 and 10 years. The

TABLE 3 Main PROMs compared between IFCD and IOD

	Oh et al. (2016)	De Souza et al. (2016)	De Kok et al. (2011)	Martínez-González et al. (2013)	Martín-Ares et al. (2016)	Brennan et al. (2010)	Katsoulis et al. (2011)	Quirynen et al. (2005)	Zitzmann and Marinello (2000)	Heydecke et al. (2003, 2004)	De Grandmont et al. (1994)	Feine et al. (1994)
Chewing function	(0)	(0)	(0)	(0)	(0)	IFCD (+)	–	IFCD (+)	(0)	(0)	(0)	IFCD (+)
Phonetic function	–	(0)	(0)	(0)	(0)	(0)	–	(0)	(0)	IOD (+)	(0)	(0)
Overall satisfaction	(0)	(0)	(0)	IFCD (+)	IFCD (+)	IFCD (+)	–	IFCD (+)	–	IOD (+)	(0)	–
Aesthetics	–	–	(0)	(0)	–	IFCD (+)	–	–	(0)	(0)	(0)	(0)
Comfort	–	–	(0)	–	–	(0)	–	(0)	(0)	(0)	–	–
Retention and stability of dentures	–	–	(0)	–	–	–	–	–	(0)	(0)	(0)	IFCD (+)
Capacity to conduct oral hygiene	–	–	IOD (+)	IOD (+)	IOD (+)	–	–	–	–	IOD (+)	–	IOD (+)
OHRQoL	(0)	–	(0)	–	–	IFCD (+) only in Psychologic	IFCD (+)	–	–	–	–	–
Social function	(0)	–	–	–	–	–	–	(0)	–	IOD (+)	(0)	–
Pain	–	(0)	–	(0)	(0)	–	–	–	–	–	–	–
Self-esteem improvement	–	(0)	–	(0)	–	–	–	–	(0)	–	–	–
Understanding of the treatment	–	(0)	–	–	–	(0)	–	–	–	–	–	–
Sense of taste	–	–	–	–	IFCD (+)	–	–	–	(0)	–	–	–
Choice of prosthesis	–	–	–	–	–	–	–	–	–	(0)	–	(0)

Note. IFCD, implant-supported fixed complete denture; IOD, implant-supported overdenture; OHRQoL, oral health-related quality of life
(0) means no significant difference between IFCD and IOD groups; (+) indicates the corresponding group showing significantly better than the other; – means not applicable

authors concluded that the reported improvements in patient satisfaction after completion of treatment could be maintained in the long term, regardless of the mode of rehabilitation, that is, IFCD or IOD.

4 | DISCUSSION

There is an increasing expectation to supplement clinical research outcomes with patients' subjective perspective of their treatment. As in previous systematic reviews in this field (De Bruyn et al., 2015), we found that the majority of eligible studies were published recently. This is not surprising, given the fact that PROMs have received increasing research attention in the recent past. The number of studies using PROMs as primary or secondary outcomes has increased significantly in the past decade, especially in reporting quality of life or patient satisfaction (De Bruyn et al., 2015; Lang & Zitzmann, 2012; McGrath et al., 2012; Strassburger, Heydecke, & Kerschbaum, 2004). Nevertheless, the number of methodologically robust trials comparing patient-reported outcomes of implant-supported fixed and removable prosthesis in fully edentulous patients remain small. Furthermore, any attempt to collectively analyse the existing studies, either statistically or in qualitative terms, has proved to be difficult due to diversity of research designs and definitions of PROMs, heterogeneity of measured outcomes, treatment protocols, and measurement techniques. In addition, differences in the restoring protocols between the same type of prosthesis (e.g., number and placement of implants, locators or bar retention, etc.), could theoretically result in different levels of invasiveness, different needs for maintenance, different frequency of complications and possibly different PROMs; however, there is little evidence in support of such differences at present (Katsoulis et al., 2011).

4.1 | Satisfaction or quality of life?

In the reviewed literature, two items are most commonly assessed as PROMs: impact of prosthesis in the "Quality of Life" and patient "Satisfaction". The current widely adopted instrument for measuring impact in the "Quality of Life" category appears to be the Oral Health Impact Profile (OHIP) and its short versions. The full OHIP questionnaire consists of 49 items that cover seven domains: functional limitation, physical pain, psychologic discomfort, physical disability, psychologic disability, social disability, and handicap (Allen & Locker, 2002). However, some authors have claimed that the OHIP is not sufficient to comprehensively present patients' perceptions of prosthetic rehabilitation (Martín-Ares et al., 2016).

While "Quality of Life" was approached with structured questionnaire items, unfortunately, a definition of "satisfaction" was not described in any of included studies. It appears that "satisfaction" is often perceived as a "common sense" outcome, which will not require any further description or definition. This widely spread perception is reflected in the diversity of measurements of patient satisfaction, and is one of the reasons of the increased heterogeneity of the outcomes. Due to the lack of a uniform or at least widely accepted definition, and a valid and reliable construct, "satisfaction" is assessed in many different formats (Sitzia, 1999). Most studies utilized a vaguely defined broad question such as "overall satisfaction", or specific questions regarding satisfaction with chewing, or speaking. The two approaches may have very different outcomes. It has been suggested that an overall "global" question tends to generate false-positive responses from patients, while specific questions might prompt patients to think deeper and give more detailed responses (Awad & Feine, 1998).

In the absence of a definition or wide understanding of "satisfaction", it is not surprising to realize that this term is often used interchangeably with "Quality of Life" (De Souza et al., 2016; Katsoulis et al., 2011; Martín-Ares et al., 2016; Martínez-González et al., 2013). In particular, some studies utilized OHIP to measure OHRQoL, but then discussed the outcomes in terms of patient satisfaction or generated conclusions about satisfaction. There is, consequently, a need to clarify whether one of these terms is actually redundant, if there is a significant overlap in the outcomes or if both of these terms have validity when assessing PROMs in clinical research. To that end, a definition of the term "patient satisfaction" or similar variations would be an invaluable contribution to this field of research. Furthermore, the factors that influence the expression of satisfaction need to be also identified and described, so as to minimize bias and confounding factors when attempting to measure it.

Allen, McMillan, and Locker (2001) compared the change effect size (pre- and post-treatment) of OHRQoL and satisfaction within IOD patients. They found the changes of OHRQoL (measuring by OHIP) were smaller than denture satisfaction (one general scale), and the correlation coefficients between these two parameters were moderate. This might indicate that the OHIP and denture satisfaction scales are capturing different outcomes. Satisfaction is perceived as simple and comprehensible outcome and thus has often been used as a surrogate outcome of PROMs, leading to instruments that are perceived to be more user-friendly for both patients and clinicians. In contrast, OHRQoL is usually measured with multidimensional variables and the concept is probably too abstract for patients and clinicians unfamiliar with PROMs.

Measurement instruments have been published for both satisfaction and OHRQoL (Allen & Locker, 2002; Michaud, De Grandmont, Feine, & Emami, 2012) and studies have acknowledged these instruments as sensitive enough to capture significant clinical differences between treatment modalities (Allen et al., 2001, 2006; Awad, Lund, Dufresne, & Feine, 2002). However, many researchers have attempted modifications or additions to common instruments. Martínez-González et al. (2013) and Martín-Ares et al. (2016) modified OHIP-14 in their studies for measuring OHRQoL. In Martínez-González et al.'s (2013) study, parameters such as halitosis; difficulty cleaning; self-consciousness when smiling; idea that treatment has been a waste of money; and

treatment has not been worth the trouble were added. Similarly, indicators of satisfaction such as the experience of treatment procedure and the fulfilment of patients' expectations have been proposed (De Souza et al., 2016; Weaver et al., 1997). These variables should not be overlooked, in particular when attempting to measure satisfaction, as there is increasing evidence that other parameters than the actual treatment outcome can significantly influence the individual's expression of satisfaction (Yao, Tang, Gao, McGrath, & Mattheos, 2014). For example, in Allen and McMillan's (2003) study, patients were less happy when they requested dental implant-supported prostheses for one edentulous jaw but given complete dentures (CDs) instead. In comparison, patients who preferred implants and received implant prosthodontic treatment were significantly more satisfied. This was the same for patients who preferred complete dentures without implants and were treated in that manner.

4.2 | The influence of patients' characteristics and background

Patient-reported outcomes measures were affected by multiple variables (Martín-Ares et al., 2016; Weaver et al., 1997). For instance, Awad and Feine (1998) demonstrated that patients' gender contributed significantly to the expression of general satisfaction. Allen and McMillan (2003) acknowledged that patients' preferences played an important role in OHRQoL and satisfaction. Patients' expectations/perception of the treatment might affect how they evaluate the success of treatment, as well (Newsome & Wright, 1999; Yao et al., 2014, 2017) . It is, therefore, evident that when measuring satisfaction, certain aspects of patients' demographic, socioeconomic and behavioural characteristics had a significant influence on the expression of satisfaction with the treatment. Unfortunately, there is presently no clear understanding on which patient characteristics would be essential to be reported together with PROMs, in order to better comprehend the outcomes. Consequently, it is no surprise that in the reviewed literature no specific patient characteristics were consistently identified as significant variables, regarding both IFCD and IOD patients. Information regarding the recruited subjects is scarce in most studies. For example, the history of previous prosthetic experiences by patients and the prosthodontic condition of the antagonistic jaw were scarcely reported. Thomason et al. (2007) proposed that the subjects included in a PROMs study should be from truly representative populations, rather than cohorts of previously dissatisfied patients. Allen et al. (2006) suggested that the use of "intention to treat" may have a placebo effect when evaluating "subjective" feeling. If patients are being proactive for implant-related treatment, they might report greater OHIP change scores than those who refuse implants. Consequently, extrapolation of conclusions should be done with caution when there is limited data in the methodology describing the patient sample and characteristics. At the same time, there is an evident need to identify critical information on patients' backgrounds that could assist in the interpretation of the observed PROMs in clinical research.

4.3 | The influence of the treatment environment and settings

Another important parameter that is often neglected is the environment in which treatment takes place. There is increasing evidence, but also widespread anecdotal perception, that patient populations from different treatment centres might differ significantly in terms of their socioeconomic backgrounds, educational level, perceptions and expectations from treatment (Berendes, Heywood, Oliver, & Garner, 2011; Ståhlnacke, Söderfeldt, Unell, Halling, & Axtelius, 2007; Yao et al., 2017). Whether treatment is delivered in government hospitals, private practice, university clinics, subsidized or fully paid care might produce a significant selection bias, as it can filter the patient sample and skew the outcomes in directions that are not easily understood. The very fact that such patients have volunteered to participate in research and that some of them are consequently offered favourable treatment terms with subsidies or other "perks" might also influence patient traits and characteristics. Having established the link between patients' perceptions and expectations with the subjective expression of "satisfaction" implies that a treatment environment and settings which can influence perceptions will also act as a significant confounding factor regarding "satisfaction" (Clow, Fischer, & O'Bryan, 1995; Yao et al., 2014, 2017). All reviewed studies in this paper were conducted in university-affiliated clinics, apart from one study that recruited patients from both private and public clinics (Oh et al., 2016). Nevertheless, there is scarce information towards understanding influences on patients' motivation for treatment such as special conditions, financial subsidies or any other conditions that would benefit study participants compared to those who paid out of pocket for care in private practice and, thus, act as confounders to the reported outcomes.

4.4 | Comparing different treatment modalities

Regarding the direct comparison of PROMs between IOD and IFCD for full-arch rehabilitations, no strong conclusions can be drawn from existing studies. Both advantages and disadvantages were reported for the two treatment modalities. The fixed prosthesis is perceived as a "part of the body" which might provide patients more security and less of a foreign body feeling than the removable option (Misch, 2014). But the IOD is relatively simple, minimally invasive, easier to clean and more affordable (De Souza et al., 2016; Martín-Ares et al., 2016).

As the direct comparison of PROMs between IFCD and IOD failed to lead to consistent conclusions, it might be even more problematic to analyse studies that assess only one or the other treatment modality, such interpretation will most likely suffer from further confounding factors and diversity of methodologies, populations and outcomes.

4.5 | Limitations

This study did not include research directly comparing IFCD versus CD, or studies measuring IOD versus CD. This might have excluded some information which could serve as indirect comparisons between IFCD and IOD. Furthermore, the potential of this review to reach valid conclusions was limited by the diversity in the quality of included studies and the inconsistency in the definition of PROMs. The quality of studies was assessed according to the design of each study, which might not be fully adequate in evaluating risk of bias or other parameters related to quality of evidence. Quantitative analysis of the data was not possible, while qualitative analysis was that of a narrative type.

5 | CONCLUSIVE REMARKS

Overall, there is a scarcity of well-designed studies comparing PROMs from IFCD and IOD treatment. When examining the data from the literature, it is difficult to conclude whether the lack of significant differences in comparing the treatment modalities is due to the actual treatment, the quality of the methodology, the environment in which the treatment took place or patient characteristics. Apart from a clear set of definitions that is urgently needed, other guidelines for introducing assessment of PROMs in clinical research would be a valuable contribution at present. Such guidelines, possibly in the form a "toolkit" could help clinical researchers to select the right tools, collect essential information related to the treatment itself including patients' backgrounds and the environment the treatment takes place. This would lead to outcomes that would be easier to interpret, extrapolate and compare**.** Such a toolkit would offer a boost to PROMs research, which is in the future should be an inherent part of all clinical research.

6 | SUMMARY OF EVIDENCE

Overall, the OHRQoL and satisfaction of edentulous patients were significantly improved after wearing implant-supported prosthesis compared to their OHRQoL and satisfaction ratings before treatment. These improvements can be found in almost all domains, including comfort, function, aesthetics, speech, self-esteem (De Kok et al., 2011; Martínez-González et al., 2013; Oh et al., 2016; Zitzmann & Marinello, 2000).

When comparing between IOD and IFCD, however, the reported outcomes were inconsistent. The majority of the reviewed studies reported that IFCD performed better in the aspects of overall satisfaction and OHRQoL (Table 3), while some authors found IODs and IFCDs were similar when comparing PROMs (Oh et al., 2016; Zitzmann & Marinello, 2000). On the other hand, Heydecke et al. (2003) showed that IODs provided better outcomes in several domains. This controversy may be due to heterogeneities among study methodologies and populations, as PROMs have been reported to be affected by numerous factors (Bryant, Walton, & MacEntee, 2015; Gallucci, Grütter, Nedir, Bischof, & Belser, 2011). In addition, the diversity of measurement tools—with some instruments not being properly validated—may also contribute to this heterogeneity. Conclusively, on the basis of current evidence, it is not possible to support a solid conclusion on which type of prosthesis would result in better PROMs. One clear conclusion appears to emerge however, as 5 studies reached an agreement on the IOD being easier to maintain oral hygiene. This might be of significance when selecting a treatment for patients with difficulties in conducting oral hygiene such as the elderly, patients with disabilities or Parkinson's disease. Meanwhile, it is also apparent that IFCD needs to have a design that allows access for efficient oral hygiene and that patients, who receive such reconstructions, must be adequately trained for their particular prosthesis.

CONFLICT OF INTEREST

The authors declared no conflict of interest and had nothing to disclose.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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APPENDIX I Search algorithm in five online databases

PUBMED

Population	**#1 = (edentulous jaw*) OR edentulous**
Intervention or exposure	#2 = (dental prosthesis implant-supported) OR dental implant?
Comparison	#3 = (fixed prosthesis) OR fixed denture* #4 = (((complete denture*) OR overdenture) OR removable denture*) OR removable prosthesis
Outcome	#5 = (((((quality of life) OR patient* centered care) OR patient* centered outcome*) OR patient* satisfaction) OR patient* preference*) OR patient* outcome*
Search combination	#1 AND #2 AND (#3 OR #4) AND #5

SCOPUS

(TITLE-ABS-KEY(patient satisfaction) OR TITLE-ABS-KEY(quality of life) OR TITLE-ABS-KEY(patient reported outcome) OR TITLE-ABS-KEY(patient preferences) OR TITLE-ABS-KEY(patient centered care)) AND TITLE-ABS-KEY(dental implant) AND TITLE-ABS-KEY(edentulous) AND (LIMIT-TO(SUBJAREA,"DENT")) AND (LIMIT-TO(LANGUAGE, "English"))

WEB OF SCIENCE

#4	#3 AND #2 AND #1 Refined by: **WEB OF SCIENCE CATEGORIES:** (DENTISTRY ORAL SURGERY MEDICINE) AND **LANGUAGES:** (ENGLISH)
#3	**TOPIC:** (edentulous) *OR* **TOPIC:** (edentulous arch) *OR* **TOPIC:** (edentulism)
#2	**TOPIC:** (dental implant*) *OR* **TOPIC:** (implant supported denture) *OR* **TOPIC:** (oral implant*) *OR* **TOPIC:** (implant supported prosthesis)
#1	**TOPIC:** (patient centered care) *OR* **TOPIC:** (patient reported outcome*) *OR* **TOPIC:** (patient satisfaction) *OR* **TOPIC:** (quality of life) *OR* **TOPIC:** (patient preference*)

EMBASE

#1	**mouth disease/or denture/or mandible/or edentulousness/or implant/or maxilla/**
#2	dental implant.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading]
#3	patient care/or "quality of life"/or outcome assessment/
#4	patient satisfaction/or doctor patient relation/or interpersonal communication/or motivation/
#5	#3 or #4
#6	#1 and #2 and #5

COCHRANE

#1	**edentulous: ti, ab, kw (Word variations have been searched)**
#2	dental implant*:ti, ab, kw or oral implant*:ti, ab, kw or implant supported prosthesis: ti, ab, kw (Word variations have been searched)
#3	patient centered: ti, ab, kw or quality of life: ti, ab, kw or "patient reported outcome":ti,ab,kw or "patient reported outcome measure":ti,ab,kw or patient satisfaction (Word variations have been searched)
#4	#1 AND #2 AND #3

APPENDIX II INCLUSION AND EXCLUSION CRITERIA

Inclusion criteria	Studies published in English;
	Studies published from 1983 until November 2016
	Quantitative study with clearly stated study design, for example, randomized controlled trial; cohort studies, cross-over studies.
	Healthy patients with fully at least one edentulous jaw treated with complete implant-supported prosthesis
Exclusion criteria	
1st round screening	Case reports or case series (less than 10 subjects)
	Expert opinions, editor comments or any kinds of articles without quantitative data;
	Reviews
2nd round screening	PROMs not being the primary or secondary study outcomes, for example, questionnaire validation
	Studies recruiting fully and partially edentulous patients without presenting separate data
	Studies involving not typical screw type implant-supported prosthesis, for example, zygomatic implant-supported dentures;
	Studies without follow-up period of at least 2 months
	Studies with insufficient data to clarify the outcomes of interest.
3rd round screening	Mini implants (implant diameter less than 3 mm)
	Study separately investigating IFCD or only IOD without comparing them

APPENDIX III

- Ia = evidence obtained from a meta-analysis of randomized controlled trails
- Ib = evidence obtained from at least one randomized controlled trial
- IIa = evidence obtained from at least one well-designed controlled study without randomization
- IIb = evidence obtained from at least one other type of well-designed quasi-experiment study
- III = evidence obtained from well-designed nonexperimental studies, such as comparative, correlational, or case studies
- IV = evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities

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REVIEW ARTICLE

WILEY CLINICAL ORAL IMPLANTS RESEARCH

Immediate loading vs. early/conventional loading of immediately placed implants in partially edentulous patients from the patients' perspective: A systematic review

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Abstract

Objectives: This systematic review aimed at answering the following PICO question: In patients receiving immediate (Type 1) implant placement, how does immediate compare to early or conventional loading in terms of Patient-Reported Outcome Measures (PROMs)?

Material and Methods: Following search strategy development, the OVID, PubMed, EMBASE, and Cochrane Database of Systematic Reviews databases were search for the relevant literature. All levels of evidence including randomized controlled trials, prospective and retrospective cohort studies, and case series of at least five patients were considered for possible inclusion. An additional manual search was performed by screening the reference lists of relevant studies and systematic reviews published up to May 2017. The intervention considered was the placement of immediate implant.

Study selection and data extraction were performed independently by two reviewers.

Results: The search yielded a list of 1,102 references, of which nine were included in this systematic review. The limited number of studies included and the heterogeneity of the data identified prevented the performance of a meta-analysis. Three studies, one of which was a randomized controlled trial, allowed the extraction of comparative data specific to the aim of the present systematic review. The remaining studies allowed only data extraction for one single treatment modality and were viewed as single cohort studies. Overall, irrespective of the PROMs chosen, patients' satisfaction was overall high with little difference between the two loading protocols. Moreover, studies indicated a positive impact on oral health-related quality of life following immediate implant placement and loading.

Conclusions: Within the limitations of the present systematic review, immediate implant placement and loading in single tooth edentulous space seems to be a well-accepted treatment modality from the patients' perspective and is worthy of consideration in clinical practice. However, the paucity of comparative data limits any definitive conclusions as to which loading protocol; immediate or early/conventional, should be given preference based on PROMs.

KEYWORDS
clinical trial, immediate dental implant loading, patient-reported outcome measures, visual analog scale

1 | INTRODUCTION

Dental implants have become a well-accepted and predictable treatment modality. From the pioneer work of Brånemark and Schroeder describing osseointegration in the 70s to the more recent digital developments in implant dentistry, our understanding in implant science has evolved. Similarly, outcome assessment of dental implants has considerably evolved.

Initially, the main outcome that was documented included implant survival. The dichotomous nature of this outcome does not allow for specific discrimination between the two extremes of this assessment parameter; that is, the implant is either in the alveolar bone or it is not. Later, a set of proposed criteria for success based on the knowledge acquired on the Brånemark implant system has been described by Albrektsson, Zarb, Worthington, and Eriksson (1986) and has been widely used. Comprehensive evaluation of implant therapy outcome included further parameters taking in account not only the dental implant but also the health of the peri-implant hard and soft tissue interface, the integrity of prosthetic reconstruction and the overall aesthetic integration of the prostheses (Belser, Buser, & Higginbottom, 2004; Belser et al., 2009; Cosyn, Thoma, Hammerle, & De Bruyn, 2017; Furhauser et al., 2005; Lang et al., 2004; Papaspyridakos, Chen, Singh, Weber, & Gallucci, 2012; Salvi & Lang, 2004).

Patients' perceptions of implant therapy outcome have gained considerable attention in the last two decades (De Bruyn, Raes, Matthys, & Cosyn, 2015). The generic term used to describe the patients' view is PROMs or Patient-Reported Outcome Measures and is defined as follows: *"report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else"* (US Department of Health and Human Services, 2006). The importance of PROMs is underlined by the fact that they may improve delivery of care as illustrated by improved patient–clinician communication, clinical outcomes and patient satisfaction (Nelson et al., 2015). Therefore, PROMs represent an important tool to develop treatment guidelines in which the patients are actively engaged.

Over the last four decades, progress made in biological understanding of implant wound healing, refinement of surgical procedures combined with technological advances related to implant design and surface developments have challenged the initial treatment guidelines that were established by the pioneers in implant dentistry. While early guidelines recommended an undisturbed healing for 3–6 months prior to prosthesis loading (Brånemark et al., 1977), protocols have been developed to shorten the overall treatment duration for the patient. The most extreme development is represented by the placement of a dental implant in single tooth gap fresh extraction socket and immediately temporized with a single implant-supported provisional restoration. In 1998; Wöhrle reported on 14 consecutive patients treated successfully with immediate implants and immediate temporization. The success with this treatment protocol has been further documents in multiple case series and small cohort studies have (Ferrara, Galli, Mauro, & Macaluso, 2006; Groisman, Frossard, Ferreira, de Menezes Filho, & Touati, 2003; Kan, Rungcharassaeng, & Lozada, 2003; Palattella, Torsello, & Cordaro, 2008; Shibly, Patel, Albandar, & Kutkut, 2010). Patient selection, risk analysis, and clinical expertise seem to be key for successful outcome (Ganeles & Wismeijer, 2004; Jivraj, Reshad, & Chee, 2005). The majority of these reports have focused on the outcome of this protocol in the aesthetic zone; that is, in the anterior maxilla. From an aesthetic standpoint, successful outcome can be achieved with immediate implant placement although mucosal midfacial recession is not uncommon (Chen & Buser, 2014).

While there seem to be no difference in implant survival rate and marginal bone level between immediate and conventional loading, from an aesthetic perspective controversial outcomes preclude any definitive conclusion (Benic, Mir-Mari, & Hammerle, 2014). The proceedings of Fifth ITI Consensus Conference concluded that, irrespective of the timing of implant placement or loading protocol, successful outcomes can be achieved and reinforced the notions that highly trained clinicians were a prerequisite for success. Based on the classic clinical outcomes reported, there are still no clear guidelines as to which treatment protocol should be favored in daily practice (Gallucci et al., 2014; Morton, Chen, Martin, Levine, & Buser, 2014). The practitioner is then faced with multiple treatment options that could lead to similar results. In such a situation, the patients' perspective may be decisive in determining the preferred treatment modality.

Therefore, the aim of this systematic review was to answer the following PICO question: In patients receiving immediate (Type 1) implant placement, how does immediate compare to early or conventional loading in terms of patient-reported outcomes?

2 | MATERIAL AND METHODS

2.1 | Protocol registration

The systematic review was registered in the PROSPERO international database on October 2016 (Registration number #49604).

2.2 | Search methodology

A health sciences librarian (M.A.W), in collaboration with the systematic review team, developed and conducted searches

in MEDLINE (OVID, 1946-present), PubMed (1809—present), EMBASE and the Cochrane Database of Systematic Reviews (Issue 5 of 12, May 2017). Search strategies were developed for MEDLINE but revised appropriately for each database to take account of differences in controlled vocabulary and syntax rules. The main concepts identified were as follows: dental implants, immediate implant loading, and treatment outcomes. Terms searched related to the concept of treatment outcomes included, but were not limited to: quality of life, visual analog scale, and patient outcome assessment. Terms searched related to the concept of dental implantation included but were not limited to edentulous jaw or mouth, endosseous dental implants, and implant-supported dental prosthesis. Terms searched related to the concept of immediate dental implant loading included but were not limited to immediate implants or functions or temporizations, and teeth-in-a-day. Results were limited to humans. No other search restrictions were made. The PubMed (1809—present) Search Strategy is described thereafter:

"partially edentulous"[tiab] OR "partial edentulism"[tiab] OR "partially dentate"[tiab] OR "dental implant*"[tiab] OR "complete edentulous"[tiab] OR "complete edentulism"[tiab] OR "total edentulous" [tiab] OR "total edentulism"[tiab] OR "totally edentulous"[tiab] OR "endosseous implant*"[tiab] OR "implant borne"[tiab] OR "edentulous jaw"[tiab] OR "edentulous mouth"[tiab] OR "Jaw, Edentulous"[Mesh] OR "Mouth, Edentulous"[Mesh] OR "Dental implantation, endosseous" [Mesh:NoExp] OR "Dental Implants"[Mesh] OR "Dental implantation"[Mesh:NoExp] OR "Dental prosthesis, implant supported"[Mesh:NoExp]
AND
"immediate implant*"[tiab] OR "all on 4"[tiab] OR "all on four"[tiab] OR "teeth in an hour"[tiab] OR "teeth in a day"[tiab] OR "immediate loading"[tiab] OR "immediate function"[tiab] OR "immediate temporization"[tiab] OR "Immediate dental implant loading"[Mesh:NoExp]
AND
"quality of life"[tiab] OR "qol"[tiab] OR "OHRQoL"[tiab] OR "OHIP-14"[tiab] OR "HRQL"[tiab] OR "visual analog scale"[tiab] OR "visual analogue scale"[tiab] OR "VAS"[tiab] OR "patient centered"[tiab] OR "PCOR"[tiab] OR "patient preference*"[tiab] OR "patient satisfaction"[tiab] OR "patient reported"[tiab] OR "patient outcome*"[tiab] OR "treatment outcome*"[tiab] OR "restoration failure*"[tiab] OR "follow up studies"[tiab] OR "follow up study"[tiab] OR "comparative effectiveness research'"[tiab]
OR
"Quality of life"[Mesh] OR "Visual analog scale"[Mesh] OR "Patient outcome assessment"[Mesh:NoExp] OR "Patient centered research outcomes"[Mesh] OR "Patient Satisfaction"[Mesh] OR "Treatment Outcome"[Mesh] OR "Dental restoration failure"[Mesh] OR "Follow-up studies"[Mesh] OR "Patient reported outcome measures"[Mesh]
AND
Humans

Reference lists of relevant studies and systematic reviews published up to May 2017 were "hand-searched" for potential relevant literature.

2.3 | Study selection

The type of studies considered for this review included randomized controlled trials, prospective and retrospective cohort studies, and case series of at least five patients. The different components of the PICO questions served as the basis for study inclusion. The patient population comprised partially edentulous patients receiving immediate dental implants (Type 1). The tested intervention under scrutiny was immediate loading, that is, within 1 week of implant placement, while the comparison group entailed early (1 week to 2 months) or conventional loading (>2 months) as previously defined by the ITI (Gallucci et al., 2014) and others (Esposito, Grusovin, Willings, Coulthard, & Worthington, 2007). Studies reporting on PROMS as defined by the FDA were considered for inclusion (US Department of Health and Human Services, 2006). Moreover, the patient-centered outcomes had to be supported by presented data in the article.

Studies reporting on "All-on-4" protocol, as initially described by Malo and coworkers (Malo, Rangert, & Nobre, 2003, 2005), and full-arch restoration were excluded for the following reasons. First, it could not be ascertained that all the implants placed according to this protocol were immediate implants (Type 1). These treatment protocols are usually used in failing dentitions of partially edentulous patients. While the remaining failing dentition is extracted immediately prior to implant placement, some implants may have been placed in long-standing edentulous healed sites (Type 4). Second, the technique used for immediate implant placement in the all-on-4 protocol calls for the placement of tilted implants with a crossarch stabilization prosthetic reconstruction which differs drastically from the immediate load of implants placed in fresh extraction socket of partially edentulous sites. Third, the crossarch stabilization represents a different biomechanical entity compared to single or short span fixed dental prostheses. Finally, indications for full-arch restoration treatment usually include patients who have experienced a failing dentition over time, which is no longer satisfactory and a more drastic and permanent therapy is sought for. The impact of such treatment cannot be combined with that of implants placed in fresh extraction socket typically involving a limited number of teeth replaced which was the focus of this review.

Studies including zygomatic implants were excluded and publications in other languages than English, German, or French were not considered.

Two investigators (G.H-B. and T.W.O.) independently screened the literature search results for possible inclusion in the systematic review. The screening was performed at the title and abstract level. Any disagreement was resolved by discussion. The same two investigators independently read the full-text articles and consensus was reached by discussion in case of disagreement. Kappa statistics was used to determine interrater agreement (Cohen, 1960).

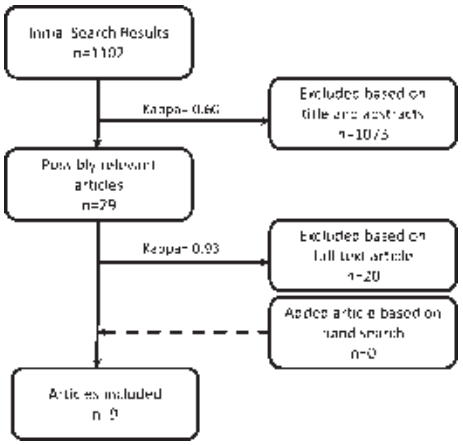

FIGURE 1 Search flow diagram

Data extraction table for included study was created and populated independently by the two investigators. Any disagreement was resolved by discussion.

3 | RESULTS

Final searches were run on 5/9/17 and resulted in 1,102 results following de-duplication. The screening of the abstracts led to the inclusion of 28 articles (k = 0.60 or "good agreement"). After evaluation of the full texts, 19 studies were excluded and a total of nine studies were included in the present systematic review (k = 0.93 or "very good agreement"). The hand search did not add any additional references (Figure 1). The reasons for exclusion of the full-text articles can be found in Table 1.

TABLE 1 Studies excluded based on full-text evaluation and reason for exclusion. *Reference list of systematic reviews were screened for other possible study inclusion

Study	Journal	Reason for exclusion
Abboud, Wahl, Guirado, and Orentlicher (2012)	The International Journal of Oral Maxillofacial Implants	No immediate implant placement
Andersen, Haanaes, and Knutsen (2002)	Clinical Oral Implants Research	No immediate implant placement
Atieh, Atieh, Payne, and Duncan (2009)*	The International Journal of Prosthodontics	Systematic review
Atieh, Payne, Duncan, de Silva, and Cullinan (2010)*	The International Journal of Oral Maxillofacial Implants	Systematic review
Barone et al. (2016)	The International Journal of Oral Maxillofacial Implants	No immediate loading
Benic et al. (2014)*	The International Journal of Oral Maxillofacial Implants	Systematic review
Bianchi and Sanfilippo (2004)	Clinical Oral Implants Research	No immediate loading
Boedeker, Dyer, and Kraut (2011)	Journal of Oral Maxillofacial Surgery	No immediate implant placement
Cosyn et al. (2011)	Journal of Clinical Periodontology	No patient-reported outcome measure
De Rouck et al. (2008a,2008b)	The International Journal of Oral Maxillofacial Implants	Review
Di Alberti et al. (2012)	The International Journal of Oral Maxillofacial Implants	No data presented to support patient satisfaction claims
Dolz, Silvestre and Montero (2014)	The International Journal of Oral Maxillofacial Implants	No immediate implant placement
Hui et al. (2001)	Clinical Implant Dentistry and Related Research	No data presented to support patient satisfaction claims
Grandi, Guazzi, Samarani, and Grandi (2013)	European Journal of Oral Implantology	No patient-reported outcome measure
Lang et al. (2007)	Clinical Oral Implants Research	No immediate loading
Malchiodi et al. (2010)	Journal of Oral Implantology	No patient-reported outcome measure
McAllister et al. (2012)	The International Journal of Oral Maxillofacial Implants	Same patient study population as Kolinski et al. (2014; which was included)
Rosa, Rosa, Francischone, and Sotto-Maior (2014)	The International Journal Prosthetic and Reconstructive Dentistry	No patient-reported outcome measure
Spies, Balmer, Patzelt, Vach, and Kohal (2015)	Journal of Dental Research	Less than 5 cases of Immediate implant placement

3.1 | Study characteristics

The data extracted from the included studies are detailed in Table 2. Of the nine included articles, three studies were randomized controlled trials (De Rouck, Collys, Wyn, & Cosyn, 2009; Felice, Pistilli, Barausse, Trullenque-Eriksson, & Esposito, 2015; Felice et al., 2011). However, only the study by De Rouck et al. (2009) included test and control groups similar to those defined in our PICO question. In the two publications by Felice et al. (2011, 2015), the test group received immediate implants (Type 1) following extraction while the control group was treated with a ridge preservation and a staged approach for implant placement (Type 4). Provided that the implant insertion torque was >35 Ncm, provisional implant restorations were placed in both treatment groups. Conversely, if the insertion torque was ≤35 Ncm, the implants were left to heal for 4 months before loading. For these two studies, only one treatment arm, that is, immediate implant placement (Type 1) with two subgroups based on nonrandomized loading protocol was considered for data extraction pertaining PROMS.

The remainder of the included studies (six studies) did not provide an adequate comparison group comprising of Type1 implant placement and conventional loading. Four of those were single-arm studies with Type 1 implant placement and immediate temporization (De Rouck, Collys, & Cosyn, 2008a, 2008b; Ferrara et al., 2006; Kolinski et al., 2014; Takeshita et al., 2015). Two studies by Raes, Cooper, Tarrida, Vandromme, and De Bruyn (2012), Raes, Cosyn, and De Bruyn (2013) were multiarms studies and only data from one arm consisting Type 1 implant placement and immediate temporization was extracted for the purpose of the present systematic review.

The PROMs reported included the use of visual analogue scale to determine patient satisfaction with regards to aesthetics (De Rouck et al., 2008a, 2008b, 2009; Kolinski et al., 2014), function, speech, sense of implant feeling like one's own and self-esteem (Kolinski et al., 2014). Other PROMs included the use of a 5-point categorical scale to evaluate function and aesthetic (Felice et al., 2011, 2015), a 10-point categorical scale to evaluate patient satisfaction (Ferrara et al., 2006), the use of close-ended questions (Felice et al., 2011,2015) and the use of Oral Health Impact Profile (OHIP) questionnaires consisting of 14 questions (Raes et al., 2012, 2013) or 54 questions specific for a Japanese population (Takeshita et al., 2015).

Three studies evaluated PROMs prior to and after treatment (Kolinski et al., 2014; Raes et al., 2012, 2013) while the remainder of the included studies only evaluated PROMs after treatment (De Rouck et al., 2008a,2008b, 2009; Felice et al., 2011, 2015; Ferrara et al., 2006; Takeshita et al., 2015). When evaluated after treatment, the timeline to report the PROMs varied between 4 months after implant placement (Felice et al., 2011) to 4 years after final crown delivery (Ferrara et al., 2006).

Given the heterogeneity in study design, in PROMs reported and time frame of reporting PROMS a qualitative review was undertaken.

3.2 | Patient-centered outcomes in studies with an available comparison group consisting of Type 1 implant placement with conventional loading

In the study by De Rouck et al. (2009), the test group received immediate implants and was restored with immediate screw-retained provisional crowns, whereas the implants in the control group were allowed to heal for 3 months before provisionalization. In both groups, final restorations were placed after 3 months of temporary loading. At the end of the study period, that is, 12 months after implant provisionalization, patients' satisfaction of the aesthetics based on a visual analog scale (from zero to ten) was recorded by asking the following question: "How would you rate your satisfaction with respect to the aesthetic outcome of your treatment?". Patients' satisfaction averaged 93% (range 82%–100%) in the test group and 91% (range 80%–96%) in the control group. Midfacial soft tissue level was stable in both groups over the study period. However, the conventionally loaded restoration group showed on average 2.5–3 times more recession as compared to the test group with a mean difference of 0.75 mm favoring immediate restoration.

Two randomized controlled trials by Felice et al. (2011, 2015) with similar methodology aimed at comparing the outcomes of immediate postextractive implants (Type 1) and implants placed in healed ridge preserved sites (Type 4). Only one arm of each study, that is, Type 1 implant placement, was within the scope of our review. In this arm, implants that were placed with an insertion torque >35 Ncm were immediately restored with a cemented provisional crown following an abutment level impression. If the torque was inferior to 35 Ncm implants were placed and left to heal for 4 months. Final cemented metal-ceramic crowns were fabricated on customized abutments 4 months after implant placement. In both studies, patients' satisfaction was recorded using a 5-point scale with regards to aesthetics and function. The questions asked were as follows: "Are you satisfied with your function of your implant-supported tooth?" and "Are you satisfied with the aesthetic outcome of the gums surrounding this implant?". For these questions, the possible answers were as follows: (a) Yes absolutely, (b) Yes partly, (c) Not sure, (d) Not really, and (e) Absolutely not. A third, close-ended question inquired if the patient would undergo the same therapy again. Felice et al. (2011, 2015) did not separate patients' responses within the immediate placement group between the implants with immediate restorations with those receiving conventionally loaded restorations. Felice et al. (2011) reported two failures in the immediate implant placement group but did not mention if they occurred in the immediately restored subgroup or the conventional loading subgroup. Nonetheless, data pertaining to patients' satisfaction were extrapolated based on the information provided in the respective studies. With regard to function, 88.2%–100% of the patients in the immediately restored subgroup answered that they were absolutely satisfied. The corresponding value for the conventional loading subgroup was 93.9%–100%. In the immediately and conventionally loaded subgroups, 0%–5.9% and 0%–3.0% of patients, respectively, were "partially satisfied" or

"unsure." For aesthetics, 100% of patients who received immediate implants answered that they were absolutely satisfied irrespective of the loading protocol. Similarly, 100% of patients stated that they would undergo the same therapy again.

3.3 | Patient-centered outcomes of studies reporting on Immediate implant placement (Type 1) and immediate loading

De Rouck et al. (2008a,2008b) followed thirty patients who received immediate implant placement and an immediate single crown screw-retained temporary restoration over a 1-year period. At the end of the study period (12 months after implant placement), patients were asked "How would you rate your satisfaction with respect to the aesthetic outcome of your treatment?" using a visual analogue scale (VAS) of 10 cm. The average satisfaction pertaining aesthetics average 93% with a range from 82% to 100%.

Ferrara et al. (2006) in a case series of 33 patients with a follow-up time up to 50 months (average 28 months) after immediate implant placement and restoration recorded patients' satisfaction using a 10-point categorical scale with the zero value corresponding to "completely unsatisfactory result" and 10 to "complete satisfaction." Patients were followed up every 3 months and satisfaction was recorded at each follow-up. No details pertaining the question asked were given in the study. The results reported an average patient satisfaction pertaining to aesthetics at the 4-year recall timeline of 9.3 ± 0.65, which included seven patients.

A 3-year multicenter case series by Kolinski et al. (2014), evaluated the following PROMs based on VAS: (a) Function, (b) Aesthetics, (c) Speech, (d) Sense of implant feeling like one's own tooth, and (e) Self-esteem.

The two extremities of the scale were 0 = poor and 100 = excellent. Kolinski et al. reported these PROMS prior to treatment, at time of implant placement, prosthesis delivery and then annually up to the 3-year follow-up visit. The mean pretreatment baseline value for function, aesthetics, speech, sense of implant feeling like one's own tooth and self-esteem were 62.2, 58.9, 80.0, 66.3 and 68.7, respectively. All the parameters increased gradually up to prosthesis delivery and remained stable throughout the study. The corresponding values at the 3-year follow-up were 93.7 ± 6.4, 89.2 ± 9.4, 93.5 ± 6.7, 87.0 ± 18.5 and 92.2 ± 7.2, which were statistically significantly different from baseline ($p < 0.001$).

Raes et al. (2012, 2013) conducted two multiarm clinical trials comparing the outcomes of Type 1 implant placement and immediate provisionalization to Type 4 implant placement and immediate provisionalization. The data for the single arm of interest, that is, Type 1 implant placement, were extracted. The assessment of PROMs was based on the shortened version of the original Oral Health Impact Profile (OHIP) questionnaire (Slade & Spencer, 1994). The questionnaire used included 14 questions (OHIP-14) with two questions assessing each of the seven dimensions including functional limitation, physical pain, psychological discomfort, physical disability, psychological disability, social disability, and handicap (Slade, 1997). Raes et al. (2012) reported that over a 1-year period, the overall OHIP-14 average score increased from baseline to 6 months and remained stable thereafter. More specifically, two dimensions, psychological discomfort and disability, decreased significantly from baseline to 1 month which indicated that patients were less self-conscious, felt less tense, found it less difficult to relax, and were more relaxed with regard to their oral condition. The physical pain dimension decreased from the 1-month to the 6-month follow-up illustrating that the patient experienced less pain and could eat comfortably.

Similarly, Raes et al. (2013) showed that the overall OHIP-14 score increased from baseline (66.25 ± 3.86) to 12 months (69.67 ± 0.62) in patients receiving immediate implant and immediate provisionalization in the aesthetic anterior maxilla (teeth 15–25).

In a retrospective study, Takeshita et al. (2015) used a modified OHIP questionnaire specifically adapted to Japanese populations with 54 questions (Yamazaki, Inukai, Baba, & John, 2007) to report on patient satisfaction. The authors converted the overall OHIP-J scores recorded into percentage of satisfaction. One year and a half after immediate implant placement and provisionalization, the reported satisfaction rate amounted to 96.7% ± 2.16 (92.6%–100%).

4 | DISCUSSION

The present systematic review sought to answer the following question: In patients receiving immediate (Type 1) implant placement, how does immediate compare to early or conventional loading in terms of patient-reported outcomes? The relevance of this question is based on the fact that there is no clinical consensus as to which treatment protocol should be favored (Gallucci et al., 2014; Morton et al., 2014).

In the medical field, patient-centered outcome research is fairly new and is focusing on valuating questions and outcomes that are important to the end-user of the research, that is, the patient. The patients' views through this research are voiced and reduces the imbalance represented in more traditional research in which the views of the empowered, the physicians and researchers, are mostly expressed. This is performed with the premise that improving the relevance of clinical research by incorporating PROMs and thereby helping disseminate new evidence will ultimately improve patient care (Frank, Basch, & Selby, 2014). The growing importance of this type of research is illustrated by a federal initiative to create the Patient-Centered Outcomes Research Institute which goals are to improve the quantity and quality of research, facilitate its dissemination and implementation with a patient-centered approach as the overarching concept (Selby & Lipstein, 2014, https://www.pcori.org/about-us accessed on 9/15/17).

In the field of implant dentistry, despite the fact that multiple consensus conferences and workshops have recommended the inclusion on patient-centered outcomes to evaluate therapy (Albrektsson & Isidor, 1994; Klinge et al., 2015; Lang, Karring, & Meredith, 2002; Lang & Zitzmann, 2012), patient-centered outcomes have only rarely been reported in the literature (Pjetursson, Karoussis, Burgin, Bragger, & Lang, 2005).

TABLE 2 Data extraction table of included studies. [In PDF format, this table is best viewed in two-page mode]

Authors (year)	Journal	Study type	Duration	Patients (*n*)	Gender	Patient age (Mean (±*SD*), range)	Treatment group(s)	Implants (*n*)	Implant site(s)
De Rouck et al. (2009)	COIR	Multicenter Randomized Controlled Trial	1 year	Group 1: 24 Group 2: 25	Group 1: 13 females 11 males Group 2: 13 females 12 males	Group 1: 55 ± 13 Group 2: 52 ± 12	Group 1: Type 1 Implant placement Immediate provisionalization Group 2: Type 1 Implant placement and delayed loading	Group 1: 24 Group 2: 25	15–25
Felice et al. (2011)	Eur J Oral Impl	Single Center Randomized Controlled Trial	4 months	Group 1: 54 Group 2: 52	32 females 22 males	Mean 48 (28–70)	Group 1: Type 1 Implant placement + Immediate provisionalization (if insertion torque >35 Ncm) and Delayed loading (at 4 months if insertion torque was ≤35 Ncm) Group2: Ridge preservation + Type 4 Implant placement + Immediate provisionalization (if insertion torque >35 Ncm)	Group 1: 54 Group 2: 52	15–25
Felice et al. (2015)	Eur J Oral Impl	Randomized Controlled Trial	1 year	Group 1: 25 Group 2: 25	Group 1: 13 females 12 males Group 2: 12 females 13 males	Group 1: 51.3 (32–71) Group 2: 53.1 (39–72)	Group 1: Type 1 Implant placement + Immediate provisionalization (if insertion torque >35 Ncm) and Delayed loading (at 4 months if insertion torque was ≤35 Ncm) Group2: Ridge preservation + Type 4 Implant placement + Immediate provisionalization (if insertion torque >35 Ncm)	Group 1: 25 Group 2: 25	15–25

(Continues)

TABLE 2 (additional columns)

Implant manufaturer	Implant insertion torque	Provisional restorations	Occlusion of provisional	Final restoration	Follow-up	Patient-centered outcomes	Comments
Nobel	At least 35 Ncm	Screw-retained provsional single crown	Cleared of centric and eccentric contacts	At 6 months after implant placement with cemented restoration	3, 6, 12 months	At the end of study period (12 months after implant provisionalization), patients were asked "How would you rate your satisfaction with respect to the aesthetic outcome of your treatment?" using an Visual analogue scale of 10 cm. 0 = not at all satisfied 10 = completely satisfied Group 1: Average 93% (range 82%–100%) Group 2: Average 91% (range 80%–96%)	
MegaGen	>35 Ncm (In Group 1: 19 of 54 were immediately provisionalized and 35 of 54 received delayed loading)	Cemented provisional single crown on temporary abutment	Non-occluding	4 months after implant placement with provisionally cemented crown on customized abutment	Final crown delivery, i.e. 4 months after loading	Patient satisfaction was recorded at the time of final crown delivery with regards to: 1) Function: "Are you satisfied with your function of your implant-supported tooth?" 2) Aesthetic:"Are you satisfied with the aesthetic outcome of the gums surrounding this implant?" Possible answers were: a)yes absolutely, b) Yes partly, c)not sure, d) not really and e)absolutely not 3) Another question (closed-ended question): "Would you undergo the same therapy again?" For function: Group 1 with immediate temporization: 88.2%–100% were "absolutely satisfied", 0%–5.9% were "partially satisfied"and 0%–5.9% were "unsure" Group 1 with delayed loading: 93.9%–100% were "absolutely satisfied", 0%–3.0% were "partially satisfied" and 0%–3.0% were "unsure" 100% of patients were "absolutely satisfied" with aesthetic and 100% would undergo the same therapy again	Patient-centered outcomes extracted only for one arm (Type 1 Implant placement). Two implants failed in Group 1. Details not given if the two implants were immediate or delayed loaded implants. *Patient satisfaction range extrapolated from data available in study.
Dentsply	>35 Ncm (In Group 1: 16 of 25 were immediately provisionalized and 9 of 25 received delayed loading)	Cemented provisional single crown on temporary abutment	Absence of contact in static and dynamic occlusion	4 months after implant placement	6 months and 1 year	Patient satisfaction was recorded at time of final crown delivery and 12 months after with regards to: 1) Function: "Are you satisfied with your function of your implant-supported tooth?" 2) Aesthetic:"Are you satisfied with the aesthetic outcome of the gums surrounding this implant?" Possible answers were: a) yes absolutely, b) Yes partly, c)not sure, d) not really and e) absolutely not 3) Another question (closed-ended question): "Would you undergo the same therapy again?" 100% of patients were "absolutely satisfied" with function and aesthetic and 100% would undergo the same therapy again	Patient-centered outcomes extracted only for one arm (Type 1 Implant placement)

(Continues)

TABLE 2 (Continued) [In PDF format, this table is best viewed in two-page mode]

Authors (year)	Journal	Study type	Duration	Patients (*n*)	Gender	Patient age (Mean (±*SD*), range)	Treatment group(s)	Implants (*n*)	Implant site(s)
De Rouck et al. (2008a, 2008b)	JCP	Case series	1 year	30	16 females 14 males	Mean 54 (24–76)	Group 1: Type 1 Implant placement Immediate provisionalization	30	15–25
Ferrara et al. (2006)	IJPRD	Case series	Up to 50 months. Average: 28 months	33	17 females 16 males	24–58	Group 1: Type 1 Implant placement Immediate provisionalization	33	14–24
Kolinski et al. (2014)	J Perio	Multicenter case series	3 years	55	31 females 24 males	52.6 ± 13.3 (19–82)	Group 1: Type 1 Implant placement Immediate provisionalization	60	3 Molars 26 Premolars 31 Maxillary anterior
Raes et al. (2012)	COIR	Prospective Multicenter Case-control study	1 year	96 Group 1: 46 Group 2: 54	55 females 41 males	42 ± 14.8 (18–72)	Group1: Type 1 Implant placement Immediate-provisionalization Group 2: Type 4 Implant placement Immediate provisionalization	Group 1: 48 Group 2: 54	15–25

(Continues)

TABLE 2 (additional columns - continued)

Implant manufaturer	Implant insertion torque	Provisional restorations	Occlusion of provisional	Final restoration	Follow-up	Patient-centered outcomes	Comments
Nobel	At least 35 Ncm	Screw-retained provsional single crown	Cleared of centric and eccentric contacts	At 6 months after implant placement with cemented restoration	1, 3, 6, 12 months	At the end of study period (12 months after implant placement), patients were asked "How would you rate your satisfaction with respect to the aesthetic outcome of your treatment?" using an Visual analogue scale of 10 cm. 0 = not at all satisfied 10 = completely satisfied Average 93% (range 82%–100%)	
Friadent	Not reported	Cemented provisional single crown on temporary abutment	No contact in maximum intercuspation and eccentric movement	At 6 months after implant placement with cemented restoration	Once a month for the first 6 months and every 3 months thereafter up to 4 years	Patient satisfaction was recorded at each follow-up (3-month recall visit) using a 10-point scale (0 = completely unsatisfactory result; 10 = complete satisfaction) Average at 4-year recall: 9.3 ± 0.65 (ecompassing 7 patients)	
Nobel	At least 35 Ncm	58 implants with single crowns 2 implants for an FDP (lost to follow-up at 3 years examination)	Temporary restoration in light or no contact with opposing dentition	Within 6 months of implant placement	3, 6 months 1, 2, 3 years	Aesthetic and function of restoration evaluated by patients at baseline (i.e. prior to treatment), implant placement, definitive prosthesis insertion, and at 1-, 2-, 3-year follow-up. VAS was used: 0 = poor, 100 = excellent Pre-operative/Baseline: Function: 62.2 Aesthetics: 58.9 Speech: 80.0 Sense of implant feeling like one's own tooth: 66.3 Self-esteem: 68.7 3-y follow-up: Function: 93.7 ± 6.4 Aesthetics: 89.2 ± 9.4 Speech: 93.5 ± 6.7 Sense of implant feeling like one's own tooth: 87.0 ± 18.5 Self-esteem: 92.2 ± 7.2 All scores increased significantly from baseline to 3-y follow-up visit ($p < 0.001$)	
Astra	Not reported	Cemented provisional single crown on temporary abutment	Not reported	At 10 weeks	Baseline, 1, 6, 12 months	OHIP-14 questionnaire ((14 questions, Scores 1–5 for a maximum of 70) for Group 1 recorded at all time points: Overall, imited oral health-related quality of life problems were reported (because they were never toothless) by these patients. Patients described a significant decrease in3 domains: Physical pain, Psychological discomfort and Psychological disablitity. Patient-reported less pain and tension, were less occupied with their teeth, were able to eat comfortably and relax over time and were less embarrassed. These improvement were mainly seen the first six months.	-Patient centered outcomes extracted only for one arm (Type 1 Implant placement)

(Continues)

TABLE 2 (Continued) [In PDF format, this table is best viewed in two-page mode]

Authors (year)	Journal	Study type	Duration	Patients (*n*)	Gender	Patient age (Mean (±*SD*), range)	Treatment group(s)	Implants (*n*)	Implant site(s)
Raes et al. (2013)	CIDRR	Prospective 3-arm clinical trial	1 year	48 Group 1: 16 Group 2: 9 Group 3: 23	21 females 27 males Group 1: 16, 6 females, 10 males Group 2: 9, 4 females, 5 males Group 3: 23, 11 females, 12 males	Group 1: 45 ± 14 (22–68) Group 2: 35 ± 15 (20–69) Group 3: 40 ± 19 (19–75)	Group1: Type 1 Implant placement Immediate-provisionalization Group 2: GBR at time of extraction, Type 4 Implant placement Immediate provisional-ization Group 3: Type 4 Implant placement Immediate provisionalization	Group 1: 16 Group 2: 9 Group 3: 23	15–25
Takeshita et al. (2015)	IJPRD	Retrospective case series	1.5 year	18	12 females 6 males	48 ± 11 (32–77)	Group 1: Type 1 Implant placement Immediate-provisionalization	21	12–22

Given the general sense that PROMs tend to be underreported for clinical situations other than two implants supporting a mandibular overdenture (De Bruyn et al., 2015) and in an effort to capture all relevant data present in the literature, the present systematic review did not chose a specific PROM as an inclusion factor to address the PICO question. This led to the inclusion of a total of nine studies using different PROMs. Only one randomized controlled trial addressed specifically the PICO question (De Rouck et al., 2009) and two further randomized controlled trials included data for both immediate and conventional loading following type 1 implant placement within the same treatment arm (Felice et al., 2011, 2015). The loading protocol was not randomized and was based on the implant placement insertion torque. Therefore, the studies by Felice et al. (2011, 2015) had to be viewed as nonrandomized for the purpose of this review. The remaining studies only included the test intervention of interest as the sole treatment investigated (De Rouck et al., 2008a,2008b; Ferrara et al., 2006; Kolinski et al., 2014; Takeshita et al., 2015) or as part of a multiarm trial in which the other treatment arms were outside the scope of the present work (Raes et al., 2012, 2012). Therefore, the majority of the included studies (six of nine) were single cohort uncontrolled studies.

All studies included in the present review reported exclusively on single tooth implant-supported restoration except for Kolinski et al. (2014). In this study, the authors reported the outcomes of 60 implants up to 3 years. Of the 60 implants placed, 58 were placed for single tooth restorations while two were placed to support a fixed dental prosthesis (FDP). Ideally, for the purpose of the present review, data related to the two implants supporting the FDP should be excluded. Unfortunately, the report by Kolinski et al., 2014 did not discriminate the outcomes based on the restorative indication, hampering the author's ability to extract the data for single tooth restorations only. Nonetheless, the authors decided to keep the study by Kolinski et al. (2014) and to report their findings based on the following rationale:

1. At baseline, the PROMs from the one patient who received immediate implants for an FDP out of a total of 55 patients was unlikely to significantly change the reported values for the overall cohort.
2. At the 3-year follow-up examination, 37 patients with 37 implants were evaluated, indicating that the patient with the two implants supported FDP had been lost to follow-up. Therefore, the PROMs reported at the 3-year timeline only included data from implant-supported single tooth restorations.
3. As a qualitative review was undertaken, the authors felt that including the study by Kolinski et al., 2014 which had the longest follow-up of all included studies would add useful information to the review which would outweigh the fact that the baseline data included a single patient who received two implants for an FDP when the remaining data included in this review only included single tooth restorations.

For data derived from controlled trials, combining results of randomized and nonrandomized controlled trials has been questioned as it has been shown that results of nonrandomized controlled trials tended to show greater treatment effects than randomized controlled trials (Ioannidis et al., 2001). While newer Network Meta-analysis may overcome this shortcoming (Cameron et al., 2015), two different sets of PROMs were used in the three comparative studies preventing pooling of the data and meaningful comparison between studies. Another shortcoming of these comparative trials was the fact that only one time point after treatment was considered for recording the PROMs

TABLE 2 (additional columns - continued)

Implant manufaturer	Implant insertion torque	Provisional restorations	Occlusion of provisional	Final restoration	Follow-up	Patient-centered outcomes	Comments
Astra	Not reported	Cemented provisional single crown on temporary abutment	Absence of centric and eccentric contacts	11–12 weeks after implant placement	Baseline, 1, 3, 6, 12 months	Based on OHIP-14 questionnaire (14 questions, Scores 1–5 for a maximum of 70) for group 1: There was a signifcant improvement in overall OHIP-14 score from baseline (66.25 ± 3.86) to 12 months (69.67 ± 0.62)	Patient-centered outcomes extracted only for one arm (Type 1 Implant placement)
Dentsply	At least 35 Ncm	Cemented provisional single crown on temporary abutment	Temporary restoration placed slightly of occlusal contact	14 weeks after implant placement	1.5 year	Based on OHIP-J (Japanese version of Oral Health Impact Profile = 49 + 5 = 54 questions, Scores 1–4, for a maximum of 216). Scores was converted in % satisfaction. Satisfaction based on OHIP-J: 96.7% ± 2.16 (92.6%–100%)	

which limited the prospective evaluation of the treatment benefits. These shortcomings were already mentioned in previous reviews (De Bruyn et al., 2015; McGrath, Lam, & Lang, 2012). Nonetheless, these studies indicated little to no difference in patient satisfaction following the two different loading protocols following immediate implant. This was irrespective of the PROMs reported which included a VAS for aesthetic satisfaction, a 5-point scale assessing function, aesthetics, and open-ended questions placement.

From the uncontrolled studies, overall patient satisfaction was high following immediate implant placement and loading. Three studies (Kolinski et al., 2014; Raes et al., 2012, 2013) reported PROMs with a baseline evaluation prior to treatment up to 1 year (Raes et al., 2012, 2013) or 3 years (Kolinski et al., 2014) after treatment. The impact of treatment could be objectified by the significant increase in the VAS scores pertaining to function, aesthetic, speech, sense of the implant feeling like one's own, and self-esteem (Kolinski et al., 2014) and by the improvement of oral health-related quality of life as measured by the OHIP-14 (Raes et al., 2012, 2013). While this information is valuable to demonstrate the positive impact of Type1 implant placement and immediate provisionalization, no clinical recommendation can be made pertaining the timing of loading as only one protocol was implemented. The psychometric properties of OHIP-14 have been well documented and the questionnaire has been validated to evaluate the outcome of clinical interventions (Allen, 2003; Slade, 1997). OHIP questionnaires presented the advantage to be standardized in comparison with other patient satisfaction questionnaires, for example, using VAS or categorical scales, which lacked standardization across studies and, thereby, hampered the ability to make any meaningful comparison between studies.

Given the sense of relative paucity of PROMs reported in the literature, the authors wanted to be as inclusive as possible and the scope encompassed all types of partial edentulism treated with either single or multiple tooth implant-supported restorations. However, the included studies reported almost exclusively on single tooth restorations. Therefore, the findings in the present review may not be extended to implant-supported fixed dental prostheses (FDPs) replacing multiple teeth. This maybe further supported by the fact that in clinical settings, the technical approach for immediate loading in extended tooth gaps may be more challenging as compared to single tooth restorations. Adjustment of the occlusion to limit the amount of forces in immediate loading situations, including full to the absence of contacts in centric and absence of excursive contacts have been reported (Schrott, Riggi-Heiniger, Maruo, & Gallucci, 2014). This may be more readily achievable for single tooth restorations as compared to longer span implant-supported FDPs. Finally, the clinical guidelines derived from the previous ITI consensus conference (Gallucci et al., 2014) recommended that immediate loading of single tooth restoration can be successfully implemented for all area except for maxillary molar regions which lacked solid scientific backup. For immediate loading of implant-supported FDPs the recommendations emphasized careful case selection and advanced clinical expertise, especially for anterior sites for which insufficient documentation had been identified. These clinical recommendations emphasize the fact that outcomes of immediate loading in single tooth sites and multiple tooth sites have to be reported separately.

A further limitation of the available literature resides in the multitude of factors likely to influence the assessment of subjective outcomes and the limited ability of the existing studies to control for confounders.

In conclusion, and within the limitations of the available literature, immediate implant placement and loading in single tooth edentulous space seemed to positively impact patients oral health-related quality of life as this therapeutic approach remains worthy of consideration in patient care. However, the paucity of comparative data limits any definitive conclusions as to which loading protocol; immediate or early/conventional, should be given preference based on PROMs.

5 | CONSIDERATION FOR FUTURE RESEARCH

There is little discussion that incorporating the patient in the decision making process of their treatment may positively impact the outcome of therapy. This underlines the importance of incorporating PROMs in clinical research. While the trend is encouraging with more studies including PROMs being published, limitations in the present review have been previously mentioned in other reports (De Bruyn et al., 2015; Lang & Zitzmann, 2012).

To overcome them the following suggestions are made:

- Evaluation of PROMs should be evidence-based tools that have been previously validated, for example, OHIP.
- Evaluation of PROMs should include at the very least two time points: a baseline, that is, prior to treatment, and a posttherapeutic assessment to allow the prospective evaluation of treatment benefit.
- Ideally, multiple assessments are desirable to potentially discriminate short-term vs long-term benefits of treatment.

Moreover, further well-controlled randomized trials are needed to possibly determine the standard of care with regard to loading protocols based on clinical and patient-reported outcome measures.

CONFLICTS OF INTEREST

No conflicts of interest are declared.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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CONSENSUS REPORT

WILEY CLINICAL ORAL IMPLANTS RESEARCH

Group 3 ITI Consensus Report: Patient-reported outcome measures associated with implant dentistry

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Abstract

Objectives: The aim of Working Group 3 was to focus on three topics that were assessed using patient-reported outcome measures (PROMs). These topics included the following: (a) the aesthetics of tooth and implant-supported fixed dental prostheses focusing on partially edentulous patients, (b) a comparison of fixed and removable implant-retained prostheses for edentulous populations, and (c) immediate versus early/conventional loading of immediately placed implants in partially edentate patients. PROMs include ratings of satisfaction and oral health-related quality of life (QHRQoL), as well as other indicators, that is, pain, general health-related quality of life (e.g., SF-36).

Materials and methods: The Consensus Conference Group 3 participants discussed the findings of the three systematic review manuscripts. Following comprehensive discussions, participants developed consensus statements and recommendations that were then discussed in larger plenary sessions. Following this, any necessary modifications were made and approved.

Results: Patients were very satisfied with the aesthetics of implant-supported fixed dental prostheses and the surrounding mucosa. Implant neck design, restorative material, or use of a provisional restoration did not influence patients' ratings. Edentulous patients highly rate both removable and fixed implant-supported prostheses. However, they rate their ability to maintain their oral hygiene significantly higher with the removable prosthesis. Both immediate provisionalization and conventional loading receive positive patient-reported outcomes.

Conclusions: Patient-reported outcome measures should be gathered in every clinical study in which the outcomes of oral rehabilitation with dental implants are investigated. PROMs, such as patients' satisfaction and QHRQoL, should supplement other clinical parameters in our clinical definition of success.

KEYWORDS
clinical research, clinical trials, patient-centered outcomes, prosthodontics, systematic reviews

INTRODUCTION

The objectives of Group 3 of the 6th ITI Consensus Conference were to provide statements and recommendations for clinicians and researchers relating to patient-reported outcome measures (PROMs). Three systematic reviews on different topics were carried out in which implant prostheses were assessed by patients using PROMs. Each review was written up as manuscript. Group 3 met to discuss the results of each review; consensus statements and clinical recommendations stemming from each review were then discussed and agreed upon, then presented to a plenary session for discussion and final agreement.

The three systematic reviews are as follows:

1. Patient-reported outcome measures focusing on aesthetics of implant- and tooth-supported fixed dental prostheses: A systematic review and meta-analysis
   Julia G. Wittneben, Daniel Wismeijer, Urs Brägger, Tim Joda, Samir Abou-Ayash
2. Patient-reported outcome measures of edentulous patients restored with implant-supported removable and fixed prostheses: A systematic review
   Coral J. Yao, Cong Cao, Michael M. Bornstein, Nikos Mattheos
3. Immediate loading vs. early/conventional loading of immediately placed implants in partially edentulous patients from the patients' perspective: A systematic review.
   Guy Huynh-Ba, Thomas W. Oates, Mary Ann H. Williams

1 | REVIEW

1. Patient-reported outcome measures focusing on aesthetics of implant- and tooth-supported fixed dental prostheses: A systematic review and meta-analysis. Wittneben et al. (2018).

1.1 | Preamble

The aim of this review was to summarize the existing evidence on the aesthetic outcome of implant-supported and tooth-supported fixed dental prostheses (FDPs) in partially edentulous patients according to PROMs. Secondary outcomes were to analyze the influence of restorative material, implant neck design, and the implementation of a provisional phase focusing on PROMs.

In all, 16 publications on implant-supported FDPs, including 19 relevant study cohorts, were identified and met the review inclusion criteria. No publications on tooth-supported FDPs met the inclusion criteria; thus, a comparison could not be performed. However, the group was able to produce consensus statements and clinical recommendations from the studies on implant-supported FDPs.

1.2 | Consensus statements

1.2.1 | Consensus statement 1

The aesthetics of implant-supported FDPs are highly rated by patients (VAS 90; 95%CI: 87.9–92.2).

**This statement was supported by: two RCTs, eight prospective cohort studies, four retrospective studies and two cross-sectional studies, including 867 patients in total.*

1.2.2 | Consensus statement 2

Mucosal aesthetics of implant supported FDPs are highly rated by patients (VAS 87; min. 73–max. 92).

**This statement was supported by: one RCT, three prospective cohort studies and one cross-sectional studies, including 315 patients in total.*

1.2.3 | Consensus statement 3

Implant neck design, that is, tissue or bone level, has no influence on patients' ratings of aesthetics: VAS 93 (95% CI: 89–96) versus VAS 89 (95% CI: 86–92)

**This statement was supported by: two RCTs, five prospective cohort studies and two cross-sectional studies, including 443 patients in total.*

1.2.4 | Consensus statement 4

Individual restorative materials have no influence on patient ratings of the aesthetics of implant supported FDPs.

**This statement was supported by: two RCTs, five prospective cohort studies, two retrospective studies and two cross-sectional studies, including 556 patients in total.*

1.2.5 | Consensus statement 5

The use of a provisional restoration had no effect on patients' ratings of the aesthetics of definitive restorations on implant supported FDPs.

**This statement was supported by: two RCTs, five prospective cohort studies and two cross-sectional studies, including 359 patients in total.*

1.2.6 | Consensus statement 6

No studies were found that reported on PROMs for tooth-supported FDPs in partially edentulous patients.

1.3 | Clinical Recommendations

1.3.1 | Can we satisfy the patient's aesthetic concerns with implant-supported fixed dental prostheses (FDPs)?

It is possible to achieve high patient satisfaction with aesthetics. It is also possible to achieve highly rated mucosal aesthetics around implants. Hence, implant-supported FDPs can be recommended.

**Based on consensus statements 1 and 2*

1.3.2 | Does the selection of tissue or bone level implants influence the patient's perception regarding aesthetics?

The individual implant choice of implant-supported FDPs has no influence on ratings of aesthetics. Therefore, the choice of implant type supporting FDPs should be based on factors other than patient ratings of aesthetics.

**Based on consensus statement 3.*

1.3.3 | Does the restorative material have an impact on the patient's perception regarding the aesthetic outcome?

The type of restorative material used in implant-supported FDPs did not influence patient ratings of aesthetics. Therefore, the choice of restorative material for implant-supported FDPs should not be based on PROMs.

**Based on consensus statement 4.*

1.3.4 | Do patients perceive an added benefit on the final aesthetic result when a provisional is used for an implant supported FDP?

The choice of implementation of a fixed implant-supported provisional should not be only based on PROMs. Regardless, according to the 2014 ITI Consensus Statement, the use of provisional implant-retained restorations in the aesthetic zone is recommended.

**Based on consensus statement 5*

1.4 | Recommendations for future research

1. Standardized reliable and valid questionnaires with similar scoring methods should be used.

2. Patient ratings should be collected without influence from the clinician performing the treatment.

2 | REVIEW

Patient-reported outcome measures of edentulous patients restored with implant-supported removable and fixed prostheses: A systematic review. Yao et al. (2018).

2.1 | Preamble

The aim of this review was to summarize the scientific evidence on implant supported removable and fixed prostheses for edentulous populations and to compare Patient-Reported Outcome Measures such as satisfaction, impact of prosthesis on oral health-related quality of life or any other PROMs reported within this field. In all, 13 studies met the inclusion criteria. Most studies reported different measures of patients' satisfaction and oral health-related quality of life PROMs. However, due to lack of standardization and high heterogeneity, no meta-analysis or collective quantitative analysis of the results was possible. On the basis of the existing evidence on all studied parameters, neither prosthetic design—fixed or removable—was rated by patients as consistently superior, with the exception of the ability to practice oral hygiene, which is perceived by patients to be superior with removable implant supported prostheses.

2.2 | Consensus Statements

2.2.1 | Consensus statement 1

PROMs are not commonly used in clinical implant research. There are currently no guidelines on what PROMs are most appropriate for implant dentistry.

**This statement was based on 13 investigations, including one RCT, seven prospective and five retrospective studies.*

2.2.2 | Consensus statement 2

The timing of PROMs assessment in the literature is inconsistent and often limited to one time point.

**This statement was based on 13 investigations, including one RCT, seven prospective and five retrospective studies.*

2.2.3 | Consensus statement 3

Reporting of patients' characteristics and sampling techniques in PROMs research is inadequate, which could limit the ability to draw conclusions in implant dentistry.

**This statement was based on 13 investigations, including one RCT, seven prospective and five retrospective studies.*

2.2.4 | Consensus statement 4

There are no differences in PROMs between Implant supported Overdentures (IOD) and Implant-supported Fixed Complete Dentures (IFCD), except for perceived maintenance of oral hygiene, which is rated higher with IODs.

**This statement was based on 13 investigations, including one RCT, seven prospective and five retrospective studies. The oral hygiene superiority of IOD is based on five investigations, including one RCT, three prospective and one retrospective studies.*

2.3 | Clinical Recommendations

2.3.1 | Should PROMs supplement clinical implant patient care?

Patient perceptions of psychosocial state, functional limitation, pain and discomfort, and expectations should be assessed before implant treatment. Clinicians are advised to use PROMs when assessing clinical outcomes.

**Based on Consensus statement 1*

2.3.2 | Should the assessment of PROMs be conducted prospectively?

Before implant treatment, a baseline assessment of patient perception of oral health-related quality of life and satisfaction should be recorded.

After treatment completion, the assessment of PROMs should be conducted prospectively at appropriate intervals, case dependent.

**Based on Consensus statement 2.*

2.3.3 | Based on PROMs, should clinicians rehabilitate fully edentulous patients with Implant-supported Overdentures (IOD) or Implant-supported Fixed Complete Dentures (IFCD)?

The decision of whether to rehabilitate a patient with fixed or removable implant prostheses cannot be based solely on PROMs. Such decisions should be guided by the specific anatomy, clinical parameters, as well as the patient's needs and wishes.

In cases in which either treatment is feasible, proper assessment of patients' expectations and desires before treatment is critical prior to deciding between fixed or removable prosthesis.

**Based on Consensus statement 4*

2.3.4 | Do patients perceive differences in their ability to maintain oral hygiene with IFCDs and IODs?

Patients report that it is easier for them to maintain oral hygiene with an implant overdenture (IOD) than with an implant fixed conventional denture (IFCD); therefore, the IOD may be preferable for certain patients.

*Based on Consensus statement 4

2.4 | Recommendations for future Research

1. More well-designed studies are needed to be able to statistically compare the ratings of PROMs for implant fixed complete dentures (IFCDs) and implant overdenture (IOD) treatment are needed.
2. Guidelines for assessing PROMs in clinical research are needed to help clinical researchers select the most appropriate outcomes and measurement instruments.
3. The use of standard PROMs instruments in every relevant well-designed study will enable more powerful and useful analytic approaches.

3 | REVIEW

Immediate loading vs. early/conventional loading of immediately placed implants in partially edentulous patients from the patients' perspective: A systematic review. Huynh-Ba et al. (2018).

3.1 | Preamble

The aim of this review was to summarize the scientific evidence on immediate and early/conventional loading of immediately placed implants and to compare them according to the results of patient-reported outcomes of satisfaction, quality of life, and other aspects of treatment. Nine studies were identified and met the selection criteria. However, due to the small number of studies and the heterogeneity of the data, a meta-analysis could not be carried out. Regardless, patient satisfaction ratings were high for both loading strategies, and both resulted in improvement in OHRQoL scores.

3.2 | Consensus statements

3.2.1 | Consensus statement 1

From the patient's perspective, there is no difference between immediate provisionalization and conventional loading. Both treatment modalities can achieve similar positive patient-reported outcomes.

This statement was based on: one RCT and two controlled clinical trials.

3.2.2 | Consensus statement 2

Based on PROMs, no evidence was found to address early loading of immediately placed implants.

This statement was based on the fact that no study was identified reporting on early loading of immediately placed implants.

3.2.3 | Consensus statement 3

Positive patient-reported outcomes can be achieved following immediate implant placement with immediate provisionalization in a single edentulous space in maxillary anterior and premolar sites.

From an occlusion standpoint, most studies reported immediate provisional restoration with no contact in centric occlusion or eccentric movement.

This statement was based on: one RCT, two controlled clinical trials and five single cohort studies.

3.2.4 | Consensus statement 4

The placement of an immediate implant-supported provisional restoration demonstrated a significant improvement in OHIP-14 score.

This statement is based on two single cohort studies

3.2.5 | Consensus statement 5

From the patient's perspective, the outcome of immediate implant-supported provisional restorations in contiguous edentulous spaces has yet to be determined.

This statement was based on the fact that no study was identified reporting PROMS for contiguous edentulous spaces.

3.2.6 | Consensus statement 6

Limited evidence is available to support immediate provisionalization based on PROMs.

This statement is based on the fact that only a third of the studies used standardized and validated tools to report PROMs.

3.3 | Clinical recommendations

3.3.1 | Based on patients' perspectives, what loading protocol can be recommended following immediate implant placement in single edentulous spaces?

Both immediate provisionalization and conventional loading can be recommended to provide patient benefit. Clinicians' preferences, expertise, specific case- and patient-related factors should be included to make this determination.

This is based on Consensus statements 1 and 4.

3.3.2 | When immediate provisionalization of immediately placed implants in single edentulous spaces is chosen, what occlusal scheme should be favoured?

Positive patient ratings have been associated with immediate provisional restoration having no contact in centric occlusion and eccentric movements. Therefore, the clinical recommendation is to

have no contact in centric occlusion and eccentric movements for immediate implant-supported provisional restorations.

**This is based on Consensus statement 3.*

3.4 | Recommendations for future research

- The choice of which PROMs to use should be restricted to those most appropriate for the study question that have been previously validated.
- At a minimum, PROMs data should be gathered at 2 time points: at baseline and at a designated point post-treatment. Ideally, multiple assessments are desirable to discriminate short-versus long-term treatment effects.
- More well-controlled randomized trials are needed to determine the appropriate standard of care with regard to loading protocols based on clinical and patient-reported outcome measures.

CONCLUSIONS

Understanding how patients respond to implant treatment is essential. The use of patient-reported outcome measures can provide the patient perspective for both practice and research objectives. The results of these reviews, in which patient-reported outcome measures were used, have provided evidence to assist clinicians when planning treatment and discussing therapeutic options with their implant patients.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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REVIEW ARTICLE

WILEY CLINICAL ORAL IMPLANTS RESEARCH

The diagnosis of peri-implantitis: A systematic review on the predictive value of bleeding on probing

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Abstract

Objectives: Bleeding on gentle probing (BOP) is the key parameter to the diagnosis of mucositis, while changes in crestal bone levels, along with clinical signs of inflammation, are required for the diagnosis of peri-implantitis. This systematic review and meta-analysis focused on the evaluation of BOP as a predictive measure for peri-implantitis.

Materials and methods: An electronic search was performed through Medline and EMBASE databases, followed by a hand search through previous reviews and reference lists. Screening, study selection, data extraction and evaluation of publication bias were conducted by two independent examiners. Clinical studies reporting on the prevalence of peri-implantitis, BOP and/or suppuration (SUP) after more than 1 year of functional loading were selected. Meta-analyses were conducted to combine the proportions of peri-implantitis among BOP- and/or SUP-positive subjects and implants across studies. Subgroups were created and compared to investigate potential sources of heterogeneity.

Results: Thirty-one studies were selected for analysis. Inconsistent definitions of peri-implantitis were reported across the studies. Twenty-nine studies reported data on implant-level and twenty publications reported on subject-level. The combined proportion of peri-implantitis was 24.1% (95% CI 19.3–29.7) in BOP-positive implants and 33.8% (95% CI 26.7–41.6) for BOP-positive cases. However, the degree of variability among studies was high; the prediction intervals were 10.3-69.3 and 6.9-57.8, respectively. Evidence of asymmetry or publication bias could not be statistically detected. Short observation periods were significantly associated with lower proportions of peri-implantitis among BOP-positive implants.

Conclusions: For BOP-positive implants, there was a 24.1% chance to be diagnosed with peri-implantitis; while for BOP-positive patients, there was a 33.8% probability to be diagnosed with peri-implantitis. This probability varied across study populations. Clinicians should be aware of the considerable false-positive rate of BOP to diagnose peri-implantitis.

KEYWORDS

bleeding on probing, implants, peri-implantitis, predictive value, systematic review

1 | INTRODUCTION

Oral implants support and maintain dental prostheses in the jaw bones. The peri-implant bone stability and the presence of an intact seal at the site of passage through the mucosa are key factors for long-term success. The tissues involved in this function can be affected by a destructive process for which more than 30 years ago the term "peri-implantitis" was proposed (Mombelli,

van Oosten, Schürch & Lang, 1987). Since then, the causes of loss of bone, the impact of infection, methods for diagnosis and therapy of peri-implantitis have been intensely debated.

The study of the diseases of the peri-implant tissues started with a theoretical framework that was built in analogy to periodontology. In periodontal diseases, specialized members of the oral microbiota dysregulate the host immune response, which results in destruction of the tissues anchoring the teeth in the jaw bone (Hajishengallis, 2014; Hajishengallis & Korostoff, 2017). Around implants, bone resorption, independent of infection, has been documented when implants are placed too deep (Hämmerle, Brägger, Bürgin & Lang, 1996) or too close to each other (Tarnow, Cho & Wallace, 2000), and after installing abutments on previously submerged implants (Adell, Lekholm, Rockler & Brånemark, 1981). Such bone loss is usually limited in time and extent and should not be misdiagnosed as peri-implantitis. Thus, one of the diagnostic challenges is to discriminate bone loss due to infection from bone "remodelling." Several studies have shown that the thresholds used to account for bone loss unrelated to infection have a substantial impact on peri-implantitis prevalence rates (Derks et al., 2016; Koldsland, Scheie & Aass, 2010; Roos-Jansåker, Lindahl, Renvert & Renvert, 2006). A consensus report published following the 8th European Workshop on Periodontology (Sanz & Chapple, 2012) defined peri-implantitis by "changes in the level of crestal bone accompanied by bleeding on probing, irrespective of peri-implant probing depth. When previous radiographs are unavailable, crestal bone loss of 2 mm after initial remodelling was recommended for diagnosis. However, a more sensitive threshold can be set when radiographs can be utilized for comparison." Unfortunately, few studies adhere to these recommendations and peri-implantitis definitions are widely variable in the literature (Lee, Huang, Zhu & Weltman, 2017).

In analogy to the physiopathology of the periodontium, it is assumed that inflammation increases the risk of bleeding from the peri-implant mucosa due to the rupture of local blood vessels after minimal trauma. Therefore, bleeding upon gentle probing with a blunt instrument (BOP) has been proposed as a sign of mucositis and/or peri-implantitis. However, the extent to which BOP, as a single observation, indicates the presence or the risk of peri-implantitis is unclear. Around natural teeth, bleeding upon probing can occur even in the absence of disease (Lang, Nyman, Senn & Joss, 1991), and its frequency increases with probing force (Karayiannis, Lang, Joss & Nyman, 1992). Around implants, marked disproportions between the incidences of BOP and clinically manifested peri-implantitis, noticeable in many studies (Mombelli, Müller & Cionca, 2012), suggest that BOP may have a high false positive rate when identifying the presence of destructive peri-implant pathology.

The utility of a diagnostic parameter depends on its value to answer a concrete diagnostic question, and on the clinical context in which this question is asked. Diagnostic tasks may include the identification of subjects and implants at risk of developing peri-implantitis, the detection of early stage disease in apparently asymptomatic individuals, the classification of disease categories, the prediction of likely response to a specific therapy, monitoring treatment efficacy and finding recurrent disease. The utility of a diagnostic parameter may not be the same in each of these situations, and therefore needs to be determined separately every time. The evaluation of a diagnostic test has several aspects. In general, primary evaluation of diagnostic tests focuses on accuracy, that is the degree to which the test correctly identifies the presence or absence of disease. In 1947, Yerushalmy proposed the indicators "sensitivity" and "specificity" for dichotomous tests (Yerushalmy, 1947). Ever since, diagnostic tools have often been primarily judged with respect to these two indicators (high sensitivity is desired in order not to miss any positive cases, whereas high specificity is sought to avoid false positives), underestimating the importance of the predictive value (the proportion of positive and negative results that are true positive and true negative results, respectively), which varies depending on the prevalence of the condition within a population, and is key for estimating utility (Mombelli, 2005).

According to the proceedings of the 7th European Workshop on Periodontology (Lang & Berglundh, 2011), the key parameter to the diagnosis of mucositis is BOP with a gentle force (<0.25 N). Changes in crestal bone levels, along with clinical signs of inflammation (BOP and/or suppuration) are required for the diagnosis of peri-implantitis. The question remains: To what extent can clinical signs of infection/inflammation identify peri-implantitis? Therefore, this review aimed to systematically evaluate the predictive value of BOP for the diagnosis of peri-implantitis.

2 | MATERIAL AND METHODS

This systematic review was conducted according to the guidelines of PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) (Moher, Liberati, Tetzlaff, Altman & Group, 2009).

2.1 | Focused question

The focused question was formulated according to the PICO principle (Needleman, 2002):

> *For persons with osseointegrated dental implants, is assessing BOP and/or suppuration after probing (SUP) as accurate (i.e., with equal or better sensitivity and specificity) as diagnosis of peri-implantitis based on bone loss after initial remodelling (i.e., identified by comparing new radiographs with radiographs taken upon completion of the prosthetic reconstruction)?*

2.2 | Eligibility criteria

Studies were included according to the following criteria:

- Clinical studies published in the English language.
- Included at least 20 human subjects with implant-supported dental reconstructions.
- Observation period of at least 12 months after functional loading.
- Clear definition of *peri-implantitis*.
- At least one case diagnosed with *peri-implantitis*.

- Cases are not selected initially based on the presence of peri-implant pathology.
- BOP and/or SUP after peri-implant probing, or the presence of *peri-implant mucositis*, clearly reported.

2.3 | Exclusion criteria

Studies not fulfilling all eligibility criteria were not included in this analysis. Reviews, in vitro and animal experiments were also eliminated. Moreover, studies were full texts could not be obtained, or if the number of peri-implantitis affected subjects or implants could not be calculated, were excluded.

2.4 | Search strategy

An electronic search was performed in the two databases MEDLINE and EMBASE to identify studies published between January 2012 and May 2017. The following MeSH terms were used: "peri-implantitis" OR "biological complication" OR "peri-implant disease."

A previous systematic review (Mombelli et al., 2012), comprising studies reported prior to 2012, was also included. This was complemented by a hand search through selected review articles and reference lists of identified studies for further potentially relevant publications.

2.5 | Quality assessment

Two reviewers (DH and NC) independently performed the methodological quality assessment of the selected studies according to the following criteria: study design, subject and implant characteristics, extent of clinical and radiographic examinations, inter-/intra-examiner calibration, completeness of follow-up and reporting drop-outs, provision of supportive periodontal treatment (SPT), accuracy of peri-implantitis definition, as well as completeness and clarity of data reporting. Local risk factors such as implant malposition, cleansability of reconstructions, excess cement and implant surface characteristics were also considered. In light of the mentioned criteria, studies were evaluated as having low, moderate or high risk of bias.

2.6 | Data extraction

The following data were extracted from each report: publication year, study design, type of patients, maintenance protocol, definitions of mucositis and peri-implantitis, mean follow-up period, number of patients and number of implants. The prevalence of BOP, peri-implant mucositis and peri-implantitis were recorded on the patient and the implant levels. Disagreement regarding data extraction was resolved with discussion. No attempts were made to contact authors in case of ambiguity in data reporting.

2.7 | Statistical analysis

The primary outcome was defined as the proportion of peri-implantitis among BOP- and/or SUP-positive subjects and implants. For the present analysis, it was assumed that BOP occurred whenever a diagnosis of peri-implant mucositis was made. If a study reported the prevalence of peri-implantitis at various time points, results of the latest follow-up were selected for analysis. For each study, the

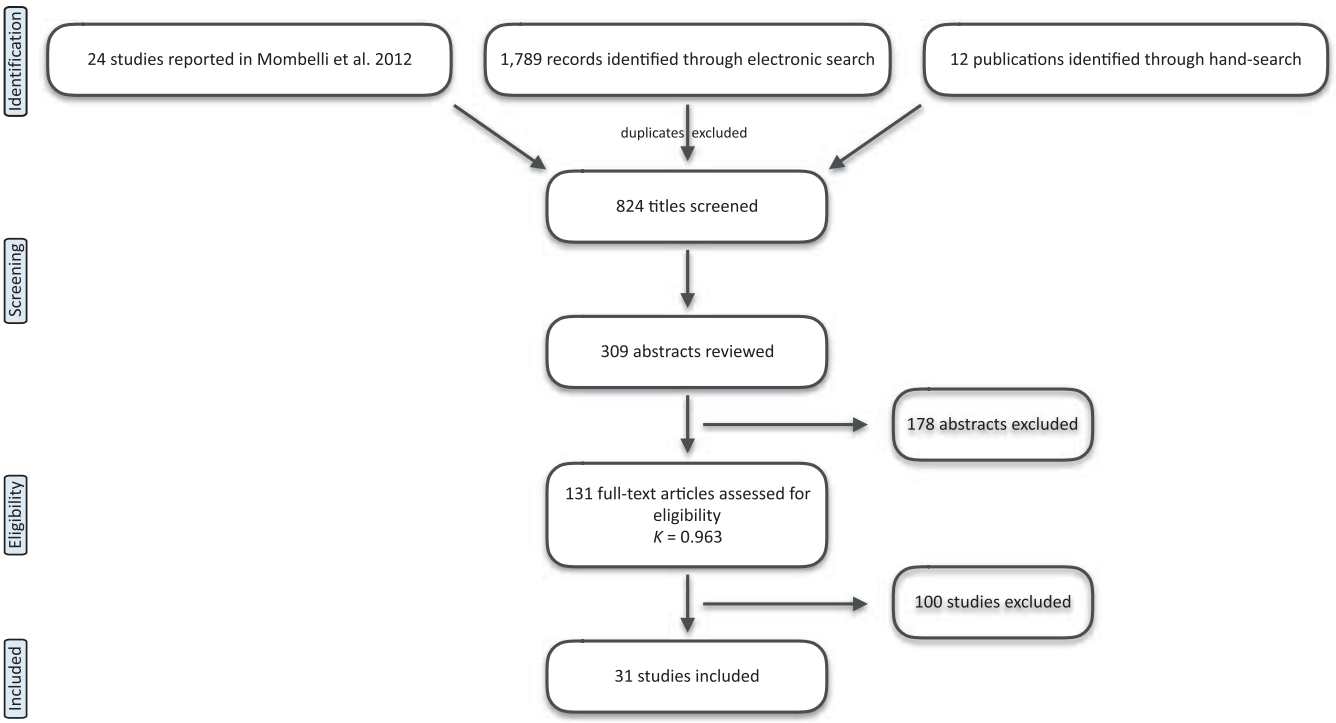

FIGURE 1 Flow chart for the search strategy

proportion of peri-implantitis was reported with Clopper-Pearson's exact 95% confidence interval. Meta-analyses were conducted to combine the proportions of peri-implantitis across studies. Models with random effects were used (Der-Simonian Laird's estimate). Statistical heterogeneity was assessed using Cochran's chi-square test with a significance level set at 0.1, and I^2 statistics. Forest plots were used to show the proportion estimated in each study with its confidence interval and the weight given to each study in the meta-analyses, along with the pooled proportion. Leave-one-out sensitivity analysis was conducted to check the robustness of the findings, and potential publication bias was investigated using funnel plots. Finally, subgroups were created and compared to investigate potential sources of heterogeneity: mean follow-up period (1–3, 3–5 and >5 years), history of periodontal disease and compliance with regular SPT. Analyses were performed using the package meta for R Statistical Software version 3.3.1 (Foundation for Statistical Computing, Vienna, Austria).

3 | RESULTS

3.1 | Study selection (Figure 1)

Initial electronic search yielded 1,789 titles published between 2012 and May 2017. Twenty-four studies were reported in Mombelli et al. (2012), and hand search produced 12 additional articles for review. After removing duplicates, 824 titles were independently screened by two examiners (DH, NC) resulting in 309 abstracts. Finally, 131 articles were reviewed in detail. Reviewers disagreed on the classification of two studies (Cohen's Kappa Index Value 0.963) and this was resolved with discussion. Ultimately, 31 publications were included in this analysis (Table 1).

3.2 | Excluded studies

Out of the 131 full-text articles evaluated, six were excluded due to sample size, two because of short observation periods and 25 because the cases were selected based on the diagnosis of peri-implantitis. Four more studies were omitted because they did not include any cases with peri-implantitis, 22 due to ambiguous data reporting on BOP/SUP or mucositis and three were not clinical studies. Five publications did not correspond to the search criteria, 23 did not provide clear definitions of peri-implantitis and 10 full-text articles were not available or abstracts corresponded to poster/oral presentations (Table 2).

3.3 | Quality assessment and risk of bias

Studies were evaluated for bias according to the previously mentioned criteria (Table 3). Three publications were considered to have a high risk of bias mainly due to unclear data reporting and/or ambiguity in their definition of peri-implantitis (Cecchinato, Parpaiola & Lindhe, 2014; Corbella, Del Fabbro, Taschieri, De Siena & Francetti, 2011; Duque, Aristizabal, Londono, Castro & Alvarez, 2016). On the other hand, 13 studies were at low risk of bias while 15 had medium risk.

3.4 | Study characteristics

3.4.1 | Case definitions

Inconsistent definitions of peri-implantitis with variable degrees of bone loss (BL) were reported. Still, each study included BOP and/or probing depth (PD) in the defining criteria. The thresholds of BL ranged between 0.2 and 3.5 mm. Three studies did not identify a cut-off level for BL (Ferreira, Silva, Cortelli, Costa & Costa, 2006; Lee et al., 2016; Rutar, Lang, Buser, Bürgin & Mombelli, 2001) while one did not take it into consideration for the definition of peri-implantitis (Corbella et al., 2011). On the other hand, Rodrigo, Martin and Sanz, (2012) required "significant" BL, defined as 3× standard deviation of repeated measures, for the diagnosis of peri-implantitis. Only eight studies used standardized intra-oral radiographs for measurement of peri-implant bone level (Cecchinato et al., 2014; Duque et al., 2016; Lehmann et al., 2013; Maximo et al., 2008; Meijer, Raghoebar, de Waal & Vissink, 2014; Rodrigo et al., 2012; Schropp, Wenzel & Stavropoulos, 2014; Swierkot, Lottholz, Flores-de-Jacoby & Mengel, 2012), while three studies utilized orthopantomograms (Marrone, Lasserre, Bercy & Brecx, 2013; Rinke, Ohl, Ziebolz, Lange & Eickholz, 2011; van Velzen, Ofec, Schulten & Ten Bruggenkate, 2015). Finally, mucositis was not defined in seven articles which only reported BOP (Table 1).

3.4.2 | Observation period

Two studies (Corbella et al., 2011; Duque et al., 2016) had a short mean follow-up period of less than 3 years, while eight reported results after 3–5 years of observation (Aguirre-Zorzano, Estefania-Fresco, Telletxea & Bravo, 2015; Canullo et al., 2016; Ferreira et al., 2006; Lee et al., 2016; Maximo et al., 2008; Passoni et al., 2014; Rodrigo et al., 2012; Rokn et al., 2017). The rest reported long-term results exceeding 5 years of functional loading (Table 1).

3.4.3 | Subject characteristics

Two studies exclusively included subjects with a history of periodontal disease (Aguirre-Zorzano et al., 2015; Daubert, Weinstein, Bordin, Leroux & Flemming, 2015), while 13 others included both healthy and periodontally treated patients. Marrone et al. even included subjects with active periodontal disease (Marrone et al., 2013). Twenty of the 31 included articles reported regular maintenance care. Various studies included further details on subjects' characteristics, such as age, smoking status and systemic diseases (Table 3). Only two studies were designed as "split-mouth": Duque et al. compared platform switching implants with conventional ones (Duque et al., 2016), while Rodrigo et al. compared immediately placed implants and delayed ones (Rodrigo et al., 2012).

TABLE 1 Characteristics of included studies [In PDF format, this table is best viewed in two-page mode]

Study	Study design	Follow-up period	Type of subjects	Prosthetic reconstruction	SPT	Health (H)	Mucositis (M)	Peri-implantitis 1 (P1)
Aguirre-Zorzano et al. (2015)	Cross-sectional	Mean 5.25 ± 3.41 years	Hx of Perio.	SC or iFDP	Regular SPT	NR	BOP	BOP/SUP, PD, BL ≥ 1.5 mm
Canullo et al. (2016)	Cross-sectional	Mean 5.9 ± 3.3 years	140/534 S with Hx of perio.	iFDP	428/534 S on regular SPT	NR	NR	PD ≥ 4 mm, BOP/SUP, BL > 3 mm
Cecchinato et al. (2014)	Prospective	1–10 years	41/100 S lost teeth due to perio.	NR	66/100 S on regular SPT	NR	BOP	Progressive BL > 0.5 mm, BOP, PD ≥ 4 mm
Cho-Yan Lee, Mattheos, Nixon and Ivanovski (2012)	Retrospective case-control	Mean 8–8.2 years years (Range 5.04–14.40)	30 perio. and 30 healthy S	SC, iFDP, overdentures	Regular SPT	NR	NR	PD ≥ 5 mm, BOP, BL > 2 mm
Corbella et al. (2011)	Prospective	Mean 18.3 months (range 6 months–5 years)	Edentulous S	Full-arch prosthesis supported by straight and tilted implants	Regular SPT	NR	Redness, swelling, BOP or spontaneous bleeding	BOP or spontaneous bleeding, PD ≥ 4 mm
Dalago et al. (2017)	Retrospective	Mean 5.64 years (range 1–14)	33/183 S had Hx of perio.	SC or iFDP	NR	NR	NR	PD > 5 mm, BOP/SUP, BL > 2 mm
Daubert et al. (2015)	Cross-sectional	Mean 10.9 ± 1.5 years (range 8.9–14.8)	Healthy and perio. S	iFDP	NR	NR	BOP/gingival inflammation	BOP/SUP, PD ≥ 4 mm, BL ≥ 2 mm
Derks et al. (2016)	Cross-sectional	Mean 8.9 ± 0.8 years	Edentulous (16%), healthy (60%) and perio. (24%) S	NR	Regular SPT	No BOP/SUP	BOP/SUP	BOP/SUP, BL >0.5 mm i.e., exceeding the measurement error (compared to initial Rx)
Duque et al. (2016)	Cross-sectional	1 year	Healthy S	SC or iFDP	NR	No BOP or BL	BOP, BL < 2 mm	BOP, PD ≥ 5 mm, BL ≥ 2 mm
Ferreira et al. (2006)	Cross-sectional	Mean 3.5 ± 1.4 years (range 6 months–5 years)	30 perio. and 182 healthy S	NR	94/212 S on regular SPT	NR	BOP or PD ≥ 5 mm without vertical BL	BOP/SUP, PD ≥ 5 mm, vertical BL

(Continues)

TABLE 1 (additional columns)

Peri-implantitis 2 (P2)	Peri-implantitis 3 (P3)		Total *n*	H (*n*)	M/BOP (*n*)	P1 (*n*)	P2 (*n*)	P3 (*n*)	M/BOP (%)	P1 (%)	P2 (%)	P3 (%)
		C	239	144	59	36			24.69	15.06		
		I	786	608	101	77			12.85	9.80		
		C	534	NR	NR	53			NR	9.93		
		I	1,507	NR	72	110			59.50	7.30		
Progressive BL > 1 mm, BOP, PD ≥ 4 mm	Progressive BL > 2 mm, BOP, PD ≥ 4 mm	C at ≥ 1 year	100	NR	NR	29	18	5	NR	29	18	5
		I	291	NR	NR	47	28	5	NR	16.15	9.62	1.72
		C After ≥ 3 years	100	NR	NR	34	17	9	NR	34	17	9
		I	291	NR	NR	51	26	10	NR	17.53	8.93	3.44
		C After ≥ 8 years	100	NR	85	40	25	11	85	40	25	11
		I	291	NR	233	75	48	20	80	25.77	16.49	6.87
PD ≥ 5 mm, BOP, BL > 3 mm		C	60	NR	NR	16	9		NR	26.67	15	
		I	117	NR	27	23	12		23.08	19.70	10.26	
		C at 6–12 months	NR	NR	NR	NR			NR	NR		
		I	216	NR	8	3			3.70	1.40		
		C at 12–18 months	NR	NR	NR	NR			NR	NR		
		I	165	NR	13	0			7.70	0		
		C at 24–36 months	NR	NR	NR	NR			NR	NR		
		I	109	NR	7	0			6.30	0		
		C	183	NR	NR	30			NR	16.40		
		I	938	NR	258	69			27.50	7.30		
		C	96	NR	46	25			48	26		
		I	225	NR	74	36			33	16		
BOP/SUP, BL > 1 mm	BOP/SUP, BL > 2 mm	C	427	98	137	192	115	62	32	45	26.93	14.52
		I	1,578	620	554	393	232	126	35.11	24.90	14.70	7.98
		C	24	NR	NR	NR			NR	NR		
		I	62	2	53	7			85.50	11.30		
		I Platform-swith	30	1	27	2			90	6.60		
		I Conventional	32	1	26	5			81.25	15.60		
		C	212	56	137	19			64.60	8.90		
		I	578	NR	362	43			62.60	7.44		

(Continues)

TABLE 1 (Continued) [In PDF format, this table is best viewed in two-page mode]

Study	Study design	Follow-up period	Type of subjects	Prosthetic reconstruction	SPT	Health (H)	Mucositis (M)	Peri-implantitis 1 (P1)
Frisch et al. (2015)	Retrospective	Mean 12.1 ± 4.93 years (range 2.37–20.35)	S with Implants exhibiting <1 mm keratinized mucosa	NR	Regular SPT	NR	BOP	BOP, PD ≥ 5 mm, BL > 3.5 mm
Frisch et al. (2013)	Retrospective	Mean 14.1 ± 2.8 years (range 10.2–18.9)	Edentulous S	Implant-supported removable double-crown dentures	Regular SPT	NR	BOP	BOP, PD ≥ 5 mm, BL > 3.5 mm after 10 years of functional loading
Koldsland et al. (2010)	Cross-sectional	Mean 8.4 ± 4.6 years	NR	NR	No	NR	BOP/SUP but no BL	BOP/SUP, PD ≥ 4 mm, BL ≥ 2 mm
Lee et al. (2016)	Retrospective	Mean 3.6 years (range 2.6–4.7)	NR	Lateral screw-retained SC	Regular SPT	NR	BOP, swelling, or redness	BOP, swelling, or redness, PD > 5 mm, BL and/or mobility
Lehmann et al. (2013)	Prospective	Mean 9.1 years (range 5.3–11.2)	Edentulous S	Implant-supported bar-retained overdentures	No	PD < 5 mm, no BOP	BOP, PD ≥ 5 mm, no pathological BL	BOP, PD ≥ 5 mm, pathological BL > 0.5 mm 1st year and > 0.2 mm each subsequent year
Marrone et al. (2013)	Cross-sectional	Mean 8.5 ± 3.2 years (range 5–18)	34 healthy S, 39 with stabilized periodontitis, and 15 with active periodontitis. 7 Edentulous	SC, iFDP, overdentures	58 S with regular SPT, 45 S with irregular SPT,	NR	BOP, PD ≤ 5 mm, BL ≤ 2 mm	BOP, PD > 5 mm, BL > 2 mm
Maximo et al. (2008)	Prospective case series	Mean 3.4 ± 2 years	Partially or fully edentulous (29%), healthy and perio. S	NR	No	PD ≤ 5 mm, no gingival inflammation, no BOP/SUP, no BL	Gingival inflammation, BOP, BL < 3 threads	PD ≥ 5 mm, BOP/SUP, BL ≥ 3 threads
Meijer et al. (2014)	Retrospective	10 years	Edentulous S	Bar-retained overdentures	Regular SPT	NR	BOP/SUP	BOP/SUP, BL ≥ 2 mm
Mir-Mari, Mir-Orfila, Figueiredo, Valmaseda-Castellon and Gay-Escoda (2012)	Cross-sectional	Mean 6.3 ± 4.3 years (range 1–18)	NR	NR	Regular SPT	No BOP, BL < 2 threads or clinical stability (BL ≥ 2 threads without BOP)	BOP, BL < 2 threads	BOP/SUP, BL ≥ 2 threads
Passoni et al. (2014)	Cross-sectional	Mean 4.7 ± 2 years (range 1–5.4)	NR	iFDP	No	NR	NR	BOP/SUP, PD ≥ 5 mm, BL > 2 mm

(Continues)

TABLE 1 (additional columns - continued)

Peri-implantitis 2 (P2)	Peri-implantitis 3 (P3)		Total *n*	H (*n*)	M/BOP (*n*)	P1 (*n*)	P2 (*n*)	P3 (*n*)	M/BOP (%)	P1 (%)	P2 (%)	P3 (%)
		C	60	NR	NR	2			NR	3.33		
		I	105	NR	38	2			36.19	1.87		
		C	22	NR	8	2			36.40	9.10		
		I	88	NR	19	7			21.40	8		
BOP/SUP, PD ≥ 4 mm, BL ≥ 3 mm		C	104	NR	41	49	12		39.40	47.10	11.70	
		I	300	NR	82	108	20		27.30	36.60	6	
		C	70	NR	NR	NR			NR	NR		
		I	73	NR	11	1			15.10	1.40		
		C	31	NR	NR	NR			NR	NR		
		I	131	121	9	1			92.37	0.76		
		C	103	33	32	38			31	37		
		I	266	103	101	61			38	23		
		C	113	58	41	14			36.30	12.40		
		I	347	210	111	26			32	7.50		
		C at 5 years	150	NR	78	25			51.90	16.90		
		I	300	NR	123	34			41.20	11.50		
		C at 10 years	150	NR	85	45			57	29.70		
		I	300	NR	141	61			47	20.30		
		C	245	102	96	40			38.80	16.30		
		I	964	494	208	88			21.60	9.10		
		C	32	3	9	20			28.13	62.50		
		I	161	16	100	45			62.11	27.95		
		S with I ≤ 5 (*n* implants)	NR	11	63	19			67.74	20.43		
		S with I > 5 (*n* implants)	NR	5	37	26			54.41	38.24		

(Continues)

TABLE 1 (Continued) [In PDF format, this table is best viewed in two-page mode]

Study	Study design	Follow-up period	Type of subjects	Prosthetic reconstruction	SPT	Health (H)	Mucositis (M)	Peri-implantitis 1 (P1)
Poli et al. (2016)	Retrospective cross-sectional	2–15 years	NR	NR	Regular SPT	No BOP/SUP or BOP at one surface only	BOP from more than one surface	BOP/SUP, PD ≥ 4 mm, BL ≥ 2 mm
Rinke et al. (2011)	Retrospective cross-sectional	Mean 68.2 months (range 2–11.2 years)	Healthy and perio. S	iFDP	58 S with regular SPT, 31 S with irregular SPT	NR	BOP, PD ≥ 4 mm	BOP/SUP, PD ≥ 5 mm, progressive BL (BL > 3.5 mm apical to implant shoulder on last Rx)
Rodrigo et al. (2012)	Prospective	5 years	7 healthy and 15 perio. S	NR	Regular SPT	NR	BOP, PD ≥ 4 mm, no significant BL	BOP, PD ≥ 4 mm, significant BL (3xSD of repeated measures)
Rokn et al. (2017)	Retrospective cross-sectional	Mean 4.43 ± 2.25 years (range 1–11)	17/134 S with Hx of perio.	iFDP	No	NR	BOP/SUP, BL ≤ 2 mm	BOP/SUP, BL > 2 mm
Roos-Jansåker et al. (2006)	Retrospective case series	9–14 years	Healthy and perio., 29.4% edentulous S	iFDP or removable prosthesis	SPT performed by reffering dentist	NR	BOP, PD ≥ 4 mm, no BL	BOP/SUP, PD ≥ 4 mm, BL ≥ 3 threads (1.8 mm)
Rutar et al. (2001)	Retrospective	5–10 years	NR	NR	Regular SPT	NR	NR	BOP/SUP, PD > 4 mm, BL
Schropp et al. (2014)	RCT	10 years	Healthy and perio. Subjects	SC (all cemented except 2 which were screw retained)	NR	NR	NR	BOP/SUP, PD ≥ 5 mm, BL > 1 mm
Swierkot et al. (2012)	Retrospective	5–16 years	35 Hx of aggressive Perio. and 18 healthy S	SC, iFDP, removable prosthesis	Regular SPT	NR	BOP, PD ≥ 5 mm, no BL	BOP, PD > 5 mm, annual BL > 0.2 mm after 1 year of loading
Trullenque-Eriksson and Guisado Moya (2015)	Retrospective	Mean 13.19 ± 3.7 years	Healthy and perio. S	NR	NR	NR	BOP/SUP, PD ≥ 5 mm, BL < 3 mm	BOP/SUP, PD ≥ 5 mm, BL ≥ 3 mm
van Velzen et al. (2015)	Prospective	10 years	Healthy and perio. S	SC, iFDP, removable prosthesis	Regular SPT	NR	NR	BOP, BL ≥ 1.5 mm
Wahlstrom, Sagulin and Jansson (2010)	Retrospective	Mean 5.1 years (range 3.3–7)	Healthy and perio. (29%) S	iFDP	Regular SPT	NR	Color and shape of mucosa, BOP, PD < 4 mm, no BL	BOP/SUP, PD ≥ 4 mm, BL > 2 mm after minimum loading of 1 year

BL, bone loss; BOP, bleeding on probing; C, control; Hx, history; I, implant; iFDP, implant supported fixed dental prosthesis; NR, not reported; PD, probing depth; RCT, randomized controlled trial; S, subject; SC, single crown; SPT, supportive periodontal therapy; SUP, suppuration.

TABLE 1 (additional columns - continued)

Peri-implantitis 2 (P2)	Peri-implantitis 3 (P3)		Total *n*	H (*n*)	M/BOP (*n*)	P1 (*n*)	P2 (*n*)	P3 (*n*)	M/BOP (%)	P1 (%)	P2 (%)	P3 (%)
		C	103	NR	NR	NR			NR	NR		
		I	421	248	173	19			41.10	4.50		
		C	89	NR	40	10			44.90	11.20		
		I	NR	NR	NR	NR			NR	NR		
		C	22	NR	NR	NR			NR	NR		
		I	68	NR	13	4			19.10	5.80		
		C	134	NR	65	27			48.50	20.10		
		I	478	NR	191	42			40	8.80		
BOP/SUP, PD ≥ 4 mm, BL ≥ 5 threads (4.3 mm)		C	218	NR	105	35			48	16	24	
		I	999	NR	160	66			16	6.60	5.60	
		C	45	NR	NR	NR			NR	NR		
		I	64	NR	51	15			80	23.43		
		C	46	NR	NR	2			NR	NR		
		I	46	NR	32	2			70	4.30		
		C	53	NR	34	17			64.15	32.10		
		I	179	NR	96	42			53	23		
		C	100	NR	14	3			14	3		
		I	242	NR	27	4			11.20	1.70		
BOP, BL ≥ 2 mm		C	169	NR	101	25	NR		59.80	14.80	NR	
		I	356	NR	162	25	15		45.50	7	4.20	
		C	46	21	10	2			21.74	4.34		
		I	116	NR	NR	NR			NR	NR		

TABLE 2 Excluded studies and reasons for exclusion

Reason for exclusion	Study (Author, year)
Study included less than 20 human subjects	Poli et al. (2017), Chang et al. (2016), Zuo et al. (2015), Quaranta et al. (2015), Li et al. (2015), Li et al. (2014)
Less than 12 months of mean functional loading	Al Jaboobi et al. (2017), Goncalves Junior et al. (2016)
Cases selected based on diagnosis of PI	Zani et al. (2016), Wang et al. (2016), Teixeira et al. (2016), Severino et al. (2016), Mardegan et al. (2016), Heitz-Mayfield et al. (2016), Renvert et al. (2015), Rakic et al. (2015), Neilands et al. (2015), Lopez-Martinez et al. (2015), Jemt et al. (2015), Guo et al. (2015), Garcia-Delaney et al. (2015), Canullo et al. (2015), Ata-Ali et al. (2015), Albertini et al. (2015), de Araujo Nobre et al. (2014a, b), Cecchinato et al. (2014), Wu et al. (2013), Raki et al. (2013), Ebadian et al. (2013), Darabi et al. (2013), Cortelli et al. (2013), Charalampakis et al. (2012)
PI not diagnosed in any of the cases	Bechara et al. (2017), Glibert et al. (2016), Frisch et al. (2015b), Guljé et al. (2014)
BOP, SUP or mucositis not clearly reported	Troeltzsh et al. (2016), Canullo et al. (2016b), Sanchez-Siles et al. (2015), Rinke et al. (2015), Papantonopoulos et al. (2015), Renvert et al. (2014), Malo et al. (2014), Fardal et al. (2013), Pjetursson et al. (2012), Roccuzzo et al. (2012), Dierens et al. (2012), Dvorak et al. (2011), Schmidlin et al. (2010), Simonis et al. (2010), Zetterqvist et al. (2010), Gatti et al. (2008), Bragger et al. (2005), Fransson et al. (2005), Baelum et al. (2004), Gruica et al. (2004), Karoussis et al. (2003), Bragger et al. (2001)
Not a clinical study	Maret et al. (2017), Schwendicke et al. (2015), Cañaveral Cavero et al. (2015)
Study not corresponding to search criteria	Sampaio-Fernandes et al. (2015), Korsch et al. (2015), Silva et al. (2014), Becker et al. (2014), Olmedo et al. (2013)
No clear definition of PI	Mencio et al. (2017), Jemt et al. (2017), Badea et al. (2017), Lopez et al. (2016), Esposito et al. (2016), Ernst et al. (2016), Cotic et al. (2016), Jervoe-Storm et al. (2015), Galindo-Moreno et al. (2015), Moreno Vazquez et al. (2014), Galindo-Moreno et al. (2014), Qu et al. (2013), Manev et al. (2013), Malo et al. (2013), Lam et al. (2013), Lachmann et al. (2013), Casado et al. (2013), Bignozzi et al. (2013), Atalay et al. (2013), Aguirre-Zorzano et al. (2013), Becker et al. (2016), Lopez-Piriz et al. (2012), Astrand et al. (2004)
Full text not available or abstracts for oral/poster presentations	de Arriba et al. (2016), Kang et al. (2015), Dastaran et al. (2015), Pigatto et al. (2014), Nobre de et al. (2014), Lombardo et al. (2014), Kim et al. (2014), Bazikyan et al. (2014), Parmar et al. (2013), Ihan Hrenet al. (2013)

3.5 | Meta-analyses of the proportion of peri-implantitis

3.5.1 | Implant-level analysis

Twenty-nine studies reported data on an implant-level. The proportion of peri-implantitis among implants presenting with BOP varied between 0% (Corbella et al., 2011) and 62.1% (Canullo et al., 2016). However, significant heterogeneity was noted (I^2 = 93.3%) and a model with random effects was used to combine the studies. Over all studies, 24.1% (95% CI 19.3–29.7) of implants presenting with BOP were diagnosed with peri-implantitis. The 95% prediction interval for the proportion of peri-implantitis among implants with BOP in a new study was 6.9% to 57.8%. The wide prediction interval is attributed to the heterogeneity of the studies (Figure 2). Leave-one-out sensitivity analysis did not reveal a specific study explaining the heterogeneity, and the pooled proportion was similar when any of the studies was removed. The funnel plot did not show evidence of asymmetry (p value = .35). No publication bias was detected (Figure 3).

In two of the retrieved studies, each participant received two different implant treatments (Duque et al., 2016; Rodrigo et al., 2012). As the types of implants are potentially associated with the risk of peri-implantitis, a sensitivity analysis was conducted by removing these two comparative studies from the meta-analyses. The exclusion of these two studies did not significantly modify the results of the meta-analysis on the implant level.

3.5.2 | Subject-level analysis

Twenty studies reported data on a subject level. The proportion of peri-implantitis among subjects presenting with BOP varied from 9.1% (Frisch, Ziebolz & Rinke, 2013) to 69% (Passoni et al., 2014). Again, significant heterogeneity was noted (I^2 = 88.9%) and a random effects model was utilized. The combined proportion of peri-implantitis in BOP-positive cases was 33.8% (95% CI 26.7–41.6). The 95% prediction interval for the proportion of peri-implantitis among subjects with BOP in a new study was 10.3% to 69.3%. Once more, the considerable heterogeneity contributed to the width of the prediction interval (Figure 4). No specific study explained the heterogeneity, and the pooled proportion was similar when any of the studies was removed. Finally, the funnel plot did not show asymmetry (p value = .57) and publication bias was not detected (Figure 5).

3.6 | Subgroup analysis

An association was found between the mean follow-up period and the proportion of implants affected by peri-implantitis (Table 4). Short observation periods (1–3 years) were significantly associated with

lower proportions of peri-implantitis among BOP-positive implants (p value < .05).

4 | DISCUSSION

This systematic review and meta-analysis focused on the evaluation of BOP as a predictive measure for peri-implantitis. In the studies included in this review, whenever bleeding occurred after probing, there was a 24% chance that the corresponding implant was diagnosed with peri-implantitis. In addition, there was a 33.8% probability that patients with BOP-positive implants were diagnosed with peri-implantitis. In other words, in the majority of instances, bleeding after probing of implants was observed in the absence of peri-implantitis. The generally high rate of BOP around implants noted in our analysis, may be attributed in part to the mechanical fragility of healthy peri-implant mucosae. Indeed, comparative assessments of teeth and implants in the same patients have indicated that, even in the absence of disease, the bleeding tendency and gingival index scores were higher at implants than at teeth (Cionca, Hashim, Cancela, Giannopoulou & Mombelli, 2016). BOP positive and negative gingival tissues have been compared histologically (Greenstein, Caton & Polson, 1981). Specimens from sites bleeding after light probing showed a significantly increased percentage of cell-rich and collagen-poor connective tissue, but no increase of blood vessel lumens. Similar information is presently unavailable for human peri-implant tissues. The documented relationship between probing force and frequency of BOP at healthy teeth (Karayiannis et al., 1992) suggests that tissue trauma due to probing with a high force may occasionally be the reason for bleeding at implants. None of the studies included in the present review used force-controlled probes. Thus, excessive probing forces, causing rupture of small blood vessels, cannot be excluded. To avoid false-positive readings, probing with controlled forces not exceeding 0.25 N have been recommended for teeth (Karayiannis et al., 1992). However, recommendations for ideal probing forces at implants can not presently be made based on currently available evidence.

Continual absence of BOP at teeth during maintenance care has been suggested as an indicator of periodontal stability. In patients incorporated in a maintenance programme for more than 2.5 years following periodontal therapy, only 1.3% dental sites that rarely bled on probing (never or only at one of six assessments) lost ≥2 mm clinical attachment. In contrast, 28% of the sites that bled frequently (5 or 6 times of six assessments) lost ≥2 mm clinical attachment (Lang, Adler, Joss & Nyman, 1990). In another study (Luterbacher, Mayfield, Brägger & Lang, 2000), 19 patients were monitored, both at teeth- and implant-levels, during 2 years of rigid maintenance care. At implants, a BOP frequency of ≥50% showed a sensitivity of 50% and specificity of 100% to indicate change in bone density or probing attachment loss. The authors reported better positive predictive values for frequent BOP at implant sites than at tooth sites. Negative predictive values indicating periodontal or peri-implant stability did not differ substantially.

This review was limited in its analysis of risk factors that could contribute to the development of peri-implantitis. Such analysis was hindered by the heterogeneity of the studies and the small number of articles evaluating a single factor in association with peri-implantitis. Six of the 31 included studies evaluated both patient and implant factors in relation to peri-implantitis (Canullo et al., 2016; Dalago, Schuldt Filho, Rodrigues, Renvert & Bianchini, 2017; Daubert et al., 2015; Derks et al., 2016; Marrone et al., 2013; Rokn et al., 2017), yet data were only presented in terms of relative risk in Daubert et al. (2015). van Velzen et al. (2015) reported on both implant and subject characteristics but did not attempt to analyse their effects on the prevalence of peri-implantitis. Only three studies (Frisch, Ziebolz, Vach & Ratka-Kruger, 2015; Passoni et al., 2014; Poli, Beretta, Grossi & Maiorana, 2016) examined the effect of keratinized mucosa on peri-implant disease. Ferreira et al. (2006), on the other hand, evaluated the effect of patient-related risk factors and plaque index on the prevalence of peri-implantitis without examining local implant factors. The diversity in diagnostic criteria and disease definition, the differences regarding length of the observation period, prosthetic reconstructions, treatment of peri-implantitis, statistical methodology and data presentation, in addition to the differences in sample selection and the variability in subjects' susceptibility to peri-implant disease, present major limitations of this meta-analysis. Despite a consensus report from the proceedings of the 8th European Workshop on Periodontology (Sanz & Chapple, 2012) recommending the use of unequivocal case definitions and the expression of outcomes at subject level, a large number of studies still fail to adhere to such directions.

The results of this analysis showed a significant association between the observation period and the proportion of implants with a mucosa bleeding after probing being affected by peri-implantitis. Yet, the reliability of such association could be questioned due to the scarcity of studies with short follow-up periods (n = 2). Nonetheless, a recent systematic review also established that a longer observation period is associated with a higher prevalence of peri-implantitis (Lee et al., 2017). It is also worth considering that one study (Corbella et al., 2011), which reported 0% prevalence of peri-implantitis after 3 years, could have affected the analysis. This was a prospective study which evaluated immediately loaded implants placed in edentulous subjects over an observation period of 4 years. The authors reported peri-implantitis affecting 1.4% of implants (three implants in two subjects) after 6–12 months of function. Surgical debridement was performed, and no further complications were reported. Hence, the lack of peri-implantitis at the 3-year follow-up. For the rest of the studies reporting data at different time points, the results of the latest follow-up were included in this report. However, this could not be applied to Corbella et al. which, at 4 years, only analysed 29 of the initial 244 implants. As 109 implants were examined at 3 years, those were the data analysed in this review. A leave-one-out statistical analysis was performed to reduce the risk of bias generated by this study, and the results did not show a statistically significant difference when Corbella et al. were omitted.

The proportion of implants with BOP being affected by peri-implantitis was not significantly associated with either periodontal history or regular maintenance care. This could be attributed to the differences in the degree of periodontal involvement, the variability in

TABLE 3 Quality assessment of the included studies [In PDF format, this table is best viewed in two-page mode]

Study ID		Design	Evidence level[a]	Details on clinical examination	Inter/Intra-examiner calibration	Details on implant characteristics	Local factors[b]
1	Aguirre-Zorzano et al. (2015)	Cross-sectional	III	No	No	Yes	No
2	Canullo et al. (2016)	Cross-sectional	III	Yes	No	Yes	Yes
3	Cecchinato et al. (2014)	Prospective	III	Yes	NC	No	NC
4	Cho-Yan Lee et al. (2012) (46)	Retrospective case-control	IIa	Yes	No	Yes	No
5	Corbella et al. (2011)	Prospective	III	Yes	No	No	No
6	Dalago et al. (2017)	Retrospective	III	Yes	No	Yes	Yes
7	Daubert et al. (2015)	Cross-sectional	III	No	Yes	Yes	Yes
8	Derks et al. (2016)	Cross-sectional	III	Yes	No	Yes	Yes
9	Duque et al. (2016)	Cross-sectional	III	Yes	Yes	Yes	No
10	Ferreira et al. (2006)	Cross-sectional	III	Yes	Yes	Yes	Yes
11	Frisch et al. (2015)	Retrospective	III	Yes	No	Yes	Yes
12	Frisch et al. (2013)	Retrospective	III	Yes	No	Yes	No
13	Koldsland et al. (2010)	Cross-sectional	III	Yes	Yes	NC	No
14	Lee et al. (2016)	Retrospective	III	No	No	Yes	No
15	Lehmann et al. (2013)	Prospective	III	Yes	No	Yes	No
16	Marrone et al. (2013)	Cross-sectional	III	Yes	No	Yes	Yes
17	Maximo et al. (2008)	Prospective case series	III	No	Yes	Yes	No
18	Meijer et al. (2014)	Retrospective	III	Yes	No	Yes	No
19	Mir-Mari et al. (2012)	Cross-sectional	III	Yes	Yes	Yes	No
20	Passoni et al. (2014)	Cross-sectional	III	Yes	Yes	NC	Yes
21	Poli et al. (2016)	Retrospective cross-sectional	III	Yes	No	NC	Yes
22	Rinke et al. (2011)	Retrospective cross-sectional	III	No	No	NC	No
23	Rodrigo et al. (2012)	Prospective	III	Yes	No	Yes	No
24	Rokn et al. (2017)	Retrospective cross-sectional	III	No	No	Yes	Yes
25	Roos-Jansåker et al. (2006)	Retrospective case series	III	Yes	No	No	No
26	Rutar et al. (2001)	Retrospective	III	Yes	No	No	No
27	Schropp et al. (2014)	RCT	Ib	Yes	Yes	No	No
28	Swierkot et al. (2012)	Retrospective	III	No	Yes	Yes	No
29	Trullenque-Eriksson and Guisado Moya (2015)	Retrospective	III	Yes	No	No	No
30	van Velzen et al. (2015)	Prospective	III	Yes	No	Yes	Yes
31	Wahlstrom et al. (2010)	Retrospective	III	Yes	No	Yes	NC

Ib, evidence from at least one randomized controlled trial; III, evidence from well-designed non-experimental studies, such as comparative, correlational or case studies; IIa, evidence from at least one well-designed controlled study without randomization. PI = Peri-implantitis. BL = Bone loss. SPT = Supportive periodontal treatment. RCT = Randomized controlled trial. NC = Not clear.

[a]According to the definitions of types of evidence originating from the US Agency for Health Care Policy and Research (1993).

[b]Risk factors for peri-implantitis such as implant malpositioning, cleansability of reconstruction, excess cement, absence of keratinized gingiva etc.

[c]Such as history of periodontal disease, oral hygiene and smoking status.

TABLE 3 (additional columns)

Standardized radiographic examination	Completeness of follow-up/report of drop outs	Details on subjects characteristics[c]	SPT reported	Definition PI with BL	Treatment of PI	Completeness/ clarity of data reporting on PI	Risk of bias
No	Yes	Yes	Yes	Yes	No	Yes	Low
No	Yes	Yes	Yes	Yes	No	No	Medium
Yes	Yes	NC	Yes	Yes	Yes	No	High
No	Yes	Yes	Yes	No	No	No	Medium
No	Yes	NC	Yes	No	Yes	No	High
No	Yes	Yes	No	Yes	No	Yes	Low
No	Yes	Yes	No	Yes	No	Yes	Low
No	Yes	Yes	No	Yes	No	Yes	Low
Yes	Yes	Yes	No	Yes	Yes	No	High
No	Yes	Yes	Yes	Yes	No	Yes	Low
No	Yes	No	Yes	Yes	No	No	Medium
No	Yes	NC	Yes	Yes	No	Yes	Low
No	Yes	No	No	Yes	No	Yes	Medium
No	Yes	No	Yes	Yes	No	No	Medium
Yes	Yes	NC	Yes	Yes	No	No	Medium
Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low
Yes	Yes	Yes	No	Yes	No	Yes	Low
Yes	Yes	No	Yes	Yes	Yes	No	Medium
No	Yes	No	Yes	Yes	No	Yes	Low
No	Yes	No	No	Yes	No	Yes	Medium
No	Yes	NC	Yes	Yes	No	No	Medium
Yes	Yes	Yes	Yes	Yes	No	No	Medium
Yes	Yes	Yes	Yes	Yes	Yes	No	Medium
No	Yes	Yes	No	Yes	No	Yes	Low
No	Yes	No	Yes	Yes	No	Yes	Medium
No	Yes	NC	Yes	Yes	Yes	No	Medium
Yes	Yes	NC	Yes	Yes	No	Yes	Low
Yes	Yes	Yes	No	Yes	No	Yes	Low
No	Yes	NC	No	Yes	No	Yes	Medium
Yes	Yes	Yes	Yes	Yes	No	Yes	Low
No	Yes	Yes	Yes	Yes	No	No	Medium

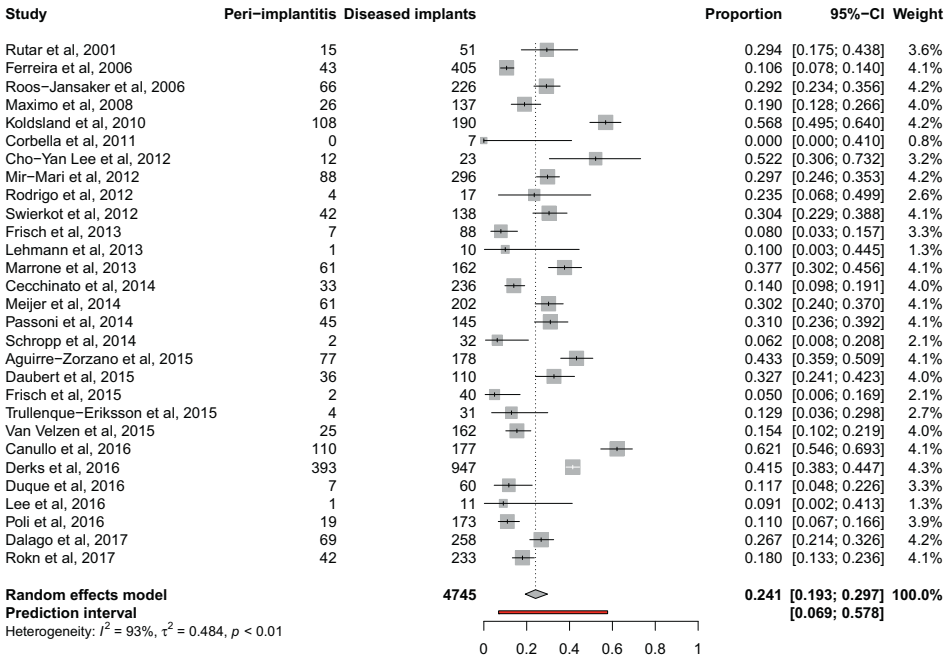

FIGURE 2 Forest plot for the proportion of peri-implantitis among implants presenting with BOP/SUP

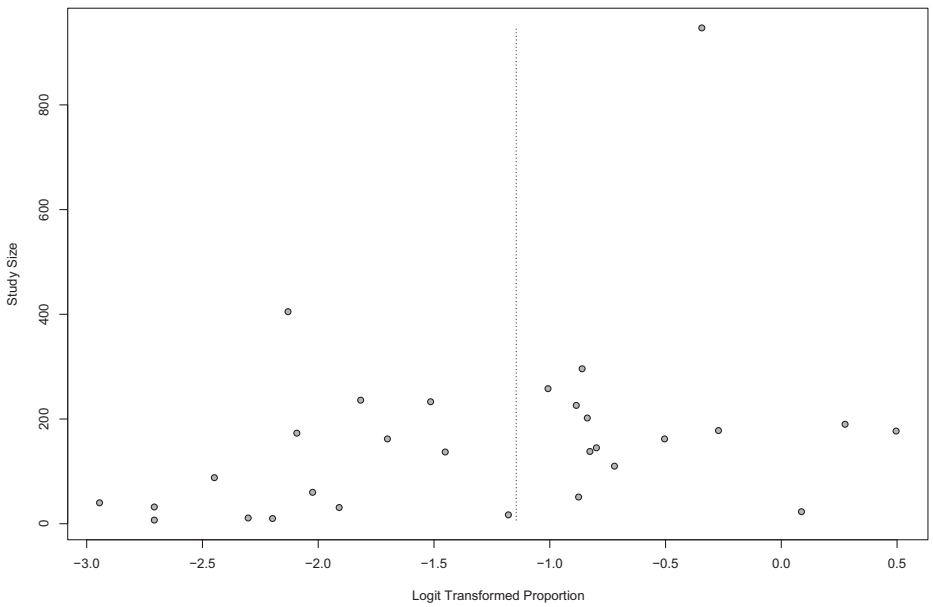

FIGURE 3 Funnel plot for publication bias in studies presenting data on implant level (n = 29 studies)

maintenance intervals and patient compliance, as well as the length of the observation period.

Attempts to classify the data according to implant risk factors or prosthetic connection's design had failed due to the extreme variability in between, and within, studies. Most studies evaluated different implant brands with extremely variable characteristics. Rough and machined surfaces were analysed, as well as tissue-level and bone-level implants, platform switching, removable and fixed reconstructions, in healthy and periodontally compromised patients, with or without regular maintenance care.

In conclusion, the present systematic review and meta-analysis demonstrated that for BOP-positive implants, there was a 24.1% chance to be diagnosed with peri-implantitis; while for BOP-positive patients, there was a 33.8% probability of being diagnosed with peri-implantitis. Clinicians should be aware of the considerable false-positive rate of BOP to diagnose peri-implantitis.

TABLE 4 Subgroup analysis on implant level

Subgroups of studies	Category	*n* studies	Pooled proportion	I^2 (%)	*p* value
Type of subjects	Healthy	2	19.5% (7.3 to 42.6)	80.6	.2409
	Healthy + Perio.	12	26.6% (18.4 to 36.7)	95.2	
	Perio.	3	35% (26.9 to 44.1)	78.0	
Regular SPT	No	4	27.3% (12.4 to 49.7)	96.2	.7125
	Yes	17	23.5% (16.9 to 31.8)	94.8	
Mean follow-up period	1–3 years	2	11.2% (5.6 to 21.2)	0	**.0439***
	3–5 years	8	25.8% (14.4 to 41.7)	96.1	
	>5 years	18	26.1% (20.8 to 32.3)	91	

*P value in bold characters indicates a statistically significant association between the pooled proportion and the length of the mean follow-up period (p value < .05)

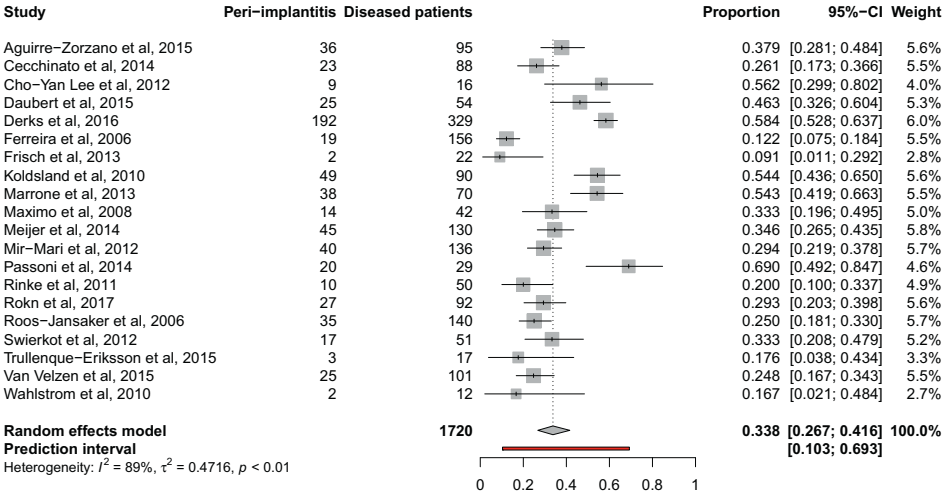

FIGURE 4 Forest plot for the proportion of peri-implantitis among subjects presenting with BOP/SUP

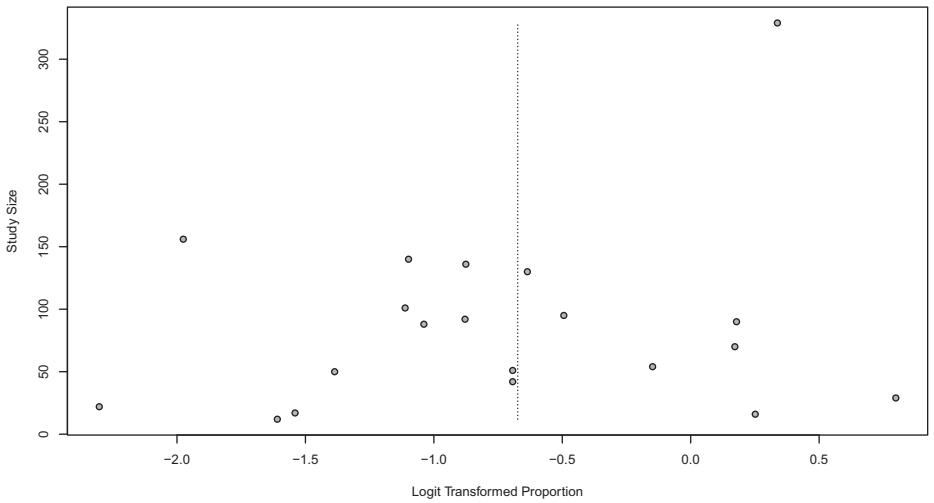

FIGURE 5 Funnel plot for publication bias in studies presenting data on subject level (*n* = 20 studies)

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CONFLICT OF INTEREST

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REVIEW ARTICLE

WILEY CLINICAL ORAL IMPLANTS RESEARCH

Long-term biological complications of dental implants placed either in pristine or in augmented sites: A systematic review and meta-analysis

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Abstract

Aim: To investigate and compare the prevalence of biological complications and failure of implants placed in pristine vs. augmented sites after a mean observation period of at least 10 years.

Materials and methods: The focused question "In patients with osseointegrated dental implants, are there differences in biological complications and implant failure at implants placed in pristine vs. augmented sites?" was addressed using the Population, Exposure, Comparison and Outcome criteria. Electronic and manual searches supplemented by the screening of the grey literature were carried out. A case definition of peri-implant mucositis and peri-implantitis had to be specified. The binary random-effects method was chosen to conduct meta-analyses. Results are presented as Forest plots with weighted mean values and 95% confidence intervals (CI). The I^2 statistic test was applied to quantify heterogeneity. The Newcastle-Ottawa Scale and the parameters provided in the Cochrane Center and CONSORT statement were used for quality assessment. The results are reported according to the PRISMA guidelines.

Results: No randomized clinical trial (RCT) comparing the outcomes of implants placed in pristine vs. augmented sites was identified. Five case-series studies, one case–control study, one cross-sectional study and one RCT were eligible for qualitative and quantitative analyses. No statistically significant differences ($p > .05$) were observed between implants placed in pristine vs. augmented sites for any outcome variables both at patient and at implant levels, respectively. High heterogeneity concerning patient sampling, case definitions of biological complications and eligibility criteria was observed.

Conclusion: The studies included in the present systematic review did not directly address the focused questions. Hence, the outcomes of the meta-analysis should be interpreted with caution due to high variability with respect to study design.

KEYWORDS

bone regeneration, clinical trials, complication, dental implants, diagnosis, guided tissue regeneration, inflammation, osseointegration, peri-implantitis, titanium

1 | INTRODUCTION

Outcomes from preclinical studies indicated that the alveolar ridge undergoes resorptive processes following tooth extraction impacting on the bony envelope for an ideal prosthetically driven implant placement (Araújo & Lindhe, 2005).

Findings in posterior extraction sites demonstrated that within 1 year, half of the alveolar ridge width is resorbed, of which 2/3 occurred during the first 3 months (Schropp, Wenzel, Kostopoulos, & Karring, 2003). Moreover, results from clinical studies showed a substantial amount of vertical bone resorption on the vestibular aspect of the alveolar process (Araújo & Lindhe, 2005; Cardaropoli, Araújo, & Lindhe, 2003; Chappuis et al., 2015). Interestingly, thickening of the soft tissue following tooth extraction was observed in sites with a facial alveolar bone thickness < 1 mm masking underlying bone deficiencies (Chappuis, Bornstein, Buser, & Belser, 2016). This fact may severely compromise optimal three-dimensional implant positioning (Atwood, 1971, 1973). Therefore, in order to achieve primary implant stability and successful osseointegration, simultaneous or staged lateral and/or vertical bone augmentation procedures are needed to manage the reconstruction of atrophic alveolar ridges (Milinkovic & Cordaro, 2014; Urban et al., 2016). Based on recent advances in regenerative technologies, bone augmentation procedures are nowadays performed with minor invasiveness due to the use of bone substitutes and barrier membranes (Kuchler & von Arx, 2014).

Recently, controversial data on the long-term survival rates of implants placed in augmented vs. pristine bone have been reported (Chappuis, Cavusoglu, Buser, & von Arx, 2017; Daubert, Weinstein, Bordin, Leroux, & Flemmig, 2015; Tran et al., 2016; Urban et al., 2016; Visser, Stellingsma, Raghoebar, Meijer, & Vissink, 2016). For example, while some studies showed comparable outcomes in terms of implant survival rates and crestal bone loss (Chappuis et al., 2017; Urban et al., 2016), other studies reported inferior outcomes for implants placed in augmented sites (Daubert et al., 2015; Tran et al., 2016; Visser et al., 2016).

A recent systematic review with meta-analysis reported subject-based estimated weighted mean prevalences and ranges for peri-implant diseases derived from longitudinal studies (Derks & Tomasi, 2015). The prevalence for peri-implant mucositis amounted to 43% ranging from 19% to 65% and for peri-implantitis to 22% ranging from 1% to 47%, respectively (Derks & Tomasi, 2015). Moreover, several cross-sectional studies reported comparable data to those conducted in longitudinal ones (Aguirre-Zorzano, Estefania-Fresco, Telletxea, & Bravo, 2015; Dalago, Schuldt Filho, Rodrigues, Renvert, & Bianchini, 2017; Daubert et al., 2015; Konstantinidis, Kotsakis, Gerdes, & Walter, 2015; Monje, Wang, & Nart, 2017; Rokn et al., 2017; Schwarz et al., 2017).

Despite the fact that placement of dental implants in conjunction with augmentation procedures is well documented and was shown to yield high predictability in terms of implant survival rates and volume stability (Buser et al., 2013; Elnayef et al., 2017), comparative knowledge between the long-term prevalence of biological complications at implants placed in pristine vs. augmented sites is lacking.

Hence, the aim of the present systematic review was to investigate and compare the prevalence of biological complications and failure of implants placed in pristine vs. augmented sites after a mean observation period of at least 10 years.

2 | MATERIAL AND METHODS

2.1 | Study registration

The review protocol was registered and allocated the identification number CRD42017049602 in the PROSPERO international prospective register of systematic reviews hosted by the National Institute for Health Research (NIHR), University of York, UK, Center for Reviews and Dissemination.

2.2 | Reporting format

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) were adopted throughout the process of the present systematic review (Moher, Liberati, Tetzlaff, & Altman, 2009; Moher et al., 2015).

2.3 | Population (P), exposure (E), comparison (C) and outcomes (O) (PECO)

2.3.1 | Population

Edentulous and partially edentulous patients with osseointegrated titanium/titanium alloy dental implants.

2.3.2 | Exposure

Dental implants placed in augmented sites prior or simultaneous to implant placement, including alveolar ridge preservation and/or vertical/lateral ridge augmentation.

2.3.3 | Comparison

Dental implants placed in sites not requiring augmentation procedures prior to or in conjunction with implant placement (i.e. pristine sites).

2.3.4 | Outcome

Primary outcome: Prevalence of biological complications (i.e., peri-implant mucositis and peri-implantitis).

Secondary outcome: Prevalence of implant failure (i.e. implant loss).

2.4 | Focused questions

The focused questions were adapted using the PECO criteria (Stone, 2002).

Primary outcome: In patients with osseointegrated dental implants, are there differences in biological complications at implants placed in pristine vs. augmented sites?

Secondary outcome: In patients with osseointegrated dental implants, are there differences in failure rates of implants placed in pristine vs. augmented sites?

2.5 | Search strategy

2.5.1 | Electronic search

A comprehensive and systematic electronic search of MEDLINE via PubMed, EMBASE via Ovid and Cochrane Central Register of Controlled Trials (CENTRAL) databases was conducted for articles published in the dental literature in English, German, French, Italian, Spanish and Portuguese up to 8 April 2017.

For the search in the PubMed library, combinations of controlled terms (MeSH and EMTREE) and keywords were used whenever possible.

For additional searches, terms not indexed as MeSH and filters were also applied:

((“bone and bones”[MeSH Terms] OR (“bone”[All Fields] AND “bones”[All Fields]) OR “bone and bones”[All Fields] OR “bone”[All Fields]) AND augmentation[All Fields]) AND (“dental health services”[MeSH Terms] OR (“dental”[All Fields] AND “health”[All Fields] AND “services”[All Fields]) OR “dental health services”[All Fields] OR “dental”[All Fields]) AND implant[All Fields] AND (10[All Fields] AND years[All Fields]) AND “humans”[MeSH Terms]

(“bone regeneration”[MeSH Terms] OR (“bone”[All Fields] AND “regeneration”[All Fields]) OR “bone regeneration”[All Fields]) AND (“dental implants”[MeSH Terms] OR (“dental”[All Fields] AND “implants”[All Fields]) OR “dental implants”[All Fields] OR (“dental”[All Fields] AND “implant”[All Fields]) OR “dental implant”[All Fields]) AND (“long”[All Fields] AND (“term”[MeSH Terms] OR (“term”[All Fields]) OR “term”[All Fields]) AND “humans”[MeSH Terms]

(((((“dental implants”[MeSH Terms] OR “dental implantation, endosseous”[MeSH Terms]) AND long-term[Title/Abstract]) OR 10 years[Title/Abstract]) AND peri-implant diseases[Title/Abstract]) OR peri-implantitis[Title/Abstract]) AND mucositis[Title/Abstract] OR peri-implant mucositis[Title/Abstract]

(implant[All Fields] AND (“dental health services”[MeSH Terms] OR (“dental”[All Fields] AND “health”[All Fields] AND “services”[All Fields]) OR “dental health services”[All Fields] OR “dental”[All Fields]) AND 10[All Fields] AND year[All Fields]) AND ((Clinical Trial[ptyp] OR Clinical Study[ptyp] OR Case Reports[ptyp] OR Controlled Clinical Trial[ptyp] OR Randomized Controlled Trial[ptyp]) AND “humans”[MeSH Terms])

2.5.2 | Manual search

A manual search of the reference lists of relevant articles published in the *Journal of Periodontology*, *Journal of Oral Rehabilitation*, *Journal of Clinical Periodontology*, *Clinical Oral Implants Research*, *International Journal of Oral & Maxillofacial Implants*, *Implant Dentistry*, *Clinical Implant Dentistry and Related Research*, *International Journal of Periodontics and Restorative Dentistry* and the *International Journal of Prosthodontics* of the last 3 years was performed.

2.5.3 | Unpublished literature search

In order to further identify potential articles for inclusion, grey literature was searched in the register of clinical studies hosted by the US National Institutes of Health (www.clinicaltrials.gov) and in the multidisciplinary European database (www.opengrey.eu).

2.6 | Study selection

2.6.1 | Inclusion criteria

The following inclusion criteria were applied:

- Clinical studies with all levels of evidence
- Case series with ≥ 20 patients at baseline
- Studies reporting on titanium/titanium alloy implants
- Studies with a mean follow-up ≥ 10 years
- Studies reporting on lateral and/or vertical augmentation procedures before or at time of implant placement
- Studies reporting on alveolar ridge preservation before implant placement
- Clinical and radiographic examinations at follow-up
- Studies including case definitions of peri-implant mucositis and peri-implantitis

2.6.2 | Exclusion criteria

The following exclusion criteria were applied:

- Preclinical studies
- Narrative reviews
- Abstracts
- Letters to editors
- Studies reporting on zirconia implants
- Studies reporting on early implant losses/complications (i.e., before implant loading)
- Studies reporting on augmentation procedures in the sinus cavity
- Studies reporting on zygomatic implants
- Studies reporting on tilted implants
- Studies reporting on distraction osteogenesis
- Studies reporting on subperiosteal implants
- Studies reporting on bicortical implants
- Studies reporting on hollow-cylinder and hollow-screw implants
- Studies reporting on patients taking medications/therapy affecting bone metabolism (i.e., bisphosphonates, radiation therapy)
- Studies reporting on patients with pathologies affecting bone metabolism (i.e., osteoporosis, osteopenia, rheumatoid arthritis)
- Studies reporting on implants placed in sites affected by tumours
- Lack of information on whether augmentation procedures were performed or not
- Studies reporting on multiple augmentation procedures in which insufficient information is available to sort the data

- Insufficient/unclear information on clinical and/or radiographic parameters leading to a case definition of peri-implant mucositis and peri-implantitis
- No author response to inquiry email for data clarification

Screening was performed independently by two reviewers (G.E.S. and A. M.). A third reviewer (C. T.) screened the selected full-text articles for consistency of the findings. A Cohen kappa score was calculated to assess interexaminer agreement (Landis & Koch, 1977). Eligibility assessment was performed firstly through titles and abstract analysis and secondly through full-text analysis. In order to avoid exclusion of potentially relevant articles, abstracts providing unclear results were included in the full-text analysis. If necessary, authors were contacted for clarifications. From all studies of potential relevance, full text was obtained for independent assessment by the two reviewers against the stated inclusion criteria. Any disagreement was resolved by discussion among the three reviewers. In the event of multiple publications on the same patient sample, relevant data on the primary and secondary outcome measures were extracted from the publication with a mean follow-up ≥ 10 years.

2.7 | Data collection

From the selected articles fulfilling the inclusion criteria, data addressing the primary and secondary outcome measures were extracted for analysis.

2.8 | Quality assessment

The Newcastle-Ottawa Scale (NOS) for assessing the quality of non-randomized, non-interventional studies was applied (Wells et al., 2011). The topics evaluated were selection of study groups, comparability of participants and outcome. Each included study received a maximum of 13 points for cohort studies and of 10 points in case–control studies.

The criteria used to evaluate the quality of the selected randomized controlled trials (RCTs) derived from the randomized clinical trial checklist of the Cochrane Center and the CONSORT (Consolidated Standards of Reporting Trials) statement, providing guidelines for the following parameters: (i) sequence generation; (ii) allocation concealment method; (iii) masking of the examiner; (iv) address of incomplete outcome data; and (v) free of selective outcome reporting. The degree of bias was categorized as low risk if all the criteria were met, moderate risk when only one criterion was missing and high risk if two or more criteria were missing (Moher et al., 2015; Schulz, Altman, Moher, & Fergusson, 2010).

2.9 | Data synthesis

Preliminary evaluation of the selected publications revealed considerable heterogeneity between the studies with respect to design and sample characteristics. Consequently, a qualitative report of the data was planned by applying descriptive methods and, if possible, a quantitative data synthesis for meta-analyses was applied.

2.10 | Data analysis

The I^2 statistic test was applied to quantify heterogeneity among studies. After grouping data with respect to the use or not of an augmentation procedure, meta-analyses were performed to estimate overall prevalence at patient and at implant levels for the following outcomes: peri-implant mucositis, peri-implantitis and implant failure, using a specific software for meta-analysis (OpenMeta[Analyst]) (open source software, Brown University of Public Health, RI, USA). The binary random-effects method was chosen. Results are presented as Forest plots with weighted mean values and 95% confidence intervals (CI). A p value <.05 was considered statistically significant.

3 | RESULTS

3.1 | Study selection

A total of 852 records were identified through the electronic search and supplemented with 32 citations from the manual search and through screening of bibliographies of relevant included/excluded articles for a total of 864 citations following removal of duplicates (Figure 1).

Upon exclusion of 692 publications based on their titles, 172 studies remained for full-text evaluation. Following exclusion of 130 studies based on abstract, 42 studies remained. Finally, based on full-text assessment, 34 studies were excluded (Table 1) yielding eight studies (Daubert et al., 2015; Donati, Ekestubbe, Lindhe, & Wennström, 2016; Roccuzzo, Bonino, Dalmasso, & Aglietta, 2014; Roccuzzo, Gaudioso, Bunino, & Dalmasso, 2014; Roccuzzo, Savoini, Dalmasso, & Ramieri, 2017; Simion, Ferrantino, Idotta, & Zarone, 2016; Tenenbaum et al., 2017; Zuffetti et al., 2016) for qualitative synthesis. Out of the final eight publications, four evaluated the prevalence of peri-implant diseases around implants placed in pristine sites (Donati et al., 2016; Roccuzzo, Bonino, et al., 2014; Tenenbaum et al., 2017; Zuffetti et al., 2016) (Table 2a), three in augmented sites (Roccuzzo, Gaudioso, et al., 2014; Roccuzzo et al. 2017; Simion et al., 2016) (Table 2b) and one in both pristine and augmented sites (Daubert et al., 2015), respectively (Table 2c). An interexaminer Cohen's kappa score of 0.93 was calculated.

3.2 | Meta-analyses

Data were extracted from the selected papers and grouped according to patient characteristics as reported in the articles (i.e., periodontal conditions, smoking history, adherence to supportive periodontal therapy, loading time). The presence or absence of an augmentation procedure was used as a covariate for the analysis.

3.3 | Prevalence of biological complications and implant failure

The number of events on the total number observed for reported biological complications was entered in the meta-analysis software. Six

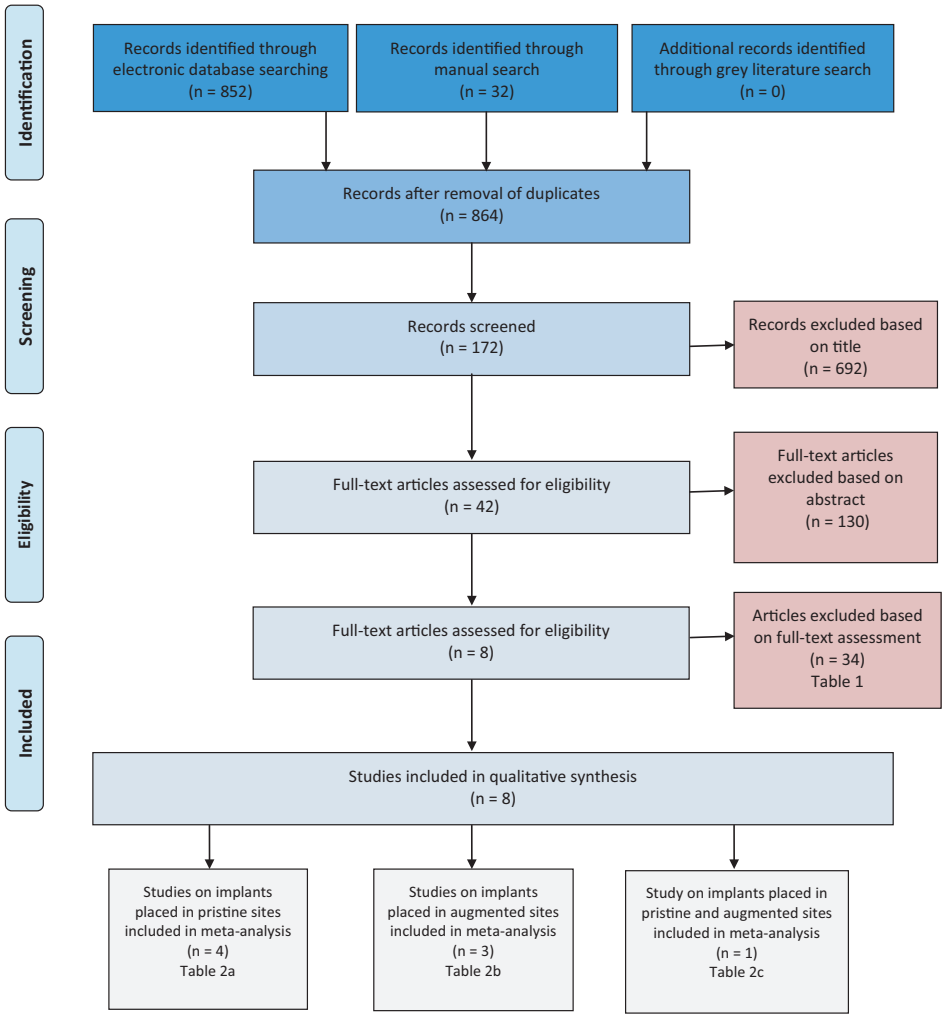

FIGURE 1 Flow diagram of the systematic review

publications provided data for estimating prevalence of peri-implant mucositis at patient level (Roccuzzo, Bonino, et al., 2014; Roccuzzo, Gaudioso, et al., 2014; Roccuzzo et al. 2017; Simion et al., 2016; Tenenbaum et al., 2017; Zuffetti et al., 2016). In those publications, data were reported according to subgrouping, resulting in seven clusters for patients with pristine and three clusters for patients with augmented sites, respectively.

Seven publications provided data on the prevalence of peri-implantitis at patient level (Donati et al., 2016; Roccuzzo, Bonino, et al., 2014; Roccuzzo, Gaudioso, et al., 2014; Roccuzzo et al. 2017; Simion et al., 2016; Tenenbaum et al., 2017; Zuffetti et al., 2016). Subgroup analysis resulted in eight clusters for patients with pristine and three clusters for augmented sites, respectively.

Seven publications provided data on mucositis and on peri-implantitis at implant level (Daubert et al., 2015; Donati et al., 2016; Roccuzzo, Gaudioso, et al., 2014; Roccuzzo et al. 2017; Simion et al., 2016; Tenenbaum et al., 2017; Zuffetti et al., 2016), with six clusters for pristine and four clusters for augmented sites, respectively.

Data on implant failure at patient level could be extracted from seven publications (Donati et al., 2016; Roccuzzo, Bonino, et al., 2014; Roccuzzo, Gaudioso, et al., 2014; Roccuzzo et al. 2017; Simion et al., 2016; Tenenbaum et al., 2017; Zuffetti et al., 2016), with eight groups for pristine sites and three groups for augmented sites, while six publications provided data for failure at implant level (Daubert et al., 2015; Donati et al., 2016; Roccuzzo, Bonino, et al., 2014; Roccuzzo et al. 2017; Tenenbaum et al., 2017; Zuffetti et al., 2016), with nine groups for pristine and two for augmented sites, respectively.

3.4 | Meta-analyses at patient level

3.4.1 | Peri-implant mucositis

The total number of patients observed was 321, 242 for pristine sites and 79 for augmented sites. The meta-analysis of prevalence of peri-implant mucositis at patient level yielded weighted mean values of 22.4% (95% CI 6%–38%) for pristine and of 19.6% (95% CI 0%–40%) for augmented sites, respectively. Heterogeneity as expressed by the I^2 test was 93% for pristine and 88% for augmented sites, respectively (Figure 2).

TABLE 1 List of excluded publications based on full-text assessment and reasons for exclusion

Publication	Reason for exclusion
Karoussis et al. (2003)	Lack of information on whether augmentation procedures were performed or not
Karoussis et al. (2004)	Lack of information on whether augmentation procedures were performed or not
Fransson, Lekholm, Jemt, and Berglundh (2005)	Mean follow-up <10 years
Roos-Jansåker, Lindahl, Renvert, and Renvert (2006a)	Lack of information on whether augmentation procedures were performed or not
Roos-Jansåker, Lindahl, Renvert, and Renvert (2006b)	Lack of information on whether augmentation procedures were performed or not
Roos-Jansåker, Renvert, Lindahl, and Renvert (2006c)	Lack of information on whether augmentation procedures were performed or not
Renvert, Roos-Jansåker, Lindahl, Renvert, and Persson (2007)	Lack of information on whether augmentation procedures were performed or not
Fransson, Wennström, and Berglundh (2008)	Mean follow-up <10 years
Fransson, Wennström, Tomasi, and Berglundh (2009)	Mean follow-up <10 years
Fransson et al. (2010)	Lack of information on clinical parameters for a case definition of peri-implantitis
Bonde, Stokholm, Isidor, and Schou (2010)	Lack of comparison between augmented and pristine sites with respect to biological complications or implant failure
Simonis, Dufour, and Tenenbaum (2010)	Lack of information on whether augmentation procedures were performed or not
Fischer and Stenberg (2012)	Lack of comparison between augmented and pristine sites with respect to biological complications or implant failure
Renvert, Lindahl, and Persson (2012)	Lack of information on whether augmentation procedures were performed or not
Gotfredsen (2012)	Lack of information on whether augmentation procedures were performed or not
Swierkot, Lottholz, Flores-de-Jacoby, and Mengel (2012)	Insufficient information for data extraction
Stoker, van Waas, and Wismeijer (2012)	Lack of information on whether augmentation procedures were performed or not
Frisch, Ziebolz, and Rinke (2013)	Lack of information on whether augmentation procedures were performed or not
Lehmann et al. (2013)	Sinus floor elevation and insufficient information for data extraction
Cecchinato, Parpaiola, and Lindhe (2014)	Lack of information on whether augmentation procedures were performed or not
Schropp, Wenzel, and Stavropoulos (2014)	Lack of information on whether augmentation procedures were performed or not
Mangano et al. (2014)	Lack of information on whether augmentation procedures were performed or not
Meijer, Raghoebar, de Waal, and Vissink (2014)	Lack of information on whether augmentation procedures were performed or not
Meyle, Gersok, Boedeker, and Gonzales (2014)	Lack of information on whether augmentation procedures were performed or not
Renvert, Aghazadeh, Hallström, and Persson (2014)	Lack of information on whether augmentation procedures were performed or not
Trullenque-Eriksson and Guisado Moya (2014)	Lack of information on whether augmentation procedures were performed or not
Trullenque-Eriksson and Guisado Moya (2015)	Lack of information on whether augmentation procedures were performed or not
Frisch, Ziebolz, Vach, and Ratka-Krüger (2015)	Lack of information on whether augmentation procedures were performed or not
French, Larjava, and Ofec (2015)	Insufficient information for data extraction
van Velzen, Ofec, Schulten, and Ten Bruggenkate (2015)	No information on clinical parameters for a case definition of peri-implantitis
Woelber, Ratka-Krueger, Vach, and Frisch (2016)	Lack of information on whether augmentation procedures were performed or not
Jemt, Karouni, Abitbol, Zouiten, and Antoun (2017)	Insufficient information for data extraction
Urban, Monje, Lozada, and Wang (2017)	Lack of information on clinical parameters for a case definition of peri-implantitis
Gurgel et al. (2017)	Insufficient information for data extraction

3.4.2 | Peri-implantitis

The total number of patients observed was 351, 272 for pristine sites and 79 for augmented sites. The prevalence of peri-implantitis at patient level was estimated to a weighted mean of 10.3% (95% CI 4%–17%) for pristine sites and of 17.8% (95% CI 0%–37%) for augmented sites. Heterogeneity as expressed by the I^2 test was 80% for pristine and 87% for augmented sites, respectively (Figure 3).

TABLE 2 Characteristics of the included studies on implants placed in (a) pristine sites, (b) augmented sites and (c) pristine and augmented sites, respectively [In PDF format, this table is best viewed in two-page mode]

(a)

Publication (year)	Study design	Mean follow-up ± *SD* (years)	Number of subjects (n)	Mean age ± *SD* (years)	Gender	Subject's characteristics	Group	Number of implants (n)	Implant system (s)	Type of restoration	Type of augmentation	Timepoint of augmentation	Augmentation material
Roccuzzo, Bonino, et al. (2014)	Prospective case series	10	32	43.3 ± 12.4	NR	ASA type I-II partially edentulous	Periodontally healthy subjects	54	Institute Straumann AG	FDPs	N	N	N
			46	53.3 ± 10.7			Subjects with moderate periodontitis	96			N	N	N
			45	52.7 ± 8.4			Subjects with severe periodontitis	102			N	N	N
Donati et al. (2016)	Prospective case series	12	31	NR	NR	ASA type I-II partially edentulous	Pristine bone	35	Astra Tech	SCs	N	N	N
Zuffetti et al. (2016)	Randomized controlled	10	25	51.6	48% females 52% males	ASA type I-II partially edentulous	Immediate loading	52	Zimmer Biomet 3i	FDPs	N	N	N
			27	51.3	62% females 48% males		Early loading	52			N	N	N
Tenenbaum et al. (2017)	Prospective case series	10.8 ± 1.7	52	63 ± 9.23	63.5% (F) 36.5% (M)	ASA type I-II partially edentulous	Pristine bone	108	Institute Straumann AG	FDPs	N	N	N

(b)

Publication (year)	Study design	Mean follow-up ± *SD* (years)	Number of subjects	Mean age ± *SD* (years)	Gender	Subject's characteristics	Group	Number of implants	Implant system	Type of restoration	Type of augmentation	Timepoint of augmentation	Augmentation material
Roccuzzo, Gaudioso, et al. (2014)	Prospective case–control	10	19	48.4	37.85% females 62.15% males	ASA type I-II partially edentulous	ARP	19	Institute Straumann AG	SCs	ARP	At tooth extraction	DBBM
			15	47.2	47% females 53% males		PB	15			N	N	N
Roccuzzo et al. (2017)	Prospective case series	10	34	48.5 ± 10.6	71% females 29% males	ASA type I-II partially edentulous	GBR	68	Institute Straumann AG	FDPs	VRA	Before implant placement	Autogenous bone block and particulated autogenous bone
Simion et al. (2016)	Retrospective case series	15 (range: 13–21 years)	33	62	30% females 70% males	Systemic conditions NR partially edentulous	GBR	91	Nobel Biocare	FDPs	VRA	Before implant placement	Autogenous bone or blood clot and DBBM

(Continues)

TABLE 2 (additional columns)

			Confounding factors								Biological complications		
Type of barrier membrane	Implant survival rate at subject level/implant level (%)	Implant failure rate at subject level/implant level (%)	Subjects with a smoking history (%)	Subjects with a history of periodontal disease (%)	FMPS (%)	% of subjects with SPT	Presence/absence of KM	Case definition of peri-implant mucositis	Case definition of peri-implantitis	Mean bone level changes (mm) ± *SD* from Baseline	Mucositis at implant level/subject level (%)	Peri-implantitis at implant level/subject level (%)	Comments
N	100%/100%	0%/0%	15.60%	0	22.1 ± 10.8	59.40%	NR	BoP+ BL ≤2 mm PPD>5 mm	BoP+, BL > 2 mm PPD> 5 mm	NR	NR/15.6%	NR/3.1%	Personal communication Analysis at subject level
	93.5%/96.9%	6.5%/3.1%	13%	100	27.7 ± 14.8	54.30%				NR	NR/36.9%	NR/15.2%	
	93.4%/97.1%	6.6%/2.9%	22.20%	100	30.4 ± 20.6	68.90%				NR	NR/24.4%	NR/42.2%	
N	89.7%/90.9%	10.3%/9.1%	NR	NR	NR	100%	NR	BOP+	BoP+ and BL ≥ 2 mm	0.67 ± 2.20 at subject level 0.61 ± 2.10 at implant level	25%/NR	8.6%/10%	Subjects enrolled in SPT up to 5 years and then dismissed to dental provider for SPT in private practice
N	96%/98.1%	4%/1.9%	NR	NR	NR	100%	NR	Heavily inflamed soft tissue without BL	BL + suppuration + heavily inflamed tissues	1.34 ± 0.55 at subject level	4%/12%	0%/0%	Immediate implants with gap >1.5 mm were filled with DBBM Implants with peri-implantitis reported in early loading group did not present signs of inflammation at time of X-ray evaluation; however BL was overt
N	100%/100%	0%/0%	NR	NR	NR		NR			1.42 ± 0.64 at subject level	0%/0%	3.8%/3.7%	
N	98.1%/99.1%	1.9%/0.9%	13%	84.61%	0.33 ± 0.67	100%	NR	BoP+	PPD>5 mm BoP+ BL>4.5 mm	NR	60.2%/73.1%	12%/15.4%	Plaque Index based on Silness & Löe (1964)

			Confounding factors								Biological complications		
Type of barrier membrane	Implant survival rate at subject level/implant level (%)	Implant failure rate at subject level/implant level (%)	Subjects with a smoking history (%)	Subjects with a history of periodontal disease (%)	FMPS (%)	% of subjects with SPT	Presence/absence of KM	Case definition of peri-implant mucositis	Case definition of peri-implantitis	Mean bone level changes (mm) ± *SD* from Baseline	Mucositis at subject level/implant level (%)	Peri-implantitis at subject level/implant level (%)	Comments
Collagen	100%/100%	0%/0%	5.20%	NR	24.4 ± 6.6%	100%	3.68 ± 1.11 mm	BoP+ BL ≤2 mm PPD>5 mm	BoP+ BL>2 mm PPD>5 mm	0.21 ± 0.42 subject level	5.2%/5.2%	0%/0%	Patients were prospectively evaluated but not randomized 13.9% of the cases received additional buccal bony contour augmentation Systemic antibiotics were used to prevent post-surgical complications 2 patients dropped out
	100%/100%	0%/0%	20%		21.5 ± 8.1%		3.93 ± 0.8 mm			0.20 ± 0.32 subject level	6.6%/6.6%	0%/0%	
Titanium-reinforced ePTFE or Titanium mesh	88.2/94.1%	11.8/5.9%	NR	PHP (53%)	PHP (26.4%)	100%	1.89 ± 1.11 mm	BOP+ BL ≤2 mm PD>5 mm	BOP+ BL>2 mm PD>5 mm	PHP: 0.43 ± 0.50	20.6%/10.3%	32.3%/16.2%	7 patients with 14 implants dropped out
				PCP (47%)	PCP (15.7%)					PCP: 0.78 ± 0.59			
Titanium-reinforced ePTFE	89.9%/96.7	9.1/3.3%	27%	18%	54%	30%	72%	Inflammation of the peri-implant mucosa without discernible progressing BL	Infection with suppuration associated with clinically significant progressing BL after the adaptive phase	1.02 ± 1.47 implant level	60.6%/44%	15.2%/9.9%	

(Continues)

TABLE 2 (Continued) [In PDF format, this table is best viewed in two-page mode]

(c)

Publication (year)	Study design	Mean follow- and range (years)	Number of subjects (n)	Mean age ± *SD* (years) at follow-up	Gender	Subject's characteristics	Group	Number of implants (n)	Implant system (s)	Type of restoration	Type of regeneration	Timepoint of augmentation	Augmentation material
							Pristine bone	153			N	N	N
Daubert et al. (2015)	Cross-sectional	10.9 ± 1.5 (8.9–14.8)	96	67.6 ± 10.6	50% females 50% males	Systemic conditions NR Partially and fully edentulous	Augmented bone	53	Zimmer Biomet 3i, Institute Straumann AG, Nobel Biocare, Brånemark System, Centerpulse Dental, Astra Tech, Sulzer Dental, Steri-Oss	Cement-retained (69.4%)/ screw-retained (30.6%) FDPs	NR	NR	Biogran®, BioOss®, AB, Osseograft™, DFDBA, BioOss® mixed with Puros®, BioOss® mixed with AB

AB, autogenous bone; ARP, alveolar ridge preservation; ASA, American Society of Anaesthesiology; BL, bone loss; BoP, Bleeding on Probing; DBBM, deproteinized bovine bone mineral; DFDBA, demineralized freeze-dried bone allograft; ePTFE, expanded Poly-Tetra-Fluor-Ethylene; FDP, fixed dental prosthesis; FMPS, full-mouth plaque score; GBR, guided bone regeneration; KM, keratinized mucosa; N, none; NR, not reported; PB, pristine bone; PCP, periodontally compromised patient; PHP, periodontally healthy patient; PPD, pocket probing depth; SC, single-unit crown; *SD*, standard deviation; SLA, sandblasted and acid-etched; SPT, supportive periodontal therapy; VRA, vertical ridge augmentation.

Astra Tech, Mölndal, Sweden; Biogran, Biomet 3i, Palm Beach Gardens, FL, USA; Biomend, Zimmer Biomet Dental, Warsaw, IN, USA.; BioOss, Geistlich Biomaterials, Wolhusen, Switzerland; Brånemark System, Nobel Biocare, Gothenburg, Sweden; Centerpulse Dental, Carlsbad, CA, USA; Institute Straumann AG, Basel, Switzerland; Nobel Biocare, Gothenburg, Sweden; Osseograft, Advanced Biotech Products Ltd., Chennai, India; Puros, Zimmer Biomet Dental, Warsaw, IN, USA; Steri-Oss, Nobel Biocare, Gothenburg, Sweden; Sulzer Dental, Carlsbad, CA, USA; Zimmer Biomet 3i, Palm Beach Gardens, FL, USA.

3.4.3 | Implant failure

The total number of patients observed was 352, 273 for pristine sites and 79 for augmented sites. The prevalence of implant failure at patient level was estimated to a weighted mean of 2.5% (95% CI 1%–4%) for pristine sites and of 3.6% (95% CI 0%–8%) for augmented sites. Heterogeneity as expressed by the I^2 test was 0% in both pristine and augmented sites, respectively (Figure 4).

3.5 | Meta-analyses at implant level

3.5.1 | Peri-implant mucositis

The total number of implants observed was 642, 415 for pristine sites and 227 for augmented sites. The prevalence of peri-implant mucositis at implant level presented a weighted mean value of 21.2% (95% CI 4%–38%) for pristine sites and of 24.6% (95% CI 6%–44%) for augmented sites. Heterogeneity as expressed by the I^2 test was 97% for pristine and 93% for augmented sites, respectively (Figure 5).

3.5.2 | Peri-implantitis

The total number of implants observed was 642, 415 for pristine sites and 227 for augmented sites. The prevalence of peri-implantitis at implant level presented a weighted mean value of 7.5% (95% CI 2%–13%) for pristine sites and of 9.7% (95% CI 4%–15%) for augmented sites. Heterogeneity as expressed by the I^2 test was 84% for pristine and 56% for augmented sites, respectively (Figure 6).

3.5.3 | Implant failure

The total number of implants observed was 739, 667 for pristine sites and 72 for augmented sites. The prevalence of failure at implant level presented a weighted mean value of 2.4% (95% CI 1%–4%) for pristine sites and of 6.5% (95% CI 0%–15%) for augmented sites. Heterogeneity as expressed by the I^2 test was 34% for pristine and 60% for augmented sites, respectively (Figure 7).

Collectively, as indicated in the Forest plots by the overlap of the 95% confidence intervals, no statistically significant differences ($p > .05$) were observed between implants placed in pristine vs. augmented sites for any outcome variables both at patient and at implant levels, respectively.

3.6 | Quality assessment

Five case-series studies (Donati et al., 2016; Roccuzzo, Bonino, et al., 2014; Roccuzzo et al. 2017; Simion et al., 2016; Tenenbaum et al., 2017), one case–control (Roccuzzo, Gaudioso, et al., 2014) and one cross-sectional study (Daubert et al., 2015) were assessed by means of the NOS (Wells et al., 2011). The mean ± standard deviation (*SD*) NOS score was 4.8 ± 1.8 for "selection" (median: 4, interquartile range

TABLE 2 (additional columns - continued)

			Confounding factors								Biological complications		
Type of barrier membrane	Implant survival rate at subject level/implant level (%)	Implant failure rate at subject level/implant level (%)	Subjects with a smoking history (%)	Subjects with a history of periodontal disease (%)	FMPS (%)	% of subjects with SPT	Presence/ absence of KM	Case definition of peri-implant mucositis	Case definition of peri-implantitis	Mean bone level changes (mm) ± *SD* from Baseline	Mucositis at subject level/ implant level (%)	Peri-implantitis at subject level/ implant level (%)	Comments
N	NR/91.5%	NR/8.5%			NR		NR			NR	NR/30.7%	NR/17.6%	
Biomend®	NR/88.7%	NR/11.3%	5.60%	NR	NR	84.37%	NR	BoP^+ and/or inflammation	BoP^+ and/or suppuration and BL ≥ 2 mm after remodelling and PPD ≥ 4 mm	NR	NR/39.6%	NR/11.3%	Author was contacted

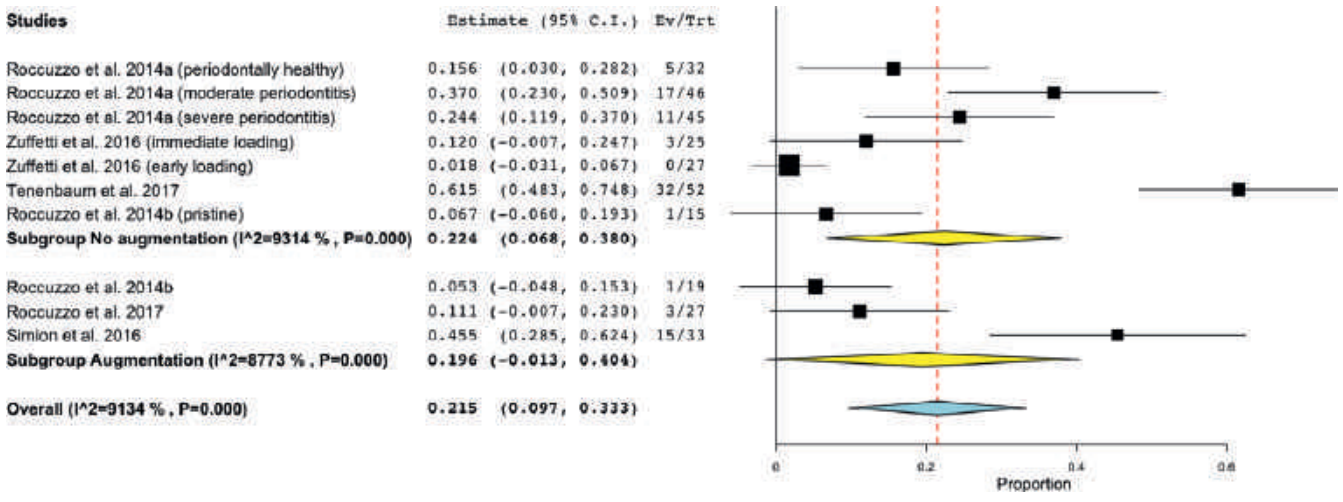

FIGURE 2 Forest plot of the weighted mean prevalence of peri-implant mucositis at patient level of implants placed in pristine vs. augmented sites

[IQR]: 0), 2.6 ± 1.6 for "comparability" (median: 1, IQR: 0) and 3.8 ± 2.8 for "exposure/outcome" (median: 3, IQR: 0.5) (Table 3).

One randomized clinical trial (Zuffetti et al., 2016) was scored according to the randomized clinical trial checklist of the Cochrane Center and the CONSORT (Consolidated Standards of Reporting Trials) statement. Two points were given to "selection of bias," one to "detection of bias" and one to "reporting bias" (Table 4).

4 | DISCUSSION

The aim of the present systematic review was to investigate and compare the prevalence of biological complications and failure of implants placed in pristine sites vs. augmented sites after a mean observation period of at least 10 years. The outcomes of the meta-analysis failed to reveal any statistically significant differences

between implants placed in pristine and augmented sites for any outcome variables both at patient and implant levels, respectively. Nevertheless, patients receiving implants in augmented sites displayed higher variability and lower predictability in terms of peri-implantitis compared with patients receiving implants in pristine sites. Even though the meta-analysis yielded its weakness from an outcome point of view, it had the merit to highlight the high heterogeneity and the limited number of studies available on this topic. Moreover, a great variability in terms of patient sampling, case definitions and eligibility criteria was observed. In fact, the studies included in the present systematic review did not directly address the focused questions or reported prospectively data on cohorts of patients treated with implants placed in augmented vs. pristine sites but reported on patients in need of implant therapy based on different eligibility criteria and case definitions. From a methodological point of view, another shortcoming of the present systematic review was the impossibility to identify randomized controlled trials (RCTs) complying with ethical guidelines. The avoidance of augmentation procedures in cases considered necessary is in contrast with the ethical principle of maintaining the same standard of care for all patients.

This limitation was overcome in a randomized controlled trial by selecting implants of different length in cases of vertical bone augmentation in the anterior mandible followed by prosthetic rehabilitation with an overdenture (Visser et al., 2016). The results of that RCT, however, indicated that implants with a length of 13–18 mm placed in mandibular sites augmented with anterior iliac crest yielded a significantly lower survival rate (88.7%) compared with that of implants with a length of 8–11 mm placed in pristine bone (98.7%) up to 15 years (Visser et al., 2016). Hence, these outcomes (Visser et al., 2016) are in partial agreement with the findings of the present systematic review as even though the meta-analysis failed to show statistical significance, failure rate was higher for implants placed in augmented sites compared with pristine sites.

It was observed that only three of eight studies included in the present systematic review reported data on the history of treated periodontitis prior to implant placement (Roccuzzo, Bonino, et al., 2014; Roccuzzo et al. 2017; Simion et al., 2016). This might stand for one of the reasons of the high variability of the outcomes in the present systematic review as history of periodontal disease is regarded as the major risk factor for peri-implantitis (Derks et al., 2016; Sanz & Chapple, 2012). Findings from several studies indicated that patients treated for chronic or aggressive periodontitis may experience more biological complications and implant failures compared with non-periodontitis patients (Aguirre-Zorzano et al., 2015; Derks et al., 2016; Monje et al., 2014; Sgolastra, Petrucci, Severino, Gatto, & Monaco, 2015; Sousa et al., 2016). In fact, outcomes of a recent publication on the effectiveness of implant therapy in a Swedish population sample indicated that significantly higher odds ratios (ORs) for moderate/severe peri-implantitis were found for patients diagnosed with periodontitis (OR 4.08) compared with periodontally healthy patients (Derks et al., 2016).

Moreover, the endpoints of periodontal therapy were shown to impact on the survival and success rates of dental implants (Pjetursson et al., 2012). The presence of residual pocket probing depths ≥5 mm and bleeding on probing scores ≥ 30% at the end of active periodontal therapy represented a significant risk of peri-implantitis and implant loss over a mean follow-up period of 7.9 years (Pjetursson et al., 2012). In addition, patients adhering to regular supportive periodontal therapy (SPT) and developing periodontal re-infections were at greater risk of peri-implantitis and implant failure compared with periodontally stable patients (Monje et al., 2016, 2017; Pjetursson et al., 2012).

All studies included in the present systematic review reported on the enrolment of patients in SPT following implant therapy. In this respect, it is well established that patients not enrolled in regular SPT suffer from higher prevalence of peri-implantitis and implant failure compared with patients enrolled in SPT (Monje et al., 2016; Roccuzzo, Bonino, et al., 2014; Rokn et al., 2017; Salvi & Zitzmann, 2014).

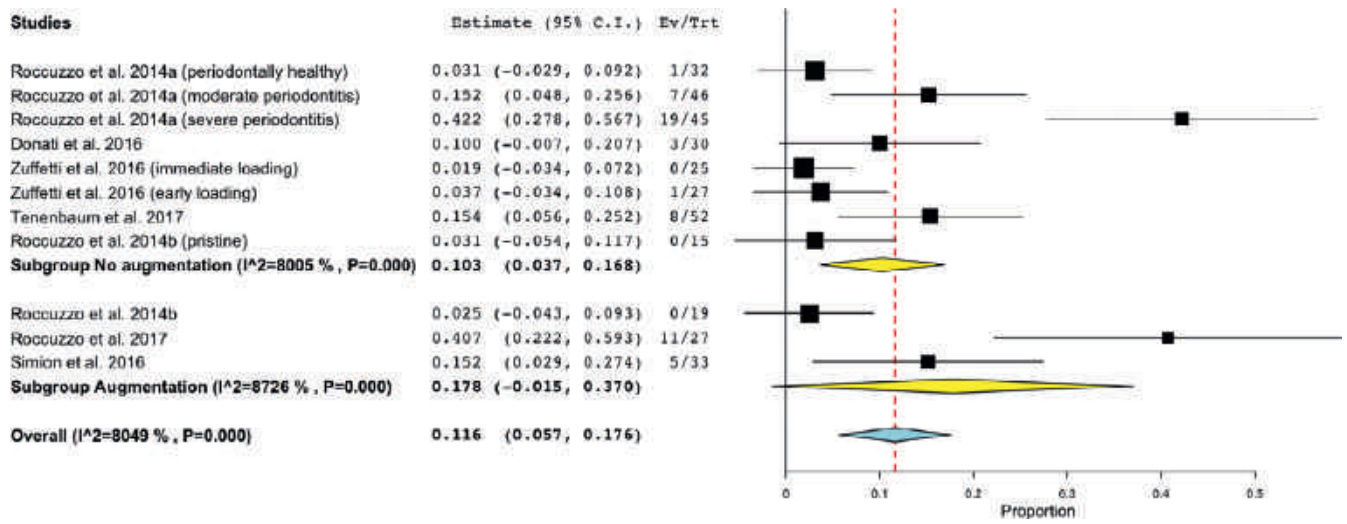

FIGURE 3 Forest plot of the weighted mean prevalence of peri-implantitis at patient level of implants placed in pristine vs. augmented sites

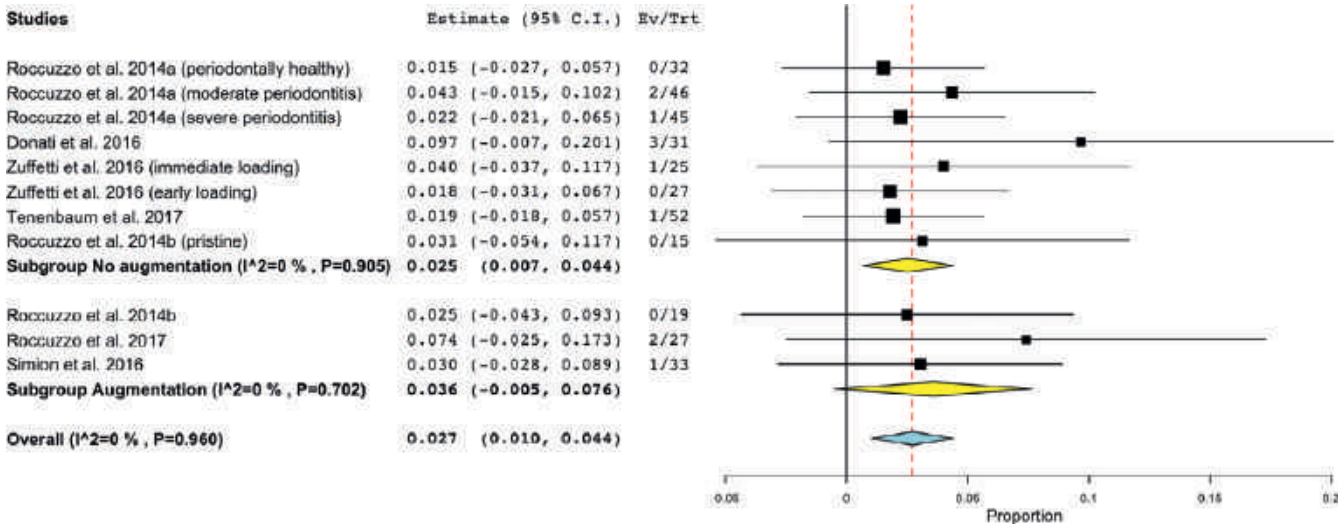

FIGURE 4 Forest plot of the weighted mean prevalence of failure at patient level of implants placed in pristine vs. augmented sites

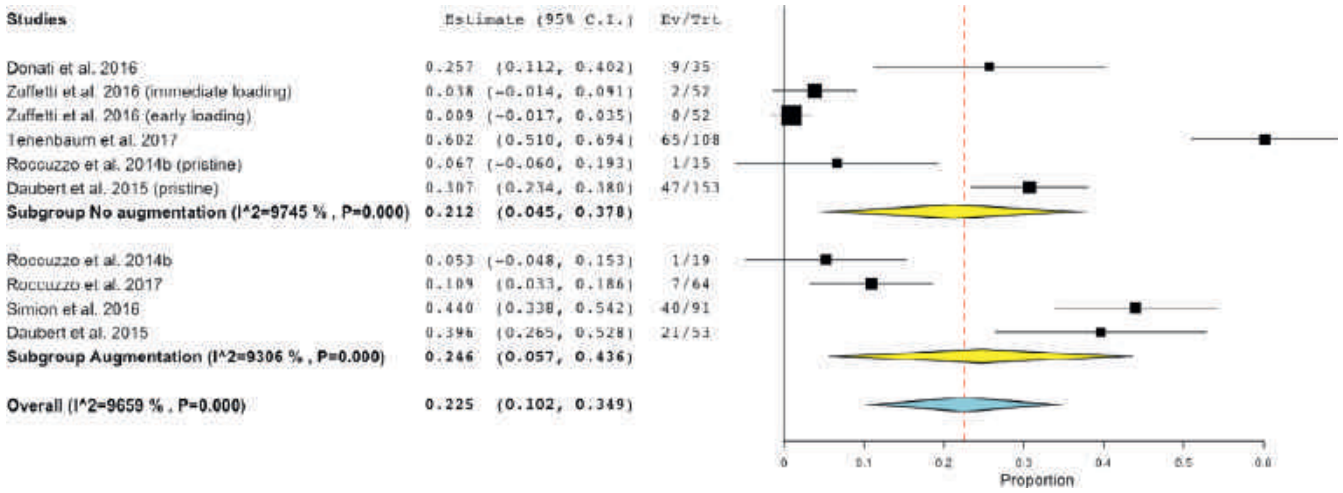

FIGURE 5 Forest plot of the weighted mean prevalence of peri-implant mucositis at implant level of implants placed in pristine vs. augmented sites

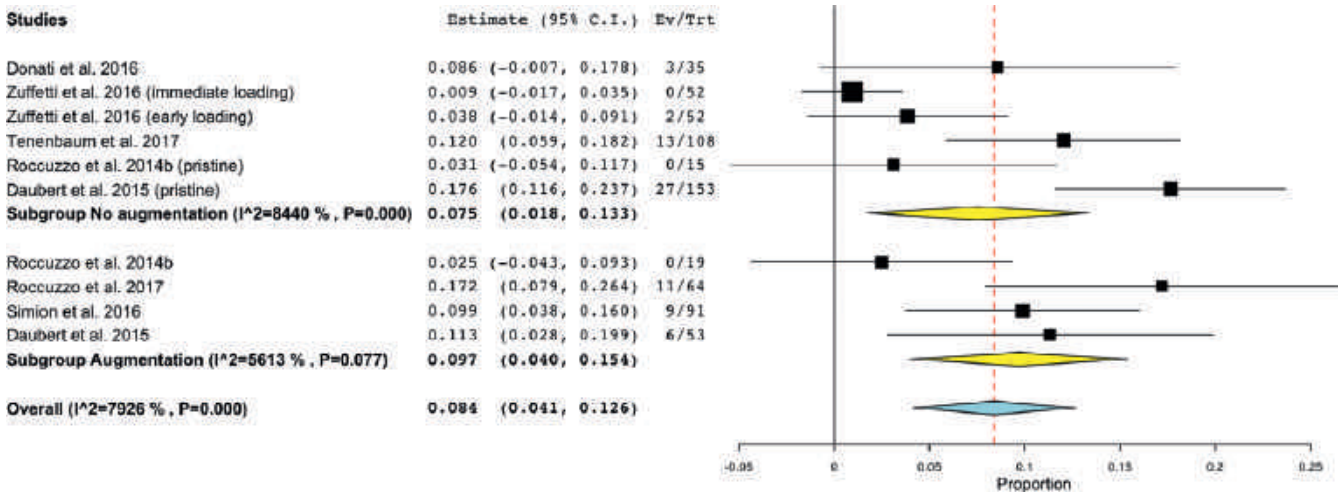

FIGURE 6 Forest plot of the weighted mean prevalence of peri-implantitis at implant level of implants placed in pristine vs. augmented sites

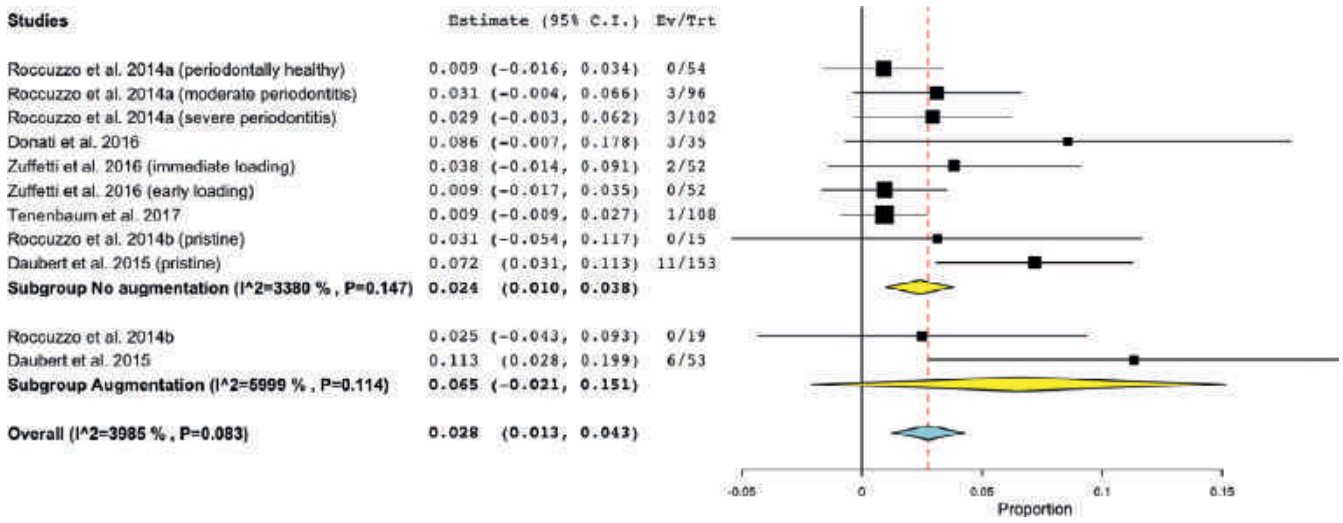

FIGURE 7 Forest plot of the weighted mean prevalence of failure at implant level of implants placed in pristine vs. augmented sites

TABLE 3 Newcastle-Ottawa Scale for assessing the quality of non-randomized, non-interventional studies

Publication	Selection	Comparability	Exposure/outcome
Roccuzzo, Bonino, et al. (2014)	★★★★	★★	★★★★
Tenenbaum et al. (2017)	★★★★	★	★
Donati et al. (2016)	★★★	★	★★★
Simion et al. (2016)	★★★★	★	★★
Roccuzzo, Gaudioso, et al. (2014)	★★★★★	★	★★★
Roccuzzo et al. (2017)	★★★★	★	★★★
Daubert et al. (2015)	★★★★	★	★★★

TABLE 4 Parameters provided in the Cochrane Center and CONSORT guidelines (Consolidated Standards of Reporting Trials) to evaluate the quality of randomized controlled trials (RCTs)

Publication	Selection of bias	Performance of bias	Detection of bias	Attrition bias	Reporting bias	Other bias
Zuffetti et al. (2016)	★★		★		★	

Different augmentation techniques (e.g., alveolar ridge preservation or vertical ridge augmentation), different materials (e.g., autogenous bone or bone substitutes) and different barrier membranes (e.g., resorbable and non-resorbable) were used in the four studies reporting on implant placement in augmented sites (Daubert et al., 2015; Roccuzzo, Gaudioso, et al., 2014; Roccuzzo et al. 2017; Simion et al., 2016). Hence, the variety of materials and protocols used for bone augmentation could not be assessed in the meta-analysis but it may be assumed that it plays a role on the long-term prevalence of biological complications and implant failure reported in the present systematic review. Findings from a recent systematic review yielded a comparable risk for wound healing complications when using resorbable (18.3%) vs. non-resorbable membranes (17.6%) (Lim, Lin, Monje, Chan, & Wang, 2017). Nevertheless, it is known that non-exposed sites achieve a six-fold greater bone gain compared with augmented sites where wound dehiscence occurred (Machtei, 2001). Hence, findings from the present systematic review should be interpreted with caution due to the impossibility to perform subset analysis to gain insight on the impact of the augmentation procedure and/or biomaterials on the prevalence of peri-implant diseases.

5 | LIMITATIONS

Despite a comprehensive and strict screening process, some limitations might bias the outcomes of the present systematic review. Firstly, to the best of the authors' knowledge, no randomized controlled trials complying with ethical principles in cases where augmentation procedures were considered mandatory could be identified. Secondly, the included studies did not directly address the focused questions

but reported on patients in need of implant therapy based on different eligibility criteria and case definitions of biological complications and more importantly, not controlling for other confounders. Lastly, the meta-analysis highlighted the high heterogeneity and the limited number of studies fulfilling the inclusion criteria of the present systematic review.

Patient samples in the included studies were quite varied, differing with respect to clinical characteristics such as history of treated periodontitis and materials used for augmentation procedures. In addition, it should be highlighted that none of the four studies including augmentation procedures adopted the same technique, enhancing the heterogeneity due to sample selection. Therefore, results from the meta-analysis should be interpreted with caution, also considering the lack of representation of different augmentation techniques used and of the variety of implant designs available, resulting in a lack of generalizability of the results.

6 | FUTURE DIRECTIONS

The conduction of case–control studies in which patients with implants placed in augmented sites are matched with patients receiving implants in pristine sites and are prospectively evaluated should be encouraged. A higher level of evidence should include the performance of prospective cohort multi-centre studies in which patients in need of implants with augmentation procedures are recruited, treated according to standardized protocols and a priori-determined materials and enrolled in regular long-term maintenance to better capture the onset of disease.

7 | CONCLUSIONS

The studies included in the present systematic review did not directly address the focused questions. Hence, the outcomes of the meta-analysis should be interpreted with caution due to high variability with respect to patient sampling, case definitions of biological complications and eligibility criteria. Nevertheless, within the limitations of the present systematic review, patients receiving implants in augmented sites displayed higher variability and lower predictability in terms of peri-implantitis compared with patients receiving implants in pristine sites. Accordingly, future clinical trials should investigate the impact of augmentation procedures on implant outcomes controlling for other potential confounders and standardizing the alveolar bony defects.

CONFLICTS OF INTEREST

The authors do not report any conflicts of interest.

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REVIEW ARTICLE

WILEY CLINICAL ORAL IMPLANTS RESEARCH

Effect of advanced age and/or systemic medical conditions on dental implant survival: A systematic review and meta-analysis

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Abstract

Objectives: This review evaluated implant survival in geriatric patients (≥75 years) and/or the impact of systemic medical conditions.

Materials and Methods: Systematic literature searches were performed to identify studies reporting on geriatric subjects with dental implants and on implant patients who had any of the seven most common systematic conditions among geriatric patients. Meta-analyses were performed on the postloading implant survival rates. The impact of systemic medical conditions and their respective treatment was qualitatively analyzed.

Results: A total of 6,893 studies were identified; of those, 60 studies were included. The fixed-effects model revealed an overall implant survival of 97.3% (95% CI: 94.3, 98.7; studies = 7) and 96.1% (95% CI: 87.3, 98.9; studies = 3), for 1 and 5 years, respectively. In patients with cardiovascular disease, implant survival may be similar or higher compared to healthy patients. High implant survival rates were reported for patients with Parkinson's disease or diabetes mellitus type II. In patients with cancer, implant survival is negatively affected, namely by radiotherapy. Patients with bone metastases receiving high-dose antiresorptive therapy (ART) carry a high risk for complications after implant surgery. Implant survival was reported to be high in patients receiving low-dose ART for treatment of osteoporosis. No evidence was found on implant survival in patients with dementia, respiratory diseases, liver cirrhosis, or osteoarthritis.

Conclusions: Implant prostheses in geriatric subjects are a predictable treatment option with a very high rate of implant survival. The functional and psychosocial benefits of such intervention should outweigh the associated risks to common medical conditions.

KEYWORDS

aging, Alzheimer's disease, bisphosphonates, cancer, cardiovascular disease, chronic obstructive pulmonary disease, cirrhosis of the liver, dementia, dental implants, depression, diabetes mellitus, geriatric, hypertensive heart disease, hyposalivation, ischemic heart disease, lower respiratory infections, medication-related osteonecrosis of the jaw, meta-analysis, neurocognitive impairment, osteoarthritis, Parkinson's disease, radiotherapy, respiratory diseases, stroke, systematic review

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1 | INTRODUCTION

Current demographic trends suggest that tooth loss now occurs in later life, and an increased number of patients will require tooth replacements at an advanced age (Hugoson et al., 2005; Stock, Jurges, Shen, Bozorgmehr & Listl, 2015). In Germany and Switzerland, more than 90% of patients aged ≥75 years have a fixed and/or removable dental prosthesis, and this age group has an increasing number of implant restorations, compared to 20 years ago (Jordan & Micheelis, 2016; Schneider, Zemp & Zitzmann, 2017). This trend was likewise reported in the Department of Oral Surgery and Stomatology at the University of Bern, School of Dental Medicine, where there is a marked increase since the year 2000 in implant surgeries in the age cohort of ≥70 years (Schimmel, Müller, Suter & Buser, 2017). It has to be borne in mind that the prevalence of systemic medical conditions and frailty increase with age, and this may influence implant survival.

Today's aged generation present new challenges in the field of implant dentistry. Old and very old patients, terms that are often used when referring to persons 75 years or older, often present with functional dependency, multimorbidity, and frailty. This may or may not present a risk for implant placement, maintenance, and ultimately survival.

The world health report on aging published by the World Health Organization (WHO) lists the most common chronic conditions in elders: cardiovascular disease (CVD) (including ischemic heart disease, stroke, and hypertensive heart disease), cancer, respiratory diseases (chronic obstructive pulmonary disease COPD, and lower respiratory infections), diabetes mellitus, cirrhosis of the liver, osteoarthritis, and conditions that involve neurocognitive impairment (unipolar depression, Alzheimer's disease, and other dementias) (WHO, 2015).

Additional risks may arise from the treatment of these medical conditions, including negative side effects. Polypharmacy as well as radiotherapy directed toward the salivary glands may cause symptoms of dry mouth. High-dose bisphosphonates prescribed for the treatment of cancer with bone metastases may present a risk for necrosis of the jaw. Lower dose bisphosphonates are prescribed for the treatment of osteoporosis, although it is not listed among the seven most prevalent chronic systemic diseases in elders.

Any of these conditions or treatments might be considered by the patient or clinician as absolute or relative contraindication for implant surgery/therapy. Risks may be related to the surgical procedure itself, osseointegration, soft tissue response, as well as the long-term survival of the implant (Bartold, Ivanovski & Darby, 2016; Bornstein, Cionca & Mombelli, 2009). Another pathway of failure may be more indirect, via neglected oral hygiene and improper implant maintenance. For example, patients with dementia are known to have lower motivation to perform regular and meticulous oral hygiene, in addition to diminished cognitive and manual skills to perform the adequate procedures (Brändli, 2012). Reduced motor skills are also well documented for patients with rheumatoid arthritis (Lawrence et al., 2008; Zhang et al., 2002) or stroke (Schimmel et al., 2011).

Implant success and survival are well documented for younger age cohorts (Schimmel, Srinivasan, Herrmann & Müller, 2014), but little is known about the effect of age on osseointegration and long-term implant survival (Srinivasan, Meyer, Mombelli & Müller, 2016). In a comprehensive review of biological, clinical, and sociological considerations, Bartold et al. (2016) acknowledge the influence of physiological aging on wound healing. However, the complex process that leads to osseointegration of titanium implants as well as the accompanying inflammatory response has been mainly studied in animals (Bartold et al., 2016). Bornstein et al. reviewed and discussed the available evidence in relation to medical conditions that may influence early and late implant failure (Bornstein, Cionca & Mombelli, 2015; Bornstein et al., 2009) and found a low level of evidence that indicates absolute or relative contraindications for implant surgery. Furthermore, little is known about the reactions of the peri-implant tissues to poor oral hygiene in geriatric patients (Holm-Pedersen, Agerbaek & Theilade, 1975; Meyer et al., 2017).

In the scope of this review, geriatric patients were defined as patients with an age of 75 years and above. The aim of this systematic review was to screen and pool the available evidence to establish:

1. The dental implant survival rate in geriatric patients.
2. The potential impacts of the most common systemic medical conditions (WHO, 2015) and their treatments on implant survival.

The focused question set for this systematic review was "In patients undergoing dental implant therapy, what is the effect of advanced age (≥75 years) and/or common systemic medical conditions on the implant survival, biological complication, and technical complication rates?"

2 | MATERIAL AND METHODS

2.1 | Protocol and registration

This systematic review and meta-analysis were conducted and reported according to the PRISMA guidelines (Moher et al., 2015). The review protocol was registered with PROSPERO: International prospective register of systematic reviews (PROSPERO 2016: CRD42016049617).

2.2 | Eligibility criteria

All human studies reporting on geriatric individuals (≥75 years) with dental implants that satisfied the listed predefined inclusion criteria (Table 1) were included in the first part of this systematic review, which analyzed implant survival. Therefore, outcomes in healthy aged people were also sought.

For the second part of this search, no age limit was applied, as a preliminary screening of the literature did not identify any studies in relation to the most common medical conditions in the elderly (WHO, 2015) if the exclusion criteria included those aged 75 years or older.

TABLE 1 PICO focus question, criteria for inclusion, sources of information, search terms, search strategy, search filters, and search dates

Focus question	**In patients undergoing dental implant therapy, what is the effect of advanced age (≥75 years) and/or common systemic medical conditions on the implant survival, biological complication, and technical complication, rates?**	
Criteria	Inclusion criteria	Dental implants placed in the completely and partially edentulous human participants
		Implant-supported fixed prostheses and implant-supported/retained removable prostheses
		Studies must specify the study design, number of participants, number of implants placed and failed, time of loading, and number of dropouts
		Implant type: solid screw-type implants
		Participants must have been clinically examined during recall
	Exclusion criteria	Age <75 years
		One-piece implants, Zygomatic implants, and pterygoid implants
		Postloading follow-up <12 months
		Narrow diameter implants or mini dental implants (implants with diameter <3 mm)
		Implants with turned or machined surface
Information sources	Electronic databases	MEDLINE (PubMed): https://www.ncbi.nlm.nih.gov/pubmed/; EMBASE: https://www.embase.com/#search; and Central Register of Controlled Trials (CENTRAL) in the Cochrane Library: http://www.cochranelibrary.com.
	Others	Popular online internet search engines (e.g., Google and Yahoo), research community websites on the internet (https://www.researchgate.net/), reference cross-checks, personal communications, and hand searches. Hand searches in dental journals were only performed for records not available electronically or without an electronic abstract
Search terms	Population	#1: (Elderly Adults) OR (Partially Edentulous) OR (Fully Edentulous) OR (Completely Edentulous) OR (Partially Edentulous Maxilla) OR (Fully Edentulous Maxilla) OR (Completely Edentulous Maxilla) OR (Partially Edentulous Mandible) OR (Fully Edentulous Mandible) OR (Completely Edentulous Mandible) OR (80 + Aged) OR (75 + Aged) OR (65 + Aged) OR (Older Patient) OR (Aged Patients)
	Intervention or exposure	#2: (dental implantation, endosseous) OR (dental implants) OR (dental prosthesis, implant supported) OR (Overdentures) OR (Removable dental prostheses) OR (fixed dental prostheses) OR (dental implantation*) OR (dental implant) OR (implants) OR (implant supported fixed dental prostheses) OR (implant supported overdentures) OR (Removable dental prostheses*) OR (Overdentures) OR (Implant supported Overdentures) OR (Implant assisted Overdentures)
	Comparison	#3: (Cardiovascular disease) OR (ischemic heart disease) OR (stroke) OR (hypertensive heart disease) OR (cancer) OR (neoplasia) OR (COPD) OR (lower respiratory infections) OR (respiratory diseases) OR (Diabetes mellitus) OR (Cirrhosis) OR (Osteoarthritis) OR (neurocognitive disorder) OR (unipolar depression) OR (Alzheimer's disease) OR (other dementias) OR (Polypharmacy) OR (Hyposalivation) OR (Dry Mouth) OR (Multi Morbidity)
	Outcome	#4: (Survival) OR (survival rate) OR (survival analysis) OR (implant survival) OR (dental implant survival rate) OR (peri implantitis) OR (periimplant mucositis) OR (peri-implant mucositis) OR (treatment failure) OR (prevalence) OR (mandibular implants failure rate) OR (maxillary implants failure rate) OR (success rate) OR (failure rate) OR (crestal bone loss) OR (periimplant bone loss) OR (bone loss) OR (periodontal conditions) OR (peri-implant conditions) OR (implant success rates) OR (implant failure rates) OR (dental implant success rate) OR (dental implant failure rates) OR (biological complications)
Filters	Language	Not applied
	Species	Humans [MeSH]
	Ages	Aged [MeSH]
	Journal categories	Dental journals

(Continues)

TABLE 1 (Continued)

Focus question	In patients undergoing dental implant therapy, what is the effect of advanced age (≥75 years) and/or common systemic medical conditions on the implant survival, biological complication, and technical complication, rates?	
Search queries run as performed in MEDLINE (PubMed)	Using search combination: #1 AND #2 AND #3 AND #4 AND Humans AND Aged = 1,207 (June 2017)†	†Detailed use of the various search terms and their combinations are presented in the Supporting Information Table
	Using search combination: #1 AND #2 AND #4 AND Humans AND Aged = 1,210 (June 2017)††	††Detailed use of the various search terms and their combinations are presented in the Supporting Information Table
	Specific Searches for systemic medical conditions and implants without any age filters (PubMed/ Medline) = 1,348 (June 2017)	1. Stroke AND Dental Implants AND Humans 2. Respiratory Diseases AND Dental Implants AND Humans 3. Cirrhosis AND Dental Implants AND Humans 4. Osteoarthritis AND Dental Implants AND Humans 5. Neuorcognitive Disorders AND Dental Implants AND Humans 6. Polypharmacy AND Dental Implants AND Humans 7. Hyposalivation OR Dry Mouth AND Dental Implants AND Humans 8. Multi morbidity AND Dental Implants AND Humans 9. Multimorbidity AND Dental Implants AND Humans 10. Cancer AND Dental Implants AND Humans 11. Cardiovascular Diseases AND Dental Implants and Humans
Search dates	January 1980–26/05/2017	Final confirmatory online search was performed on 9 June 2017. No further online searches were performed after this date

2.3 | Information sources

Three electronic databases were searched: MEDLINE (PubMed), EMBASE, and CENTRAL. Hand searches of dental journals were performed for records that were not accessible electronically or for those records without an electronic abstract available. Further searches resulting from reference cross-checks were performed to identify studies that were not discovered online. Further attempts to maximize the pool of relevant studies and avoid any erroneous exclusion involved posting queries on research community websites (https://www.researchgate.net/) and, personal communications sent to selected authors. The final update for all the electronic searches was performed on June 9, 2017.

2.4 | Search strategy

The search strategy was designed and set up by two experts in database searches (Table 1). An initial electronic search was performed by a single reviewer (MS). Then the search was repeated by a second reviewer (GMK) to confirm the number of discovered articles by the search strategy. The search terms employed were either medical subject headings (MeSH) terms or keywords classified under general (all fields) category. The search terms were then combined with an "OR," and PICO categories were combined using "AND" to create a final logic search query (Supporting Information Table).

2.5 | Study selection

All relevant studies were included in this review, if they fulfilled the inclusion criteria. A title and abstract screening was performed by two investigators independently (MS and GMK). A final list of studies was put forth for full-text analysis and data extraction, only after a mutual agreement between the two investigators; disagreements, if any, were resolved by means of a consensus discussion. In cases of identified studies reporting on the same cohort at different time points, only the most recent publication was included in the review.

2.6 | Data collection process

The investigators (MS and GMK) extracted data from the included studies independently and were reciprocally blinded. During data extraction, for any uncertainty involving the extracted variable, a consensus was always reached by both investigators before finalizing the extracted data. In cases of significant doubts, corresponding authors were contacted for confirmation of the extracted information. The data items extracted from the included studies are specified in Tables 2–9.

2.7 | Missing data

Information was requested by email from the corresponding authors of included studies for missing or unclear data. In case of a nonresponse, email reminders were sent. A nonresponse from the corresponding author ultimately resulted in the exclusion of the study from the review.

2.8 | Risk of bias and quality assessment of the included studies

The Cochrane collaboration's tool and the Newcastle-Ottawa scales were used for the assessment of the risk of bias and quality

TABLE 2 List of RCTs and prospective studies reporting on dental implant therapy in elderly patients (75 years and above)

Study (first author)	Publication year	Loading protocol	Implant system	Observation period (in months)	Number of patients (*n*)	Mean age (in years)	Total number of implants failed/ placed in the study period (*n*)	Number of patient (implants) dropouts during the study period (*n*)	Number of implants survived (total)	Calculated implant survival rate (SR%)	Edentulous state of the jaw rehabilitated	Prosthesis type
Becker	2016	Not specified	Nobel Biocare	12	31	83.0 (♀ = 16), 84.0 (♂ = 15)	2/59	0 (0)	57 (59)	96.61	Not specified	Not specified
Bressan	2014	Immediate	Ankylos	24	5	79.0	0/20	0 (0)	20 (20)	100.00	Completely edentulous	Complete fixed on 4 implants.
Cakarer	2011	Conventional	Astra-tech, Straumann, Nobel, Frialit, Swiss-Plus, Biohorizons, Bio-Lok	Up to 60	16	75.56	1/42	0 (0)	41 (42)	97.62	Completely edentulous	2-IOD
de Carvalho	2013	Immediate	Nobel Biocare, Lifecore, Biomet 3i, Globtek	12–180	45	75+	1/45	0 (0)	44 (45)	97.77	Partially edentulous	Fixed
Hoeksema	2015	Conventional	Straumann	120	7	75+	0/14	5 (10)	4 (4)	100	Completely edentulous	2-IOD
Maniewicz	2017	Early	Straumann	60	17	87.06	2/36	12 (24)	10 (11)	90.91	Completely edentulous	2-IOD
Müller	2015	Early	Straumann	60	18	75.33	0/36	8 (16)	20 (20)	100.00	Completely edentulous	2-IOD

Note. RCTs: randomized controlled trials.

[a]Calculated as per the raw data supplied by the author for the end of the study period while not considering implant dropouts as failures; ♂: men; ♀: women; 2-IOD: implant overdenture retained by two implants. [b]Reported for 1 year only (excluding machined surface implants); 75+: exact age was not provided, but the minimum age was confirmed by the authors as over 75 years.

TABLE 3 Peri-implant marginal bone loss (PI-MBL), technical, and biological complications reported by the included RCTs and prospective studies

Study (first author)	Publication year	PI-MBL in millimeters	Technical/mechanical complications (*n*)	Biological complications (*n*)	Calculated annual bone loss in millimeters
Becker	2016	0.1 (annual)	n.r.	n.r.	0.1
Bressan	2014	0.4 (over 2 years)	*n* = 0	*n* = 2 Peri-implant mucositis	0.2
Cakarer	2011	n.r.	*n* = 2 1 Prosthesis fracture 1 Clips activation	*n* = 1 Mucosal enlargement around ball attachment	n.a.
de Carvalho	2013	1.0 (over 5 years)	*n* = 0	*n* = 0	0.20
Hoeksema	2015	0.51 (at 1 year)	*n* = 0	*n* = 0	0.51 (first year postloading)
Maniewicz	2017	0.17 (annual)	n.r.	n.r.	0.17
Müller	2015	0.61 (over 5 years)	n.r.	n.r.	0.12

Note. *n*: number of events; n.r.: not reported; n.a.: not applicable; RCTs: randomized controlled trials.

assessment of the included RCTs and prospective cohort/case–control studies, respectively (Higgins & Green, 2011; Wells et al., 2014).

2.9 | Summary measures

2.9.1 | Primary outcome measure

The primary outcome measure in this review was calculated implant survival based on the reported number of implants placed and failed. This calculation provided the event rate in the first year postloading. Implants in dropout patients and in those patients not available for follow-up were censored. Implant survival rate was assessed in the context of patient age and medical status. Implant failure has been defined as loss or removal of implant for any reason, and the timing of the failure has been described for the purpose of this review as either early, delayed, or late (ten Bruggenkate, Asikainen, Foitzik, Krekeler & Sutter, 1998). The loading protocols described in this review have been adopted as per the definitions of a previously published review (Schimmel et al., 2014).

2.9.2 | Secondary and tertiary outcome measures

Mean annual peri-implant marginal bone loss (PI-MBL), biological complications and any associated technical and/or mechanical complications were set as secondary and tertiary outcome parameters.

2.10 | Synthesis of results

Kappa (κ) statistics were calculated to confirm the interinvestigator agreement for the various extracted parameters. A meta-analysis was performed on the included prospective studies for implant survival rates at 1 and 5 years postloading. The weighted means across the studies were calculated using a fixed-effects model. Heterogeneity across the included studies was assessed using the *I*-squared statistics (I^2 statistics). For the purpose of the meta-analyses, case reports or case series reporting on less than 10 patients were excluded as the inclusion of individual participant data (IPD) would require a different statistical approach (Stewart et al., 2015). The meta-analysis was performed using a meta-analysis software (CMA, version 3.0; Biostat, Englewood, NJ, USA), with confidence intervals set to 95% (95% CI).

2.11 | Risk of publication bias and additional analyses

The risk of publication bias was explored across the included studies using a funnel plot (Sterne & Egger, 2001). PI-MBL, biological complications, technical/mechanical complications, and implant survival related to the medical status of the patients were reported descriptively.

3 | RESULTS

3.1 | Study selection

The search queries identified a total of 6,893 studies from the three electronic databases. After an initial sweep to eliminate duplicates and articles not relevant to the focus question followed by title and abstract screening, a combined total of 680 studies were selected for full-text analysis. Initially, 46 relevant articles were shortlisted for inclusion in the review. After subsequent hand searches, reference cross-checks, and information from other sources and authors, an additional 16 articles were identified. Four authors provided novel subanalyses from their published cohorts to report only on patients aged 75 years or older (Antoun, Karouni, Abitbol, Zouiten & Jemt, 2017; Bressan & Lops, 2014; Hoeksema, Visser, Raghoebar, Vissink & Meijer, 2016; Ormianer & Palti, 2006). A final total of 62 relevant articles were included in the review for data extraction. The flow of the entire search and the article identification process is shown in Figure 1.

TABLE 4 Studies reporting on implant survival in patients with cardiovascular diseases

Study (first author)	Publication year	Study design	Investigated condition	Observation period (months)	Number of patients (*n*)	Mean age in years	Total number of implants placed in the study period (*n*)	Total number of implants failed in the study period (*n*)	Number of implants survived (total)	Calculated implant survival rate (SR%)[†]	Time of failure (months)
Alsaadi[a]	2008	Cross-sectional	Hypertension	n.r.	n.r.	56.2	119	2	117	98	1–6
			Nonhypertension	n.r.	n.r.	56.2	601	12	589	98.32	
			Cardiac problems	n.r.	n.r.	56.2	68	0	68	100	
			No cardiac problems	n.r.	n.r.	56.2	652	14	638	97.85	
Wu X[a]	2016	Cohort	Antihypertensive drugs	84	142	57.7	327	2	325	99.39	Up to 60
			No antihypertensive drugs	84	586	57.7	1,172	48	1,124	95.90	

Note. n: number; n.r.: not reported.

[a]Different study groups within the same study reported in separate rows.

3.2 | Study characteristics

3.2.1 | Studies included for meta-analysis

From the included final list of 62 publications, seven prospective studies reported exclusively on geriatric cohorts aged ≥75 years (Becker, Hujoel, Becker & Wohrle, 2016; Bressan & Lops, 2014; Cakarer, Can, Yaltirik & Keskin, 2011; de Carvalho, de Carvalho & Consani, 2013; Hoeksema et al., 2016; Maniewicz Wins et al., 2017; Müller et al., 2015) (Table 2). Among these, there was one RCT (Müller et al., 2015), one prospective controlled clinical trial (Hoeksema et al., 2016), and five prospective case series (Becker et al., 2016; Bressan & Lops, 2014; Cakarer et al., 2011; de Carvalho et al., 2013; Maniewicz Wins et al., 2017). These three prospective studies were included in the meta-analysis for 1-year postloading implant survival in a geriatric population, aged 75 years or older; while six of these studies also provided information for inclusion in the meta-analysis for the 5 year postloading implant survival (de Carvalho et al., 2013; Maniewicz Wins et al., 2017; Müller et al., 2015).

3.2.2 | Studies included for descriptive analysis

The remaining 53 studies reported on cohorts with the most common systemic medical conditions or their respective treatment and their effect on implant survival. The analyses included both, the individual medical conditions and their treatment effects. Although these studies report on all-age cohorts, they were still included in this review because no studies were identified for cohorts aged 75 years and over.

3.3 | Synthesis of results

3.3.1 | Inter-investigator agreement

The calculated κ-range was 0.637–1.000, and 0.800–1.000, for the different stages of the search process, and the various parameters of the extracted data, respectively, which is defined as good to almost perfect reliability between the two independent investigators (MS and GMK).

3.3.2 | Meta-analysis of the included studies: Implant survival in geriatric subjects

A meta-analysis was performed for the postloading implant survival rates calculated for observation periods at 1 year (Becker et al., 2016; Bressan & Lops, 2014; Cakarer et al., 2011; de Carvalho et al., 2013; Hoeksema et al., 2016; Maniewicz et al., 2017; Müller et al., 2015). The fixed-effects model revealed an overall 1-year postloading implant survival of 96.7% (95% CI: 94.3, 98.7; I^2 = 0.00%; n = 7 studies; Figure 2). Three studies provided information for a 5-year meta-analysis and revealed an overall postloading implant survival of 96.1% (95% CI: 87.3, 98.9; I^2 = 0.00%, Figure 3) (de Carvalho et al., 2013; Maniewicz et al., 2017; Müller et al., 2015). According to the funnel plot analysis, a possible publication bias across the studies included in the meta-analysis was explored and ruled out (Figure 4).

3.3.3 | Calculated annual peri-implant bone loss

The calculated annual peri-implant bone loss was reported to range from 0.1 mm annually (Becker et al., 2016) to 0.51 mm during the first year postloading (Hoeksema et al., 2016) for geriatric subjects aged ≥75 years (Table 3).

3.4 | Medical conditions and their treatment

3.4.1 | Cardiovascular disease (including ischemic heart disease, stroke, hypertensive heart disease)

Implant survival in relation to CVD or associated treatment was reported in two studies (Table 4). In particular, Wu et al. (2016) reported a higher survival rate of implants in patients treated with antihypertensive therapy. In contrast, Alsaadi, Quirynen, Komarek and van Steenberghe (2008) did not find an influence of hypertensive heart disease on implant survival.

3.4.2 | Cancer

Radiotherapy

The effects of radiotherapy for the treatment of cancer in the head and neck region on implant survival were included in this systematic review. Seventeen studies were identified which met the inclusion and exclusion criteria (Table 5) (Arcuri, Fridrich, Funk, Tabor & LaVelle, 1997; Bodard et al., 2011; Buddula et al., 2012; Cuesta-Gil et al., 2009; Eckert, Desjardins, Keller & Tolman, 1996; Ernst et al., 2016; Fenlon et al., 2012; Gander, Studer, Studer, Gratz & Bredell, 2014; Heberer, Kilic, Hossamo, Raguse & Nelson, 2011; Hessling et al., 2015; Korfage et al., 2014; Linsen, Martini & Stark, 2012; Mancha de la Plata et al., 2012; Mericske-Stern, Perren & Raveh, 1999; Pompa et al., 2015; Sammartino, Marenzi, Cioffi, Tete & Mortellaro, 2011). Most of the studies reported on implants placed after radiotherapy (Arcuri et al., 1997; Bodard et al., 2011; Ernst et al., 2016; Gander et al., 2014; Heberer et al., 2011; Hessling et al., 2015; Korfage et al., 2014; Linsen et al., 2012; Mancha de la Plata et al., 2012; Pompa et al., 2015; Sammartino et al., 2011). Only two studies also included patients with implants placed prior to radiotherapy (Hessling et al., 2015; Mericske-Stern et al., 1999).

Survival rates were reported to range between 57.1% for immediately placed implants into vascularized grafts with subsequent radiotherapy (Fenlon et al., 2012) and 97.9% (Heberer et al., 2011).

Most investigators reported a time lapse between radiotherapy and implant placement of more than 12 months; however, some utilized a shorter delay (Ernst et al., 2016; Heberer et al., 2011; Korfage et al., 2014; Sammartino et al., 2011).

Antiresorptive therapy

Patients with bone metastases, including breast and prostate cancer or those suffering from multiple myeloma often receive high-dose intravenous antiresorptive therapy (ART) that may be associated with medication-related osteonecrosis of the jaw (MRONJ) (Jacobsen et al., 2013; Kwon et al., 2014). A recent review supports the statement that dental implant treatment is contraindicated in these patients because of the greatly increased risk of MRONJ (Lazarovici et al., 2010).

In a different context, ART is a very common treatment for osteoporosis. The current systematic search identified 14 articles that provided information about the implant survival in patients treated with ART for osteoporosis and osteopenia (Table 6) (Bell & Bell, 2008; Fugazzotto, Lightfoot, Jaffin & Kumar, 2007; Goss, Bartold, Sambrook & Hawker, 2010; Grant, Amenedo, Freeman & Kraut, 2008; Griffiths, 2012; Jacobsen et al., 2013; Koka, Babu & Norell, 2010; Kwon et al., 2014; Lopez-Cedrun et al., 2013; Martin et al., 2010; Memon, Weltman & Katancik, 2012; Shabestari et al., 2010; Siebert, Jurkovic, Statelova & Strecha, 2015; Tallarico, Canullo, Xhanari & Meloni, 2016; Zahid, Wang & Cohen, 2011). Another two articles reported on mixed indications, including malignancies (Jacobsen et al., 2013; Kwon et al., 2014). In studies of osteoporotic patients managed with ART, reported implant survival rates were predominately high. The prevalence of MRONJ in these patient cohorts was rarely specified (Fugazzotto et al., 2007; Goss et al., 2010; Griffiths, 2012; Shabestari et al., 2010; Siebert et al., 2015; Zahid et al., 2011).

Hyposalivation

The effect of hyposalivation on implant survival was only reported for patients with Sjögren's syndrome, rather than in cancer patients with radiotherapy (Table 7) (de Mendonca Invernici et al., 2014; Korfage et al., 2016; Oczakir, Balmer & Mericske-Stern, 2005; Spinato, Soardi & Zane, 2010; Weinlander, Krennmair & Piehslinger, 2010). Survival rates were reported to be 100% (de Mendonca Invernici et al., 2014; Oczakir et al., 2005; Spinato et al., 2010; Weinlander et al., 2010), with the exception of a recent comparative study, which reported a small number of early implant failures (Korfage et al., 2016).

3.4.3 | Respiratory diseases (chronic obstructive pulmonary disease COPD and lower respiratory infections)

No articles reporting on implant survival in patients with COPD or other respiratory diseases were identified in the search.

3.4.4 | Diabetes mellitus

A number of recent prospective cohort studies reported on the survival of implants in adult patients with diabetes mellitus, mainly Type 2 (Table 8) (Aguilar-Salvatierra et al., 2016; Alsaadi et al., 2008; Dowell, Oates & Robinson, 2007; Erdogan et al., 2015; Eskow & Oates, 2017; Oates et al., 2014; Peled, Ardekian, Tagger-Green, Gutmacher & Machtei, 2003). Calculated survival rates were reported to range from 86.3% (24-month observation period) (Aguilar-Salvatierra et al., 2016) to 100% (12 months) (Oates et al., 2014). Poor control (Hb_{A1c} ≥ 8.0%) may have an influence.

TABLE 5 Studies reporting on implant survival in patients with cancer treated with radiotherapy in the neck and head region [In PDF format, this table is best viewed in two-page mode]

Study (first author)	Publication year	Study design	Radiation dose (Gy)	Time of placement	Observation period (in months)	Number of patients (*n*)
Arcuri	1997	Retro	56–65	>12 months post-Ra	12–60	4
Bodard	2011	Retro	n.r.	n.r.	27.5	23
Buddula	2012	Retro	50.2–67.5	41 months post-Ra (mean)	60.0	48
Cuesta-Gil	2009	Retro	50–60	pre-Ra or >12 months post-Ra	6–108	79
Eckert	1996	Retro	20–65	post-Ra	n.r.	21
Ernst	2016	Retro	55–72	6 months post-Ra	52.9	17
Fenlon	2012	CS	65	pre-Ra	n.r.	12
Gander	2014	Retro	56–76	42 months post-Ra (mean)	20.0	21
Heberer	2011	Pros	≤72	>6 months post-Ra	14.4	20
Hessling	2015	Retro	40	pre-Ra	<60	21
Hessling	2015	Retro	61–66	post-Ra	<60	28
Korfage	2014	Follow-up	n.r.	>6 months post-Ra	45.6	100
Linsen	2012	Retro	36–60	mean: 41.0 months post-Ra	60.0	34
Mancha de la Plata	2012	Retro	50–70	33.4 months post-Ra 23 pat pre-Ra	6–96 (mean 45)	30
Mericske-Stern	1999	Follow-up	50–74	pre-Ra	12–84	4
Pompa	2015	Retro	≤50	12 months post-Ra	Mean 22.9	12
Sammartino	2011	Pros	50	Mean 9.4 months post-Ra	<36.0	77

Note. n.r.: not reported; *n*: number; Retro: retrospective study; CS: case series; Pros: Prospective study; post-Ra: implant postradiotherapy; pre-Ra: placement preradiotherapy; Early: before implant loading; Late: after implant loading; SR: calculated survival rate.

TABLE 6 Studies reporting on implant survival in patients treated with antiresorptive drugs because of osteoporosis and/or cancer treatment [In PDF format, this table is best viewed in two-page mode]

Study (publication year)	Study design	Route	Indication for ART	Duration of ART before/no onset of MRONJ (months)
Bell (2008)	Retro	Oral	n.r.	No onset (ART 6-132)
Fugazzotto (2007)	Retro	Oral	n.r.	No onset (ART: mean: 39.6)
Goss (2010)	CS	Oral	Osteoporosis	MRONJ in 10 weeks to 120
Grant (2008)	CS	Oral	Osteoporosis	No onset (ART: mean: 38)
Griffiths (2012)	RCT	Oral	n.r.	None with ART
Jacobsen (2013)	CS	Oral + IV	Malignancy (*n* = 9)/ osteoporosis (*n* = 5)	MRONJ in 38–50 months after implant placement
Koka (2010)	Retro	Oral	Osteoporosis/Osteopenia	No onset (ART 72)
Kwon (2014)	CS	Oral + IV	Osteoporosis/multiple myeloma	MRONJ in 3-82
Lopéz-Cedrún (2013)	Retro	Oral	Osteoporosis/Polymyalgia/ rheumatic	MRONJ in 6-120
Martin (2010)	Retro	Oral	Osteoporosis	No onset
Memon (2012)	Retro	Oral	Osteoporosis	No onset (ART: 0–36+)
Shabestari (2010)	Retro	Oral	Osteoporosis	No onset (ART before placement: 0–60; ART after placement: 0–36)
Siebert (2015)	Pros	IV	Osteoporosis	No onset (ART: mean: 36)
Tallarico (2015)	Pros	Oral	Osteoporosis	No onset (ART: mean: 36)
Zahid (2011)	Retro	Oral	Osteoporosis	No onset (ART 18-192)

Note. n.r.: not reported; Retro: retrospective study; RCT: randomized clinical trial; CS: case series; Pros: prospective study; ART: antiresorptive therapy; Route: route of administration; IV: intravenous administration; Early: before implant loading; Late: after implant loading; SR: calculated survival rate.

TABLE 5 (additional columns)

Mean age (in years)	Total number of implants placed in the study period (*n*)	Total number of implants failed in the study period (*n*)	Number of implants survived (*n*)	Calculated implant survival rate (SR%)	Time of failure (months)
51	18	1	17	94.4	n.r.
n.r.	75	n.r.	n.r.	80.0	n.r.
60.2	271	33	238	87.8	n.r.
52	395	75	320	81.0	n.r.
n.r.	111	9	102	91.9	n.r.
n.r.	88	3	85	96.6	2 in 12, 1 in 48
n.r.	35	15	20	57.1	<6
64.15	84	12	72	85.7	2–18
61.1	97	2	95	97.94	Early
55	95	2	93	97.89	2 in 24
55	128	6	122	95.3	1 in 24, 5 in 60
55.7	318	27	291	91.5	n.r.
n.r.	127	8	119	93.7	n.r.
55.5	225	23	203	90.2	n.r.
n.r.	17	2	15	88.2	n.r.
51	51	12	39	76.5	n.r.
55.8	172	20	152	88.4	<12 months

TABLE 6 (additional columns)

Number of patients (*n*)	Mean age in years	Follow-up period (months)	Number of implants placed (*n*)	Number of implants failed (*n*)	Time of failure (months)	SR (%)
42	n.r.	7–89	100	5	Multiple time points	95
61	51–83	12–24	169	0	n.r.	100
7	65.7	n.r.	19	9	n.r.	52.6
115	67.4	<96	468	2	Early	99.6
10	62	<18	14	0	n.r.	100
12	n.r.	60	23	n.r.	20.9	
55	71	n.r.	121	1	n.r.	99.2
19	67.3	>60	n.r.	18	n.r.	
9	66	<36	57	10	1–96.0	82.5
589	70.2	n.r.	44 in 16 patients	26 in 16 patients	1–132	40.9
100	66	n.r.	153	10	Early	93.5
21	53	<96	46	0	n.r.	100
12	54+	12	60	0	n.r.	100
32	64.4	36–72	98	1	Early	98.98
26	56	2–78	51	3	Early	94.12

TABLE 7 Studies reporting on implant survival in patients with hyposalivation

Study (first author)	Publication year	Study design	Investigated condition	Observation period (in months)	Number of patients (*n*)	Mean age in years	Total number of implants placed in the study period (*n*)	Total number of implants failed in the study period (*n*)	Number of implants survived (*n*)	Calculated implant survival rate (SR%)	Time of failure
Korfage[a]	2016	Retro	Sjögren's	45.6	50 (♀ = 46, ♂ = 4)	67	140	4	136	97.1	Early
		Retro	Healthy controls	60.0	50 (♀ = 46, ♂ = 4)	66	125	0	125	100	n.a.
de Mendonça	2014	Case report	Sjögren's	72	1	58	2	0	2	100	n.a.
Oczakir	2005	Case series	Sjögren's	24–60	2	63.5	12	0	12	100	n.a.
Spinato	2010	Case report	Sjögren's	12	1	62	6	0	6	100	n.a.
Weinlander	2010	Retro	Sjögren's + RA	57.7	4	55.6	21	0	21	100	n.a.

Note. ♀: Women; ♂: Men; n.r.: not reported; Retro: retrospective study; Early: before implant loading; Late: after implant loading; SR: calculated survival rate; n.a.: not applicable.

[a]Different study groups within the same study reported in separate rows.

3.4.5 | Cirrhosis of the liver

No articles reporting on implant survival in patients with cirrhosis of the liver were identified by the search criteria.

3.4.6 | Osteoarthritis

No articles reporting on implant survival in patients with osteoarthritis were discovered by the search criteria.

3.4.7 | Neurocognitive impairment (unipolar depression, Alzheimer's disease and other dementias, and Parkinson's disease)

The search revealed no data regarding implant survival in patients with Alzheimer's disease or other forms of dementia. Studies addressing other forms of neurocognitive impairment and implant survival are listed in Table 9 (Chu, Deng, Siu & Chow, 2004; Deniz, Kokat & Noyan, 2011; Ekfeldt, Zellmer & Carlsson, 2013; Heckmann, Heckmann & Weber, 2000; Jackowski et al., 2001; Packer, Nikitin, Coward, Davis & Fiske, 2009; Wu et al., 2014). One study reported higher implant failure rates in patients taking selective serotonin reuptake inhibitors for depression compared to nonusers of SSRIs (Wu et al., 2014). Case reports and case series with a limited number of participants reported on patients with Parkinson's disease with calculated survival rates ranging between 82.1% (Packer et al., 2009) and 100% (Chu et al., 2004; Heckmann et al., 2000).

4 | DISCUSSION

4.1 | Principal findings

This review identified high implant survival rates in geriatric patients aged 75 years and older. The 1 and 5-year implant survival rates are similar to those reported in younger cohorts (Al-Nawas et al., 2012; Müller et al., 2015), irrespective of the clinical indications or loading protocol (Benic, Mir-Mari & Hammerle, 2014; Papaspyridakos, Chen, Chuang & Weber, 2014; Schimmel et al., 2014; Schrott, Riggi-Heiniger, Maruo & Gallucci, 2014). It is important to note that the 1-year survival rates reflect implants failing to osseointegrate, and therefore, it could be suggested that advanced age does not seem to negatively affect osseointegration.

Clinical decision-making should take into consideration the oral and systemic health of every patient with comorbidities in form of an individualized risk assessment comprising a close collaboration with medical specialists and the family doctor. Implant placement in oncologic patients must be performed with caution and, if at all, an adequate refractory period postradiotherapy (>12 months) should be respected. Individualized treatment planning including assessment of radiation protocol must be carefully tailored and should be performed in a specialist setting; however, the risk of osteonecrosis cannot be ruled out. Implant placement in patients receiving high-dose ART is contraindicated.

TABLE 8 Studies reporting on implant survival in patients with diabetes mellitus

Study (first author)	Publication year	Study design	Investigated condition related to diabetes	Observation period (in months)	Number of patients (*n*)	Mean age (in years)	Total number of implants placed in the study period (*n*)	Total number of implants failed in the study period (*n*)	Number of implants survived (total)	Calculated implant survival rate (SR%)	Time of failure
Aguilar-Salvatierra[a]	2016	Pros	HbA1c ≤ 6, Type 2	24	33	59	33	0	33	100	n.a.
			HbA1c = 6.1–8.0, Type 2	24	30	57	30	1	29	96.6	Late
			HbA1c = 8.0–10, Type 2	24	22	61	22	3	19	86.3	Late
Alsaadi[a]	2008	CS	Type 1	n.r.	n.r.	56.2	1	1	0	0	Early
			Type 2	n.r.	n.r.	56.2	24	1	23	95.83	n.r.
Dowell[a]	2007	Cohort (Pros)	Type 2	4	25	51–81	38	0	38	100	n.a.
			No	4	10	29–61	12	0	12	100	n.a.
Erdogan[a]	2015	Pros	HbA1c = 6.1–7.5, Type 2	>12	12	52.6	22	0	22	100	n.a.
			No	>12	12	49.5	21	0	21	100	n.a.
Eskow[a]	2017	Observational	HbA1c 6–7.9, Type 2	24	9	59.9	21	0	21	100	n.a.
			HbA1c ≥ 8.0, Type 2	24	11	59.9	38	2	36	94.74	n.r.
Oates[a]	2014	Cohort (Pros)	HbA1c ≤ 5.9, Type 2	12	50	64	100	1	99	99	n.r.
			HbA1c = 6.0–8.0, Type 2	12	47	64	94	1	93	98.9	n.r.
			HbA1c ≥ 8.1, Type 2	12	20	64	40	0	40	100	n.a.
Peled	2003	CS	Type 2 diabetes	60	41	n.r.	141	8	133	94.33	Early: 6; Late: 2

Note. *n*: number; n.a.: not applicable; Pros: prospective study; n.r.: not reported; Retro: retrospective study; CS: case series; Early: before implant loading; Late: after implant loading; SR: calculated survival rate.

[a]Different study groups within the same study reported in separate rows.

TABLE 9 Studies reporting on implant survival in patients with neurocognitive impairment

Study (first author)	Publication year	Study design	Investigated condition	Observation period (in months)	Number of patients (*n*)	Mean age in years	Total number of implants placed in the study period (*n*)	Total number of implants failed in the study period (*n*)	Number of implants survived	Calculated implant survival rate (SR%)	Time of failure
Chu	2004	Case report	Parkinson's disease	12	1	83	4	0	4	100	n.a.
Deniz	2009	Case report	Huntington's disease	12	1		2	0	2	100	n.a.
Ekfeldt	2013	Pros	Acquired neurologic disabilities	120	22	44	70	12	58	82.86	n.r.
Heckman	2000	Case report	Parkinson's disease	28–42	3	75.7	9	0	9	100	n.a.
Jackowski	2001	Case report	Huntington's disease	12	1		2	0	2	100	n.a.
Packer	2009	Pros	Parkinson's disease	3	9	63	28	5	23	82.14	n.r.
Wu[a]	2014	Retro	51 Depression treated with SSRIs	72	51	56.4	94	10	84	89.36	n.r.
			No SSRIs		439		822	38	784	95.38	n.r.

Note. n.r.: not reported; Retro: retrospective study; SSRIs: selective serotonin reuptake inhibitors; Early: before implant loading; Late: after implant loading; SR: calculated survival rate; n.a.: not applicable; n.r.: not reported.

[a]Different study groups within the same study reported in separate rows.

Although ranking among the most common diseases in geriatric patients, there is no evidence on implant dentistry on conditions including cirrhosis of the liver, osteoarthritis, or respiratory diseases and sparse knowledge on patients with neurocognitive impairment and their respective treatments. This may constitute a potential risk for implant surgery, osseointegration and implant survival; for example, the use of glucocorticoids might induce osteoporosis and thus, influence bone healing (Krennmair, Seemann & Piehslinger, 2010). With multiple chronic conditions present, their effect on implant treatment becomes complex and poorly understood.

4.1.1 | Cardiovascular disease

The main concern in patients with CVD may be related to the general risk in performing invasive surgery because of prescribed anticoagulants or changes in blood pressure due to vasoconstrictor containing local anaesthetics.

Interestingly, the current review identified one study that reported the positive impact of antihypertensive drugs on implant survival (Wu et al., 2016). The authors hypothesize that this may be related to the positive effect of such drugs including beta-blockers, thiazide diuretics, ACE inhibitors, and ARBs on bone metabolism, which constitutes an interesting field for further research.

4.1.2 | Radiotherapy

The use of head and neck radiotherapy has been associated with a reduced survival rate of implants. In many cases, implants may be the only possibility of a prosthetic restoration, aiming for the patient's functional rehabilitation, social reintegration and psychological well-being (Müller, Schadler, Wahlmann & Newton, 2004). A recent review suggests that recently improved protocols of administering therapeutic radiation doses carry less risk for implant failure and MRONJ, compared to traditional protocols (Schiegnitz, Al-Nawas, Kammerer & Grotz, 2014).

4.1.3 | Antiresorptive therapy and osteoporosis

Antiresorptive therapy with agents that have long-lasting effects on bone metabolism can also be a major obstacle for implant surgery. Patients with Cancer with bone metastases (e.g., from breast or prostate cancer) or with multiple myeloma often receive high-dose intravenous ART. Dental implant treatment is often contraindicated in these patients because of the strongly increased risk of MRONJ (Lazarovici et al., 2010).

Osteoporosis patients, on the other hand, receive ART at much lower doses. As their risk of MRONJ is much lower, implants are increasingly utilized in these patients (Chadha, Ahmadieh, Kumar & Sedghizadeh, 2013). The risk of MRONJ in osteoporosis patients on low-dose bisphosphonates is estimated to be 0.7 per 100,000 person-years of exposure, and fewer than 100 cases of MRONJ after

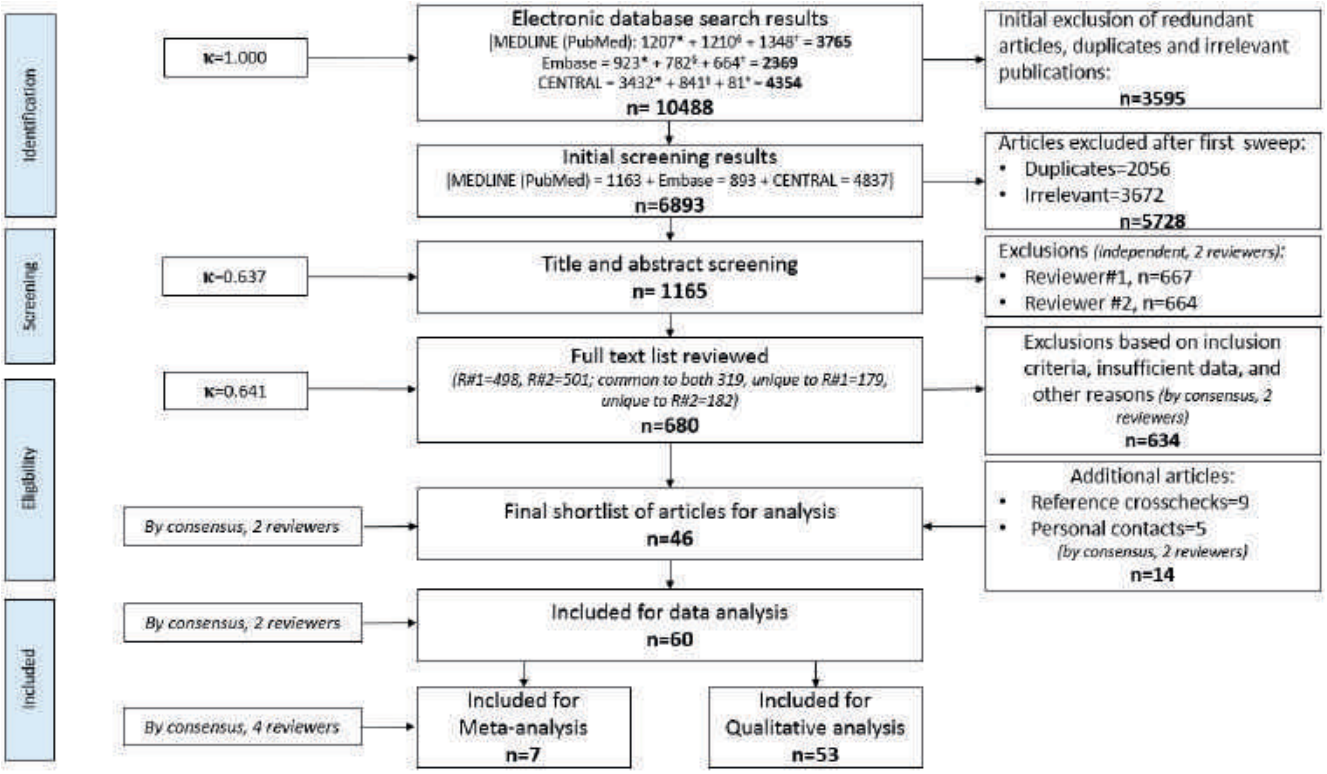

FIGURE 1 The search flow diagram, for the systematic literature search and selection process according to the PRISMA guidelines (*n*, number of articles; κ, Kappa statistics for interinvestigator agreement; R#1, reviewer 1; R#2, Reviewer 2; *, search results for studies with elderly cohort aged ≥75 years AND dental implants AND common medical conditions; §, search results for studies with elderly cohort aged ≥75 years AND dental implants without common medical conditions; †, search results for studies with cohort with dental implants AND common medical conditions without the age (≥75 years) filter]

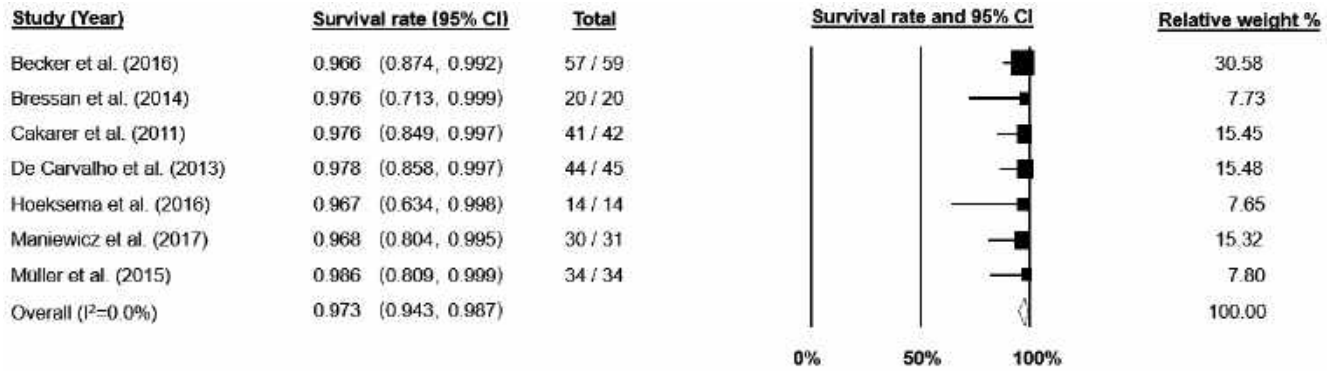

FIGURE 2 Forest plot showing the 1-year postloading implant survival rate (CI, confidence interval)

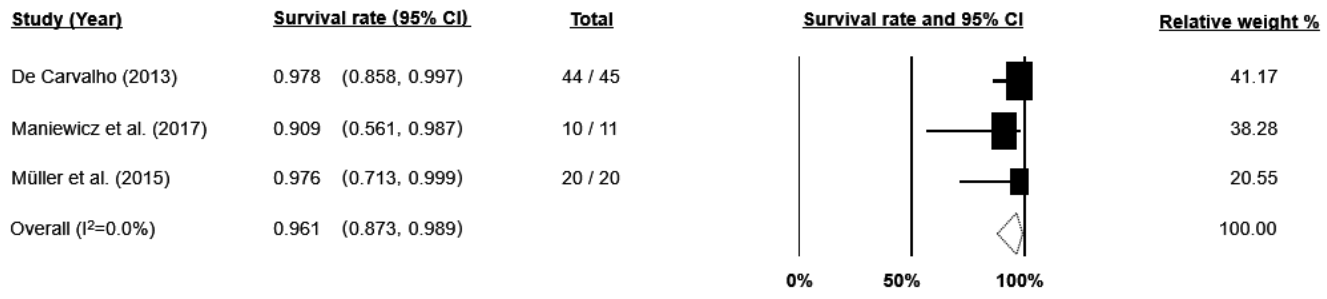

FIGURE 3 Forest plot showing the 5-year postloading implant survival rate (CI, confidence interval)

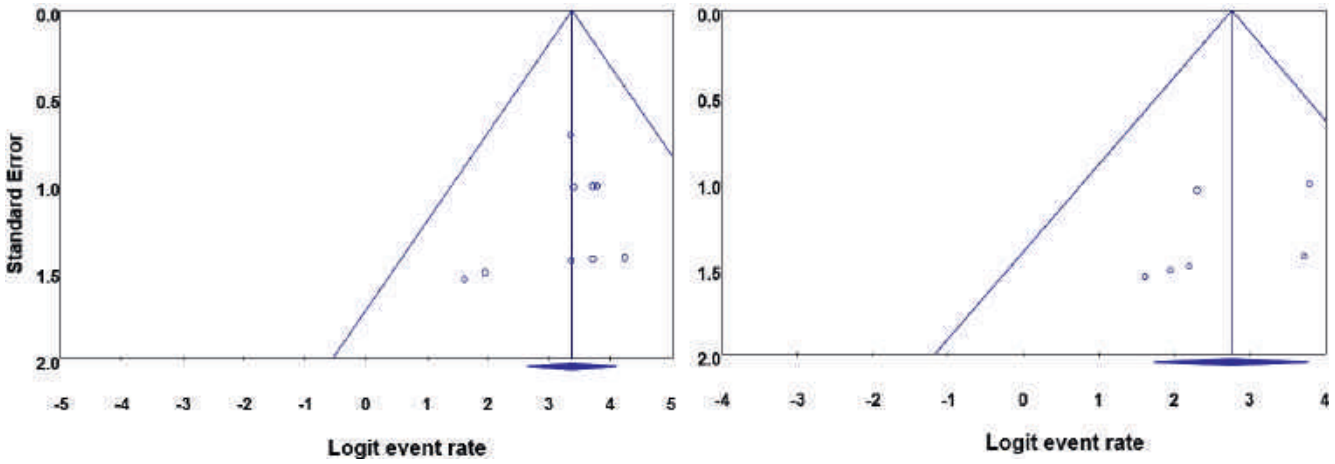

FIGURE 4 Funnel plot of the included prospective studies in the 1-year (a) and in the 5-year (b) analyses showing no publication bias

implant therapy in this group of patients have been reported (Ata-Ali, Ata-Ali, Penarrocha-Oltra & Galindo-Moreno, 2014).

Until now, there is no evidence that the intravenous low-dose administration carries a greater risk of MRONJ than oral medication, but precautions should be taken when planning and performing implant surgery (Schimmel et al., 2017). Moderate level evidence suggests that patients suffering from osteoporosis have a higher incidence of tooth loss (Anil, Preethanath, AlMoharib, Kamath & Anand, 2013). This may be related to a higher level of osteoclastic activity and a less dense bony structure, favoring progress of periodontal bone resorption in response to gingival inflammation (Wang & McCauley, 2016).

4.1.4 | Hyposalivation

Hyposalivation is very frequent among geriatric patients, not only as a consequence of radiotherapy, but mainly as a consequence of polypharmacy. However, no study dealt directly with the influence of this condition on the survival, not to mention success, of implants and implant prosthesis, which constitutes a major knowledge gap in gero-implantology.

There are, however, studies that have investigated the influence of Sjögren's syndrome on implant survival. A very recent comparative study from Korfage et al. (2016) indicated that the condition may be related to a higher risk of early implant failure.

4.1.5 | Diabetes

Type 2 diabetes signifies the body's resistance and inability to produce adequate amounts of insulin. It is the most common form of the disease in geriatric patients. Among other symptoms, Type 2 diabetics can experience microvascular and vascular damage as well as an impaired wound healing. Patients are more susceptible to periodontitis and tooth loss (Persson, 2017). The main marker of glycemic control in diabetic patients is hemoglobin A_{1C} (HbA_{1c}), and numerous studies identified in this review demonstrate that HbA_{1c} levels above 8% may result in reduced implant survival compared to lower levels.

4.2 | Strengths and weaknesses of the review

Prospective clinical studies on implants placed in geriatric patients are scarce. This may be due to a series of logistical challenges where older patients would require examination and treatment in their own home or a residential institution. In addition, older patient cohorts are extremely heterogeneous, as "not all old are old" (Bürger, 1960). The discrepancy between the biological and the numerical age can expand dramatically in advanced age, as the long-term effects of nutrition, lifestyle choices, socioeconomic status, and disease experience accumulate over a lifetime.

The search for eligible studies for this systematic review was limited by the fact that a large body of evidence published in the 1980s and 1990s from prospective geriatric studies studied implants with turned/machined titanium surfaces. These surfaces are not relevant in daily practice anymore; hence these studies were excluded from this review. Further weakness arises from the use of filters in our search that might have inadvertently omitted some relevant articles. The search truncations were not elaborately used for more search terms in "all fields," hence, this could have further limited the search yield. Furthermore, the search process of this review did not include conference proceedings. As the focus of this systematic review was not only on age, but also on comorbidity, a general lack of reporting on the medical status of study participants was noted in many papers, which further reduced the available evidence for highlighting the effect of the most common chronic conditions and their treatment in elderly patients.

Initially, a further exclusion criterion for this systematic search was a minimum sample of 10 participants for each included study. During the abstract screening, it became obvious that many studies would therefore have to be excluded. Relevant evidence would remain unreported in this review, for example, in relation to neurocognitive impairment where evidence is extremely scarce. It was, therefore, decided to remove this exclusion criterion post hoc. However, for the meta-analyses, studies reporting on single cases or case series with less than 10 cases were still excluded, as Stewart

et al. (2015) proposed in the CONSORT-IPD statement the inclusion of IPD would require a different approach.

Unfortunately, patient-reported outcome measures are not included in the analysis for this systematic review due to underreporting of the factors in most implant studies.

The strength of this review is the limitation of the participants included to those aged of 75 years and older. Previous reviews exist on the use of implants in medical compromised patients (Beikler & Flemmig, 2003; Bornstein et al., 2009, 2015), but none have previously focused on the impact of health status in combination with aging and frailty. Despite a comprehensive, meticulous, and systematic search, this review did not identify any studies on implant survival in relation to medical conditions in purely geriatric patients. Hence, this review too was not able to investigate the combined effect of age and chronic disease, and it was post hoc decided to report on any-age implant survival rates in the most common geriatric medical conditions. Yet, knowledge on the interactions of old age, medical conditions, and implant survival or even success would be essential for clinical decision-making and meticulous reporting on medical conditions in elder study participants should be encouraged for future studies on implant survival.

Although this review did not reveal age as a risk factor for osseointegration, immunosenescence can potentially compromise the body's defense mechanisms where the bacterial load around implants challenges the health of the peri-implant mucosa. The term immunosenescence refers to the aging of the immune system. It was suggested that the human immune system declines in effectiveness with age (Preshaw, Henne, Taylor, Valentine & Conrads, 2017). This can be a significant issue for functionally impaired older patients when oral hygiene is neglected (Meyer et al., 2017).

A further factor to be considered is that the implants in patients lost to follow-up were excluded from the survival analysis. However, reporting on the uncensored survival rates could have possibly overwhelmed the results in a negative direction, providing an unrealistically negative picture. Dropout rates are high in geriatric studies, due to the high prevalence of medical conditions, functional impairment, and death. The bias introduced using censored data (the "unknown") on potential knowledge gain, might be more important in geriatric studies than elsewhere in the literature.

4.3 | Clinical relevance of the findings of this systematic review

A particularly pertinent aspect of this review is the clinical relevance of the survival rate of implants in view of the patient's life expectancy and morbidity. For patients affected with head and neck cancer, implants may be the only means to achieve a psychosocial and functional rehabilitation (Müller et al., 2004). Given the undoubted benefits of an implant retained restoration compared to removable alternatives for oncology patients, the use of implants may even be justified when implant survival rates are significantly below those reported for healthy patients. A similar viewpoint may apply to patients with hyposalivation, as wearing a conventional denture may be almost impossible due to a lack of retention and pain caused by the intaglio surface rubbing on the dry and sensitive mucosa. Again, clinical decision-making must not only be based on the survival rate, but rather on the patient's subjective gain in quality of life, comfort, and overall well-being which should outweigh the associated risks. This review provides a valuable insight into the survival rates of implants which are vitally important to advise patients as part of the consent procedure prior to undertaking any intervention.

However, it should be noted that in elderly patients, implant success is rarely assessed in a relevant manner. An implant may be perfectly osseointegrated, but a patient with complex implant prostheses who is dependent on help for the activities of daily living may not wear or clean it anymore, because the management is too complex. This cannot be considered a successful treatment in this patient population (Müller & Schimmel, 2016).

4.4 | Implications for research

Substantial underreporting was noted on several important medical conditions in geriatric patients, which may have an impact on implant survival. Future, high-quality research is needed with comprehensive recording of study participants' medical conditions, and standard protocols for reporting these comorbidities should be defined based on the outcome of this systematic review.

The current review reveals an important knowledge gap when it comes to implant therapy in elderly and geriatric patients. For some of the most common geriatric medical conditions such as cancer and diabetes, there is evidence available in relation to implant surgery and implant prostheses—however, almost exclusively from younger patient groups. This limits the relevance of the findings for geriatric patients, who often take multiple medications and present with immunosenescence (Lopez-Otin, Blasco, Partridge, Serrano & Kroemer, 2013) or delayed wound healing due to qualitative or quantitative protein-energy malnutrition (Schimmel, Katsoulis, Genton & Müller, 2015).

5 | CONCLUSIONS

The provision of implant-supported/retained prostheses in geriatric subjects is a predictable treatment option with a high rate of implant survival. The functional and psychosocial benefits of an implant restoration should outweigh the reported relative risks associated with common medical conditions and their respective treatments.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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REVIEW ARTICLE

WILEY CLINICAL ORAL IMPLANTS RESEARCH

Clinical outcomes of peri-implantitis treatment and supportive care: A systematic review

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Abstract

Objectives: To report the clinical outcomes for patients with implants treated for peri-implantitis who subsequently received supportive care (supportive peri-implant/periodontal therapy) for at least 3 years.

Material and methods: A systematic search of multiple electronic databases, grey literature and hand searching, without language restriction, to identify studies including ≥10 patients was constructed. Data and risk of bias were explored qualitatively. Estimated cumulative survival at the implant- and patient-level was pooled with random-effects meta-analysis and explored for publication bias (funnel plot) at different time intervals.

Results: The search identified 5,761 studies. Of 83 records selected during screening, 65 were excluded through independent review (kappa = 0.94), with 18 retained for qualitative and 13 of those for quantitative assessments. On average, studies included 26 patients (median, IQR 21–32), with 36 implants (median, IQR 26–45). Study designs (case definitions of peri-implantitis, peri-implantitis treatment, supportive care) and population characteristics (patient, implant and prosthesis characteristics) varied markedly. Data extraction was affected by reduced reporting quality, but over 75% of studies had low risk of bias. Implant survival was 81.73%–100% at 3 years (seven studies), 74.09%–100% at 4 years (three studies), 76.03%–100% at 5 years (four studies) and 69.63%–98.72% at 7 years (two studies). Success and recurrence definitions were reported in five and two studies respectively, were heterogeneous, and those outcomes were unable to be explored quantitatively.

Conclusion: Therapy of peri-implantitis followed by regular supportive care resulted in high patient- and implant-level survival in the medium to long term. Favourable results were reported, with clinical improvements and stable peri-implant bone levels in the majority of patients.

KEYWORDS

dental implants, dental restoration failure, long-term care, meta-analysis, peri-implantitis, periodontal maintenance, supportive periodontal therapy, surgical treatment, survival, systematic review

1 | INTRODUCTION

Peri-implantitis is defined as the presence of inflammation in the soft tissues in addition to loss of supporting bone around an osseointegrated implant (Lindhe & Meyle, 2008). Controversy regarding the global prevalence of peri-implantitis exists largely due to the wide range of case definitions used across studies (Salvi, Cosgarea & Sculean, 2017). Nevertheless, it is recognized that peri-implantitis is not an uncommon finding. A recent cross-sectional study identified patients from the Swedish implant register (n > 24,716) who had implants in situ for 9 years and assessed the prevalence of moderate to severe peri-implantitis to be 15% (Case definition: bleeding on probing (BOP), suppuration and >2 mm of peri-implant bone loss) in 596 patients who attended a clinical examination out of 900 invitees (Derks et al., 2016); and a recent systematic review estimated a prevalence of 22% (Derks & Tomasi, 2015) across 11 studies.

Furthermore, there is general concern that the incidence of peri-implantitis may increase as more implants are being placed by a greater number of clinicians with varying expertise. Therefore, as highlighted in the 11th European Workshop for Periodontology (Tonetti, Chapple, Jepsen & Sanz, 2015), there is a need for research to identify effective protocols for prevention and treatment of peri-implantitis. In addition, evaluation of effective supportive care protocols to maintain peri-implant tissue health once peri-implantitis is treated is also required.

Heitz-Mayfield and Mombelli (2014) in 2014 investigated peri-implantitis treatment success at 12 months in a systematic review of seven studies, concluding that whilst favourable short-term outcomes were reported in the majority of patients; nonresolution, progression or recurrence could also occur.

Numerous peri-implantitis treatment protocols with clinical efficacy have been documented, including nonsurgical, surgical, resective, regenerative and combined approaches. However, the most effective management protocol across the general population or in specific patient groups has not been identified (Chan, Lin, Suarez, MacEachern & Wang, 2014; Daugela, Cicciu & Saulacic, 2016; Esposito, Grusovin & Worthington, 2012b; Heitz-Mayfield & Mombelli, 2014; Khoshkam et al., 2013, 2016; Mahato, Wu & Wang, 2016; Renvert, Polyzois & Rutger Persson, 2013; Suarez-Lopez Del Amo, Yu & Wang, 2016). It is likely that heterogeneity related to study design, patient characteristics, defect characteristics, implant design, prosthesis design, operator experience, clinical protocols, outcome measures and disease definitions have complicated data assessment. In addition, length of follow-up is a significant confounding factor, with Esposito and coworkers finding that recurrence of peri-implantitis occurred in up to 100% of cases in some of the study environments (Esposito et al., 2012b). In contrast, Renvert and coworkers found that stable clinical results could be achieved up to 5 years after initial therapy but highlighted that adequate oral cleanliness across this period appeared to be an essential prerequisite (Renvert et al., 2013).

Authors agree that extended follow-up periods are required to allow adequate assessment of stable treatment outcomes over time (Heitz-Mayfield & Mombelli, 2014; Khoshkam et al., 2016; Mahato et al., 2016).

The role of supportive periodontal therapy (SPT) in stabilizing periodontal disease over the long term has been accepted for many years (Lindhe & Nyman, 1984; Matuliene et al., 2008), with recent evidence also concluding that "erratic" SPT attendees had a significantly higher risk of tooth loss compared with those who attended regularly (Lee, Huang, Sun & Karimbux, 2015). Regarding peri-implant outcomes and supportive therapy, Monje and coworkers investigated outcomes across 13 studies, finding that less frequent supportive care was correlated with an increased incidence of peri-implantitis at the implant level. However, this finding was confounded by whether there was a history of periodontal disease (Monje et al., 2016).

It is hypothesized that over the long term, supportive care influences the outcome of implants in general and those that have been treated for peri-implant disease specifically.

The aim of this systematic review was to explore the question: In patients with osseointegrated dental implants, who were enrolled in supportive peri-implant/periodontal therapy (SPT) for at least 3 years, following treatment for peri-implantitis, what proportion of patients and implants is estimated to experience success, survival or peri-implantitis recurrence?

2 | MATERIALS AND METHODS

The focus question, PICO, search design and selection process are outlined in Tables 1 and 2 and are summarized below. The proposed methods were registered with PROSPERO (CRD42017071602), and reporting has been guided by PRISMA. The search was completed in April 2017. Multiple electronic databases (MEDLINE (Ovid), Embase (Ovid), The Cochrane Library, Nonindexed OVID citations), grey literature (conference proceedings, expert contact, study registers), reference lists (included articles, relevant reviews) and selected journals were scrutinized systematically, without language restriction to identify relevant data for independent review. Dedicated electronic search strategies combined textwords, indexing terms (MESH or EMTREE), multipurpose fields, adjacency operators, truncations and Boolean operators.

Selection criteria were broad during identification and screening to decrease search specificity (low agreement between investigators anticipated, decreased risk of omitting relevant articles) and specific during inclusion to increase search precision (high agreement between investigators anticipated, relevant articles included). Clinical investigations where at least 10 participants with osseointegrated implants that required treatment for peri-implantitis and who were subsequently enrolled in a SPT for at least 3 years were included. Review articles were excluded.

The primary outcome was survival at the patient and implant level. Secondary outcomes were success, peri-implantitis recurrence, and implant loss at the patient and implant level. To report those outcomes, number of patients and implants in each category were extracted at 3 years, and other time intervals if reported. Outcome definitions were:

TABLE 1 Search strategy and selection criteria

Focus question	In patients with osseointegrated dental implants who have been enrolled in a supportive periodontal/peri-implant programme (SPT) for at least 3 years following treatment of peri-implantitis, what is the implant failure rate or recurrence of peri-implantitis?
Population	Patients with osseointegrated dental implants that were diagnosed with and received treatment by investigators for peri-implantitis
Intervention	Enrolment in SPT for a minimum of 3 years following treatment for peri-implantitis
Comparison	Nil
Outcome	Implant loss for any reason (failure), recurrence of peri-implantitis
Language	No restriction
Search date	Completed in April 2017
PROSPERO	CRD42017071602 registration number
Database search, No language restriction	
Databases	MEDLINE (Ovid), Embase, Nonindexed citations (Ovid), The Cochrane Library. See further details in Table 2
Supplementary hand search	
Journals *(Jan 2015—April 2017)*	Clinical Oral Implants Research
	International Journal of Oral and Maxillofacial Implants
	Clinical Implant Dentistry and Related Research
	International Journal of Prosthodontics
	Journal of Prosthetic Dentistry
	Journal of Periodontology
	Journal of Clinical Periodontology
References	Included articles and identified reviews
Grey literature search	
Conference proceedings	EAO, 2016
	EuroPerio, 2015
	Perio Master Clinic, European Federation of Periodontology, 2017
	ITI World Symposium, Basel 2017
	American Academy of Periodontology, 2016, 2017
	Academy of Osseointegration 2017
	Osteology Australasia 2017
Contact with experts	Authors of included articles; researchers with a known interest in peri-implantitis research
Study registers	Australia & New Zealand (ANZCTR, http://www.anzctr.org.au)
	China (ChiCTR, http://www.chictr.org.cn)
	EU (EU-CTR, https://www.clinicaltrialsregister.eu) Germany (DRKS, http://www.drks.de)
	UK (ISRCTN, http://www.isrctn.com)
	USA (ClinicalTrials.gov)
	Search terms: periimplantitis, peri-implantitis or peri-implantitis identified 79 studies, with 2 potentially relevant investigations
Selection process	
Inclusion criteria	Clinical investigations of any study design related to the focus question
	Minimum 10 patients followed for at least 3 years
	Must specify: number of participants, number of implants, follow-up duration, number of failures, definition for peri-implantitis
Contact with authors	Research potentially met the inclusion criteria, but full-text article was unavailable
	Research potentially met the inclusion criteria, but data reporting was incomplete or unclear
	Research identified through grey literature search
Exclusion criteria	Topic not relevant to the focus question
	Reviews
	In vitro study
	Animal study
	Insufficient patient numbers
	Insufficient follow-up
	Insufficient participant information, and no response from investigators when seeking clarification
	Previous investigations reporting on the same patient population (excluded, but retained for reference)
Identification process	Records were reviewed by at least two investigators independently, disagreements were resolved by discussion, and authors were contacted for clarification when required
	Records in languages other than English that potentially fulfilled inclusion criteria were translated initially by the investigators, colleagues or "Google Translator." No investigations met the inclusion criteria, and therefore no formal translations were completed

- Survival—implant presence, regardless of the health of the surrounding tissues.
- Success—if defined by the authors.
- Peri-implantitis recurrence—if defined by the authors.
- Implant loss—implants that were removed for any reason, including those unrelated to peri-implantitis.

The data extraction form, risk of bias assessment form and explanatory instructions were drafted, trialled (two investigators) modified (two investigators) and completed (in duplicate, independently). Discrepancies were resolved by discussion, with authors also contacted to seek additional information.

Data extraction included the methodology, participant demographics, implant details, author's outcome definitions, peri-implantitis treatment method, SPT method, primary outcomes, secondary outcomes and other unexpected outcomes that could be of interest.

TABLE 2 Electronic database search strategies

Databases	Search strategy	Description
MEDLINE (Ovid)	*(peri-implant adj3 disease*).mp or (peri-implant adj3 infection*).mp or implantitis.mp or ((Dental implants.mp and (bone loss*).mp)) or ((Dental implants.mp and (suppurat*).mp))*	The multipurpose (.mp) field was used to search words used by authors in the title, original title and abstract as well as indexing terms allocated to the bibliometric record. OVID operators "OR", "AND" and "ADJ" allowed terms to be combined exclusively (AND), inclusively (OR) or specifically (ADJ3: retrieving records where terms were within 3 words of each other). For example, "Peri-implant adj3 disease*" retrieves both "peri-implant disease" and "Diseases of the peri-implant tissues"
MEDLINE(R) Epub Ahead of Print, In-Process & Other NonIndexed Citations and Ovid MEDLINE(R) (Ovid)	*((peri-implant adj3 disease*) or (peri-implant adj3 infection*) or implantitis or ((Dental adj3 implants) and (bone adj3 loss*)) or ((Dental adj3 implants) and suppurat*)).mp*	Nonindexed records were searched with the search philosophy outlined for MEDLINE (Ovid). The search differs, because the records are not yet indexed with MeSH terms. However, the ".mp" field was used to structure the search as it also identifies data in textword fields
Embase (Ovid)	*((peri-implant adj3 disease*) or (peri-implant adj3 infection*) or implantitis or ((Dental adj3 implants) and (bone adj3 loss*)) or ((Dental adj3 implants) and suppurat*)).mp. or (Tooth implants.sh. and bone loss*.mp.) or (Tooth implants.sh. and suppurat*.mp.)*	Embase records were searched with the search philosophy outlined for MEDLINE (Ovid). However, MeSH and EMTREE terms differed for implant subject headings and the MeSH term "Dental implant" was substituted for the EMTREE term "Tooth implant"
The Cochrane Library	*(peri implant disease:ti,ab,kw) OR (peri implant infection*:ti,ab,kw) OR (implantitis:ti,ab,kw) OR (bone loss*:ti,ab,kw and dental implants:ti,ab,kw) OR (suppurat*:ti,ab,kw and dental implants:ti,ab,kw)*	Cochrane fields of ".ti", ".ab" and ".kw" were used to search the title, abstract and index term for the Cochrane Library

Note. mp (multipurpose field: title, original title, abstract, subject heading, name of substance, and registry word fields); adj3 (adjacency operator: retrieves records where terms are within 3 words of each other); * (truncation operator); sh (MeSH subject heading field), ab (abstract field), ti (title field), kw (keyword field).

Risk of bias was assessed on a modified Newcastle–Ottawa Scale (NOS). The criteria were customized for number of study groups (one or multiple) and assessment of subjective outcomes specific to this review (peri-implant probing, radiograph assessment, peri-implantitis recurrence definition and failure definition) (Table 3). The impact of potential bias on outcomes was explored qualitatively.

2.1 | Statistics and data presentation

Research details were tabulated and discussed qualitatively. Where available, implant- and patient-level survival and success across 3, 4, 5 and 7 years was tallied. The number of implants and patients at the study inception, and those that became lost to follow-up, failed or experienced recurrence were tallied to calculate survival and success. Those lost to follow-up were assumed to occur randomly across time (nonsystematic), with life-table analysis and Greenwood's formula used to calculate the estimated cumulative survival (ECSurv), estimated cumulative success (ECSucc) and 95% confidence interval (CI). Confidence intervals that extended beyond 100% were truncated.

Data was weighted and pooled with meta-analysis (Stata 11.2, StataCorp) where appropriate. Heterogeneity was assessed with Cochran's Q ($p < 0.1$ indicated reduced homogeneity) and *I*-squared (variation in summary estimate that may be attributable to heterogeneity). Fixed or random-effects (if there was reduced statistical homogeneity) meta-analysis was used to calculate the pooled summary estimate and 95% CI. A funnel plot investigated whether publication or other small-study biases may have been present.

3 | RESULTS

3.1 | Systematic search

The systematic search flow is outlined in Figure 1. Of 5,754 studies from multiple electronic databases, six studies from grey literature searches and one study from hand searching were screened (total n = 5,761). Eighty-three records were identified as potentially relevant during screening, 65 records were excluded through independent full-text review (Kappa = 0.94). All corresponding researchers were contacted to request clarification or further information. Four records were excluded as double-data, with the most relevant data retained for analysis (Froum, Rosen, Wang, Froum & Vinayak, 2018; Romeo, Lops, Chiapasco, Ghisolfi & Vogel, 2007; Roos-Jansåker, Lindahl, Persson & Renvert, 2011; Schwarz, Hegewald, John, Sahm & Becker, 2013). Eighteen studies were included in qualitative assessments, with 13 in quantitative assessments. Additional records were consulted if data had been presented in related publications, and these are listed in Table 4.

A single investigator identified records from multiple electronic databases, sought grey literature and completed the hand search. Two independent investigators completed screening (Kappa = 0.25, low agreement as anticipated, reflecting the wide variety of

potentially relevant articles gathered) and eligibility assessments (Kappa = 0.94, high agreement).

3.2 | Qualitative assessment

3.2.1 | Study characteristics

Table 4 describes the main features of the individual studies including: study design and setting; population characteristics; peri-implantitis case definition; peri-implantitis treatment provided; and supportive care during follow-up. The majority of studies (n = 15) were small convenience samples (range 16–38 participants, 19–86 implants) of patients referred for peri-implantitis treatment. One study followed 100 participants with 179 implants (Carcuac et al., 2017), and two studies followed 100 (Froum, Froum & Rosen, 2015) and 245 participants (Charalampakis, Rabe, Leonhardt & Dahlen, 2011) respectively, but it was unclear how many were followed for at least 3 years. Average participant age ranged between 44.9 and 66.3 years, with age ranges also reported from 22 to 87 years.

Studies were prospective (n = 16) and retrospective (n = 2), followed one participant group (n = 11) or multiple participant groups (n = 7), and were completed in University (n = 9), private practice (n = 6) and combined environment (n = 3).

3.2.2 | Outcomes

Studies reported outcomes of implant success (n = 5, Table 5), survival (n = 13, Figures 2 and 3) and disease recurrence (n = 2) at the implant-level, patient-level or both. No studies evaluated patient-reported outcomes.

3.2.3 | Methodological Heterogeneity

Peri-implantitis definitions, peri-implantitis treatment protocols, success definitions and recurrence definitions varied considerably between groups, contributing to marked methodological heterogeneity between studies. However, participants were treated equally within studies and within study groups, reducing heterogeneity within the data. The between-study variations impact on how results are interpreted, inter-related and translated into practice.

Across the studies, all peri-implantitis case definitions included the presence of clinical signs of inflammation and bone loss, but the thresholds defined for bone loss and probing depths were heterogeneous.

Peri-implantitis treatment protocols differed across all categories: pretreatment phase; surgical approach (i.e., resective, regenerative, combination); implant surface decontamination method; biomaterials used; adjunctive treatment (e.g., soft tissue grafting); and peri-operative antimicrobials.

Definitions for success were reported by five studies and varied markedly (Table 5). For this reason, it was not possible to assess implant- and patient-level success quantitatively. Studies with strict definition generally reported lower success figures, but studies with less strict definitions did not necessarily achieve better outcomes. The ECSucc calculated from the data reported in each study for "successfully" treated implants ranged from 34% to 57% (at 3 years), 71% to 75% (at 5 years) and 7% to 41% (at 7 years) across studies. However, at these time points, the majority of implants survived, and remained in situ (Figure 2).

Disease "recurrence" was described in two of the 18 papers (Heitz-Mayfield et al., 2016; Serino, Turri & Lang, 2015). Heitz-Mayfield and coworkers defined recurrence of disease where implants required additional treatment (i.e., with PD > 5 mm with concomitant BoP or suppuration and/or continued bone loss), which occurred in 12% (three of 24 patients) at 5 years. Serino and coworkers reported that none of the implants (86 patients) which obtained healthy peri-implant tissues following treatment had recurrence of disease, which was described as increased probing depth (Serino et al., 2015).

3.2.4 | Supportive care protocols

Few studies provided detailed information about the supportive care regimen during follow-up, while some described the recall frequency; operator; instrumentation; and individual risk analysis performed. One study used soft tissue grafting during supportive care to augment keratinized peri-implant mucosa for some patients (Roccuzzo, Pittoni, Roccuzzo, Charrier & Dalmasso, 2017). No studies compared supportive care protocols.

3.2.5 | Factors influencing treatment outcome

Two studies reported treatment success for different implant surfaces (Carcuac et al., 2017; Roccuzzo et al., 2017; Table 5). In one study implants with a rough titanium plasma-sprayed surface (TPS) had lower success at 7 years than implants with a moderately rough surface (sandblasted large-grit acid etched [SLA]), but similar survival (Roccuzzo et al., 2017). In the second study implants with modified implant surfaces had lower success at 3 years compared to implants with a nonmodified surface (Carcuac et al., 2017).

3.2.6 | Risk of bias assessment

The 18 included studies were assessed for methodological risks that may impact on the results (Figure 4). The NOS was modified to apply to both multiple and single group studies. Ten studies reported on a single patient group and eight reported on multiple patient groups.

Fourteen of the studies (78%) met over 80% of the criteria and were considered to have low risk of bias. All studies included participants in a manner that reduced risk of bias (Domain 1: Selection), with the participants comparable with each other within all studies (Domain 2: Comparability). However, assessments of outcomes were not always standardized and definitions of outcome measures were not always clearly reported across the studies (Domain 3: Outcome). Over 80% (16 of 18) of the studies did not clearly define peri-implantitis

TABLE 3 Risk of bias assessment form, modified from NOS. Studies with more than one group could attract 13 stars (*), and studies with a single group could attract 12 stars (*)

	Topic	Question	Details
Selection			
1	Representativeness	Are the patients in the study representative of similar patients who would present with peri-implantitis to a private practice, university or hospital? 1. Yes, generally representative of the average patient who may need treatment in a private practice, university clinic or hospital clinic? (*) 2. No, it is a selected group (e.g. Nurses, volunteers, students) 3. Unclear, there is no description of how the cohort was selected	
2	Second group representativeness	*Does the study have two groups? If yes, answer this question. If no, skip this question and continue with Question 3.* If there are two cohorts, was the second cohort 1. Drawn from the same community as the first cohort (*) 2. Drawn from a different source 3. Unclear, There is no description of how the second cohort was selected	
3	Ascertainment of exposure	How do you know that the group was exposed? 1. Secure record (e.g. Surgical record, Clinical Notes, Author provided the exposure etc.) (*) 2. Structured interview (*) 3. Written self-report 4. Unclear, No description	
4	When did the outcome occur	Is it clear that the outcome of interest (see definition above) was not present at the start of the study? 1. Yes (*) 2. No	
Comparability			
5	Different cohorts	*Does the study have two groups? If yes, answer this question. If no, skip this question and continue with Question 6.* Are subjects in different cohorts comparable with each other? 1. Yes. This is because cohorts were randomly selected with allocation concealment (**) 2. Yes. Although selection was nonrandomized, authors adjusted for/reported/excluded/considered more than one important confounding factor. Please list the factors in the "details" column. (**) 3. Yes. Although selection was nonrandomized, authors adjusted for/reported/excluded/considered one important confounding factor only. Please list the single factor in the "details" column. (*) 4. No, subjects in each cohort appeared to differ substantially from each other. 5. No, details were not reported	
6	Same cohort	*Does the study have one group? If yes, answer this question. If no, skip this question and continue with Question 7.* Are subjects within the same cohort comparable with each other? 1. Yes. This is because authors adjusted for/reported/excluded/considered more than one important confounding factor. Please list the factors in the "details" column. (**) 2. Yes. This is because authors adjusted for/reported/excluded/considered one important confounding factor only. Please list the single factor in the "details" column. (*) 3. No, subjects appeared to differ substantially from each other in the same group. 4. No, details were not reported	
Outcomes			
7	Subjective outcomes	How were the subjective outcomes assessed (probing, radiographic bone loss)? 1. Independent blind assessment with calibrated examiners (*) 2. Nonblinded assessment with calibrated examiners, because blinding was not appropriate or practical (*) 3. Non calibrated multiple examiners 4. Self-report, by patient 5. Unclear, no description	

(Continues)

TABLE 3 (Continued)

	Topic	Question	Details
8	Probing	Was peri-implant probing standardized? Yes (*) No	
9	Radiographs	Were radiographs standardized? Yes (*) No	
10	Recurrence	Were criteria for peri-implantitis "recurrence" clearly reported? Yes (*) No	
11	Failure	Were reasons/criteria for implant removal clearly reported? Yes (*) No	
12	Follow-up completeness	Was the follow-up long enough for outcomes to occur? 1. Yes (*) (State the maximum follow-up in the "details" box) 2. No	
13	Loss to follow-up	Was the follow-up of the cohorts adequate? 1. Complete follow-up, with all subjects accounted for (*) 2. Some subjects were lost to follow-up, but in your opinion this was unlikely to introduce bias or be the result of selective reporting. Authors provided reasons for lost to follow-up where practical and these indicate that such losses were unlikely to introduce bias. (State the number that were lost to follow-up and the total number in the study; the percentage lost to follow-up; reasons for lost to follow-up in the details box) (*) 3. Follow-up rate was high, and there was no description of those lost 4. Unclear, not reported	

recurrence, over a quarter (five of 19) did not clearly standardize the radiographic technique and another quarter (five of 19) did not clearly standardize the probing technique. These factors impact on how results can be generalized to other patient populations.

3.3 | Quantitative assessment

Quantitative assessment of survival at the implant- (n = 13 studies, Figure 2) and patient-levels (n = 12 studies, Figure 3) are outlined below. There was heterogeneity between studies in the reporting of treatment outcomes. While all included studies reported on implant-level survival, the reason for implant loss/removal was not always stated.

Four studies reported at two time points each: Heitz-Mayfield et al. (2016) (3 year, 5 year), Roccuzzo et al. (2017) (3 year through personal communication, 7 year), Roos-Jansåker, Persson, Lindahl & Renvert (2014) (3 year, 5 year) and Schwarz, John, Schmucker, Sahm & Becker (2016) (4 year, 7 year).

Two studies reported data cumulatively, and were included in pooled summaries corresponding to their mean time in situ: Froum, Froum & Rosen (2012) (3 year results, $\mu = 3.7$), and Zablotsky (1998) (4 year results, $\mu = 4.5$).

Seven studies reported on single, and six studies reported on multiple treatment groups. Of those six studies, results of each group were reported separately (n = 1; Schwarz, Sahm, Bieling & Becker, 2009), results of the test group only were reported because the control group was observed for less than 3 years (n = 1; Romeo et al., 2005) and results were combined because authors observed no differences between groups (n = 4; Carcuac et al., 2017; Khoury & Buchmann, 2001; Roos-Jansåker et al., 2014; Schwarz et al., 2016).

Implant survival across seven studies at 3 years ranged from 81.73% (lower 95% CI) to 100% (upper 95% CI). Implant survival across three studies (one with two groups) at 4 years ranged from 74.09% (lower 95% CI) to 100% (upper 95% CI). Implant survival across four studies at 5 years ranged from 76.03% (lower 95% CI) to 100% (upper 95% CI). Implant survival across two studies at 7 years ranged from 69.63% (lower 95% CI) to 98.72% (upper 95% CI).

Patient-level survival across eight studies at 3 years ranged from 78.64% (lower 95% CI) to 100% (upper 95% CI). Patient-level survival across three studies (one with two groups) at 4 years ranged from 71.29% (lower 95% CI) to 100% (upper 95% CI). Patient-level survival across three studies at 5 years ranged from 56.14% (lower 95% CI) to 100% (upper 95% CI). Patient-level survival across two studies at 7 years ranged from 69.63% (lower 95% CI) to 98.42% (upper 95% CI).

Pooled meta-analysis results showed implant-level ECSurv of 99.95% at 3 years (n = 7 studies), 99.97% at 4 years (n = 3 studies) and 91.82% at 5 years (n = 4 studies). Corresponding 95% CIs

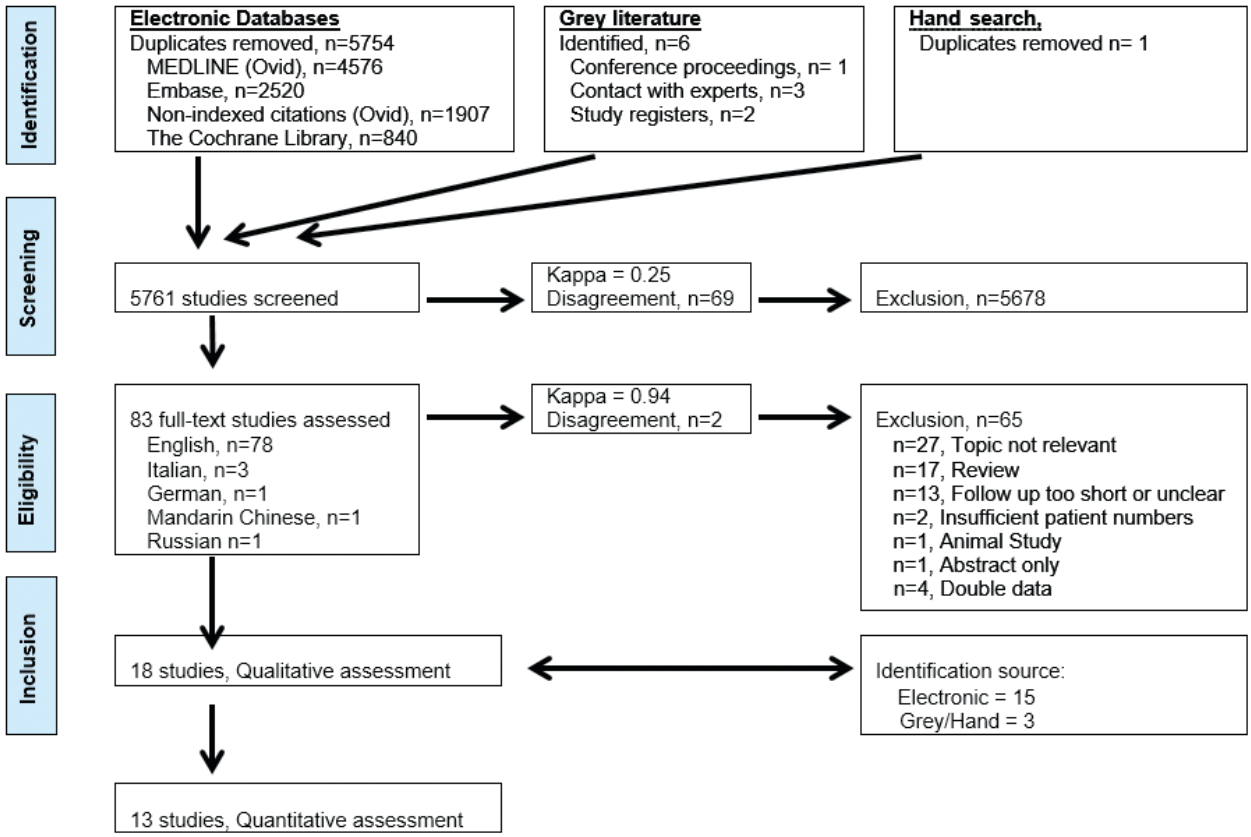


FIGURE 1 PRISMA systematic search flow diagram

estimating the precision of the mean summary effect are reported in Figures 2 and 3. Pooled meta-analysis results showed patient-level ECSurv of 99.99% at 3 years (n = 8 studies), 99.99% at 4 years (n = 3 studies) and 86.08% at 5 years (n = 3 studies). Corresponding 95% CIs estimating the precision of the mean summary effect are reported in Figures 2 and 3. Data at 7 years was not pooled, as there were less than 3 studies. Across the 13 implant-level studies and 12 patient-level studies, seven groups reported no implant losses (and 100% survival). It is likely that this has markedly influenced the pooled weighting and overestimated the true effect.

A combined funnel plot (Figure 5) explored the point estimate versus the standard error of implant-level survival in the 3 year (blue legend, n = 7 studies), 4 year (red legend, n = 4 studies), 5 year (green legend, n = 4 studies) and 7 year (yellow legend, n = 2 studies) subgroups. Data for nine studies appeared once in the plot, and data for four studies appeared twice in the plot (n = 3, reported at multiple time points, n = 1, two study groups analysed). Seven studies reported 100% survival and these data points are clustered at the peak of three of the funnels (3, 4 and 5 year). Data was skewed or potentially skewed at all time points, meaning that it was likely that small patient cohorts with less favourable outcomes existed, but remained either unpublished or difficult to find. Therefore, the pooled results likely overestimate the true clinical effect and care should be taken when applying the pooled estimate to patient groups.

4 | DISCUSSION

This review assessed clinical outcomes in patients treated for peri-implantitis who were enrolled in a supportive care program for at least 3 years, with 3, 4, 5 and 7 year results collated. This review shows that after 3, 4, 5, and 7 years the great majority of patients enrolled in a supportive care program (SPT), with regular professional biofilm removal at both implants and teeth, will not lose their implants. This review did not aim to identify the most effective peri-implantitis treatment protocol or supportive care regimen, or to quantify risk factors that may modify outcomes. However, as there was considerable heterogeneity within and between studies with respect to the study design (peri-implantitis definition, outcome definitions, treatment protocols, supportive care protocols) and population characteristics (patient, implant and prosthesis characteristics), these factors are examined further in the discussion.

The perception among clinicians that peri-implantitis treatment is unpredictable and may not lead to successful clinical outcomes is not uncommon. In a systematic review (Esposito, Grusovin & Worthington, 2012a) it was found that recurrence of peri-implantitis in up to 100% of treated cases occurred in some studies with a follow-up longer than 1 year. In contrast, the present systematic review shows that favourable treatment outcomes documented in studies with 12-month results (Heitz-Mayfield & Mombelli, 2014) may be

TABLE 4 Study description

	Study details			Treatment provided		
Authors/Year	**Design**	**Population baseline**	**Inclusion**	**Initial peri-implantitis treatment**		**Supportive care**
1. Bach et al. (2000)	Prospective, two groups Private practice Operators—NR Funding: NR Follow-up: 5 yrs	Patients: n = 30 G1: n = 15 G2: n = 15 Implants: NR Prostheses: NR	Inclusion Criteria: Evidence of marginal bone loss, PD > 5 mm, overall BoP, Clinical signs of inflammation Exclusion Criteria: Serious illness, alcohol abuse, nicotine use, lack of compliance	Pretreatment phase: Yes Surgical treatment: Combination RES + regenerative	Adjunctive treatment: Mucogingival corrections, if necessary Surface decontamination: Gp1: NR, Gp2: Diode laser Peri-operative Antibiotics: NR	SPT operator: NR SPT frequency: 6 months SPT description: Dental hygiene + diode laser
2. Behneke et al. (2000)	Prospective, one group University Single Operator—periodontist Funding: NR Follow-up: 3 yrs	Patients: n = 17 6 M, 11 F Mean age: 51.7 yrs Implants: n = 25 Straumann Prostheses: NR	Inclusion Criteria: Peri-implantitis crater defects, PD > 5 mm, crater-like BL < 90% implant length Exclusion Criteria: No systemic illnesses	Pretreatment phase: Yes Iodine irrigation for 4 weeks Surgical treatment: Regenerative ABG block (n = 18) ABG particulate (n = 7)	Adjunctive treatment: No Surface decontamination: APB Peri-operative Antibiotics: MTR	SPT operator: NR SPT frequency: 3 months for the first year, then annually SPT description: Regimen unclear, OHI as required
3. Carcuac et al. (2017) Related publication: Carcuac et al. (2016)	Prospective RCT, four groups University Multiple operators; 5 periodontists Funding: Swedish Research Council Follow-up: 3 yrs	Patients: n = 100 35 M, 65 F Mean age 66.3 (21–60 yrs) Implants: n = 179 Prostheses: NR	Inclusion Criteria: Advanced peri-implantitis—PD ≥6 mm, BoP/SUP, bone loss >3 mm Exclusion Criteria: compromised general health, systemic antibiotic therapy during past 6 months	Pretreatment phase: Yes Professional supramucosal cleaning/OHI Surgical treatment: RES: pocket elimination Gp 1: ATB+/CHX+ Gp 2: ATB+/CHX- Gp 3: ATB-/CHX+ Gp 4: ATB-/CHX-	Adjunctive treatment: No Surface decontamination: titanium curettes, saline (Gp2 & 4)/CHX (Gp 1 & 3) Peri-operative Antibiotics: In Gp 1 & 2	SPT operator: Referring clinician SPT frequency: 3 -4 monthly SPT description: 1st year—OHI every 3 months. Thereafter according to individual needs
4. Chang, Park, Kim, Kim and Lee (2015)	Retrospective, 1 group University Operators—NR Funding: NR Follow-up: 5 yrs	Patients: n = 16 10 M, 6 F Mean age: 56.2±10.6 yrs Hx treated PDD n = 12 DM + CVD n = 3 CVD n = 3 Implants: n = 31 Prostheses: SICs = 5, FDPs = 26	Inclusion Criteria: PD >4 mm, BL >2 mm, BoP/PUS, Plaque Exclusion Criteria: NR	Pretreatment phase: NR Nonsurgical treatment: Curettage of the granulation tissue	Adjunctive treatment: Retreatment 1–8 times Surface decontamination: ErYAG Laser + CHX irrigation + MIN ointment injection Peri-operative Antibiotics: NR	SPT operator: Hygienist SPT frequency: 3–5 month SPT description: NR

(Continues)

TABLE 4 (Continued)

	Study details			Treatment provided		
Authors/Year	**Design**	**Population baseline**	**Inclusion**	**Initial peri-implantitis treatment**		**Supportive care**
5. Charalampakis et al. (2011)	Retrospective Multiple operators Funding—Oral Microbiology Gothenburg Follow-up: 9 months to 13 yrs. 45 patients ≥ 4 yrs	Patients 245 (45 patients followed for ≥4 yrs) Implants: NR Prostheses: NR	Inclusion Criteria: BOP/Sup with PD ≥5 mm and bone loss ≥1.8 mm after 1 year in function Exclusion Criteria: NR	Pretreatment phase: NR Nonsurgical (46 patients) Surgical treatment: 6 different surgical approaches used RES, regenerative (various materials)	Adjunctive treatment: NR Surface decontamination: Various antiseptics (NaCl, H_2O_2, CHX, iodine) Peri-operative Antibiotics: Various, based on microbiological testing results Some local antibiotics	SPT operator: multiple SPT frequency: 3 monthly for first year then annually SPT description: OHI patient motivation, supragingival plaque control, "subgingival scaling" at implant sites with residual bleeding
6. Deppe, Horch and Neff (2007)	Prospective, 4 groups University Operators—NR Funding: NR Follow-up: 5 yrs	Patients: n = 32 Implants: n = 73 G1: n = 17, G2: n = 22 G3: n = 15, G4: n = 19 IMZ, Frialit, Brånemark, Straumann Prostheses: Cement and screw retained SICs and FDPs	Inclusion Criteria: PD >5 mm, progressive BL or BoP Exclusion Criteria: NR	Pretreatment phase: Yes Non surgical debridement + CHX rinsing Surgical treatment: Multiple G1: Regenerative (TCP, ABG, ePTFE) G2: RES G3: Regenerative (TCP, ABG, ePTFE) G4: RES	Adjunctive treatment: No Surface decontamination: G1 & G2: APB + CO_2 Laser G3 & G4: APB Peri-operative Antibiotics: No	SPT operator: NR SPT frequency NR SPT description: NR
7. Froum et al. (2012) Related publications: Froum et al. (2015, 2018)	Prospective, 1 group Private practice Single operator Funding: NR Follow-up: 3 to 7.5 yrs	Patients: n = 38 18 M, 20 F Mean age: approx. 58 yrs, range 29–81 yrs Implants: n = 51 8 brands: S Prostheses: NR	Inclusion criteria: PD >6 mm, BoP, BL >4 mm Exclusion Criteria: DM, OP, chemotherapy, radiation therapy	Pretreatment phase: Yes FMD 1 month prior surgery Surgical treatment: Regenerative EMD, XBM, PDGF, CM CTG (if KT <2 mm)	Adjunctive treatment: No Surface decontamination: CFC, TC, APB, CHX Peri-operative Antibiotics: AMX/CLI for 10 days	SPT operator: NR SPT frequency: 2–3 monthly SPT description: Rubber cup polishing 2 month post-op. interproximal brush soaked in CHX 3× day
8. Froum et al. (2015) Related publications: Froum et al. (2012, 2018)	Prospective, 1 group Private practice Operators—NR Funding: NR Follow-up: up to 10 yrs	Patients: n = 100, unknown for ≥3 yrs 47 M, 53 F Implants: n = 170, unknown for ≥3 yrs Prostheses: NR	Inclusion Criteria: BoP, PD ≥5 mm, BL ≥3 mm from implant platform Exclusion Criteria: DM, OP, BIP chemotherapy radiation therapy	Pretreatment phase: Yes Surgical treatment: Regenerative EMD or PDGF XBM, CM CTG (if KT <2 mm)	Adjunctive treatment: Additional surgical procedure if required Surface decontamination: MIN, TET, CHX, APB Peri-operative Antibiotics: NR	SPT operator: NR SPT frequency: 2–3 month SPT description: NR

(Continues)

TABLE 4 (Continued)

	Study details			Treatment provided		
Authors/Year	**Design**	**Population baseline**	**Inclusion**	**Initial peri-implantitis treatment**		**Supportive care**
9. Heitz-Mayfield et al. (2016) Related publication: Heitz-Mayfield et al. (2012)	Prospective, 1 group Multi-centre Private practice & University Multiple operators Funding: ITI grant Follow-up: 5 yrs	Patients: n = 24 13 M, 11 F Mean age: 56±8.5 yrs Hx treated PDD n = 8 Smokers n = 6 Implants: n = 36 Various brands Prostheses: Cement and screw-retained SICs and FDPs	Inclusion Criteria: BL ≥2 mm + PD ≥5 mm + BoP/PUS Exclusion Criteria: Inadequate implant, restoration contours, uncontrolled DM, heavy smokers	Pretreatment phase: Yes FMPS < 25% & FMBS < 25% Surgical treatment: Access flap	Adjunctive treatment: No Surface decontamination: TC + saline Peri-operative Antibiotics: AMX and MTR for 7 days	SPT operator: Periodontist SPT frequency: 3 monthly for 12 months, then at least 6 monthly according to patient's needs SPT description: Motivation, OHI, FMD
10. Khoury & Buchmann (2001)	Prospective, 3 groups Private practice & University Single operator Funding: NR Follow-up: 3 yrs	Patients: n = 25 Gp1: n = 12, Gp2: n = 20, Gp3: n = 9 3 M, 22 F Mean age: 48.2 ± 6.3 yrs Implants: n = 41 IMZ, Friadent Prostheses: FDPs and RDPs	Inclusion Criteria: BL >50% Exclusion Criteria: NR	Pretreatment phase: Yes 0.2% CHX irrigation Implant scaling + systemic ATB Weekly OHI prophylaxis program Surgical treatment: Regenerative Gp 1: ABG (n = 12) Gp 2: ABG + ePTFE (n = 20) Gp 3: ABG + CM (n = 9)	Adjunctive treatment: No Surface decontamination: CHX, CA, H_20_2, saline Peri-operative Antibiotics: Various, 6 months prior surgery	SPT operator: NR SPT frequency: 3–6 month SPT description: Regimen unclear, OHI as required
11. Mercado et al. (2018)	Prospective, 1 group Private practice Single operator Funding: National Health and Medical Research Council Follow-up: 3 yrs	Patients: n = 30 11 M, 19 F Mean age: 44.9±11 yrs Implants: n = 30 Brånemark TiUnite, Astra Tech, Straumann SLA Prostheses: Cement or screw-retained SICs	Inclusion Criteria: BoP/PUS, BL > 20%, PD > 4 mm, Implants >2 yrs in function Exclusion Criteria: DM, OP, pregnant/lactating, autoimmune disorders, warfarin intake, >2 implants, UPD, smoking	Pretreatment phase: Yes Surgical treatment: Regenerative (XMB + EMD + DOX mix) + CTG (n = 8)	Adjunctive treatment: CTG (n = 8) Surface decontamination: DOX 100 mg mixed with XMB Peri-operative Antibiotics: No	SPT operator: Periodontist SPT frequency: 3–4 month SPT description: OHI, FMD with mild ultrasonic implant debridement

(Continues)

TABLE 4 (Continued)

	Study details			Treatment provided		
Authors/Year	**Design**	**Population baseline**	**Inclusion**	**Initial peri-implantitis treatment**		**Supportive care**
12. Roccuzzo et al. (2017)	Prospective, 1 group Private practice Single operator Funding: NR Follow-up: 7 yrs	Patients: n = 26 11 M, 15 F Mean age: 60±7.9 yrs Hx treated PDD Smokers N = 4 Implants: n = 26 Straumann, 12 SLA & 14 TPS Prostheses: Cement retained SICs and FDPs	Inclusion Criteria: Crater-like BL, PD ≥6 mm Exclusion Criteria: Poor implant placement, HC, adjacent defects, Implant mobility	Pretreatment phase: Yes FMPS < 20% & FMBS < 20% Surgical treatment: Regenerative DBBMC	Adjunctive treatment: CTG when no KT Surface decontamination: EDTA gel (24%) + CHX gel (1%) Peri-operative Antibiotics: AUG 1 g twice a day, for 6 days	SPT operator: Dental hygienist + Periodontist SPT frequency: According to individual risk assessment SPT description: Motivation, OH reinstruction, FMD Additional treatment ATB, FGG
13. Romeo et al. (2005)	Prospective, 2 groups University Multiple operators Funding: NR Follow-up: 3 yrs	Patients: n = 17 Gp1: n = 10, Gp2: n = 7, 2 smokers >10 cig./day Implants: n = 35 Straumann, TPS: HS n = 11, S n = 24 Prostheses: NR	Inclusion Criteria: PD >4 mm, BoP/PUS, Evident BL Exclusion Criteria: Implant mobility	Pretreatment phase: Yes Systemic ATB and FMD Surgical treatment: Resective Gp1: RES + IPP (10 pts, 19 impl.) Gp2: RES (7 pts, 16 impl.); Not followed for 3 yrs	Adjunctive treatment: NR Surface decontamination: MTR gel + TET solution Peri-operative Antibiotics: AMX	SPT operator: NR SPT frequency: NR SPT description: Regimen unclear
14. Roos-Jansåker et al. (2014) Related publications: Roos-Jansåker et al. (2007, 2011)	Prospective, 2 groups University Single operator Funding: NR Follow-up: 5 yrs	Patients: n = 36 Gp1: n = 17 7 M, 10 F Mean age: 65.6±7.4 yrs Smokers n = 12 Gp2: n = 19 5 M, 12 F Mean age: 66.3±6.8 yrs Smokers n = 13 Implants: n = 65 G1: n = 29, G2: n = 36 Astra Tech, Brånemark Prostheses: Screw retained SICs and FDPs	Inclusion Criteria: BL ≥1.8 mm, BoP/PUS Exclusion Criteria: Horizontal bone loss or no crater-like bone defect	Pretreatment phase: Yes Surgical treatment: Regenerative Gp 1: PCC + RSM (n = 19) Gp 2: PCC (n = 17)	Adjunctive treatment: NA Surface decontamination: H_2O_2 Peri-operative Antibiotics: AMX and MET for 10 days	SPT operator: NR SPT frequency: 3 month SPT description: OHI and rubber cup polishing

(Continues)

TABLE 4 (Continued)

	Study details			Treatment provided		
Authors/Year	**Design**	**Population baseline**	**Inclusion**	**Initial peri-implantitis treatment**		**Supportive care**
15. Schwarz et al. (2009) Related publications: Schwarz et al. (2006, 2008)	Prospective, 2 groups University Single operator Funding: NR Follow-up: 4 yrs	Patients: n = 22 Gp1: n = 11 Gp2: n = 11 8 M, 14 F Mean age: 54.4±12.5 yrs Implants: n = 22 7 brands: S Prostheses: NR	Inclusion Criteria: PD > 6 mm, intrabony BL > 3 mm Exclusion Criteria: Implant mobility, occlusal overload, no KM, UPD, poor OH, DM, OP, heavy smokers (> 10 cig./day), HS	Pretreatment phase: Yes Non surgical debridement with PS, CHX irrigation & gel Surgical treatment: Regenerative Gp1: NHA+ CM Gp2: NBM	Adjunctive treatment: NR Surface decontamination: PC Peri-operative Antibiotics: No	SPT operator: 2 of the authors SPT frequency Fortnightly for 2 month, Monthly until 6 month, then 6 monthly until 48 month SPT description: Supragingival professional implant/tooth cleaning OHI
16. Schwarz et al. (2017) Related publications: Schwarz et al. (2012, 2013)	Prospective, 2 groups University Single operator Funding: NR Follow-up: 7 yrs	Patients: n = 32 Gp1: n = 16 Gp2: n = 16 11 M, 21 F Mean age: 60.8±10.9 yrs Implants: n = 38 10 different brands Prostheses: NR	Inclusion Criteria: PD > 6 mm, Intrabony BL > 3 mm Exclusion Criteria: HC, Implant mobility, unhealthy patients, UPD, lack of proper periodontal maintenance, heavy smokers (> 10 cig./day)	Pretreatment phase: Yes Surgical treatment: Combined Regenerative XMB (Bio-Oss), CM (BioGide) + resective (IPP)	Adjunctive treatment: CTG when no KT Surface decontamination: Gp 1: ER:YAG laser (ERL), PC + saline GP 2: PC + saline Peri-operative Antibiotics: AMX for 5 days	SPT operator: Single operator first 6 month One visit annually, University, Maintenance provided by the referring practitioner SPT frequency 2 weeks during the first 2 month, then monthly until 6 month, then yearly SPT description: OHI, professional cleaning
17. Serino et al. (2015) Related publications: Serino et al. (2011)	Prospective, 1 group University Multiple operators—periodontists Funding: NR Follow-up: 5 yrs	Patients: n = 31 13 M, 11 F Mean age: 63.2±8.7 yrs Smokers n = 8 Implants: n = 86 Astra, ITI, Brånemark: S Prostheses: Screw-retained restorations removed before treatment	Inclusion Criteria: PPD ≥ 6 mm, BoP/PUS, BL ≥ 2 mm Exclusion Criteria: BIP	Pretreatment phase: Yes Supra/subgingival debridement, adjustment prosthesis if required Surgical treatment: Combined Access flap + RES	Adjunctive treatment: No Surface decontamination: US + CHX irrigation Peri-operative Antibiotics: CLI for 7 days	SPT operator: Periodontist SPT frequency: 6 month SPT description: Supragingival plaque control Sub-gingival scaling at implants with residual pockets using US metal tips instrument under CHX 0.12% irrigation

(Continues)

TABLE 4 (Continued)

	Study details			Treatment provided		
Authors/Year	**Design**	**Population baseline**	**Inclusion**	**Initial peri-implantitis treatment**		**Supportive care**
18. Zablotsky (1998)	Retrospective, 1 group Private practice Operators—NR Funding: NR Follow-up: 3 yrs	Patients: n = 21 Age range: 22–87 yrs Implants: n = 42 Multiple brands, various surfaces: TPS n = 22, HA HS n = 15, Ti n = 5 Prostheses: NR	Inclusion Criteria: Implant stability (periotest values <10), BL <70%, PD >4 mm, BoP/PUS, previously treated with hard and/or soft tissue augmentation Excessive BL BoP/PUS Exclusion criteria: NR	Pretreatment phase: Yes LDD: Actisite (n = 8) Systemic ATB (n = 6) Surgical treatment: Multiple 17 GBR, 11 RES, 9 STG, 5 combination	Adjunctive treatment: Unstable implants were retreated Surface decontamination: CA Peri-operative Antibiotics: NR	SPT operator: NR SPT frequency: 3–4 month SPT description: NR

BL: bone loss; PD: probing depth; BoP: bleeding on probing; NR: not reported; SUP/PUS: suppuration.
Population baseline: FDP: fixed dental prosthesis; HA: hydroxyapatite-coated implants; Hx treated PDD: history of treated periodontal disease; HS: hollow-screw; RDP: removable dental prosthesis; S: screw-shaped; SIC: single-implant crown, Ti: titanium; TPS: titanium plasma-sprayed; HC: Hollow cylinder.
Inclusion/Exclusion criteria: BIP: bisphosphonate therapy; DM: diabetes mellitus; CVD: cardiovascular diseases; OP: osteoporosis; UPD: untreated periodontal disease.
Antibiotics: AMX: amoxicillin; ATB: antibiotics; AUG: augmentin; CLI: clindamycin; DOX: doxycycline; LDD: local delivery device; MIN: minocycline; MTR: metronidazole; TET: tetracycline.
Surgical treatment and regenerative materials: ABG: autogenous bone graft; CM: collagen membrane; DBBMC: demineralized bovine bone mineral with collagen; EMD: enamel matrix derivate; ePTFE: expanded polytetrafluoroethylene membrane; GBR: guided bone regeneration; NBM: natural bone mineral; NHA: nanocrystalline hydroxyapatite; PCC: phytogenic calcium carbonate (Algipore); PDGF: platelets derived growth factor; RES: resective; RSM: resorbable synthetic membrane; STG: soft tissue grafting; TCP: beta-tricalcium phosphate; XBM: xenogenic bone mineral (Bio-Oss).
Adjunctive treatment: FGG: free gingival graft; CTG: connective tissue graft; KT: keratinized tissue.
Surface decontamination: CA: citric acid; CHX: chlorhexidine; EDTA: ethylenediamine tetra-acetate; IPP: implantoplasty; PC: plastic curette; PS: plastic scaler; TC: titanium curettes; US: ultrasonic instrumentation.
Supportive care: APB: air-powder abrasive with sodium bicarbonate powder; FMD: full-mouth debridement; OHI: oral hygiene instruction.

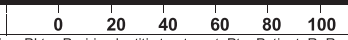
TABLE 5 Implant-level success for the longest follow-up time reported, and success definitions as reported

		Peri-implantitis				Results at the longest follow-up time							
Date	Author	Tx	Group	Time in situ	Imp N	LTF N	Succ N	Recur N	Fail N	ECSucc (%)	Lower 95% CI	Upper 95% CI	Success Criteria
2017	Carcuac et al.	Res	4 Groups combined	3 years	179	31	40	NR	20	33.94	26.69	41.20	Success = No BL > 0.5 mm, +PD ≤5 mm, + No BoP + No Sup
2018	Mercado F, Hamlet S, Ivanovski S	R	1 Group	3 years	30	0	17	NR	0	56.67	38.93	74.41	Success = No further BL + No BoP + No Sup + PD <5 mm + Recession of <0.5–1.5 mm
1998	Zablotsky MH.	Various	1 Group	3.5 years to 7.0 years, μ=4.5 years	42	4	32	NR	4	85.00	73.93	99.07	Not clearly reported
2015	Serino G, Turri A, Lang NP.	Res	1 Group	5 years	86	8	58	9	11	75.61	66.32	84.9	Success = PD < 4 mm + No BoP + No Sup
2016	Heitz-Mayfield LJ et al.	Access flap	1 Group	5 years	36	8	19	5	4	71.88	56.30	87.46	Success = No further BL + No PD ≥5 mm with BoP +No Sup
2017	Roccuzzo M et al.	R	Gp 1: TPS	7 years	14	2	2	NR	2	7.69	0.00	22.18	Success = No further BL + PD ≤5 mm + No BoP + No Sup
			Gp 2: SLA		12	0	7	NR	2	41.67	13.77	69.56	

Peri-implantitis abbreviations: R: regenerative, Recur: recurrence, Res: resective, Tx: treatment.

Other abbreviations: BL: bone loss, BoP: bleeding on probing, ECSucc: estimated cumulative success, LTF: loss to follow-up, N: number, NR: not reported, PD: peri-implant probing depth, Succ: success, Sup: suppuration, TPS: titanium plasma sprayed, SLA: sandblasted large grit acid-etched.

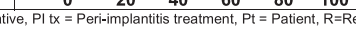
Author	Date	PI Tx	Time (yr) in situ	Imp N	LTF N	Surv N	Fail N	ECSurv %	Lower 95%CI	Upper 95%CI	Weight
Khoury F, Buchmann R.	2001	R	3	41	0	41	0	100.00	99.80	100.00	24.88
Romeo E et al.	2005	Res	3	19	0	19	0	100.00	99.80	100.00	24.88
Froum SJ, Froum SH, Rosen PS.	2012	R	3 to 7.5 μ=3.7	51	0	51	0	100.00	99.80	100.00	24.88
Heitz-Mayfield LJ, et al.	2016	NR	3	36	4	30	2	94.12	86.20	100.00	0.12
Mercado F, Hamlet S, Ivanovski S	2017	R	3	30	0	30	0	100.00	99.80	100.00	24.88
Roccuzzo M, et al.	2017	R	3	26	1	23	2	92.16	81.73	100.00	0.07
Carcuac O. et. al.	2017	Res	3	179	31	128	20	87.77	82.75	92.79	0.30
	I-squared = 77.9%, P<0.001 Weights are from random effects analysis							**99.95**	**99.67**	**100.00**	**100.00**
Zablotsky MH.	1998	C	3.5 to 7.0 μ=4.5	42	4	34	4	90.00	80.71	99.29	0.16
Schwarz F et al	2009	R	4	11	0	11	0	100.00	99.80	100.00	49.88
Schwarz F et al	2009	R	4	11	0	11	0	100.00	99.80	100.00	49.88
Schwarz F et al	2016	R	4	38	17	17	4	86.44	74.09	98.79	0.09
	I-squared = 67%, P=0.028 Weights are from random effects analysis							**99.97**	**99.60**	**100.00**	**100.00**
Roos-Jansaker AM et al	2014	R	5	45	15	30	0	100.00	99.80	100.00	31.51
Chang HY et al	2015	NS	5	31	0	28	3	90.32	79.91	100.00	21.97
Serino G, Turri A, Lang NP.	2015	Res	5	86	8	67	11	86.59	79.22	93.96	25.88
Heitz-Mayfield LJ et al	2016	NR	5	36	8	24	4	87.50	76.03	98.97	20.64
	I-squared = 85.4%, P<0.001 Weights are from random effects analysis							**91.82**	**82.95**	**100.00**	**100.00**
Schwarz F et al.	2016	R	7	38	19	15	4	85.96	73.20	98.72	NA
Roccuzzo M et al	2017	R	7	26	2	20	4	84.00	69.63	98.37	NA
	I-squared = 0%, P=0.84 Less than 3 studies, Meta analysis not completed							**NA**	**NA**	**NA**	**NA**



C=Combination, ECSurv=Estimated cumulative survival, LTF=Loss to follow up, NR=Non-Regenerative, PI tx=Peri-implantitis treatment, Pt = Patient, R=Regenerative, Res=Resective, Surv=Survival

FIGURE 2 Forest plot of the estimated cumulative survival of dental implants treated for peri-implantitis across 3, 4, 5 and 7 years

Author	Date	PI Tx	Time (yr) in situ	Pt N	LTF N	Surv N	Fail N	ECSurv %	Lower 95%CI	Upper 95%CI	Weight
Khoury F, Buchmann R.	2001	R	3	25	0	25	0	100.00	99.80	100.00	19.98
Romeo E et al.	2005	Res	3	10	0	10	0	100.00	99.80	100.00	19.98
Froum SJ, Froum SH, Rosen PS.	2012	R	3 to 7.5 μ=3.7	38	0	38	0	100.00	99.80	100.00	19.98
Roos-Jansaker AM et al	2014	R	3	38	6	32	0	100.00	99.80	100.00	19.98
Heitz-Mayfield LJ et al.	2016	NR	3	24	2	20	2	91.30	79.78	100.00	0.02
Mercado F, Hamlet S, Ivanovski S	2017	R	3	30	0	30	0	100.00	99.80	100.00	19.98
Roccuzzo M, et al.	2017	R	3	26	1	23	2	92.16	81.73	100.00	0.03
Carcuac O. et. al.	2017	Res	3	100	17	70	13	85.79	78.64	92.95	0.06
	I-squared = 64.1%%, P=0.0.007 Weights are from random effects analysis							**99.99**	**99.81**	**100.00**	**100.00**
Zablotsky MH.	1998	C	3.5 to 7.0 μ=4.5	21	2	17	2	90.00	76.85	100.00	0.06
Schwarz F et al	2009	R	4	11	0	11	0	100.00	99.80	100.00	49.95
Schwarz F et al	2009	R	4	11	0	11	0	100.00	99.80	100.00	49.95
Schwarz F et al	2016	R	4	32	11	17	4	84.91	71.29	98.53	0.05
	I-squared = 56.7%, P=0.074 Weights are from random effects analysis							**99.99**	**99.68**	**100.00**	**100.00**
Roos-Jansaker AM et al	2014	R	5	38	13	25	0	100.00	99.80	100.00	39.15
Serino G, Turri A, Lang NP.	2015	Res	5	31	4	19	8	72.41	56.14	88.68	30.36
Heitz-Mayfield LJ et al	2016	NR	5	24	4	16	4	81.82	65.71	97.93	30.49
	I-squared = 87.5%, P<0.001 Weights are from random effects analysis							**86.08**	**67.17**	**100.00**	**100.00**
Schwarz F et al.	2016	R	7	32	13	15	4	84.31	70.20	98.42	NA
Roccuzzo M et al	2017	R	7	26	2	20	4	84.00	69.63	98.37	NA
	I-squared = 0%, P=0.98 Less than 3 studies, Meta analysis not completed							**NA**	**NA**	**NA**	**NA**



C=Combination, ECSurv=Estimated cumulative survival, LTF=Loss to follow up, NR=Non-Regenerative, PI tx = Peri-implantitis treatment, Pt = Patient, R=Regenerative, Res=Resective, Surv=Survival

FIGURE 3 Forest plot of the estimated cumulative survival of dental implants in patients treated for peri-implantitis across 3, 4, 5 and 7 years

		SELECTION				COMPARABILITY		OUTCOME							TOTAL
		1	2	3	4	5	6	7	8	9	10	11	12	13	
		Representativeness	Second group representativeness	Ascertainment of exposure	When did the outcome occur	Different cohorts	Single cohort	Subjective outcomes	Probing	Radiographs	Recurrence	Failure	Follow up completeness	Loss to follow up	
Studies with a single group															
Behneke A, Behneke N, d'Hoedt B	2000	★	NA	★	★	NA	★★	?	★	★	✖	★	★	★	10/12
Chang HY et al	2015	★	NA	★	★	NA	★★	★	★	★	✖	★	★	★	11/12
Charalampakis G et al	2011	★	NA	★	★	NA	★	✖	✖	✖	✖	★	★	?	6/12
Froum SJ, Froum SH, Rosen PS.	2015	★	NA	★	★	NA	★★	★	★	★	✖	★	★	★	11/12
Froum SJ, Froum SH, Rosen PS.	2012	★	NA	★	★	NA	★★	★	★	★	✖	★	★	★	11/12
Heitz-Mayfield LJ et al	2016	★	NA	★	★	NA	★★	★	★	★	★	★	★	★	12/12
Mercado F, Hamlet S, Ivanovski S	2017	★	NA	★	★	NA	★★	★	★	★	★	★	★	★	12/12
Roccuzzo M et al	2017	★	NA	★	★	NA	★★	★	★	★	✖	★	★	★	11/12
Serino G, Turri A, Lang NP	2015	★	NA	★	★	NA	★★	★	★	✖	★	★	★	★	11/12
Zablotsky MH	1998	★	NA	★	★	NA	★★	?	✖	✖	✖	★	★	★	8/12
Studies with more than one group															
Bach G et al	2000	★	★	★	★	★	NA	?	✖	✖	✖	★	★	?	8/13
Carcuac et al	2017	★	★	★	★	★★	NA	★	★	★	✖	★	★	★	12/13
Deppe H, Horch HH, Neff A	2007	★	★	★	★	✖	NA	✖	✖	✖	✖	★	★	✖	6/13
Roos-Jansaker AM et al	2014	★	★	★	★	★★	NA	★	✖	★	✖	★	★	★	11/13
Schwarz F et al	2016	★	★	★	★	★★	NA	★	★	★	✖	★	★	✖	11/13
Schwarz F te al	2009	★	★	★	★	★★	NA	★	★	★	✖	✖	★	★	11/13
Khoury F, Buchmann R.^	2001	★	★	★	★	★	NA	★	★	★	✖	★	★	★	11/13
Romeo E et al*	2005	★	★	★	★	★★	NA	★	★	★	✖	★	★	★	12/13

^3 groups in paper, but the authors combined the results during reporting
* 2 groups in the paper, but one was used for this analysis because the control group was followed for less than 3 years.
Green: Criteria fulfilled; Orange: Unclear if criteria fulfilled; Red: Criteria not fulfilled; NA: Not applicable.

FIGURE 4 Risk of bias assessment results, modified from NOS. Studies with more than one group could attract 13 stars (*), and studies with a single group could attract 12 stars (*).

maintained over the medium to long term (3–7 years), when patients are enrolled in a supportive care program.

4.1 | 3–7-year outcomes

Across the studies, anti-infective treatment protocols aimed at implant surface decontamination with or without a reconstructive approach using bone graft/substitutes resulted in clinical improvements for the majority of patients and implants. It should be recognized however, that some studies in this review documented the need for additional interventions (connective tissue grafting, surgical intervention, systemic antimicrobials) in some patients, to achieve the desired outcome (Roccuzzo et al., 2017) or manage disease recurrence (Heitz-Mayfield et al., 2016; Zablotsky, 1998).

The 3-year treatment outcomes were favourable with high patient- and implant-level survival. However, in several studies where multiple follow-up time points were available, additional implant loss was noted with time due to disease progression resulting in the removal of the implants (Froum et al., 2015; Heitz-Mayfield et al., 2016; Roccuzzo et al., 2017).

The implant-level and patient-level pooled meta-analyses showed that over 90% of implants in over 85% of patients that had treatment were expected to still have their implants after 5 years. At 7 years there was less evidence, but data still indicated that over 80% of patients with treated implants might retain their implants. Although results are not definitive, the review suggests that anti-infective protocols will stabilize those infections for the medium- to long term for the majority of patients, and as such, pursuing treatment could be considered to be worthwhile.

Five papers defined success, with each using composite criteria relating to BoP, suppuration, and probing depth (n = 5), bone level (n = 4) and recession (n = 1). Due to the heterogeneity of success criteria, it was not possible to pool data or make meaningful comparisons. While complete resolution of disease, as defined by the total absence of BoP, may not be a requirement for treatment success, one study observed that absence of bleeding/suppuration on probing was predictive of stable bone levels 3 years after treatment (Carcuac et al., 2017).

Across the 18 studies, disease recurrence was not commonly discussed or defined. Recession of the peri-implant mucosa following treatment was documented in two studies, (Heitz-Mayfield et al., 2016; Mercado, Hamlet & Ivanovski, 2018) which might impact on aesthetics,

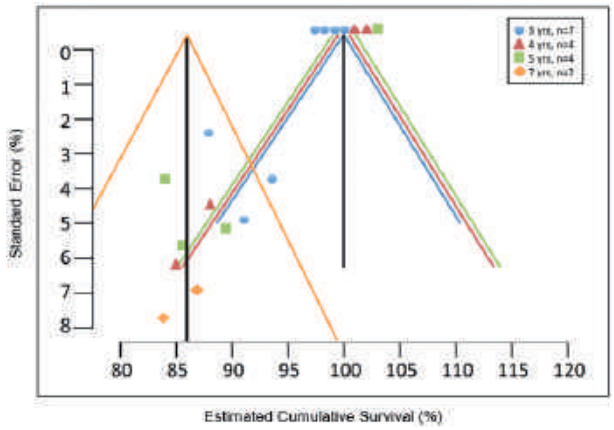


FIGURE 5 Funnel plot, analysed by implant-level survival outcomes across 3 year (blue line), 4 year (red line), 5 year (green line) and 7 year (yellow line) subgroups

phonetics and comfort. However, patient-reported outcome measures (PROMs) such as aesthetic outcomes; quality of life; and patient satisfaction; as well as cost satisfaction analyses were not reported in the included studies. These outcomes are relevant to clinical decisions and would be important areas to address in future research.

The quality of conduct of the included studies was generally high, with over 75% assessed to have low risk of bias. However, the quality of reporting in some areas, in particular outcome definitions was low. This hindered data extraction and has reduced the potential utility of this systematic review.

4.2 | Anti-infective treatment

Anti-infective treatment protocols described included a pretreatment phase (nonsurgical supramucosal biofilm removal) followed by decontamination of the implant surface using a range of techniques with and without antiseptics. Implant surface decontamination was performed during surgical access. Peri-operative systemic antimicrobials were prescribed in the majority of studies. Postoperative infection control included the use of antiseptic rinsing for periods of several weeks following treatment. Supportive care protocols all involved professional biofilm removal at implants and teeth at varying time intervals from three monthly to annually. Some studies described recall frequency based on an individual risk assessment. There was no indication that recall frequency was related to patient attrition. While there were no studies comparing supportive care protocols it appears that the regular and thorough removal of biofilm at implants and teeth is necessary for a positive treatment outcome.

4.3 | Confounding factors

Local factors which may influence local plaque control and hence the outcome of peri-implantitis treatment include: implant placement/positioning; prosthesis design; presence of keratinized mucosa; implant surface and design. The association between inadequate access for oral hygiene due to prosthesis design/contours, and the presence of peri-implantitis was previously demonstrated (Serino & Strom, 2009). It is also important to consider access for adequate local plaque control after the peri-implantitis has been treated. Two studies in the present review excluded patients with implants considered inappropriate to treat due to either poor implant positioning (Roccuzzo et al., 2017) or inadequate contour of the prosthesis (Heitz-Mayfield et al., 2016). In some instances, it may be appropriate to remake the implant prosthesis or remove the implant if there is no possibility to achieve adequate plaque control.

While the majority of studies in this systematic review did not report full-mouth plaque scores (FMPS), low FMPS (<20%) such as those reported by (Heitz-Mayfield et al., 2016) may be important in achieving sufficient infection control and treatment success.

A number of studies in the systematic review incorporated a soft tissue graft as part of the treatment procedure (Bach, Neckel, Mall & Krekeler, 2000; Froum et al., 2012, 2015; Mercado et al., 2018) or during supportive care (Roccuzzo et al., 2017). It has been suggested that the absence of an adequate band of keratinized peri-implant mucosa may negatively influence treatment outcomes due to discomfort when performing oral hygiene resulting in increased plaque accumulation (Roccuzzo, Grasso & Dalmasso, 2016).

Implant design and surface characteristics may also influence the treatment outcome. Most studies included a variety of implant designs and surfaces and it was not possible to evaluate the effect on treatment outcome due to the heterogeneity. One study found that success following resective peri-implantitis treatment was affected by implant surface characteristics. Implants with a nonmodified ("turned") surface achieved success more frequently than implants with modified surfaces at 3 years (Carcuac et al., 2017). In another study with 7 years follow-up of reconstructive peri-implantitis treatment using a bone substitute (deproteinized bovine bone mineral with 10% collagen), patients with TPS implant surfaces had lower implant survival and success than those with a SLA implant surface (Roccuzzo et al., 2017).

Other possible confounding factors that could not be assessed in this review due to heterogeneity, low participant numbers and nonreporting include: patient systemic factors (e.g., diabetes, cardiovascular disease); medications; history of periodontitis; smoking status and prosthesis design.

4.4 | Limitations of the review

This review sought published and unpublished data across the peri-implantitis treatment field. Three of the included studies (20%) were identified through grey literature. This is a substantial number and indicates that multiple teams are actively researching in this field. Therefore, it is possible that additional grey data exists, but was unintentionally overlooked during the search. It also suggests that knowledge in this field will continue to evolve, possibly quickly, and care should be taken to interpret results from this review in the light of more recent evidence that was not available at its inception.

The outcomes from this review are limited by the heterogeneity between studies. The utility of results from this review is limited by the outcome measure, survival. Other outcome measures could not be assessed. Survival does not account for surrounding tissue health, tissue appearance, or patient satisfaction. Although peri-implantitis treatment can retain implants for patients, a surviving implant in one patient might be markedly different to a surviving implant in another patient.

5 | CONCLUSIONS

The results of this review confirm that peri-implantitis can be successfully treated in patients adhering to a supportive care programme which involves professional biofilm removal at implants and teeth. High survival rates can be achieved in the medium to long term. Implant surface may influence the treatment outcomes. Some implants in some patients may require retreatment, adjunctive therapies or implant removal.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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CONSENSUS REPORT

WILEY CLINICAL ORAL IMPLANTS RESEARCH

Group 4 ITI Consensus Report: Risks and biologic complications associated with implant dentistry

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Abstract

Objectives: The aim of Working Group 4 was to address topics related to biologic risks and complications associated with implant dentistry. Focused questions on (a) diagnosis of peri-implantitis, (b) complications associated with implants in augmented sites, (c) outcomes following treatment of peri-implantitis, and (d) implant therapy in geriatric patients and/or patients with systemic diseases were addressed.

Materials and methods: Four systematic reviews formed the basis for discussion in Group 4. Participants developed statements and recommendations determined by group consensus based on the findings of the systematic reviews. These were then presented and accepted following further discussion and modifications as required by the plenary.

Results: Bleeding on probing (BOP) alone is insufficient for the diagnosis of peri-implantitis. The positive predictive value of BOP alone for the diagnosis of peri-implantitis varies and is dependent on the prevalence of peri-implantitis within the population. For patients with implants in augmented sites, the prevalence of peri-implantitis and implant loss is low over the medium to long term. Peri-implantitis treatment protocols which include individualized supportive care result in high survival of implants after 5 years with about three-quarters of implants still present. Advanced age alone is not a contraindication for implant therapy. Implant placement in patients with cancer receiving high-dose antiresorptive therapy is contraindicated due to the associated high risk for complications.

Conclusions: Diagnosis of peri-implantitis requires the presence of BOP as well as progressive bone loss. Prevalence of peri-implantitis for implants in augmented sites is low. Peri-implantitis treatment should be followed by individualized supportive care. Implant therapy for geriatric patients is not contraindicated; however, comorbidities and autonomy should be considered.

KEYWORDS

augmentation, complication, geriatric, implant survival, peri-implantitis, supportive care, systemic conditions

1 | INTRODUCTION

The objectives of Group 4 of the 6th ITI Consensus Conference were to provide statements and recommendations for clinicians and researchers relating to risks and biologic complications in implant dentistry. Four systematic reviews formed the basis for discussion within the working group and were prepared and reviewed prior to the consensus conference. The systematic reviews were discussed within the group, and minor modifications, as required, were made to the manuscripts. The working group formed consensus statements and clinical recommendations which were then presented and accepted following further discussion and modifications when required by the plenary. Recommendations for future research were also prepared by the working group. The four systematic reviews are listed below.

The Diagnosis of Peri-implantitis: A systematic review on the predictive value of bleeding on probing (Hashim, Cionca, Combescure, Mombelli, 2018).

Long-term biological complications of dental implants placed either in pristine or in augmented sites: A systematic review and meta-analysis (Salvi, Monje, Tomasi, 2018).

Clinical outcomes of peri-implantitis treatment and supportive care: A systematic review (Roccuzzo, Layton, Roccuzzo, Heitz-Mayfield, 2018).

Effect of advanced age and/or systemic medical conditions on dental implant survival: A systematic review and meta-analysis (Schimmel, Srinivasan, McKenna, Müller, 2018).

2 | THE DIAGNOSIS OF PERI-IMPLANTITIS: THE PREDICTIVE VALUE OF BLEEDING ON PROBING

2.1 | Preamble

Bleeding on probing has been proposed as one of the signs of mucositis and/or peri-implantitis. This review aimed to systematically evaluate the predictive value of the presence or absence of bleeding on probing (BOP) alone for the diagnosis of peri-implantitis.

Thirty-one clinical studies reporting on the prevalence of peri-implantitis, BOP and/or suppuration (SUP) after at least 1 year of functional loading were selected. Meta-analyses were conducted to combine the proportions of peri-implantitis among BOP and/or SUP-positive subjects and implants across studies up to 18 years.

Subgroups were created and compared to investigate potential sources of heterogeneity.

For BOP-positive patients, there was a 34% probability to be diagnosed with peri-implantitis (prediction interval 10% to 69%). On average, 24% of implants which presented with BOP across these studies were diagnosed with peri-implantitis. The prediction interval ranged from 7% to 58%. Thus, we can assume that the effect size varied across populations. Longer observation periods were significantly associated with higher proportions of peri-implantitis among BOP-positive implants, reflecting increasing prevalence with time.

This review was limited in its analysis by the heterogeneity of the populations and the variable definitions of peri-implantitis.

2.2 | Consensus statements

2.2.1 | Consensus statement 1

The positive predictive value of BOP alone for the diagnosis of peri-implantitis for each implant ranges from about 7%–58%, depending on the prevalence in the population. This means, if 100 implants present with BOP, between 7 and 58 implants may have peri-implantitis. This statement is based upon the prediction interval of 6.9%–57.8% bounding the weighted mean (24.1%) calculated across 29 studies identified as part of this review.

2.2.2 | Consensus statement 2

The positive predictive value of BOP alone increases with time after loading. This probably indicates that the prevalence of peri-implantitis increases with time after loading. Shorter observation periods have lower rates of peri-implantitis, while longer observation periods have higher rates of peri-implantitis. This statement is based on the reduced positive predictive value of BOP identified across two studies with 1- to 3-year mean follow-up compared with 27 studies with more than a 3-year mean follow-up.

2.3 | Clinical recommendations

2.3.1 | What are the key criteria to diagnose the presence of peri-implantitis?

BOP alone is insufficient for the diagnosis of peri-implantitis. The diagnosis of peri-implantitis requires the evaluation of inflammation/infection and progressive bone loss that can vary between implants and patients.

2.3.2 | What does the predictive value of a diagnostic test mean in clinical practice?

If a site bleeds after probing, there is a chance that the implant may have peri-implantitis. The probability that this is the case is called the positive predictive value. Clinicians should be aware that the positive predictive value of a diagnostic test may vary and is related to the prevalence of the disease within the specific patient population. In specific patient populations where the prevalence of peri-implantitis may be increased, the predictive value may be higher than in a general patient population.

2.4 | Recommendations for future research

- To investigate the presence of BOP as a risk factor for the development of peri-implantitis, specifically designed longitudinal studies are required.
- Biological conditions of human BOP-positive and negative peri-implant tissues should be investigated, on a histological and molecular level, to better understand the underlying causes of bleeding upon probing.
- The documented relationship between probing force and frequency of BOP at healthy teeth suggests that tissue trauma due to probing with an inappropriate force may occasionally be the reason for bleeding at implants. However, recommendations for ideal probing forces at implants can presently not be made due to lack of evidence. There is a need for clinical studies determining the impact of various factors affecting outcomes of peri-implant probing.
- Future research should investigate the utility of different assessments of bleeding, such as a bleeding index, rather than using a dichotomous evaluation of BOP.
- Research should explore the possibility of combining other diagnostic tools with BOP to increase the predictive value.

3 | LONG-TERM BIOLOGICAL COMPLICATIONS OF DENTAL IMPLANTS PLACED EITHER IN PRISTINE OR IN AUGMENTED SITES

3.1 | Preamble

Placement of dental implants in conjunction with augmentation procedures is well documented and has been shown to yield high predictability in terms of implant survival rates and volume stability. However, a comparison between the long-term prevalence of biological complications at implants placed in pristine sites (sites not requiring augmentation prior to or in conjunction with implant placement) versus augmented sites is lacking.

This systematic review investigated and compared the prevalence of biological complications and failure (loss) of implants placed in pristine versus augmented sites after a mean observation period of at least 10 years. The following focused questions were addressed:

- In patients with osseointegrated dental implants, are there differences in biological complications at implants placed in pristine versus augmented sites?
- In patients with osseointegrated dental implants, are there differences in failure rates of implants placed in pristine versus augmented sites?

The systematic review included 8 investigations (1 RCT, 1 case–control study, 1 cross-sectional study, 5 case series). The mean number of patients included across the studies was 56.9 (range: 15–96 patients), while the mean number of implants was 113.5 (range: 15–153 implants) with a mean follow-up of 11.1 years (range: 10–15 years).

Various augmentation techniques (e.g., lateral and/or vertical augmentation, augmentation prior to or at the time of implant placement, and alveolar ridge preservation procedures prior to implant placement), as well as a range of augmentation materials (e.g., autogenous bone and bone substitutes) and barrier membranes (e.g., resorbable and nonresorbable) were included in the four studies reporting on implant placement in augmented sites. All included studies reported that patients were enrolled in supportive care following implant therapy.

No statistically significant differences were observed between implants placed in pristine versus augmented sites for any outcome variable both at patient and implant level. High heterogeneity concerning patient sampling, case definitions of biological complications and eligibility criteria were observed.

Sufficient data were available to perform meta-analyses for the primary outcome (biological complications) and secondary outcome (implant failure).

3.2 | Consensus statements

3.2.1 | Consensus statement 1

There is evidence that patients receiving implants in augmented sites may display a comparable prevalence of peri-implant mucositis compared with patients receiving implants in pristine sites. Patients with implants placed in pristine sites have a prevalence of peri-implant mucositis of 22.4% (95% CI: 6%–38%) compared with a prevalence of 19.6% (95% CI: 0%–40%) for patients with implants in augmented sites.

This statement is based on 1 RCT, 1 case–control study, and 4 case series studies.

3.2.2 | Consensus statement 2

There is evidence that the long-term prevalence of peri-implantitis in patients with implants in pristine sites and augmented sites is low. The prevalence of peri-implantitis in patients with implants in augmented sites is more variable and less predictable compared with the prevalence in patients with implants in pristine sites. The weighted mean prevalence of peri-implantitis in patients with implants in augmented sites was 17.8% (95% CI: 0%–37%) compared with that of 10.3% (95% CI: 4%–17%) in patients with implants in pristine sites.

This statement is based on 1 RCT, 1 case–control study, and 4 case series studies.

3.2.3 | Consensus statement 3

There is some evidence that the long-term prevalence of implant failure (loss) in patients with implants in pristine sites and augmented sites is low.

The weighted mean prevalence of implant failure (loss) in patients with implants in augmented sites was 3.6% (95% CI: 0%–8%) compared with that of 2.5% (95% CI: 1%–4%) in patients with implants in pristine sites.

This statement is based on 1 RCT, 1 case–control study, and 4 case series studies.

3.2.4 | Consensus statement 4

In patients with a history of treated periodontitis (moderate and severe) receiving implant therapy in pristine sites, compliance with regular supportive care yields lower long-term implant failure (loss) compared with patients not complying with regular supportive care.

This statement is based on 1 study.

3.2.5 | Consensus statement 5

There is limited evidence concerning the effect of regular supportive care in patients with a history of treated periodontitis receiving implants in augmented sites.

This statement is based on 1 study.

3.3 | Clinical recommendations

3.3.1 | For the long-term monitoring of biological complications, at what time points should implants placed in augmented sites be assessed?

The time of completion of the implant-supported prosthesis should be used as a baseline for assessment. Similar to implants placed in pristine sites, implants placed in augmented sites should have time-points for subsequent assessments determined by the individual risk profile of the patient.

3.3.2 | Do patients with implants in augmented sites require specific supportive care?

Patients with implants in augmented and pristine sites should both be enrolled in regular supportive care. Special consideration should be given to periodontally susceptible patients with implants placed in augmented sites.

3.4 | Recommendations for future research

- The influence of factors including defect morphology, augmentation technique, and augmentation materials (bone substitutes and barrier membranes) on the occurrence of biologic complications should be investigated in observational and randomized controlled trials.
- The impact of implant placement in augmented versus pristine sites on the development of biological complications and implant failure

(loss) needs to be investigated in randomized controlled clinical trials.

- The impact of compliance with supportive care in patients with implants placed in augmented sites on the development of long-term biological complications and implant failure (loss) needs to be investigated in well-designed observational studies and randomized controlled clinical trials.

4 | OUTCOMES OF PERI-IMPLANTITIS TREATMENT FOLLOWED BY SUPPORTIVE CARE

4.1 | Preamble

There is a need to establish effective treatment protocols for the management of peri-implantitis to achieve stable long-term outcomes. The 5th ITI Consensus found successful 12-month outcomes following peri-implantitis treatment could be achieved in a limited number of studies (Heitz-Mayfield, Needleman, Salvi & Pjetursson, 2014). In these studies, although favorable short-term peri-implantitis treatment outcomes were reported in the majority of patients and implants, nonresolution of peri-implantitis, disease recurrence, progression of bone loss and implant loss were also reported. The majority of studies reported treatment outcomes inconsistently. Few studies reported medium to long-term outcomes. Furthermore, the effect of supportive care (supportive peri-implant/periodontal therapy, SPT) on treatment outcomes was not addressed.

Therefore, the aim of this systematic review was to evaluate the clinical outcomes for patients with implants treated for peri-implantitis who subsequently received supportive care for at least 3 years.

The primary outcome was survival (both at implant and patient level), defined as the presence of the implant, regardless of the health of the surrounding tissues. Secondary outcomes were implant success and peri-implantitis recurrence, if defined by the authors.

The results of this systematic review are based on 18 studies, of which 13 could be used for quantitative assessments. On average, 26 patients (median, IQR 21–32) with 36 implants (median, IQR 26–45) were included in those 13 studies. Sufficient data were available to perform meta-analyses of the primary outcome.

4.2 | Consensus statements

4.2.1 | Consensus statement 1

In patients successfully treated for peri-implantitis, an individualized supportive care program, including professional and self-performed biofilm removal at implants and teeth, is associated with positive medium- to long-term outcomes.

This statement is based on the results of 18 studies.

4.2.2 | Consensus statement 2

Under current peri-implantitis treatment protocols, which include supportive care, about three-quarters of implants treated for peri-implantitis may still be present after 5 years. These outcomes might be affected by patient, implant-, prosthesis-, and treatment-related factors.

This statement is based on 13 studies, presenting an estimated cumulative implant survival of 76%–100% across 4 studies at 5 years and of 70%–99% across 2 studies at 7 years.

4.2.3 | Consensus statement 3

Although limited, there is evidence that implant surface can affect the medium- to long-term stability of peri-implantitis treatment outcomes.

This statement is based on the findings of two studies. One study found reduced success outcomes of implants with TPS (titanium plasma sprayed) compared with SLA (sandblasted large-grit acid-etched) surfaces over 7 years. One study found reduced outcomes of moderately rough compared with turned/minimally rough implant surfaces over 3 years.

4.2.4 | Consensus statement 4

Despite receiving regular supportive care, certain patients may require retreatment, adjunctive therapies, and/or implant removal due to disease progression or recurrence.

This statement is based on 2 studies that reported peri-implantitis recurrence and 5 studies that reported on treatment success.

4.3 | Clinical recommendations

4.3.1 | What definition of peri-implantitis treatment success is practical in clinical practice?

Peri-implantitis treatment success is defined as stable peri-implant bone levels, absence of probing depths >5 mm, and no bleeding or suppuration on probing.

Success in clinical practice, however, may be defined as the absence of progression of the disease, regardless of whether clinical parameters adhere to the above strict success criteria.

In addition, patients may also require that their implant reconstructions are aesthetic, comfortable, and easy to clean in order to consider the treatment a success.

4.3.2 | What clinical signs indicate that there is recurrence of peri-implantitis?

After having achieved resolution of peri-implantitis, the presence of bleeding and/or suppuration on probing together with an increase in probing depth may indicate recurrence of disease. A radiograph may be indicated if a diagnosis remains unclear.

4.3.3 | What peri-implantitis treatment protocols could be considered appropriate to use in daily clinical practice?

Certain steps should be followed during the active treatment of peri-implantitis as outlined in the 5th ITI Consensus Statements (Heitz-Mayfield et al., 2014). These steps include:

1. Thorough assessment and diagnosis.
2. Control of modifiable local and systemic risk factors for peri-implantitis.
3. Nonsurgical debridement.
4. Early reassessment of peri-implant health, generally within 1-2 months
5. Surgical access if resolution has not been achieved, including:
   - Open flap debridement
   - Thorough surface decontamination of the implant and associated prosthetic components.
   - Option of regenerative/reconstructive or resective approaches
   - Appropriate postoperative anti-infective therapy
6. Supportive care tailored to the patient risk profile, most likely 3–6 monthly.

4.3.4 | What supportive care protocols can be considered appropriate to use in daily clinical practice?

Various supportive care protocols have been proposed. It is recommended to provide individualized supportive care according to the patient's needs and risk profile.

Supportive care should include oral hygiene measures, biofilm removal, monitoring oral health, and reduction in modifiable risks related to peri-implantitis. Every effort should be made to motivate the patient and facilitate their ability to maintain plaque control both at implants and teeth, aiming for a low full mouth plaque score (FMPS <20%).

4.3.5 | Are there any implant variables that could influence long-term outcomes of an implant successfully treated for peri-implantitis?

Clinicians should be aware that implant surface characteristics may have an impact on treatment success. Other implant and prosthetic variables may also impact on treatment success, requiring modification of the supportive care program.

4.4 | Recommendations for future research

- Studies should use consistent definitions for peri-implantitis treatment success, survival, nonresolution, and recurrence.
- Studies to evaluate different protocols for supportive care following peri-implantitis treatment are required.
- Studies to evaluate the efficacy of different methods of professional biofilm removal, self-performed oral hygiene, and supportive care intervals are required.
- Studies to evaluate the influence of patient-, implant-, and prosthesis-related factors on supportive care protocol choice, following peri-implantitis treatment, are required.
- Studies to evaluate the influence of patient-, implant-, and prosthesis-related factors on the long-term outcomes of patients in supportive care following peri-implantitis treatment are required.
- Health economic and cost–utility analyses for supportive care programs following peri-implantitis treatment are required.
- Patient-reported outcomes (e.g., oral health-related quality of life, patient preference, and aesthetics) for peri-implantitis treatment protocols that include supportive care should be evaluated.

5 | EFFECT OF ADVANCED AGE, AND/OR SYSTEMIC MEDICAL CONDITIONS ON DENTAL IMPLANT SURVIVAL

5.1 | Preamble

Today's aged generation presents new challenges in the field of implant dentistry. Implant patients of advanced age often present with functional dependency, systemic medical conditions (comorbidities), and frailty. In addition, the aging of the immune system, termed immunosenescence, may result in a compromised host defense to a bacterial challenge at dental implants which adversely affects peri-implant health.

Furthermore, the presence of systemic conditions and treatment of these conditions may present a risk for implant placement, maintenance of peri-implant health, and ultimately implant survival. The most common systemic conditions in geriatric patients, as reported by the World Health Organization (WHO) in 2015, are cardiovascular disease (CVD), cancer, respiratory diseases, diabetes mellitus, liver cirrhosis, osteoarthritis, and conditions that involve neurocognitive impairment.

This systematic review addressed the focused questions: "In patients undergoing dental implant therapy, what is the effect of advanced age (≥75 years) and/or common systemic medical conditions on implant survival and biologic complication rates?"

The systematic review included evidence from 60 studies, of which 7 provided sufficient information to perform meta-analyses based on the primary outcome - implant survival in geriatric patients (≥75 years). One-year implant survival was based on 7 prospective studies with a mean of 35 implants, and 5-year implant survival was based on 3 prospective studies with a mean of 25 implants.

The remaining 53 studies reported on implant survival in patients with the most common systemic medical conditions and their respective treatments (CVD, radiation therapy, antiresorptive therapy (ART), hyposalivation/dry mouth, diabetes mellitus, and neurocognitive impairment), irrespective of the patients' age.

Annual mean peri-implant marginal bone loss (PI-MBL) was reported in seven studies.

5.2 | Consensus statements

5.2.1 | Consensus statement 1

Advanced age alone (≥75 years) is not a contraindication for implant therapy.

This statement is based on 7 prospective studies.

5.2.2 | Consensus statement 2

Peri-implant marginal bone loss (PI-MBL) in geriatric patients is low and similar to other age groups after one to 5-year follow-up.

This statement is based on 7 prospective studies, where PI-MBL was calculated to be between 0.1 mm and 0.2 mm annually over a recall period of up to 5 years and 0.51 mm for the first-year after loading.

5.2.3 | Consensus statement 3

Few studies in implantology focus on geriatric patients (≥75 years) and systemic medical conditions (comorbidities) common in old age.

5.2.4 | Consensus statement 4

Evidence suggests, that in patients with cardiovascular disease (CVD), including ischemic heart disease, stroke, and hypertensive heart disease, implant survival is similar to patients without CVD.

This statement is based on one cross-sectional and one cohort study. The calculated implant survival ranges from 98% to 100% in patients with CVD.

5.2.5 | Consensus statement 5

In patients with head and neck cancer, implant survival may be negatively affected by radiotherapy. Treatment protocols for implant placement in irradiated patients have been developed.

In oncology patients receiving high-dose antiresorptive therapy (ART), implant surgery carries a high risk for postoperative complications and is contraindicated. High-dose ART is described as any ART treatment administered in oncology patients with bone metastases. In oncology patients, the long-term effects of chemotherapy on oral tissues have not been investigated.

This statement is based on 16 studies on radiotherapy and on two studies on ART focussing on the development of medication-related osteonecrosis of the jaw (MRONJ). No studies reported on the effects of chemotherapy alone.

5.2.6 | Consensus statement 6

Treatment for cancer is commonly associated with hyposalivation. Hyposalivation is also commonly associated with polypharmacy and Sjögren's syndrome. While implant survival in patients with Sjögren's syndrome is reported to be very high, the effect of cancer treatment and polypharmacy has not been reported.

This statement is based on 5 studies.

5.2.7 | Consensus statement 7

In adult patients with diabetes mellitus type II, high implant survival rates may be achieved.

This statement is based on 7 studies for patients in the mean age range of 49.5–64 years.

5.2.8 | Consensus statement 8

Patients with conditions involving neurocognitive impairment (unipolar depression, Alzheimer's disease and other dementias, and Parkinson's disease) can experience high implant survival rates.

This statement is based on 7 studies, including 4 case reports. The mean age ranged from 44 to 83 years and an observation period of 3–72 months.

5.2.9 | Consensus statement 9

No evidence was identified related to other diseases that are common among the elderly (WHO, 2015) such as liver cirrhosis, respiratory diseases and osteoarthritis, in relation to implant therapy.

5.3 | Clinical recommendations

5.3.1 | Is there an upper age limit for implant therapy?

In geriatric patients, implant therapy may be considered irrespective of age. Implant and prosthesis maintenance must be assured by the patient and/or care provider.

5.3.2 | Which common comorbidities comprise contraindications for implant placement?

High-dose antiresorptive therapy (ART) poses a serious risk for postoperative complications and is a contraindication for implant surgery. If treated at all, these patients should be managed in a specialist setting.

5.3.3 | Which common comorbidities comprise risks for implant placement?

Comorbidities such as cancer, diabetes mellitus, and conditions involving neurocognitive impairment may carry risks for implant therapy. An individual risk assessment is necessary before considering implant surgery for these patients. Implant patients with comorbidities should be managed in close collaboration with a supervising physician with regular follow-up.

In patients with diabetes mellitus, oral hygiene should be closely monitored along with glycemic control and associated comorbidities of the disease.

5.3.4 | Which information must be taken into account when planning implant therapy for geriatric patients with common systemic diseases?

While there is no evidence to preclude geriatric patients (≥75 years) from implant therapy it is advisable to perform an individual risk assessment for patients with comorbidities. In geriatric patients, a holistic approach is required which should include assessment of functional dependency in addition to related limitations for the use of implant-supported prostheses and the ability to perform oral hygiene measures. The progression of existing systemic disease and dependency as well as the patient's life expectancy should be considered in the context of availability of competent care.

5.3.5 | What are the risks and benefits associated with implant therapy in geriatric patients and patients suffering from the most common diseases in geriatric patients?

Implants may be considered in elderly and medically compromised patients when they can provide substantial functional and psychosocial benefits, which must outweigh the associated risks, cost, and burden of treatment.

5.3.6 | What public health issues are important to consider for successful implant therapy in geriatric patients?

When older patients lose independence, the availability of trained manpower in the caring professions is a potential limiting factor for implant therapy. Opportunities for education and additional training focused on oral health should be provided for those involved in caring for dependent persons.

5.4 | Recommendations for future research

- Future research should focus on evaluation of clinical outcomes of implant therapy in patients with advanced age and comorbidities with detailed and standardized reporting of systemic conditions and related therapies.
- Studies to address predictors for successful implant therapy in geriatric patients during patient selection, prior to implant therapy are required.
- Future research is required to study the mechanisms of immunosenescence and its effect on peri-implant health and osseointegration in geriatric patients.
- Future research is required to evaluate optimal implant–prosthesis design to facilitate oral hygiene measures for maintenance of peri-implant health in geriatric patients.
- Evaluation of access to quality oral health care for immobile and dependent persons is required to develop health policies for the provision of a minimum standard of oral care in aged care.

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REVIEW ARTICLE

WILEY CLINICAL ORAL IMPLANTS RESEARCH

Static computer-aided implant surgery (s-CAIS) analysing patient-reported outcome measures (PROMs), economics and surgical complications: A systematic review

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Abstract

Objective: To systematically evaluate the scientific literature for patient-reported outcome measures (PROMs) in static computer-aided implant surgery (s-CAIS).

Methods: A PICO strategy was executed using an electronic (MEDLINE, EMBASE, CENTRAL), plus manual search up to 15-06-2017 focusing on clinical studies investigating s-CAIS with regard to patients' pain & discomfort, economics and/or intra-operative complications. Search strategy was assembled from multiple conjunctions of MeSH Terms and unspecific free-text words. Assessment of risk of bias in selected studies was made at a "trial level" applying the Cochrane Collaboration Tool and the Newcastle–Ottawa Assessment Scale, respectively.

Results: The systematic search identified 112 titles. Seventy abstracts were screened, and 14 full texts were included for analysis. A total of 484 patients were treated with s-CAIS for placement of 2,510 implants. Due to the heterogeneity of the included studies, meta-analyses could not be performed.

Conclusions: The number of identified studies investigating s-CAIS for PROMs was low. Scientifically proven recommendations for clinical routine cannot be given at this time; however, the number of clinical complications with s-CAIS seems to be negligible and comparable to conventional implant surgery. s-CAIS may offer a beneficial treatment option in edentulous cases if a flapless approach is applicable. Nevertheless, the economic effects in terms of time efficiency and treatment costs are unclear. Clinical investigations with well-designed RCTs investigating PROMs with standardized parameters are compellingly necessary for the field of s-CAIS.

KEYWORDS

static computer-aided implant surgery (s-CAIS), guided surgery, patient-reported outcome measures, systematic review, virtual implant planning

1 | INTRODUCTION

A restorative-oriented treatment concept is key for success in implant therapy with predictable outcomes in an interdisciplinary approach that manages the competences of prosthodontics, periodontology, oral surgery, radiology, and dental technology. Optimal 3D implant positioning is mandatory to achieve these goals (Chen & Buser, 2014).

Conventional freehand implant placement is challenged by difficult interpretation and secondary transfer of 2D radiographic

diagnostics into the 3D clinical situation plus a limited visualization of the operative field of interest in general (Kourtis, Kokkinos & Roussou, 2014). However, computer-assisted workflows with 3D imaging and virtual simulations offer powerful instruments for treatment planning, further surgical placement and prosthetic rehabilitation with respect to both anatomic as well as restorative parameters. A thorough preoperative planning will free the clinician's mind allowing more time to concentrate on the patient and the tissue handling (Marchack & Chew, 2015).

Today, several systems are available for the translation of a virtually planned implant scenario to the clinical situation. For static computer-aided implant surgery (s-CAIS), static surgical implant guides are currently most often applied—in contrast to dynamic systems for navigation (Vercruyssen, Fortin, Widmann, Jacobs & Quirynen, 2014).

s-CAIS involves either a guided pilot drilling approach or a fully guided protocol for the entire drilling sequence regularly including implant placement through the surgical guide. The indications range from single-unit rehabilitation concepts to complete edentulous patients for mono- or bimaxillary treatment. The surgical implant guides can be distinguished according to their functional design, whether tooth-retained, mucosa-, or bone-supported or in any type of combination. In addition, the surgical placement can be performed completely flapless with soft tissue punches, or open flap varying from small crestal incisions up to the preparation of a full-thickness mucoperiosteal flap with complete exposure of the alveolar bone (Laleman et al., 2016).

Computer-aided methods realize the 3D visualization of the implant recipient site including the neighboring anatomical structures. Prior to any invasive treatment, the clinician has the opportunity to gain insights into the patient's individual situation considering prosthetic and surgical requirements. Complex and invasive treatment steps can be anticipated in advance for a predictable and safe outcome (Pozzi, Polizzi & Moy, 2016).

Recent systematic reviews focused mainly on accuracy and precision for static guided implant surgery with a mean overall inaccuracy of the final implant 3D position of 1.1 mm at the entry point, 1.4 mm at the implant apex, and an average angular deviation of 3.9 degrees, respectively (Jung et al., 2009; Schneider, Marquardt, Zwahlen & Jung, 2009; Tahmaseb, Wismeijer, Coucke & Derksen, 2014; Vercruyssen, Hultin et al., 2014). Besides these technical analyses, information on patients' convenience, surgical and/or prosthetic complications, time efficiency, and cost-benefit-analyses, as so-called reported outcome measures (PROMs), are scarce.

Therefore, the aim of this systematic review was to analyse the scientific literature to evaluate PROMs, economics, and intra-operative complications of s-CAIS compared with conventional implant placement.

2 | MATERIAL AND METHODS

This systematic review was conducted in accordance with the guidelines of Preferred Reporting Items of Systematic Reviews and Meta-Analyses (PRISMA; Moher, Liberati, Tetzlaff & Altman, 2009).

2.1 | Search strategy

Based on the PICO criteria, a search strategy was developed and executed using an electronic search. The PICO question was formulated as follows: "In patients receiving implants, is static computer-aided implant surgery (s-CAIS) beneficial in terms of patient-reported outcomes, economics and surgical complications?"

Any virtual implant planning system using a 3D software application in combination with implant placement by means of a CAD/CAM-processed surgical guide was defined as s-CAIS. Implant placement either freehand or assisted by a laboratory manually produced template was defined as conventional implant surgery.

A systematic electronic search of PubMed MEDLINE, EMBASE, CENTRAL, including the gray-literature of Google Scholar, up to 2017-06-15 was performed for English-language publications in dental journals. Search syntax was categorized in population, intervention, comparison, and outcome; each category was assembled from a combination of Medical Subject Headings [MeSH Terms] as well as free-text words in simple or multiple conjunctions:

(((((((dental implants [MeSH Terms]) OR (endosseous implant*) OR (dental implant*)))) OR (((dental implantation, endosseous [MeSH Terms]) OR (implant placement*) OR (implant insertion*) OR (implant surgery*))))) AND ((((((computer-aided surgery [MeSH Terms]) OR (computer-assisted surgery [MeSH Terms])))) OR ((guided surgery OR guided implant placement OR computer-guided OR ((drill guide OR template) AND computer) OR surgical template OR simplant OR coDiagnostiX OR SMOP OR nobel guide)))) AND ((((dental implantation, endosseous [MeSH Terms]) OR (implant placement*) OR (implant insertion*) OR (implant surgery*))))) AND ((((((patient outcome assessment [MeSH Terms]) OR (patient-centered outcomes [MeSH Terms]) OR (satisfaction*)))) OR (((economics [MeSH Terms]) OR (costs, cost analysis [MeSH Terms]) OR (efficiency [MeSH Terms])))) OR (((complications [MeSH Terms]) OR (adverse event*) OR (safety*)))) [Figure 1].

Additional manual searches of the bibliographies of all full-text articles and related reviews, selected from the electronic search, were also performed. Furthermore, manual searching was conducted in the following journals:

Clinical Implant Dentistry & Related Research, Clinical Oral Implants Research, Dentomaxillofacial Radiology, European Journal of Oral Implantology, Implant Dentistry, International Journal of Oral & Maxillofacial Implants, Journal of Clinical Periodontology, Journal of Computerized Dentistry, Journal of Dental Research, Journal of Oral & Maxillofacial Surgery, Journal of Oral Implantology, Journal of Periodontal & Implant Science, and Journal of Periodontology.

2.2 | Inclusion/exclusion criteria

This review was based on reports from randomized controlled trials, prospective or retrospective cohort studies as well as case–control studies and case series retrieved by the systematic literature search outlined above.

Detailed inclusion criteria for study selection were as follows:

Population	**Fully or partially edentulous patients treated with dental implants** **#1** – ((dental implants [MeSH Terms]) OR (endosseous implant*) OR (dental implant*))
Intervention	**Implant planning using computer-aided software applications for surgical placement** **#2** – ((computer-aided surgery [MeSH Terms]) OR (computer-assisted surgery [MeSH Terms])) **#3** – (guided surgery OR guided implant placement OR computer guided OR ((drill guide OR template) AND computer) OR surgical template OR simplant OR codiagnostix OR SMOP OR nobel guide)
Comparison	**Conventional (non-computer-aided) treatment protocols** **#4** – ((dental implantation, endosseous [MeSH Terms]) OR (implant placement*) OR (implant insertion*) OR (implant surgery*))
Outcome	**Patient-reported outcomes; economics, as (time-) efficiency & cost analysis; complications** **#5** – ((patient outcome assessment [MeSH Terms]) OR (patient-centered outcomes) OR (satisfaction*)) **#6** – ((economics [MeSH Terms]) OR (costs, cost analysis [MeSH Terms]) OR (efficiency [MeSH Terms])) **#7** – ((complications [MeSH Terms]) OR (adverse event*) OR (safety*))
Search combination	**(#1 or #4) AND (#2 or #3) AND (#5 or #6 or #7)**

FIGURE 1 Search strategy according to the focused PICO question

- Clinical trials only;
- Studies at all levels of evidence, except expert opinions;
- Case report(s) including at least 10 patients;
- Studies reporting on digital implant planning including the used systems (software, applications, techniques etc.) based on (cone beam) CT imaging for static guided implant surgery under consideration of the PROMs:
    - Discomfort and pain; and/or
    - Economics (in terms of time efficiency); and/or
    - Intra-operative complications (surgical and prosthetic).

In addition, explicit exclusion criteria were as follows:

- Animal studies;
- Insufficient information on defined outcome criteria;
- Absence of objective parameters;
- Multiple publications on the same patient population;
- No author response to inquiry email for data clarification;
- Zygoma, pterygoid, and/or orthodontic implant planning.

2.3 | Data extraction

Three reviewers independently screened (T.J., W.D., and S.K.) the retrieved titles and abstracts according to the defined outcomes. Disagreements were resolved by discussion. Following this, abstracts of all agreed titles were obtained and screened again for meeting the inclusion criteria. The selected articles were then obtained in full texts. If any titles and abstracts did not provide sufficient information regarding the inclusion criteria, the full texts were obtained as well. Again, disagreements were resolved by discussion. Finally, the selection based on in-/exclusion was made for the full-text articles.

Data were extracted independently by the three reviewers using a data extraction form. Disagreement was resolved by discussion. Following information was collected for further analysis:

- Author(s), year of publication, trial design;
- Defined outcome(s);
- Number of included subjects and implants plus calculated ratio of implants per subject;
- Follow-up in months, patient dropout(s), and number of implant failures;
- Implant indication(s) and jaw localization;
- Implant system(s) and virtual implant planning software;
- Timing of implant placement;
- Flap design;
- Design of the implant guide(s) plus fabrication technique(s);
- Timing of prosthetic loading and type of restoration.

Included studies were divided into subgroups according to their defined outcomes:

(i) "pain & discomfort"; (ii) economics, in terms of "time efficiency"; as well as (iii) "intra-operative complications."

The reported results of the studies were specified according to the defined outcomes on a patient level, and if feasible, a meta-analysis was conducted.

Assessment of risk of bias in individual studies was made at a "trial level" including random sequence generation, allocation concealment, blinding, completeness of outcome data, selective reporting, and other bias using the Cochrane Collaboration Tool (http://ohg.cochrane.org) for randomized controlled trials (RCTs). A judgment of risk of bias was assigned if one or more key domains had a high or unclear risk of bias. For non-randomized studies, the Newcastle–Ottawa Assessment Scale (http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp) was applied to evaluate the selection of the study groups, the comparability of the groups, and the ascertainment of either the outcome of interest.

3 | RESULTS

3.1 | Included studies

The systematic search was completed on 2017-06-15, and results are current as of this date (Figure 2). Of the 112 titles retrieved by the search, 70 abstracts were further screened, and successively, 42 full texts identified. A total of 28 full texts were excluded from the final analysis (Annex I).

The reasons for exclusion were as follows:

- Not matching study outcome (n = 10);
- Case report(s) with <10 patients (n = 6);
- No clinical trial (n = 5);
- No virtual implant planning and/or static guided implant surgery (n = 5);
- Multiple publications reporting on duplicated patient data (n = 2).

Finally, 14 full texts were included for data extraction (Abad-Gallegos et al. 2011; Arisan et al. 2010; di Torresanto et al. 2014; Fortin et al. 2006; Komiyama et al. 2008; Marra et al. 2013; Meloni et al. 2010; Merli et al. 2008; Nikzad & Azari 2010; Nkenke et al. 2007; Pomares 2010; Pozzi et al. 2014; Sannino & Barlattani 2016; Vercruyssen et al. 2014; Annex II). Included studies were judged to be of sufficient quality considering the specific study design. Figure 3a,b displays assessments of the risk of bias for included studies (Figure 3a,b).

Detailed information of each study is tabularized for general data, implant-specific characteristics, surgical, and prosthetic treatment protocols including virtual planning, and defined outcomes in Tables 1–3. Publication dates ranged from 2006 to 2016. Study types were categorized in RCTs (n = 4), retrospective cohort studies (n = 5),

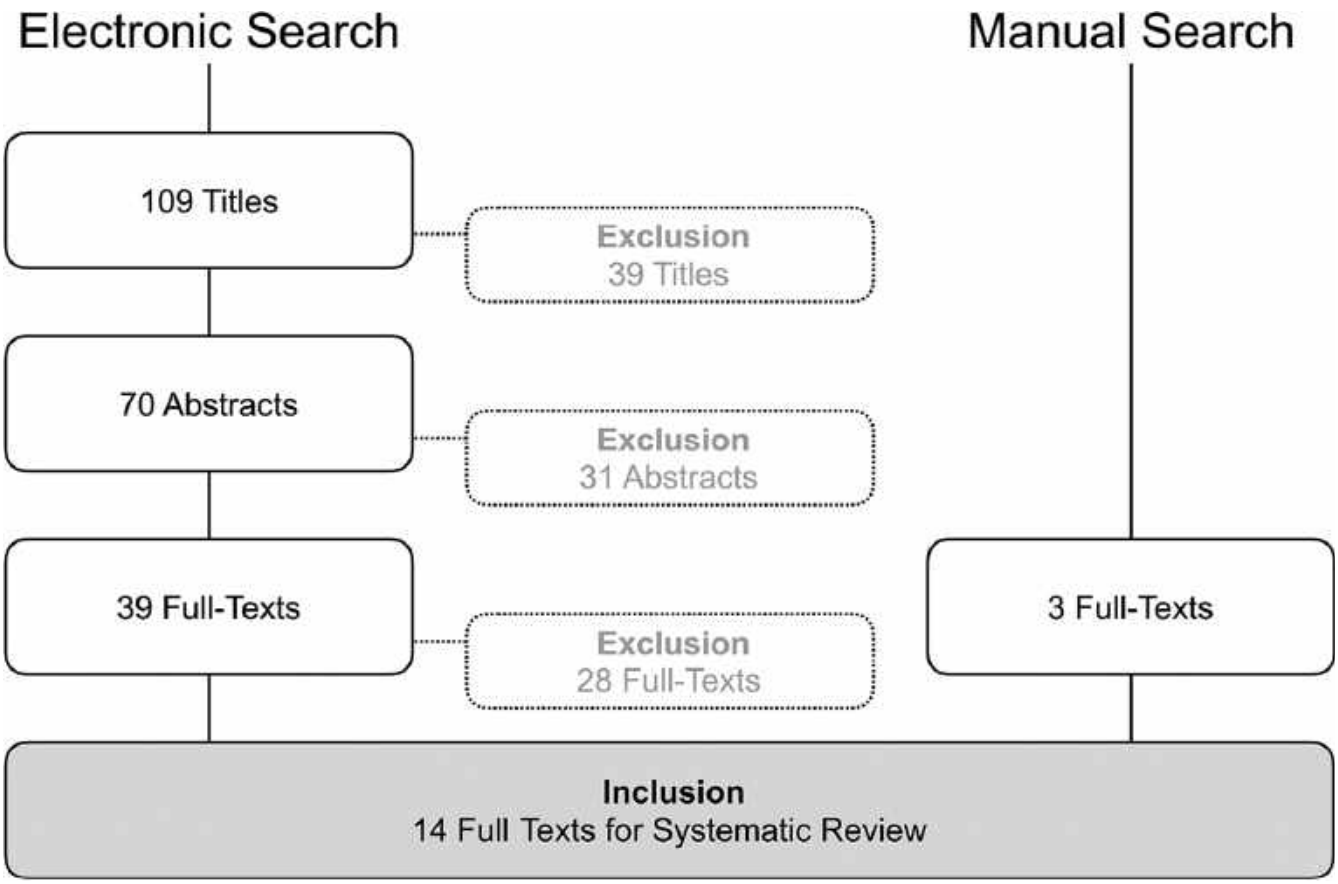

FIGURE 2 Flowchart of the systematic search results

(a)

(b)

	Selection [max. 4 stars]	Comparability [max. 2 stars]	Outcome [max. 4 stars]
Nkenke, et al. (2007)	★★★★	★	★★★
Komiyama, et al. (2008)	★★★★	—	★★
Merli, et al. (2008)	★★★★	—	★★
Meloni, et al. (2010)	★★★★	—	★★★
Nikzad & Azari (2010)	★★★★	—	★★
Pomares (2010)	★★★★	—	★★★
Abad-Gallegos, et al. (2011)	★★★★	—	★★
Marra, et al. (2013)	★★★★	—	★★★
di Torresanto, et al. (2014)	★★★★	—	★★
Sannino & Barlattani (2016)	★★★★	—	★★★

FIGURE 3 (a) Presentation of risk of bias evaluation for included RCTs according to the Cochrane Collaboration's tool (http://ohg.cochrane.org). (b) Presentation of risk of bias evaluation for included non-RCTs according to the Newcastle–Ottawa assessment scale (http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp)

prospective cohort studies (n = 4) and case series (n = 1). A total of 484 patients were treated with 2,510 dental implants resulting in a calculated ratio of 5.2 implants per patient. Six patient dropouts were reported, whereas five studies did not reveal any dropout information. Follow-up ranged from 0 days up to 44 months, in which 54 implants were lost (Table 1).

Nobel Clinician was the most often used implant planning software (n = 5), followed by Procera (n = 4), Simplant (n = 2), CADImplant, and Materialise (n = 1), respectively. Nine studies applied one single implant system, two studies multiple systems, and three studies gave no specific information. Nobel Biocare was the most often applied implant system (n = 7). The design of the used implant guide varied from mucosa-supported (n = 8), combined mucosa- plus bone-supported (n = 4), to solely tooth-supported (n = 1); one study did not specify the guide design (Table 2).

Ten studies reported on treatment protocols for edentulous patients, three studies for both, edentulous and partially dentate patients, and one study for partially dentate patients. Most often studies reported on implants placed in both jaws (n = 7), followed by studies using s-CAIS only in the maxilla

TABLE 1 General data of the 14 included trials: study design, defined outcome(s), number of subjects, and implants as well as ratio of implants per patient, follow-up period, and patient dropouts

No.	Study (year)	Study design	Outcome(s)	No. subjects	No. implants	No. implants/patient	Follow-up (months)	Patient dropouts
1.	Fortin et al. (2006)	RCT (2 arms)	Patient satisfaction (Surg)	30 (+30 controls)	80 (+72 controls)	2.7 (AVG) (+2.4 controls)	0.25	Not reported
2.	Nkenke et al. (2007)	Prospective case-control study	Patient satisfaction (Surg)	5 (+5 controls)	30 (+30 controls)	6 (+6 controls)	12	0
3.	Komiyama et al. (2008)	Prospective cohort study	Complications (Surg+Prosth)	29	176	6.1 (AVG)	44	Not reported
4.	Merli et al. (2008)	Case series	Patient satisfaction (Surg); Time efficiency (Surg+Prosth); Complications (Surg)	13	89	6.9 (AVG)	8	1
5.	Arisan et al. (2010)	RCT (3 arms)	Patient satisfaction (Surg); Time efficiency (Surg)	37 (+21 test-1|+16 test-2) (+15 controls)	341	6.6 (AVG) (+4.7 test-1|+6.3 test-2) (+9.4 controls)	0.25	Not reported
6.	Meloni et al. (2010)	Retrospective cohort study	Patient satisfaction (Surg)	15	90	6	18 (6 mo recall)	0
7.	Nikzad & Azari (2010)	Prospective cohort study	Patient satisfaction (Surg)	16	57	3.6 (AVG)	12 (1,3,6,12 mo recall)	Not reported
8.	Pomares (2010)	Retrospective cohort study	Patient satisfaction (Surg); Time efficiency (Surg+Prosth)	30	195	6.5 (AVG)	12 (1,3,6,12 mo recall)	0
9.	Abad-Gallegos et al. (2011)	Retrospective cohort study	Patient satisfaction (Surg); Complications (Surg)	19	122	6.4 (AVG)	Not reported	Not reported
10.	Marra et al. (2013)	Retrospective cohort study	Patient satisfaction (Surg); Time efficiency (Surg+Prosth)	30	312	10.4 (AVG)	36 (12 mo recall)	0
11.	Pozzi et al. (2014)	RCT (2 arms)	Patient satisfaction (Surg); Time efficiency (Surg+Prosth); Complications (Surg)	25 (+26 controls)	103 (+99 controls)	4.1 (AVG) (+3.8 controls)	12	0
12.	di Torresanto et al. (2014)	Prospective cohort study	Patient satisfaction (Surg)	15	60	4	24 (6 mo recall)	5
13.	Vercruyssen et al. (2014)	RCT (3 arms)	Patient satisfaction (Surg); Time efficiency (Surg)	59	314	5.3 (AVG)	0	Not reported
14.	Sannino & Barlattani (2016)	Retrospective cohort study	Time efficiency (Surg+Prosth)	85	340	4	36 (12 mo recall)	0

TABLE 2 Implant-specific data summarizing software implant planning, design, and fabrication of implant guides, used implant systems and implant failures

No.	Study (year)	Software implant planning	Design implant guide	Fabrication implant guide	Implant system	No. implant failures
1.	Fortin et al. (2006)	CADImplant	Not reported	Mixed	Not reported	0
2.	Nkenke et al. (2007)	Procera	Mucosa-support	Stereolithography	Not reported	0
3.	Komiyama et al. (2008)	Procera	Mucosa-pin-support	Stereolithography	Nobel Biocare	19
4.	Merli et al. (2008)	Procera 1.6	Mucosa-pin-support	Not reported	Nobel Biocare	5
5.	Arisan et al. (2010)	3D StendCad/ Simplant	Mucosa- & bone-support	Stereolithography	Thommen (*n* = 180); Xive (*n* = 161)	0
6.	Meloni et al. (2010)	Nobel Guide	Mucosa-pin-support	Not reported	Nobel Biocare	2
7.	Nikzad & Azari (2010)	Simplant 10.0	Tooth-support	Stereolithography	Straumann (*n* = 19); Zimmer (*n* = 13); Easy Implant (*n* = 13); Astra (*n* = 12)	2
8.	Pomares (2010)	Procera 1.6/2.0	Mucosa-pin-support	Stereolithography	Nobel Biocare	4
9.	Abad-Gallegos et al. (2011)	Nobel Guide	Tooth- & mucosa-pin-support	Stereolithography	Not reported	10
10.	Marra et al. (2013)	Nobel Guide	Mucosa-pin-support	Stereolithography	Nobel Biocare	6
11.	Pozzi et al. (2014)	Nobel Guide	Tooth- & mucosa-pin-support	Stereolithography	Nobel Biocare	0 (+1 controls)
12.	di Torresanto et al. (2014)	SimPlant 9.0	Mucosa-pin-support	Stereolithography	Camlog	0
13.	Vercruyssen et al. (2014)	Materialise + Facilitate	Mucosa- & bone-support	Stereolithography; conventional	Astra	0
14.	Sannino & Barlattani (2016)	Nobel Guide	Mucosa-pin-support	Stereolithography	Nobel Biocare	5

(*n* = 3) and mandible (*n* = 3), and one study did not include information about the implants' location. Seven studies compared a flapless approach vs. conventionally raised flap design, and the remaining other seven studies described only flapless s-CAIS (Table 3).

3.2 | Descriptive analysis

Of the 14 selected studies, the following PROMs could be distinguished as follows:

- 12 studies exploring "pain & discomfort" (A);
- six studies calculating "time efficiency" (B); and
- seven studies investigating "intra-operative complications" (C).

Multiple outcome categories were incorporated in three studies focusing on all criteria described above; three studies on "pain & discomfort" plus "intra-operative complications," and two on the combination of "pain & discomfort" plus "time efficiency"; further, single outcomes were solely allocated each for "pain & discomfort" (*n* = 4), "time efficiency" (*n* = 1) and "intra-operative complications" (*n* = 1), respectively (Table 4–6).

Different research techniques and methods were used, and the timing of evaluation of defined patient-centered outcomes with or without follow-up period varied largely. Due to the heterogeneity of the included studies, a direct comparison among the identified publications was not deemed possible; and subsequently, a meta-analysis could not be performed. Therefore, the review of the included full texts followed a descriptive analysis. No additional analyses were performed.

3.2.1 | (A) Pain & discomfort

Within the 12 included studies investigating pain & discomfort, different methodological approaches specified (sub-) outcomes and

TABLE 3 Data showing detailed information with regard to implant indication, jaw localization, flap design, timing of implant placement, type of restoration, and timing of prosthetic loading

No.	Study (year)	Implant indication	Jaw localization	Flap design	Timing implant placement	Prosthetic restoration	Timing prosthetic loading
1.	Fortin et al. (2006)	Partial & complete edentulous	Maxilla & mandible	Flap & flapless	Not reported	Not reported	Not reported
2.	Nkenke et al. (2007)	Complete edentulous	Maxilla	Flapless (controls with flap)	Type 4	Not reported	Mixed
3.	Komiyama et al. (2008)	Complete edentulous	Maxilla & mandible	Flapless	Not reported	Fixed	Immediate
4.	Merli et al. (2008)	Complete edentulous	Maxilla	Flap & flapless	Types 3; 4	Fixed screw-retained	Immediate
5.	Arisan et al. (2010)	Complete edentulous	Not reported	Flap & flapless	Type 4	Not reported	Not reported
6.	Meloni et al. (2010)	Complete edentulous	Maxilla	Flapless	Types 3; 4	Fixed screw-retained	Immediate
7.	Nikzad & Azari (2010)	Partial edentulous	Mandible	Flapless	Type 4	Fixed	Conventional
8.	Pomares (2010)	Complete edentulous	Maxilla & mandible	Flap & flapless	Types 2; 3; 4	Fixed	Immediate
9.	Abad-Gallegos et al. (2011)	Partial & complete edentulous	Maxilla & mandible	Flapless	Not reported	Fixed	Mixed
10.	Marra et al. (2013)	Complete edentulous	Maxilla & mandible	Flapless	Not reported	Fixed screw-retained	Immediate
11.	Pozzi et al. (2014)	Partial & complete edentulous	Maxilla & mandible	Flap & flapless	Types 1; 3; 4	Fixed screw-retained	Immediate
12.	di Torresanto et al. (2014)	Complete edentulous	Mandible	Flapless	Type 4	Removable	Conventional
13.	Vercruyssen et al. (2014)	Complete edentulous	Maxilla & mandible	Flap & flapless	Not reported	Mixed	Not reported
14.	Sannino & Barlattani (2016)	Complete edentulous	Mandible	Flapless	Types 1; 4	Fixed screw-retained	Immediate

subjective evaluation analyses during various follow-up protocols were described (Abad-Gallegos et al. 2011; Arisan et al. 2010; di Torresanto et al. 2014; Fortin et al. 2006; Marra et al. 2013; Meloni et al. 2010; Merli et al. 2008; Nikzad & Azari 2010; Nkenke et al. 2007; Pomares 2010; Pozzi et al. 2014; Vercruyssen et al. 2014; Table 4).

Post-surgery pain occurrence was the most often defined outcome for convenience assessment of s-CAIS. The consumption of painkillers was the method of choice to evaluate the quantity and quality of pain in a total of six studies (Arisan et al. 2010; Fortin et al. 2006; Merli et al. 2008; Nkenke et al. 2007; Pozzi et al. 2014; Vercruyssen et al. 2014). Merli et al. (2008) noticed a median consumption rate of two painkillers per patient for the treatment with s-CAIS in the complete edentulous maxilla; with a range of 0–7 painkillers. Fortin et al. (2006) stated that painkiller consumption was significantly lower for s-CAIS with flapless surgery compared with conventional implant placement with an open-flap procedure (p = .03). Arisan et al. (2010) reported on the influence of the guide design and the consumption of painkillers. Patients who were treated with mucosa-supported guides in a flapless approach demonstrated a significantly reduced intake of painkillers (n = 4) compared with those treated with bone-supported guides and conventionally raised full-thickness flap (n = 11; Figure 4).

Other studies quantified pain using visual analogue scales (VAS; Arisan et al. 2010; di Torresanto et al. 2014; Nikzad & Azari 2010; Nkenke et al. 2007). Again, heterogeneity was present among these studies as different scales and questionnaires for pain assessment were applied. Nikzad & Azari (2010) reported on the postoperative development of the patients' pain intensity after 2 and 7 days,

TABLE 4 Results of n = 12 included trials reporting on "pain & discomfort"

No.	Study (year)	Outcome
1.	Fortin et al. (2006)	Post-surgery pain occurrence: test < controls (p < .01*) | Post-surgery pain decrease: test < controls (p = .05*) | Consumption of painkillers: test < controls (p = .03*) | Number of patients feeling pain at all: test 57% vs. controls 80%
2.	Nkenke et al. (2007)	Post-surgery "discomfort & pain": (6 h, 1 day, 7 days) consumption of painkillers | VAS (1 day): repetition of the procedure; bleeding; duration of surgery; recommendation of procedure | Face scanning for analysis of soft tissue swelling (upper lip & cheeks)
4.	Merli et al. (2008)	Post-surgery: (3 days) five patients no pain/eight mild pain; six patients no swelling/seven mild swelling | Average consumption of painkillers: 2 (range: 0 – 7)
5.	Arisan et al. (2010)	Average consumption of painkillers: mucosa-supported guide n = 4 vs. bone-supported guide n = 11 vs. controls n = 10 | Overall VAS pain score: mucosa-supported guide < bone-supported guide (p < .01*) < controls (p < .001*)
6.	Meloni et al. (2010)	Post-surgery "discomfort & pain": (3 days) 10 patients no pain/five mild pain; seven patients no swelling/eight mild swelling
7.	Nikzad & Azari (2010)	Mean pain score: (2 days) VAS 35 points; (7 days) VAS 10 points | Post-surgery pain occurrence: (2 days /7 days) no pain 6.2%/81.2%; moderate pain 81.2%/6.2%; high pain 6.2%/6.2%; unbearable pain 6.2%/6.2%
8.	Pomares (2010)	No postoperative complications (pain, inflammation, or hematoma) | No postoperative problems (phonetic, aesthetic, or chewing ability)
9.	Abad-Gallegos et al. (2011)	Post-surgery comfort: poor 5.3%; good 42.1%; very good 31.6%; excellent 21.1%
10.	Marra et al. (2013)	Post-surgery discomfort, such as swelling and pain, was negligible
11.	Pozzi et al. (2014)	Post-surgery pain occurrence: test 0.32 (SD 0.56) vs. controls 0.92 (SD 0.74) (p = .002*) | Post-surgery swelling occurrence: test 0.48 (SD 0.65) vs. controls 1.00 (SD 0.85) (p = .024*) | Painkiller consumption: test 2.08 (SD 1.35) vs. controls 3.00 (SD 1.90) (NS p = .082)
12.	di Torresanto et al. (2014)	VAS: pain during surgery 2.4 (SD 0.84); pain after Surgery 1.3 (SD 0.64); swelling/bleeding 0.6 (SD 0.70)
13.	Vercruyssen et al. (2014)	Painkiller consumption | Swelling | Surgical time [Little difference could be found between postoperative discomfort of flapless vs. non-flapless-guided surgery, and in comparison with conventional implant placement; tendency of more pain in conventional and flapped protocols; duration of surgery is shortened with flapless-guided implant placement]

TABLE 5 Results of n = 6 included trials reporting on "time efficiency"

No.	Study (year)	Outcome
4.	Merli et al. (2008)	Average time planning: 145 min (70–370 min) | Average surgical time: 53 min (35–72 min) | Average prosthetic time: 85 min (20–210 min)
5.	Arisan et al. (2010)	Average surgical time: mucosa-supported guide 23.53 min (SD 5.48) vs. bone-supported guide 60.94 min (SD 13.07) vs. controls 68.71 min (SD 11.40)
8.	Pomares (2010)	Average surgical time: 15–45 min | Average prosthetic time: 60–150 min
10.	Marra et al. (2013)	Average surgical + prosthetic time: 90–150 min
11.	Pozzi et al. (2014)	Average surgical time: test 42.68 min (SD 21.44) vs. controls 42.31 min (SD 23.33) (NS p = .953) | Average prosthetic time: test 51.40 min (SD 3.34) vs. controls 50.40 min (SD 15.34) (NS p = .859)
14.	Sannino & Barlattani (2016)	Average surgical time "all-on-4" edentulous mandibles flapless-guided implant surgery: 15–25 min | Average prosthetic time immediate loading provisional screw-retained cross-arch prosthesis: 30–50 min

respectively. Mean VAS pain scores were 35 points after 2 days and 10 points after 7 days (with a scale definition of: "no pain" = 0 points up to "maximum pain" = 100 points). Secondary, pain categories were divided into "no pain," "moderate pain," and "high pain." Mean results were 6.2% vs. 81.2% for "no pain" after 2 days and 7 days, 81.2% vs. 6.2% "moderate pain," and 6.2% vs. 6.2% for "high pain," respectively.

The degree of post-surgical swelling was an alternative parameter for the estimation of patients' discomfort for the treatment with s-CAIS. Meloni et al. (2010) stated after 3 days of s-CAIS with a flapless procedure that 47% of the patients had no swelling, while 53% suffered from mild swelling.

Pomares (2010) observed no postoperative complications, such as pain, inflammation, or hematoma, and also no phonetic, aesthetic, or

TABLE 6 Results of $n = 7$ included trials reporting on "intra-operative complications"

No.	Study (year)	Outcome
3.	Komiyama et al. (2008)	Prosthetic fitting: five of 29 cases could not be immediately treated with fixed cross-arch screw-retained reconstructions; and three of 29 cases needed extensive occlusal adjustments of the implant reconstruction | Surgical guide fracture ($n = 3$)
4.	Merli et al. (2008)	Prosthetic fitting: four of 13 cases could not be immediately treated with fixed cross-arch screw-retained reconstructions | Surgical guide fracture ($n = 1$)
6.	Meloni et al. (2010)	Prosthetic fitting: two of 15 cases could not be immediately treated with fixed cross-arch screw-retained reconstructions
8.	Pomares (2010)	Surgical guide fracture ($n = 3$)
9.	Abad-Gallegos et al. (2011)	Lack of primary implant stability 26.3% | Lack of primary stability precluded the placement of an immediate provisional prosthesis in four cases | All implant failures occurred in complete edentulous cases and after immediate loading
11.	Pozzi et al. (2014)	Explicit statement that no intra-surgical complications occurred
12.	di Torresanto et al. (2014)	Prosthetic fitting: five of 15 cases could not be treated according to the study protocol with mandibular locator-retained over dentures | Lack of keratinized peri-implant mucosa in eight of 40 implants

chewing ability problems. Marra et al. (2013) summarized that patients' postoperative discomfort such as swelling and/or pain was negligible.

3.2.2 | (B) Time efficiency

Six studies defined time efficiency of s-CAIS as outcome (Arisan et al. 2010; Marra et al. 2013; Merli et al. 2008; Pomares 2010; Pozzi et al. 2014; Sannino & Barlattani 2016; Table 5).

Only one study calculated the time used for the implant planning software. Merli et al. (2008) described an average time of 145 min per case for virtual planning for the treatment with fixed screw-retained prostheses in the edentulous maxilla.

The reported average duration of the implant surgery using a s-CAIS approach varied from 15 min up to 72 min (Merli et al. 2008; Arisan et al. 2010; Pomares 2010; Pozzi et al. 2014; Sannino & Barlattani 2016). Here, a RCT showed that s-CAIS using mucosa-supported guides in a flapless approach in complete edentulous maxillary cases was significantly faster (23.53 min; SD 5.48) compared with bone-supported guides using a conventionally raised full-thickness flap (60.94 min; SD 13.07) and controls with a conventional approach (68.71 min; SD 11.40), respectively (Arisan et al. 2010). In contrast, another RCT could not observe any significant differences between s-CAIS (42.68 min; SD 21.44) vs. conventional surgery (42.31 min; SD 23.33) for the rehabilitation of partially and fully edentulous patients (Pozzi et al. 2014).

Within the included studies, the average prosthetic time immediately after surgery varied widely from 20 to 210 min (Merli et al. 2008; Pomares 2010; Pozzi et al. 2014; Sannino & Barlattani 2016). However, even within single studies, the duration for the prosthetic protocol was heterogeneous: Merli et al. (2008) reported 20 to 210 min and Pomares (2010) 60 to 150 min.

For the "all-on-4" concept in edentulous mandibles, Sannino & Barlattani (2016) reported an average surgical time with flapless-guided implant placement of 15 to 25 min, and an average prosthetic time for the treatment of immediate loaded provisional screw-retained cross-arch prostheses of 30 to 50 min (Figure 5).

3.2.3 | (C) Intra-operative complications

Seven studies reported on complications, either for the surgical protocol or the immediate implant-prosthetic reconstruction (Abad-Gallegos et al. 2011; di Torresanto et al. 2014; Komiyama et al. 2008; Meloni et al. 2010; Merli et al. 2008; Pomares 2010; Pozzi et al. 2014; Table 6).

The total number of surgical complications at implant placement was 12 out of 408 interventions using s-CAIS (2.9%). In detail, the reported complications were the lack of primary implant stability ($n = 5$; Abad-Gallegos et al. 2011), and fractures of the implant guide ($n = 7$; Komiyama et al. 2008; Merli et al. 2008; Pomares 2010).

With regard to the immediate insertion of the (provisional) implant-prosthetic reconstruction, three studies reported on problems placing full-arch prostheses in a correct position in five of 29 cases (Komiyama et al. 2008), four of 13 cases (Merli et al. 2008), and two of 15 cases (Meloni et al. 2010), respectively. Di Torresanto et al. (2014) observed a lack of keratinized peri-implant mucosa in 20% of the implants placed in edentulous mandibles with a flapless approach using s-CAIS.

4 | DISCUSSION

The trend of digitization is a ubiquitous sensation today; both, in social media and in dentistry (Schoenbaum, 2012; Weston, 2016). In general, the digital dental impact can be categorized into (i) clinical performance using different tools and applications investigating feasibility; (ii) technical accuracy and precision of virtual simulations and the translation into reality; (iii) PROMs for analysis of safety- and convenience-related treatment protocols; and (iv) changing learning methods in the field of higher university dental education (Joda, Ferrari, Gallucci, Wittneben & Bragger, 2017).

Digital protocols are increasingly influencing implant treatment concepts (Patel, 2010; van Noort, 2012). Since the introduction of s-CAIS, technical accuracy, and its clinical applicability have been

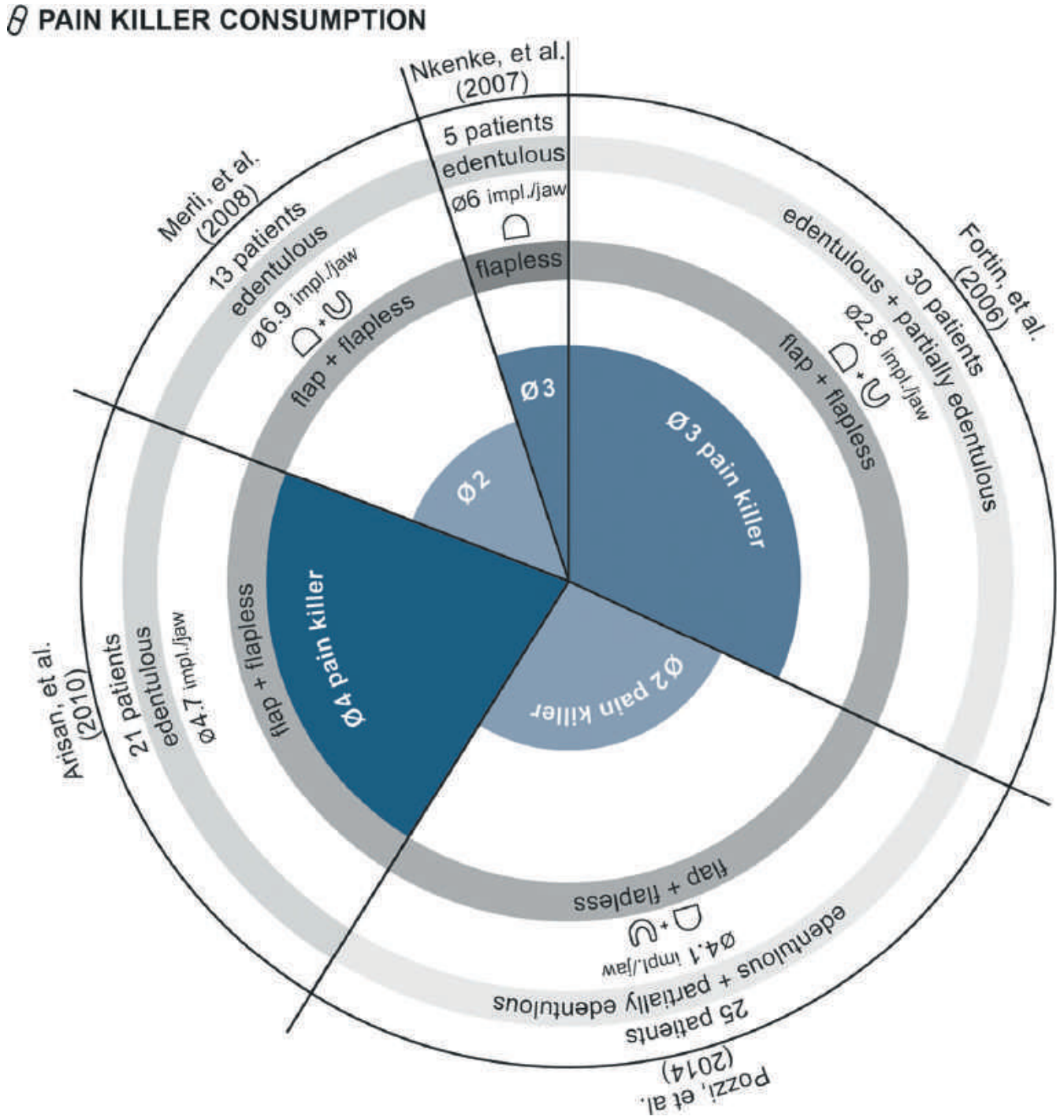

FIGURE 4 Pie chart depicting included studies with major trial characteristics analysing "pain & discomfort" with regard to patients' painkiller consumption for the treatment with CAIS

investigated in several reports and trials, and these results were summarized in no fewer (systematic) reviews so far (Jung et al., 2009; Schneider et al., 2009; Tahmaseb et al., 2014; Vercruyssen, Hultin et al., 2014). However, the scientific output of clinical studies analysing s-CAIS with regard to PROMs is low.

The systematic search of this review revealed a total of 14 studies, which met the defined inclusion criteria. Only four RCTs could be identified, whereas most trials were classified as cohort studies with a lower level of evidence. Due to the heterogeneity of included trials with various study designs, implant indications, applied virtual implant planning software, fabrication systems, and treatment protocols, no meta-analyses could be performed.

Pain is a qualitative human impression, extremely patient-dependent, and therefore, a very subjective criterion for the evaluation of medical/dental treatments in general. Most studies selected the number of painkillers taken as surrogate parameter for

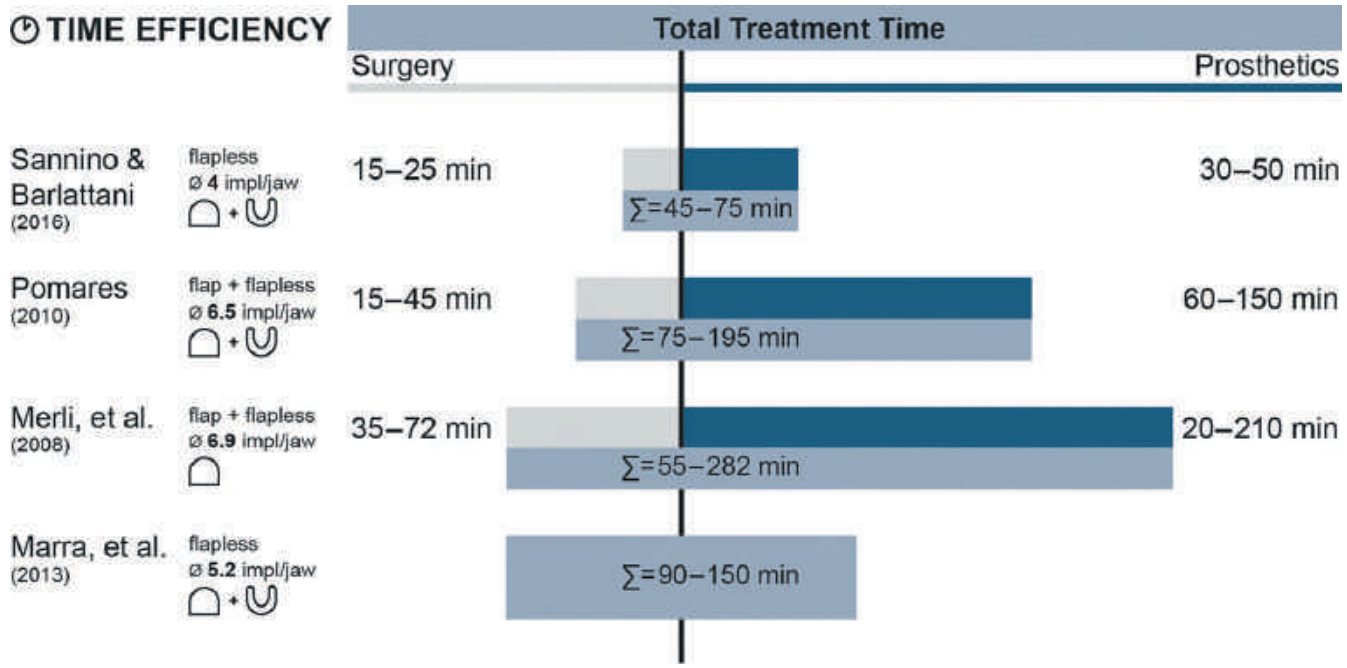

FIGURE 5 Bar graph showing included studies with major trial characteristics analysing "time efficiency" split in surgical + prosthetic treatment for the treatment with CAIS

quantification of comfort on a patient-based level for the treatment with s-CAIS. Unfortunately, no standardized protocols were used for the assessment of painkiller consumption with varying time points and no exact specifications of type of medication. Some studies reported on occurrence of pain operating a dichotomic index "yes/no" or with graduated categories, such as severe, mild, or no pain. Others used trial-specific visual analog scales (VAS) for registering patients' level of pain & discomfort. One study tried to visualize time-related swelling after s-CAIS using facial scanning and a superimposition technique.

With regard to the heterogeneous evaluation methods of patients' pain & discomfort, it can be concluded that the number of clinical complications was negligible and equivalent to conventional implant surgery. Especially, the use of s-CAIS combined with mucosa-supported guides for flapless implant placement may be beneficial in edentulous cases by means of postoperative pain intensity and related analgesic drug intake. Although the data cannot support this clearly, the improved comfort seems to be more associated with the flapless procedure than with the application of s-CAIS per se (Arisan et al. 2010).

Clinical chair time needed for s-CAIS varied largely between the included studies from 15 min up to 72 min. Due to the diverse implant indications of partially dentate vs. complete edentulous patients in combination with different flap designs, and consecutively, mucosa- and bone-supported guides in the maxilla or mandible, no comparisons between the studies could be made. Nevertheless, a positive correlation may occur between lower scores of patients' pain & discomfort and reduced duration of surgery.

The time needed for the prosthetic rehabilitation with immediate (provisional) reconstructions showed a widespread range of 20 to 210 min, indicating a sort of study protocol-based inaccuracy for the transfer of the virtual planning to the final 3D positioning of the implant(s). Maybe as a consequence, three cohort studies described problems placing full-arch prostheses in 11 of 57 cases, resulting in a success rate of 81% for immediate implant-prosthetic rehabilitation of edentulous patients.

Fracture of the surgical guide was only a rare problem, but this issue has to be considered as a major complication with a high risk for the overall success of the treatment. In such a scenario, the clinical team must be able to switch to conventional implant protocols, or the surgery has to be canceled and repeated at an additional appointment.

Yet it is important to consider the time spent by the dental team before the surgical procedure itself, especially the virtual planning process and necessary technical production of the guide. As a secondary economic factor, no trial could be identified estimating the direct costs, a cost-benefit-ratio, or a cost-time-analysis for the patient and/or the dentist.

Overall, the economic effects in terms of time efficiency and treatment costs seem to be unclear at this time; either based on the heterogeneity of the included studies which made a direct comparison impossible or simply on lacking evidence. Also, the additional exposure to radiation can be an important factor in the decision for a s-CAIS procedure.

The advancement of computer technology allows new treatment options. At present, s-CAIS protocols are feasible using complete digital workflows with superimposition technique of a virtual prosthetic setup (STL) with 3D rendering of the cone-beam computed tomography (DICOM) without prior radiographic templates (Flügge et al. 2017). This development approximates the interfaces of surgical and prosthetic treatment steps, from the virtual planning, plotted implant guides, to the CAD/CAM-based design, including production of the final prosthetic reconstruction (Joda &

Buser, 2013). As a result, economic factors, such as treatment and interdisciplinary planning time, but also the entire treatment itself could be shortened realizing a simplified treatment concept with predictable treatment outcomes under consideration of the individual patients' situation (Laleman et al., 2016). Major advantages might arise to reduce production costs, improve time efficiency, and to satisfy patients' perceptions and expectations in a modernized treatment concept. Therefore, s-CAIS might have the potential to become a game changer in implant therapy (Pozzi et al., 2016).

Selecting appropriate indications is a prerequisite, and the correct application of s-CAIS is absolutely crucial for the success of the overall therapy, and finally, for a satisfied patient reaching a predictable implant treatment outcome (Joda & Bragger, 2016). For virtual implant planning and consecutively implant placement using static s-CAIS, a teamwork approach is even more important and equally affects the prosthodontist, the oral surgeon, and the dental technician (Di Giacomo, Cury, de Araujo, Sendyk & Sendyk, 2005; Fortin, Isidori & Bouchet, 2009). Here, an increasing learning curve of the entire team has to be considered, and the level of treatment quality might be dependent on the operators' experience combined with the used implant system, the software application, and processing technology for s-CAIS guide production (Rungcharassaeng, Caruso, Kan, Schutyser & Boumans, 2015; Sarment, Al-Shammari & Kazor, 2003).

5 | CONCLUSIONS

Overall, the number of identified studies investigating s-CAIS for PROMs was low. The included studies presented heterogeneous trial designs, various therapy indications and applied techniques, which focused on different PROMs. Therefore, scientifically proven recommendations for PROMs cannot be given using s-CAIS at this time.

However, the number intra-operative complications with s-CAIS seems to be negligible and comparable to conventional implant surgery. s-CAIS may offer a beneficial treatment option in edentulous cases if a flapless approach is applicable. Nevertheless, the economic effects in terms of time efficiency and treatment costs are unclear. Clinical investigations with well-designed RCTs investigating PROMs with standardized parameters for the assessment of pain & discomfort, time efficiency & costs, as well as complications, are compellingly necessary in the field of s-CAIS.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the supporting information tab for this article.

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ANNEX I

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ANNEX II

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REVIEW ARTICLE

WILEY CLINICAL ORAL IMPLANTS RESEARCH

The accuracy of different dental impression techniques for implant-supported dental prostheses: A systematic review and meta-analysis

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Abstract

Aim: This systematic review and meta-analysis were conducted to assess and compare the accuracy of conventional and digital implant impressions. The review was registered on the PROSPERO register (registration number: CRD42016050730).

Material and Methods: A systematic literature search was conducted adhering to PRISMA guidelines to identify studies on implant impressions published between 2012 and 2017. Experimental and clinical studies at all levels of evidence published in peer-reviewed journals were included, excluding expert opinions. Data extraction was performed along defined parameters for studied specimens, digital and conventional impression specifications and outcome assessment.

Results: Seventy-nine studies were included for the systematic review, thereof 77 experimental studies, one RCT and one retrospective study. The study setting was in vitro for most of the included studies (75 studies) and in vivo for four studies. Accuracy of conventional impressions was examined in 59 studies, whereas digital impressions were examined in 11 studies. Nine studies compared the accuracy of conventional and digital implant impressions. Reported measurements for the accuracy include the following: (a) linear and angular deviations between reference models and test models fabricated with each impression technique; (b) three-dimensional deviations between impression posts and scan bodies respectively; and (c) fit of implant-supported frameworks, assessed by measuring marginal discrepancy along implant abutments.) Meta-analysis was performed of 62 studies. The results of conventional and digital implant impressions exhibited high values for heterogeneity.

Conclusions: The available data for accuracy of digital and conventional implant impressions have a low evidence level and do not include sufficient data on in vivo application to derive clinical recommendations.

KEYWORDS

computer-aided design, digital implant impressions, implant impressions, intraoral scanning

1 | INTRODUCTION

This systematic review examines current literature on the accuracy of conventional and digital implant impression methods published between 2012 and 2017. Conventional and digital implant impressions transfer the intraoral position of dental implants to a working cast. Digital impressions use optical methods to acquire implant positions and display them in a virtual model. Conventional methods use impression material and impressions copings to transfer implant positions to a stone cast with implant analogs in original implant positions.

The position of dental implants is recorded and transferred to a working stone cast for the manufacturing of implant-supported prosthesis (Lee, So, Hochstedler, & Ercoli, 2008). The correct transfer of each implant position in relation to neighboring implants or teeth is paramount for the design and fit of implant-supported prosthesis and therefore for long-term success of implant therapy avoiding mechanical and biological complications (Kunavisarut, Lang, Stoner, & Felton, 2002; Sahin, Cehreli, & Yalcin, 2002; Wang, Leu, Wang, & Lin, 2002).

The conventional workflow for dental implant impressions involves screw-retained impression copings that are attached to the implant and impression trays loaded with impression material. Impression copings are either retained in the cured impression material (pick-up method) (Di Fiore et al., 2015; Papaspyridakos et al., 2012; Pera, Pesce, Bevilacqua, Setti, & Menini, 2016) or remain in the implants and are repositioned in the respective regions in the impression after it is removed from the mouth (transfer method) (Calesini et al., 2014; Ibrahim & Ghuneim, 2013). Replacement of transfer copings after removal of the impression from the mouth may be facilitated by plastic caps seated on transfer copings that are retained in the impression (Abdel-Azim, Zandinejad, Elathamna, Lin, & Morton, 2014; Gökçen-Rohlig, Ongül, Sancakli, & Sermet, 2014).

The pick-up method is performed with open impression trays. To remove the impression with copings, the screw retention must be loosened. This is achieved through holes in the impression tray that are located on top of the impression coping. The transfer method is performed with closed impression trays, as no access to the screw-retained copings is required. Pick-up impression copings are frequently splinted to each other with acrylic resin or other materials or structures (bars, straws or dental floss) before adding impression material (Martínez-Rus, García, Santamaría, Özcan, & Pradíes, 2013; Ongül, Gökçen-Röhlig, Şermet, & Keskin, 2012; Zen et al., 2015). The rigid connection of multiple impression copings is applied to avoid movement of impression copings in the elastic impression material. A higher impression accuracy with splinted impression copings compared to nonsplinted copings has been reported (Al Quran, Rashdan, Abu Zomar, & Weiner, 2012; Filho, Mazaro, Vedovatto, Assuncao, & dos Santos, 2009; Hariharan, Shankar, Rajan, Baig, & Azhagarasan, 2010; Heidari, Fallahi, & Izadi, 2016; Zen et al., 2015).

Digital implant impressions are a new method for the acquisition of implant positions and may replace conventional implant impressions and stone cast production (Amin et al., 2016; Karl, Graef, Schubinski, & Taylor, 2012; Papaspyridakos et al., 2016). With digital implant impressions, the conventional workflow for the manufacturing of implant-supported prosthesis is avoided and the utilization of CAD/CAM technology is initiated. Digital impression summarizes multiple optical technologies to attain the position of dental implants in a virtual model (Giménez, Özcan, Martínez-Rus, & Pradíes, 2014, 2015a,b; Giménez, Pradíes, Martínez-Rus, & Özcan, 2015). Analog to conventional implant impressions, scan bodies are connected to dental implants, creating an accessible surface for optical acquisition (Flügge, Att, Metzger, & Nelson, 2017). The position of implant scan bodies within the dental arch is recorded with intraoral scanning devices and results in a virtual stone cast displaying the scan bodies. With the knowledge of scan body dimensions, the spatial position of each implant connected to a scan body is reconstructed. Based on the virtual position of implants, prostheses are virtually designed and may be manufactured using CAM technology (Aktas, Özcan, Aydin, Şahin, & Akça, 2014; Katsoulis et al., 2013). Depending on the optical scanning technology, a titanium oxide powder may be required on intraoral surfaces (Abdel-Azim et al., 2014; Karl et al., 2012; Vandeweghe, Vervack, Dierens, & De Bruyn, 2017).

To take advantage of virtual design tools and novel computer-aided production processes of implant-supported frameworks, stone cast with implant analogs may as well be scanned using optical scanners. In this case, a conventional implant impression is used to transfer the implant position from the mouth to a stone cast and scan bodies are connected to dental implant analogs in the model. The model is placed in a model scanner and optically recorded (Aktas et al., 2014; Flügge et al., 2017; Katsoulis et al., 2013; Stimmelmayr, Guth, Erdelt, Edelhoff, & Beuer, 2011).

The transfer of implant positions with conventional, intraoral optical or extraoral optical methods is the starting point for the production process of implant-supported prosthesis. Multiple studies examined and compared the accuracy of different implant impression techniques. However, intraoral implant positions must be transferred to an extraoral reference model for the assessment of the accuracy of intraoral impressions. The technique with the least assumed error is used to create a reference model and novel methods are compared with the previously created reference model (Andriessen, Rijkens, van der Meer, & Wismeijer, 2014; Papaspyridakos et al., 2016). Therefore, accuracy assessment of intraoral impressions is limited to the comparison of different techniques. The term accuracy refers to the trueness, describing the closeness of a measurement to the actual value, and by the precision, describing the closeness of multiple measurement results.

This review examines studies on the accuracy and on the precision of different digital impressions versus conventional implant impressions techniques. Digital impression techniques include direct intraoral scanning using intraoral scanning devices, extraoral scanning of stone casts using either intraoral scanning devices or extraoral scanning of stone casts using dental laboratory scanners.

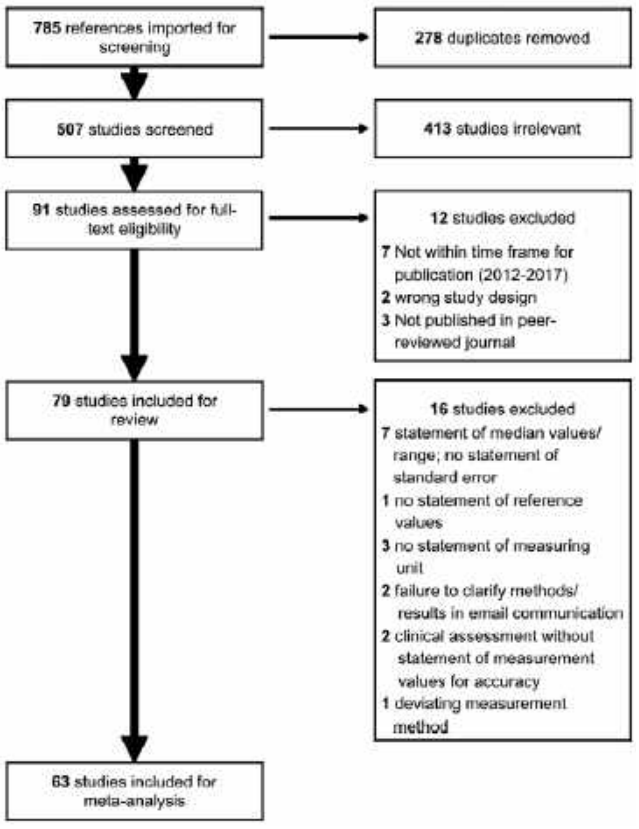

FIGURE 1 Flowchart of the search process adhering to PRISMA

2 | MATERIAL AND METHODS

This systematic literature review was performed adhering to Transparent Reporting of Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Figure 1). The review was registered on the PROSPERO register (registration number: CRD42016050730).

2.1 | Pico question

The focused PICO (Population, Intervention, Comparison, Outcome) question was: "Are digital impressions as accurate as conventional impressions for dental implant restorations?"

2.2 | Search strategy

The systematic search was conducted on PubMed MEDLINE, CENTRAL, EMBASE and Google Scholar databases using the (MeSH) keywords relevant for the focused question. The search was limited to a time frame of recent 5 years from January 1, 2012, to the date of search (March 1, 2017). Additional hand searching was performed of the following journals: Clinical Implant Dentistry and Related Research, Clinical Oral Implants Research, Implant Dentistry, International Journal of Oral and Maxillofacial Implants, Journal of Clinical Periodontology, Journal of Computerized Dentistry, Journal of Implantology and Journal of Periodontology.

The used search terms were as follows: ((((dental implants [MeSH Terms]) OR dental implant*)) AND ((dental impression technique [MeSH Terms]) OR dental impression technique*)) AND ((((dimensional measurement accuracy [MeSH Terms]) OR impression accuracy) OR accuracy) OR dimensional measurement accuracy). The search strategy and terms were modified in accordance with the searched database.

Inclusion criteria were defined as follows:

- Studies at all levels of evidence, except expert opinion
- Experimental and clinical studies
- Case reports with at least five patients
- In vitro and in vivo studies
- Publications in peer-reviewed journals

Studies with the following characteristics were excluded:

- Multiple publications based on the same patient population
- Animal studies

2.3 | Study selection and quality assessment

Most included studies (78 of 79 studies) were neither randomized/nonrandomized controlled trials nor controlled clinical trials. Therefore, quality assessment according to PRISMA was not performed.

2.4 | Data extraction

Two reviewers (TF, PW) independently screened titles and abstracts of all studies retrieved from the above-mentioned search strategy and voted for inclusion or exclusion, respectively. Conflicts were resolved in discussion with a third reviewer (BG). Subsequently, full-text screening was performed and studies were excluded when failed to meet the inclusion criteria or fall into the category of exclusion criteria. Six studies not published in the regarded time frame were excluded, two case reports were excluded because of wrong study designs, and two studies not published in peer-reviewed journals were excluded.

The following data were extracted from each study:

- Study designs: Randomized/nonrandomized controlled trial, retrospective study, case series, experimental study
- Study settings: in vivo, in vitro
- Impression technologies: digital, conventional
- Tooth status in the implant impression-taking region: single-unit case, partially edentulous or completely edentulous arch, number and distribution of implants.
- Angulation and vertical position of implants
- Implant systems and types of implant–abutment interface
- Operator experience

- Impression levels: implant level, abutment level
- Digital impressions
  - Optical scanning devices
  - Scan body manufacturers and features
  - Splinting or nonsplinting
  - Powder application
- Conventional impressions
  - Impression tray designs
  - Impression coping manufacturers and features
  - Impression material
- Assessment methods
  - Linear deviation
  - Angular deviation
  - 3D surface deviation
  - Marginal discrepancy (of restorations)
- Outcome reporting
  - Accuracy
  - Precision
  - Fit (of restorations)

2.5 | Meta-analysis

Random-effect models were used for meta-analysis of each subgroup to compare results of conventional and digital implant impression systems using Stata software (Stata 14.2, StataCorp).

3 | RESULTS

Seventy-nine studies were included in this systematic review. The study design was assessed and resulted in three groups: 77 experimental studies, one retrospective study (Perez-Davidi, Levit, Walter, Eilat, & Rosenfeld, 2016) and one randomized controlled clinical trial (Pozzi, Tallarico, Mangani, & Barlattani, 2013) (Table 1).

Most studies were performed in vitro using experimental stone, metal or resin models with implants or laboratory analogs, respectively (75 studies). One study examined digital impressions in vitro using formalin-conserved human mandibles (Corominas-Delgado et al., 2015). One randomized controlled clinical trial (Pozzi et al., 2013), one retrospective study (Perez-Davidi et al., 2016) and two experimental studies (Andriessen et al., 2014; Papaspyridakos et al., 2012) were performed in vivo (Table 2).

Digital impressions were studied in 11 studies, whereas 59 studies focused on conventional impressions. Digital and conventional impressions were directly compared in nine studies (Table 3).

Impression techniques were studies in various edentulous status. Sixty-three studies examined completely edentulous arches with two implants (13 studies), three implants (one study), four implants (27 studies), five implants (three studies) and six implants (18 studies), respectively. Twelve studies with partially edentulous arches had specimens with one implant (one study), two implants (eight studies) and with two and five implants, respectively (one study). Two studies included partially and completely edentulous arches (Sabouhi, Bajoghli, & Abolhasani, 2015; Sabouhi, Bajoghli, Dakhilalian, Beygi, & Abolhasani, 2016), one study included completely edentulous arches and a single-unit restoration (Abdel-Azim et al., 2014). Two studies assessed a single unit (Aktas et al., 2014; Lee, Betensky, Gianneschi, & Gallucci, 2015). One study included patients with various indications for implant therapy (Perez-Davidi et al., 2016).

TABLE 1 Summary of study designs for all included studies

Study design	Number of studies
RCT	1
Nonrandomized controlled clinical trial	–
Experimental study	77
Retrospective study	1
Case series	–

TABLE 2 Summary of study settings

Study setting	Number of studies
In vitro	75
In vivo	4

TABLE 3 Summary of impression technologies applied in included studies

Technology	Number of studies
Digital impression	11
Digital vs. conventional impression	9
Conventional impression	59

3.1 | Angulation and vertical position of implants

Out of 79 studies, 18 studies evaluated impression accuracy of parallel implants; 11 studies used specimens with angulated implants, 24 studies did not state angulation of implants and two studies had specimens with a single implant. Twenty-four studies focused on the comparison of impression accuracy for parallel and angulated implants. Regardless of various impression techniques, conventional implant impressions of angulated implants were significantly less accurate compared to parallel implants (Akalin, Ozkan, & Ekerim, 2013; Heidari et al., 2016; Kurtulmus-Yilmaz, Ozan, Ozcelik, & Yagiz, 2014; Mpikos et al., 2012; Ng, Tan, Teoh, Cheng, & Nicholls, 2014; Shim, Ryu, Shin, & Lee, 2015; Siadat, Alikhasi, Beyabanaki, & Rahimian, 2016; Tsagkalidis, Tortopidis, Mpikos, Kaisarlis, & Koidis, 2015). However, other studies reported that different implant angulations showed no significant difference in impression accuracy (Calesini et al., 2014; Ehsani, Siadat, & Alikhasi, 2013; Hazboun, 2013; Howell, McGlumphy, Drago, & Knapik, 2013; Lin, Harris, Elathamna, Abdel-Azim, & Morton, 2015).

Likewise, digital impressions of angulated implants did not show a significantly different impression accuracy compared to parallel implants (Giménez et al., 2014, 2015a,b; Giménez, Pradíes et al., 2015; Papaspyridakos et al., 2012). Lin et al. (2015) observed higher impression accuracy of digital implant impressions with implant divergence when comparing with parallel implants.

TABLE 4 Summary of studies of digital implant impressions [In PDF format, this table is best viewed in two-page mode]

Author	Study type	Specimen	No. of implants	Angulation of implants	Vertical position of implants	Implant System	Fixture	Operator
Aktas et al. (2014)	In vitro	Single unit	1	-	Not stated	Straumann TL	Implant	Not stated
Corominas-Delgado et al. (2015)	Ex vivo	Edentulous	6	Not stated	Not stated	Adin Touareg	Implant	Not stated
Flügge et al. (2017)	In vitro	Partially edentulous	2	Not stated	Not stated	Camlog, Straumann BL/TL	Analog	Not stated
Flügge et al., 2016;	In vitro	Partially edentulous	2; 5	Not stated	Not stated	Straumann BL/TL	Analog	Not stated
Giménez et al. (2014)	In vitro	Edentulous	6	12, 22, 17, 27:parallel 15, 25: 30°	12: 4 mm sub; 22: 2 mm sub; 15, 25, 17, 27: equigingival	Certain 4, Biomet 3i	Implant	Experienced Inexperienced
Giménez et al. (2015a)	In vitro	Edentulous	6	12, 22, 17, 27:parallel 15, 25: 30°	12: 4 mm sub; 22: 2 mm sub; 15, 25, 17, 27: equigingival	Certain 4, Biomet 3i	Implant	Experienced Inexperienced
Giménez et al. (2015b)	In vitro	Edentulous	6	12, 22, 17, 27:parallel 15, 25: 30°	12: 4 mm sub; 22: 2 mm sub; 15, 25, 17, 27: equigingival	Certain 4, Biomet 3i	Implant	Experienced Inexperienced
Giménez, Pradíes et al., 2015	In vitro	Edentulous	6	12, 22, 17, 27:parallel 15, 25: 30°	12: 4 mm sub; 22: 2 mm sub; 15, 25, 17, 27: equigingival	Certain 4, Biomet 3i	Implant	Experienced Inexperienced
Katsoulis et al. (2013)	In vitro	Edentulous	6	11, 13, 21, 23: parallel 15, 25: 10°	Not stated	Nobel Replace	Analog	Not stated
Stimmelmayr, Erdelt et al., 2012; Stimmelmayr, Güth et al., 2012	In vitro	Edentulous	4	Not stated	Not stated	Camlog	Implant/analog	Not stated
Vandeweghe et al. (2017)	In vitro	Edentulous	6	46–44:0.6° 44–42: 1.7° 42–43:4.6° 32–34: 4.8° 34–36:4.2°	Not stated	IBT Southern Implants	Implant	Not stated

The majority of studies of conventional implant impressions (55 studies) did not examine the vertical position of implants. The equigingival (BalaMurugan & Manimaran, 2013) or supragingival (Sabouhi et al., 2015, 2016) placement of implants was stated, however, not evaluated for the impression accuracy. Implants were placed at depths of 0, 1 and 3 mm and examined along with other specifications for conventional implant impressions (Martínez-Rus et al., 2013). However, the effect of depth was not evaluated independently from other factors.

Four studies using digital impressions examined the vertical position of implants (equigingivally; 2 and 4 mm subgingivally). The implant depth did not affect impression accuracy in any of these studies (Giménez et al., 2014, 2015a,b; Giménez, Pradíes et al., 2015).

3.2 | Operator experience

Few studies of conventional implant impression accuracy stated experience of operators (Ghahremanloo, Seifi, Ghanbarzade, Abrisham, & Javan, 2017; Gupta, Narayan, & Balakrishnan, 2017; Perez-Davidi et al., 2016). In a clinical study, impressions were performed by senior dentists and residents, respectively. The accuracy of each impression technique was evaluated by assessing the fit of implant-supported frameworks in periapical radiographs. There was no difference in fit between three different impression techniques when performed by senior dentists. However, ill-fitting frameworks were observed significantly more often when manufactured with an impression technique involving intraoral splinting of copings to impression trays performed by residents (Perez-Davidi et al., 2016).

TABLE 4 (additional columns)

Impression level	Optical scanning device	Scan body manufacturer	Scan body features	Splinting	Powder	Outcomes
Implant level	inEos, inLab, Cerec 3D	Straumann synOcta abutment	synOcta abutment	-	Powder	Significant differences in marginal gaps for inEos, CEREC and inLab scanners
Implant level	CBCT	LOC-i	Screw retained	Not splinted	No powder	CBCT valid for impression-taking for full-mouth rehabilitations with implants
Implant level	D250	Camlog, Straumann	Cylindrical, screw retained	Not splinted	No powder	Precision of extraoral scanning is dependent on scan body surface design and geometry
Implant level	iTero, Trios, TrueDef	Straumann	Cylindrical, screw retained	Not splinted	Powder/no powder	Digital full-arch impressions less precise than quadrant impressions
Implant level	iTero	Createch	Cylindrical, screw retained	Not splinted	No powder	Quadrant scanning more accurate than full-arch scanning; inexperienced more accurate than experienced operator
Implant level	Cerec AC Bluecam (Version 4.0)	Createch	Cylindrical, screw retained	Not splinted	No powder	Quadrant scanning more accurate than full-arch scanning
Implant level	Lava COS	Createch	Cylindrical, screw retained	Not splinted	Powder	No significant influence of operator experience, implant depths and angulation
Implant level	3D Progress, ZFX Intrascan	Createch	Cylindrical, screw retained	Not splinted	No powder	Scanning systems not suitable for multi-implant impressions
Implant level	I Metric 3D; Nobel Procera	Nobel Procera	Cylindrical, screw retained	Not splinted	Powder/no powder	High precision of fit of CAD/CAM titanium bars from photogrammetric and laser scanning
Implant level	Everest	Camlog	Cylindrical, screw retained	Not splinted	Powder/no powder	Scan body fit more reproducible on lab analogs compared to original implants
Implant level	Lava COS, True Def, Omnicam, Trios	Proscan	Cylindrical, screw retained	Not splinted	Powder/no powder	Highest accuracy for TrueDef and Trios; Lava COS not suitable for multi-implant and full-arch scanning

Four studies of digital implant impressions techniques examined the influence of operator experience with digital impression techniques on impression accuracy. A significant difference was found between experienced and inexperienced operators with one inexperienced operator yielding significantly lower impression accuracy compared to two experienced operators and one other inexperienced operator (Giménez et al., 2014). However, in another study, inexperienced operators performed significantly better for impression accuracy compared to experienced operators with another intraoral scanning device (Giménez et al., 2015a,b; Giménez, Pradíes et al., 2015). In a further study, a significant higher accuracy of digital impression by experienced operators was documented in the beginning of the scanning series. After completing all consecutive scans, the difference between experienced and inexperienced operators was not significant anymore (Giménez et al., 2015a,b; Giménez, Pradíes et al., 2015). The use of two other scanning devices did not result in significant differences for digital impression accuracy for experienced and inexperienced operators (Giménez et al., 2015a,b; Giménez, Pradíes et al., 2015).

3.3 | Optical scanning devices

Multiple optical scanners for direct intraoral optical scanning and for extraoral scanning of stone casts were examined in the included studies.

Several studies studied the accuracy of extraoral optical scanners with different technologies, such as blue and white light scanners (inEos, CEREC inLab, Sirona Dental Systems, Germany) and (Everest Scan Pro KaVo, Germany) (Aktas et al., 2014; Stimmelmayr, Erdelt, Guth, Happe, &

TABLE 5 Summary of studies comparing digital and conventional implant impressions [In PDF format, this table is best viewed in two-page mode]

Author	Study type	Specimen	No of implants	Angulation of implants	Vertical position of implants	Implant System	Fixture	Operator	Impression level
Abdel-Azim et al. (2014)	In vitro	(partially) edentulous	4, 2	Not stated	Not stated	Straumann TL	Implant	Not stated	Abutment level
Amin et al. (2016)	In vitro	Edentulous	5	Not stated	Not stated	Straumann BL	Implant	Inexperienced	Implant level
Andriessen et al. (2014)	In vivo	Edentulous	2	Not stated	Not stated	Straumann TL	Implant	Not stated	Implant level
Bergin et al. (2013)	In vitro	Edentulous	5	Not stated	Not stated	Nobel Replace	Analog	Not stated	Implant level
Karl et al.	In vitro	Partially edentulous	2	Not stated	Not stated	Straumann TL	Implant	Not stated	Implant level
Lee et al. (2015)	In vitro	Partially edentulous	1	Not stated	Not stated	Straumann BL	Implant	Not stated	Implant level
Lin et al.	In vitro	Partially edentulous	2	Parallel; 15° 30; 45	3	Straumann TL	Analog	Not stated	Implant level
Ono et al. (2013)	In vitro	Edentulous	4	Not stated	Not stated	Nobel (Brånemark RP)	Analog	Not stated	Implant level
Papaspyridakos et al., 2016	In vitro	Edentulous	5	31, 33, 41, 43: parallel 35: 10° 45: 15°	Not stated	Straumann BL	Analog	Not stated	Implant level

Beuer, 2012; Stimmelmayr, Güth, Erdelt, Edelhoff, & Beuer, 2012); laser scanner (D250, 3Shape, Denmark) (Flügge et al., 2017); photogrammetric scanner (Imetric 3D, Switzerland) and photogrammetric technology using a digital camera (Nikon D90, NY, USA) (Bergin, Rubenstein, Mancl, Brudvik, & Raigrodski, 2013); conoscopic holography (NobelProceraTM Scanner, Nobel Biocare, Sweden) (Katsoulis et al., 2013) and an optical tracking device (Micron Tracker 2, Claron Technology, Canada) (Ono et al., 2013).

One study used CBCT technology (LOC-I, ENGimage) for acquisition of implant positions (Corominas-Delgado et al., 2015). The studied intraoral scanning devices were as follows: Trios (3Shape, Denmark) (Flügge, Att, Metzger, & Nelson, 2016; Papaspyridakos et al., 2016; Vandeweghe et al., 2017); Cerec (Bluecam and Omnicam devices, Sirona, Germany) (Aktas et al., 2014; Amin et al., 2016; Giménez et al., 2015a,b; Giménez, Pradíes et al., 2015; Vandeweghe et al., 2017); iTero (Cadent, CA, USA) (Abdel-Azim et al., 2014; Flügge et al., 2016; Giménez et al., 2014; Lee et al., 2015; Lin et al., 2015); TrueDefinition (3M Espe, USA) (Amin et al., 2016; Flügge et al., 2016; Vandeweghe et al., 2017); LavaCOS (3M Espe, USA) (Giménez et al., 2015a,b; Giménez, Pradíes et al., 2015; Karl et al., 2012; Vandeweghe et al., 2017); 3D Progress (MHT) (Giménez et al., 2015a,b; Giménez, Pradíes et al., 2015); and ZFX Intrascan (Zimmer) (Giménez et al., 2015a,b; Giménez, Pradíes et al., 2015).

TABLE 5 (additional columns)

Digital					Conventional					
Optical scanning device	Scan body manufacturer	Scan body features	Splinting	Powder	Tray design	Tray production	Impression copings	Impression material	Splinting	Outcomes
iTero	Not stated	Not stated	Not splinted	Powder	Closed	Custom	Transfer plastic caps	Polyvinyl siloxane		Marginal discrepancy: single-unit lower for conventional; full arch: lower for digital
Omnicam TrueDef	Straumann	Cylindrical, screw retained	Not splinted	Powder/no powder	Open	Custom	Original pick-up, screw retained	Polyether	Splinted	Digital more accurate than conventional True Definition more accurate than Omnicam scanner
iTero	Straumann	Two-piece, screw-retained	Not splinted	No powder	Not stated	Not stated	Not stated	Not stated	Not stated	Digital impressions to inaccurate for production of frameworks
Digital camera	Custom	Two spheres on vertical shaft	Not splinted	No powder	Open	Not stated	Screw-retained	Not stated	Splinted	Similar accuracy of photogrammetry and conventions method
Lava COS	Straumann	Abutment	Not splinted	Powder	Open	Custom	Original pick-up, screw retained	Polyether	Not splinted	Digital as precise as conventional for fabrication of framework on implants
iTero	Straumann	Two-piece, screw-retained	-	No powder	Closed	Not stated	Not stated	Polyvinyl siloxane	Not splinted	Significant differences for digital and conventional for vertical implant position
iTero	Straumann	Two-piece, screw-retained	Not splinted	No powder	Open	Custom	Straumann screw retained	Polyvinyl siloxane	Not splinted	Digital less accurate than conventional impressions
Micron Tracker 2	Custom	Paper +titanium flags	Not splinted	No powder	Open	Custom	Original screw-retained	Polyvinyl siloxane	Splinted	Accurate acquisition of implant position with novel optical method for extraoral model scans
Trios	Straumann	Cylindrical, screw retained	Not splinted	No powder	Open	Custom	Original pick-up, screw retained	Polyvinyl siloxane	Splinted/non-splinted	Digital as accurate as conventional implant impressions

3.4 | Scan bodies

The majority of studies used original implant scan bodies for intraoral and extraoral optical scanning (Amin et al., 2016; Flügge et al., 2016, 2017; Katsoulis et al., 2013; Lee et al., 2015; Lin et al., 2015; Papaspyridakos et al., 2016; Stimmelmayr, Erdelt et al., 2012; Stimmelmayr, Güth et al., 2012). Besides original scan bodies, generic scan bodies (Corominas-Delgado et al., 2015; Giménez et al., 2014, 2015a,b; Giménez, Pradíes et al., 2015; Vandeweghe et al., 2017) or abutments (Aktas et al., 2014; Karl et al., 2012) were used for optical scanning. Photogrammetric acquisition of implant positions was realized with custom-made scan bodies (Bergin et al., 2013; Ono et al., 2013). The used scan body was not disclosed by Abdel-Azim et al. (2014); the retention of custom scan bodies was not disclosed by Ono et al. (2013). All other authors used screw-retained scan bodies analog to conventional impression copings (Amin et al., 2016; Bergin et al., 2013; Corominas-Delgado et al., 2015; Flügge et al., 2016, 2017; Giménez et al., 2014, 2015a,b; Giménez, Pradíes et al., 2015; Karl et al., 2012; Katsoulis et al., 2013; Lee et al., 2015; Lin et al., 2015; Papaspyridakos et al., 2016; Stimmelmayr, Erdelt et al., 2012; Stimmelmayr, Güth et al., 2012; Vandeweghe et al., 2017). The most commonly used scan

bodies among all studies had a cylindrical design (Aktas et al., 2014; Amin et al., 2016; Flügge et al., 2016, 2017; Giménez et al., 2014, 2015a,b; Giménez, Pradíes et al., 2015; Karl et al., 2012; Katsoulis et al., 2013; Papaspyridakos et al., 2016; Stimmelmayr, Erdelt et al., 2012; Stimmelmayr, Güth et al., 2012; Vandeweghe et al., 2017). Original scan bodies used in two studies differed from the cylindrical design with a short lower part and an angled top part (Lee et al., 2015; Lin et al., 2015). For photogrammetric acquisition, two different designs were examined: a vertical shaft with one sphere close to the implant and another sphere at the coronal end of the shaft (Bergin et al., 2013) and scan flags manufactured from either titanium or paper with a pattern on the surface and different sizes of the flag surface (Ono et al., 2013). Scan bodies were never splinted for extraoral or intraoral scanning. The application of powder was performed in accordance with instructions by each manufacturer.

All studies on digital implant impressions and digital and conventional implant impressions are summarized in Tables 4 and 5.

3.5 | Conventional impressions

Conventional implant impressions were performed with the open tray method (Akalin et al., 2013; Aldosari, 2014; Aldosari et al., 2015; Amin et al., 2016; de Avila, de Matos Moraes, Castanharo, Del'Acqua, & de Assis Mollo, 2014; Bergin et al., 2013; Beyabanaki, Shamshiri, Alikhasi, & Monzavi, 2015; Buzayan, Baig, & Yunus, 2013; Di Fiore et al., 2015; Ehsani et al., 2013; Geramipanah, Sahebi, Davari, Hajimahmoudi, & Rakhshan, 2015; Ghahremanloo et al., 2017; Ghanem, Nassani, Baroudi, & Abdel Fattah, 2015; Gupta et al., 2017; Heidari et al., 2016; Lin et al., 2015; Marotti et al., 2014; Ongül et al., 2012; Ono et al., 2013; Papaspyridakos et al., 2012; Perez-Davidi et al., 2016; Pozzi et al., 2013; Pujari, Garg, & Prithviraj, 2014; Selvaraj, Dorairaj, Mohan & Simon, 2016; Vigolo, Mutinelli, Fonzi & Stellini, 2014; Vojdani, Torabi, & Ansarifard, 2015; Zen et al., 2015), the closed tray method (Abdel-Azim et al., 2014; Calesini et al., 2014; Del'acqua, de Avila, Amaral, Pinelli, & de Assis Mollo, 2012; Gökçen-Rohlig et al., 2014; Ibrahim, Fouad, Elewa, & Mustafa, 2014; Ibrahim & Ghuneim, 2013; Karl et al., 2012; Lee et al., 2015; Reddy, Prasad, Vakil, Jain, & Chowdhary, 2013) or both the open and closed tray methods for comparison of the accuracy (Al Quran et al., 2012; Alikhasi, Siadat, Beyabanaki, & Kharazifard, 2015; Alikhasi, Siadat, & Rahimian, 2015; de Avila, Barros, Del'Acqua, Castanharo, & Mollo Fde, 2013; BalaMurugan & Manimaran, 2013; Chang, Vahidi, Bae, & Lim, 2012; Haghi, Shiehzadeh, Nakhaei, Ahrary, & Sabzevari, 2017; Hazboun, 2013; Howell et al., 2013; Karl & Palarie, 2014; Mpikos et al., 2012; Nakhaei, Madani, Moraditalab, & Haghi, 2015; Ng et al., 2014; Pera et al., 2016; Rutkunas, Sveikata, & Savickas, 2012; Sabouhi et al., 2015, 2016; Shankar et al., 2016; Shim et al., 2015; Siadat et al., 2016). Two studies did not use trays and compared stress induced by splinting two impression posts on dental implants with different splinting materials and techniques to each other (Lopes-Júnior, de Lima Lucas, Gomide, & Gomes, 2013a,b).

Impression copings were selected according to implant specifications and tray design. Pick-up impression copings for open tray impressions, conical screw-retained impressions copings and screw-retained copings with plastic caps retained in the impression for closed tray impressions as well as Encode abutments and original implant abutments were used for conventional impressions. Pick-up copings with screw retention for open tray impression techniques were used in 23 studies. In 36 studies, the authors compared different impression copings with each other; however, screw-retained copings with plastic caps were only studied in one study and conical transfer copings were not used exclusively in any study. Two studies did not disclose the used impression copings (Papaspyridakos et al., 2012; Reddy et al., 2013).

Impression materials were polyvinylsiloxane, vinylsiloxanether, polyether or condensation silicone. Polyvinylsiloxane materials were used in 26 studies (Abdel-Azim et al., 2014; Al-Abdullah, Zandparsa, Finkelman, & Hirayama, 2013; Alikhasi, Siadat, Beyabanaki et al., 2015; Alikhasi, Siadat, & Rahimian, 2015; de Avila et al., 2013, 2014; BalaMurugan & Manimaran, 2013; Beyabanaki et al., 2015; Calesini et al., 2014; Del'acqua et al., 2012; Di Fiore et al., 2015; Ehsani et al., 2013; Geramipanah et al., 2015; Ghahremanloo et al., 2017; Heidari et al., 2016; Howell et al., 2013; Ibrahim et al., 2014; Lee et al., 2015; Lin et al., 2015; Marotti et al., 2014; Nakhaei et al., 2015; Ono et al., 2013; Pozzi et al., 2013; Sabouhi et al., 2016; Shim et al., 2015; Siadat et al., 2016; Zen et al., 2015), whereas polyether was used in 22 studies (Al Quran et al., 2012; Aldosari, 2014; Aldosari et al., 2015; Alikhasi, Bassir, & Naini, 2013; Amin et al., 2016; Ghanem et al., 2015; Hazboun, 2013; Ibrahim & Ghuneim, 2013; Karl et al., 2012; Martínez-Rus et al., 2013; Mpikos et al., 2012; Ng et al., 2014; Ongül et al., 2012; Papaspyridakos et al., 2012; Pera et al., 2016; Perez-Davidi et al., 2016; Rashidan, Alikhasi, Samadizadeh, Beyabanaki, & Kharazifard, 2012; Selvaraj et al., 2016; Stimmelmayr, Erdelt et al., 2012; Stimmelmayr, Güth et al., 2012; Tarib et al., 2012; Tsagkalidis et al., 2015; Vigolo et al., 2014), and vinylsiloxanether and condensation silicone were each used in one study (Eliasson & Ortorp, 2012). Sixteen studies compared any combination of the aforementioned impression materials (Akalin et al., 2013; Alikhasi, Siadat, Beyabanaki et al., 2015; Alikhasi, Siadat, & Rahimian, 2015; Buzayan et al., 2013; Chang et al., 2012; Ebadian, Rismanchian, Dastgheib, & Bajoghli, 2015; Gökçen-Rohlig et al., 2014; Gupta et al., 2017; Haghi et al., 2017; Karl & Palarie, 2014; Kurtulmus-Yilmaz et al., 2014; Pujari et al., 2014; Reddy et al., 2013; Rutkunas et al., 2012; Shankar et al., 2016; Vojdani et al., 2015; Wegner, Weskott, Zenginel, Rehmann, & Woestmann, 2013).

Splinting of impression copings was studied and compared with nonsplinting of impression copings in numerous studies. Thirty-two studies used nonsplinted impression copings (Akalin et al., 2013; Aldosari, 2014; Aldosari et al., 2015; Alikhasi et al., 2013; Alikhasi, Siadat, Beyabanaki et al., 2015; Alikhasi, Siadat, & Rahimian, 2015; BalaMurugan & Manimaran, 2013; Calesini et al., 2014; Ebadian et al., 2015; Ehsani et al., 2013; Eliasson & Ortorp, 2012; Geramipanah et al., 2015; Ghahremanloo et al., 2017; Gökçen-Rohlig et al., 2014; Haghi et al., 2017; Howell et al., 2013; Ibrahim et al., 2014; Karl & Palarie, 2014; Karl et al., 2012; Lee et al., 2015; Lin et al., 2015; Marotti et al., 2014; Mpikos et al., 2012; Nakhaei et al., 2015; Ng et al., 2014; Rashidan et al., 2012; Reddy et al., 2013; Sabouhi et al.,

TABLE 6 Analysis of linear and 3D surface deviations (μm) measured for conventional and digital impressions

			Conventional impression				Digital impression			
Clinical situation	Implant distribution	Implant angulation	No. of (sub-) studies	Mean	CI	Heterogeneity (%)	No. of (sub-) studies	Mean	CI	Heterogeneity (%)
Edentulous	Neighboring implants	Unknown	4	86.8	−8.4–181.9	63.3				
	Quadrant	Parallel	10	40.0	29.6–50.3	97.6	6	24.2	13.3–35.1	45.2
		21–45 degrees					6	19	10.7–27.3	66.7
	Full arch	Unknown	67	77.7	64.9–90.5	96.4				
		Parallel	62	97.1	93.2–100.9	100.0	12	51.0	28.0–74.0	69.0
		1–20 degrees	26	42.0	36.5–47.5	97.7				
		21–45 degrees	24	212.0	158.5–265.5	97.8	6	54.9	5.8–103.9	81.2
	Unknown implant distribution	21–45 degrees	18	431.6	285.0–578.2	94.3				
Partially edentulous	Neighboring implants	Parallel	7	26.7	24.0–29.5	98.7				
		1–20 degrees	20	28.7	26.3–31.2	99.0	4	11.9	4.1–19.8	82.5
		21–45 degrees	4	46.5	35.8–57.2	98.4				
	Quadrant	Parallel	7	37.1	28.7–46.5	92	1	304.0	278.6–329.4	0
		1–20 degrees	2	73.1	54.4–91.8	0	8	57.9	37.8–78.0	98.5
		21–45 degrees	1	82	40.8–123.2	0	1	158.0	102.8–213.2	0
		Unknown	4	37.1	21.4–52.8	90.1				
	Full arch	Parallel	3	31.6	9.7–53.6	45.7				
		1–20 degrees					2	21.0	1.7–40.3	0
		21–45 degrees	3	74.3	29.2–119.4	43	2	37.0	10.7–63.3	0

2015; Shim et al., 2015; Siadat et al., 2016; Vojdani et al., 2015; Wegner et al., 2013), whereas seven studies used splinted impression copings for open tray impressions (Amin et al., 2016; Bergin et al., 2013; Di Fiore et al., 2015; Gupta et al., 2017; Ono et al., 2013; Rutkunas et al., 2012; Selvaraj et al., 2016) and one study splinted conical transfer copings for closed tray impressions. Twenty-five studies compared splinted and nonsplinted impression techniques (Al-Abdullah et al., 2013; de Avila et al., 2013, 2014; Beyabanaki et al., 2015; Buzayan et al., 2013; Chang et al., 2012; Del'acqua et al., 2012; Ghanem et al., 2015; Hazboun, 2013; Heidari et al., 2016; Ibrahim & Ghuneim, 2013; Kurtulmus-Yilmaz et al., 2014; Martínez-Rus et al., 2013; Ongül et al., 2012; Papaspyridakos et al., 2012; Pera et al., 2016; Perez-Davidi et al., 2016; Pujari et al., 2014; Sabouhi et al., 2016; Shankar et al., 2016; Stimmelmayr, Erdelt et al., 2012; Stimmelmayr, Güth et al., 2012; Tarib et al., 2012; Tsagkalidis et al., 2015; Vigolo et al., 2014; Zen et al., 2015).

3.6 | Outcome assessment

The accuracy outcome was examined by measuring deviations between reference models and test models or by assessing the fit of frameworks on test models that were manufactured on reference models. Accuracy assessment comprised (a) measurement of linear and angular deviations or three-dimensional surface deviations, respectively, between reference models and test models; (b) measurement of marginal discrepancy between abutments and implant-supported frameworks; (c) measurement of strain after connection of implant-supported frameworks on test models.

For the assessment of linear and angular distances between implants, reference models and test models were measured with coordinate measuring machines (CMM) (Alikhasi et al., 2013; Alikhasi, Siadat, Beyabanaki et al., 2015; Alikhasi, Siadat, & Rahimian, 2015; BalaMurugan & Manimaran, 2013; Bergin et al., 2013; Beyabanaki et al., 2015; Buzayan et al., 2013; Di Fiore et al., 2015; Ebadian et al., 2015; Ehsani et al., 2013; Geramipanah et al., 2015; Ghahremanloo et al., 2017; Gupta et al., 2017; Heidari et al., 2016; Martínez-Rus et al., 2013; Mpikos et al., 2012; Nakhaei et al., 2015; Ng et al., 2014; Rashidan et al., 2012; Selvaraj et al., 2016; Shankar et al., 2016; Siadat et al., 2016; Tsagkalidis et al., 2015; Vojdani et al., 2015; Wegner et al., 2013). Other authors used microscopes (Akalin et al., 2013; Aldosari, 2014; Aldosari et al., 2015; Chang et al., 2012; Ghanem et al., 2015; Haghi et al., 2017; Ibrahim & Ghuneim, 2013), digital micrometers (Al Quran et al., 2012; Tarib et al., 2012), a profile projector (Vigolo et al., 2014) or a laser measuring machine (Eliasson & Ortorp, 2012) to measure implant positions in conventional stone casts and compare them between reference and test models. Measurements of linear distances were also performed on standardized photographs of conventional models (Hazboun, 2013; Ibrahim & Ghuneim, 2013; Rutkunas et al., 2012).

Virtual measurements of implant distances and angulations were performed after optical digitization of stone casts produced from conventional impressions (Gökçen-Rohlig et al., 2014; Howell et al., 2013; Lin et al., 2015; Ongül et al., 2012; Ono et al., 2013; Pera et al., 2016; Pozzi et al., 2013; Sabouhi et al., 2015, 2016; Shim et al., 2015; Stimmelmayr, Erdelt et al., 2012; Stimmelmayr, Güth et al., 2012) or after performing optical impressions with various intraoral scanners (Flügge et al., 2016, 2017; Giménez et al., 2014, 2015a,b; Giménez, Pradíes et al., 2015; Stimmelmayr, Erdelt et al., 2012; Stimmelmayr, Güth et al., 2012; Vandeweghe et al., 2017).

In other studies, impression accuracy was assessed with virtual measurement of three-dimensional surface deviations between scan bodies/impressions posts mounted on implants in reference models and test models (Amin et al., 2016; Calesini et al., 2014; Kurtulmus-Yilmaz et al., 2014; Lee et al., 2015; Papaspyridakos et al., 2012).

The accuracy of implant-supported frameworks produced on master models and fitted on test models was assessed using different measurement protocols. Authors used strain gauges to measure the strain in a framework after the placement on implant abutments (BalaMurugan & Manimaran, 2013; Karl & Palarie, 2014; Karl et al., 2012; Zen et al., 2015). Marginal discrepancy between abutment and framework was measured using microscopes (Abdel-Azim et al., 2014; de Avila et al., 2013, 2014; Del'acqua et al., 2012; Marotti et al., 2014; Zen et al., 2015), optical comparators (Al-Abdullah et al., 2013; Pujari et al., 2014; Reddy et al., 2013), a surface profilometer (Fernandez et al., 2013), an electron microscope (Katsoulis et al., 2013) or standardized photographs (Ono et al., 2013). The three-dimensional fit of frameworks was examined by lining of caps and measurement of lining material thickness (Aktas et al., 2014). Frameworks on implants in formalin-conserved human mandibles were assessed by probing of the gap, interpreting fit on periapical radiographs and photographs (Corominas-Delgado et al., 2015). In vivo studies assessed the gap between frameworks and abutments using periapical radiography (Perez-Davidi et al., 2016) or clinical examination using a dental probe (Pozzi et al., 2013).

3.7 | Meta-analysis

Seventy-nine studies of the accuracy of conventional and digital impression accuracy were included in the systematic review. Mean values and standard errors for linear and angular distances or three-dimensional surface deviations as well as marginal discrepancy and strain were included for the analysis.

Sixteen studies were excluded from meta-analysis due to differences in reporting of results in the following situations. (a). Studies stating the median values and range (Beyabanaki et al., 2015; Buzayan et al., 2013; Pera et al., 2016; Vigolo et al., 2014) or the mean values without the standard error (Andriessen et al., 2014; Calesini et al., 2014; Papaspyridakos et al., 2016). (b). Mean deviations could not be calculated and included for analysis, when authors stated absolute interimplant distances in test models without distances in reference models (Reddy et al., 2013). (c). The documentation of deviations without the measuring unit (Alikhasi, Siadat, Beyabanaki et al., 2015; Alikhasi, Siadat, & Rahimian, 2015; Mpikos et al., 2012; Shankar et al., 2016). (d). Failure of communication when email contact with the authors was attempted for clarification of methods and results (Alikhasi, Siadat, Beyabanaki et al., 2015; Alikhasi, Siadat, & Rahimian, 2015; Siadat et al., 2016). (e). Studies with clinical and radiological assessment of implant-supported frameworks in vivo (Perez-Davidi et al.,

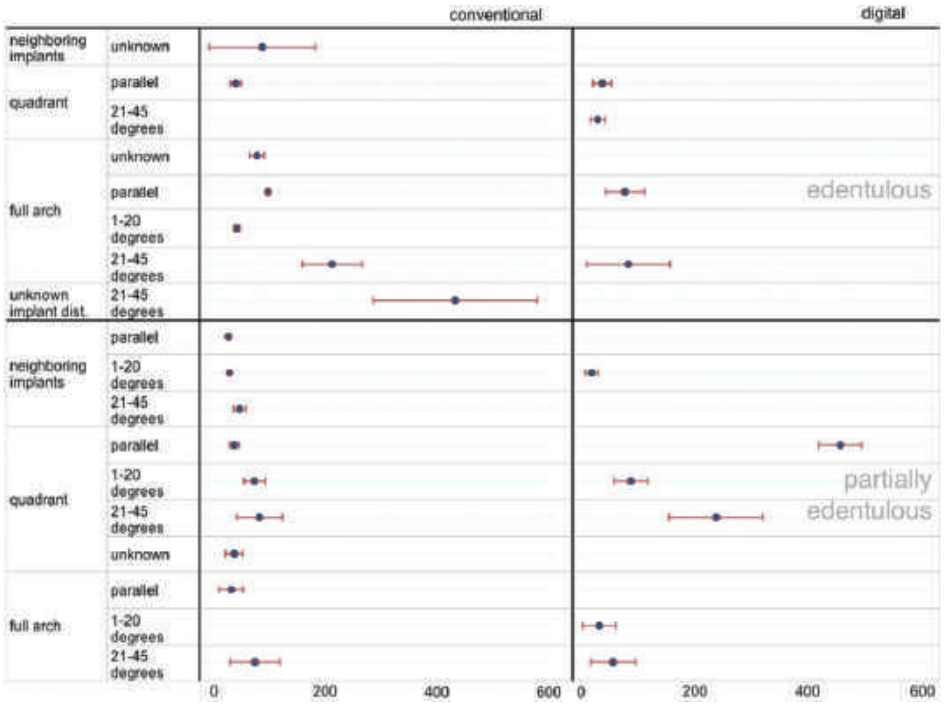

FIGURE 2 Forest plot of results for linear and 3D surface deviations (μm) measured for conventional and digital impressions

2016) and in vitro (Corominas-Delgado et al., 2015) were not included in meta-analysis, because they did not state a numerical value for accuracy. (f). The examination of fit by measuring the thickness of lining material between framework caps and implant abutments was excluded from meta-analysis, as values measured with this method were not comparable with marginal discrepancy values (Aktas et al., 2014). Therefore, meta-analysis was performed with 63 studies.

Studies were grouped for the clinical edentulous situations (edentulous jaws, partially edentulous jaws, single-unit restorations), the distribution of implants within the jaw (neighboring implants, implants in one quadrant and implants in the complete dental arch) and the angulation of implants (parallel, 1–20 degrees and 21–45 degrees).

Linear and surface deviations (Table 6, Figure 2), angular deviations (Table 7) and marginal discrepancy (Table 8) of conventional and digital impressions are displayed.

Studies of conventional impressions mostly included edentulous conditions and implants distributed within the complete dental arch. Mean linear and surface deviations of 97.1 μm (CI 93.2–100.9 μm) and angular deviations of 2.0° (CI 1.6–2.0°) for parallel implants and 77.7 μm (CI 64.9–90.5 μm) and 0.6° (CI 0.4–0.7°) for implants with unknown angulation were reported. However, high heterogeneity of 100% and 96.4% for linear and surface deviations and 95.9% and 97.0% for angular deviations were found. High linear and surface deviations for conventional impressions were reported for implants with an unknown position in the dental arch and interimplant angulations of 21–45 degrees (mean: 431.6 μm, CI 285.0–578.2 μm). Fewer studies of digital impressions of edentulous jaws with parallel implants distributed within the complete dental arch were available and resulted in linear and surface deviations of 51 μm (CI 28.0–74.0 μm) and heterogeneity of 69%.

Conventional impressions of partially edentulous jaws mostly evaluated neighboring implants resulting in mean linear and surface deviations of 28.7 μm (CI 26.3–31.2 μm) and mean angular deviations of 0.2° (CI 0.2–0.3°). Fewer studies of digital impressions were available resulting in mean deviations of 11.9 μm (CI 4.1–19.8 μm) and 0.4° (CI 0.3–0.4°). High deviations were observed in a single study of digital impressions of parallel implants within one quadrant (mean: 304.0 μm; CI: 278.6–320.4 μm; mean 1.6°; CI: 1.3–1.9°) and angulated implants (21–45 degrees) within one quadrant (mean: 158.0; CI: 102.8–213.2 μm; mean: 1.2, CI: 0.8–1.7°) (Figure 3).

Marginal discrepancies for frameworks manufactured from conventional impressions were between 18.3 and 141.5 μm in edentulous arches, 78.1 μm in partially edentulous arches and 24.9 μm for single units. Digital impressions resulted in mean marginal discrepancies of frameworks between 19.0 and 70.2 μm in edentulous arches, 11.9 and 304.0 μm in partially edentulous arches and 66.1 μm for single units (Figure 4).

4 | DISCUSSION

The systematic review on the accuracy of conventional and digital implant impressions is mainly based on experimental studies with a low evidence level, except one randomized controlled clinical trial and one retrospective study focusing on the accuracy of conventional impressions. All studies of digital implant impressions published within the considered time frame (2012–2017) were experimental.

Most studies were conducted in vitro and are therefore compromised in their informative value for the clinician. Only four

TABLE 7 Angular deviations (degrees) measured in conventional and digital impressions

			Conventional impression				Digital impression			
Clinical situation	Implant distribution	Implant angulation	No. of (sub-) studies	Mean	CI	Heterogeneity (%)	No. of (sub-) studies	Mean	CI	Heterogeneity (%)
Edentulous	Quadrant	Parallel	2	0.4	0.2–0.6	0				
		1–20 degrees	13	0.6	0.08–1.0	95.5				
		21–45 degrees	11	0.7	0.4–1.0	29.7				
	Full arch	Unknown	43	0.6	0.4–0.7	97.0				
		Parallel	20	2.0	1.6–2.4	95.9				
		1–20 degrees	16	1.4	1.1–1.8	97.8				
		21–45 degrees	6	2.0	0.9–3.1	99.2				
	Unknown implant distribution	21–45 degrees	8	5.8	4.8–6.9	41.4				
Partially edentulous	Neighboring implants	Parallel	7	0.2	0.18–0.2	99.6				
		1–20 degrees	20	0.2	0.2–0.3	99.5	4	0.4	0.3–0.4	84.5
		21–45 degrees	4	0.3	0.2–0.4	97.6				
	Quadrant	Parallel	1	0.6	0.5–0.8	0.0	1	1.6	1.3–1.9	0
		1–20 degrees	2	0.7	0.5–0.9	0.0	8	0.4	0.2–0.6	97.7
		21–45 degrees	1	0.8	0.5–1.1	0.0	1	1.2	0.8–1.7	0
	Full arch	1–20 degrees					2	0.1	0.01–0.1	0
		21–45 degrees					2	0.3	0.1–0.5	82.7

TABLE 8 Marginal discrepancy (μm) between frameworks and abutments in test models produced from conventional and digital impressions

			Conventional impression				Digital impression			
Clinical situation	Implant distribution	Implant angulation	No. of (sub-) studies	Mean	CI	Heterogeneity (%)	No. of (sub-) studies	Mean	CI	Heterogeneity (%)
Edentulous	Quadrant	Parallel	1	141.5	100.1–182.9	0	6	24.2	13.3–35.1	45.2
		1–20 degrees	4	18.3	17.5–19.1	11.9				
		21–45 degrees					6	19	10.7–27.3	66.7
	Full arch	Unknown	14	29.8	26.2–33.4	99.9	8	70.2	52.6–87.7	87.2
		Parallel	9	121.8	91.3–152.2	97.3	12	51.0	28.0–74.0	69.0
		21–45 degrees					6	54.9	5.8–103.9	81.2
Partially edentulous	Neighboring implants	1–20 degrees					4	11.9	4.1–19.8	82.5
	Quadrant	Parallel					1	304.0	278.6–329.4	0
		1–20 degrees					8	57.9	37.8–78.0	98.5
		21–45 degrees					1	158.0	102.8–213.2	0
		Unknown	3	78.1	64.7–91.5	86.7				
Single unit		na	4	24.9	21.9–28.0	0	4	66.1	45.9–86.3	72.6

studies examined impression accuracy in vivo, thereof three studies of conventional impressions (Papaspyridakos et al., 2012; Perez-Davidi et al., 2016; Pozzi et al., 2013) and one study of digital impressions (Andriessen et al., 2014). The major obstacle for conducting in vivo studies might be the lack of a suitable protocol to assess accuracy of intraoral impressions. The intraoral position of dental implants must be recorded and reproduced in a model using any impression technique to obtain a reference model. However, the technique to obtain a reference model is already associated with an error that introduces a bias to the assessment of the impression technique to be assessed in a study (Michalakis, Stratos, Hirayama, Pissiotis & Touloumi, 2009). The heterogeneity of results for conventional implant impressions in vitro implies that even the techniques and materials selected for conventional implant impressions (impression tray design, implant coping, impression material, splinting) influence the accuracy of the reference models.

In contrast, in vitro studies include reference models and test models that are measured with the same devices (CMM, microscope, digital micrometers, standardized photographs). The accuracy is measured as the deviation between reference and test models. Authors of in vivo studies used different assessment protocols to derive results from in vivo application of digital impressions and conventional impressions. In vivo studies often failed to report numerical values for the accuracy of implant impressions. Perez-Davidi et al. (2016) studied implant-supported frameworks and assessed the fit of frameworks on periapical radiographs. The results were stated as fit or unfit and are therefore not comparable with in vitro results. However, the informative value is high as the complete workflow including impression and framework production is considered. Further studies including reliable methods for outcome reporting are necessary. Pozzi et al. (2013) compared different conventional implant impression protocols and assessed implant failure, prosthesis failure, patient satisfaction as well as marginal bone level changes, interimplant discrepancy, chair time for fitting of frameworks, sulcus bleeding, plaque score in a randomized controlled clinical trial over 3 years. Comparable results for plaster impressions and splinted impressions with vinyl polysiloxane were documented. Comparison of the results within this systematic review was not possible due to the lack of comparable data.

Andriessen et al. (2014) and Papaspyridakos et al. (2012) produced a reference model using a conventional impression techniques and compared test models with reference models to obtain numerical values for impression accuracy in vivo. Papaspyridakos et al. (2012) fabricated implant-supported prosthesis on the basis of intraoral impressions in vivo. Splinted and nonsplinted conventional impressions were compared to a reference model fabricated from a verification jig. The accuracy of the verification jig was not examined; however, the comparison of reference models and test models fabricated with two different impression techniques resulted in mean deviations between 9 and 53 μm and were therefore comparable with impression accuracy obtained by other authors in vitro (Table 6).

Andriessen et al. examined digital intraoral impressions in vivo and compared them to reference models fabricated from conventional intraoral impressions. The intraoral optical scanning of 25 patients resulted in 21 virtual models that could be used for evaluation.

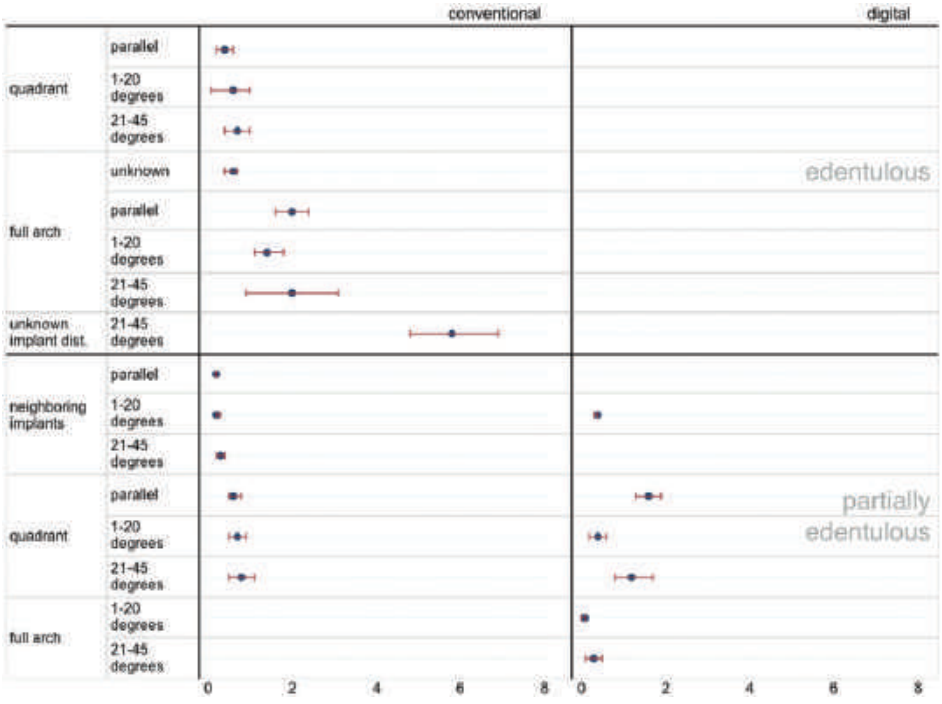

FIGURE 3 Forest plot of results for angular deviations (degrees) measured in conventional and digital impressions

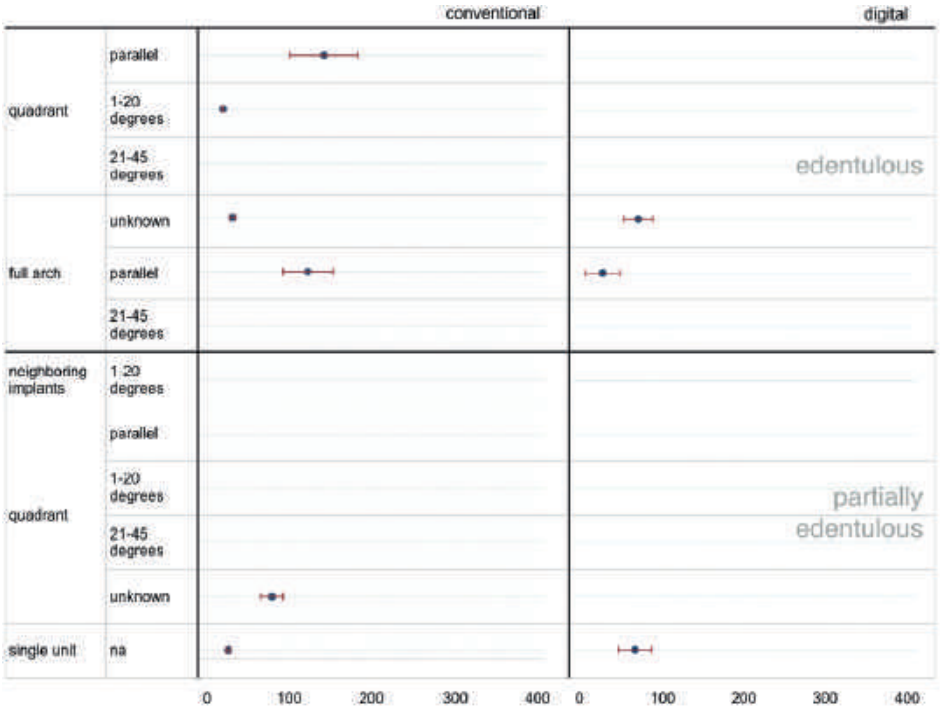

FIGURE 4 Forest plot of results for marginal discrepancy (μm) between frameworks and abutments in test models produced from conventional and digital impressions

In four patients, intraoral scanning could not produce virtual models due to wrong stitching of single images obtained with the scanner. Stitching of images is performed automatically by the scanning device; however, single images must overlap and present morphological characteristics to be stitched. The lack of intraoral characteristics for stitching in edentulous jaws implies that the use of scan body splinting could be a very helpful tool for optical scanning of implants, especially with long distances in between implants. However, none of the studies of intraoral optical impressions examined splinting of scan bodies. The same intraoral scanning device was used in other in vitro studies, but the stitching error was not found in vitro (Abdel-Azim et al., 2014; Flügge et al., 2016; Giménez et al., 2014; Lee et al.,

2015; Lin et al., 2015). Other optical scanning devices might be associated with higher inaccuracies when used intraorally; however, there is no data on other scanning devices for implant impressions in vivo. Previous studies on intraoral optical scanning of teeth suggested that limited space within the oral cavity, saliva flow and humidity cause lower precision of scanning devices compared to extraoral application (Ender, Attin, & Mehl, 2015; Flügge et al., 2016).

Regardless of the study setting, digital impressions were examined in 11 studies, digital and conventional impressions were compared in nine studies, and conventional impressions were examined in 59 studies. Studies that documented results for deviation of reference models and test models were included in the meta-analysis. The comparison of deviations resulting from conventional and digital impressions suggests that digital implant impressions are as accurate as conventional implant impressions. Conventional impressions are more accurate for partially edentulous jaws than for completely edentulous jaws for linear and angular deviations. The influence of implant distribution and implant angulation on conventional impression accuracy could not be determined with the included studies. The heterogeneity of the results implies that specifications of each included study must be regarded for analysis. The accuracy of digital implant impressions does not differ for edentulous and partially edentulous jaws. Results are less heterogeneous; however, only a small number of studies of digital implant impressions are available for analysis.

Due to a lack of standardized value for passive fit of implant frameworks, the interpretation of results may not be based on defined requirements for impression accuracy (Kan, Rungcharassaeng, Bohsali, Goodacre, & Lang, 1999; Swallow, 2004). Framework design and fabrication as well as impression accuracy are decisive for the fit of frameworks. Marginal discrepancies of 30 up to 150 μm between frameworks and abutments have been stated as acceptable to prevent biological and technical complications (Jemt, 1991; Klineberg & Murray, 1985). It was suggested that implants move up to 50 μm in bone (Kim, Oh, Misch, & Wang, 2005). Therefore, a maximum misfit of 50 μm at each implant might be considered as clinically tolerable (Andriessen et al., 2014). The suggested thresholds are already passed over prior to framework production, when reviewing the linear and angular deviations resulting from conventional and digital impressions in the included studies. Studies examining the fabrication of implant-supported frameworks on reference models and measurement of marginal gap between abutment and framework cover multiple steps in the production process of implant-supported prosthesis. Marginal discrepancies of implant-supported frameworks were below the suggested thresholds for some indications (conventional impressions: mean 21.9–141.5 μm; digital impressions: mean 11.9–304.0 μm). However, these studies were performed in vitro and a higher level of inaccuracy should be expected for in vivo impression and framework production.

The data extracted for the systematic review and meta-analysis are limited as it is mostly derived from experimental studies with low evidence level. The in vitro setup of the majority of studies reduces the informative value of the data for the clinician. The decision to use conventional or digital implant impressions should be based on available data for accuracy of each impression technique. Therefore, evidence-based data and clinical trials are necessary to support clinical guidelines. The current literature does not provide high-quality evidence to support the selection of conventional and digital impression techniques of implants.

5 | CONCLUSIONS

Limited high-quality evidence is available for the study of conventional and digital implant impressions. Interpretation of results is restricted by study settings and study designs.

Some preliminary conclusions, however, can be drawn.

There is some evidence that regardless of various impression techniques, conventional implant impressions of angulated implants are significantly less accurate compared to parallel implants. Digital impressions of angulated implants, however, do not show a significantly different impression accuracy compared to parallel implants.

There is evidence showing that the scan protocol has an impact on the accuracy and precision of digital impressions. Based on the present data, this effect may not be assigned to the experience of the operator.

Clinical guidelines cannot be derived based on the presented data. Further studies focusing on the in vivo use of conventional and digital implant impressions with study protocols to reliably assess impression accuracy are needed. The performance of clinical studies and RCTs is suggested to raise evidence level for impression procedures.

CONFLICTS OF INTEREST

The author has no conflicts of interest to declare in relation to this article.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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REVIEW ARTICLE

WILEY CLINICAL ORAL IMPLANTS RESEARCH

Accuracy of linear measurements on CBCT images related to presurgical implant treatment planning: A systematic review

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Abstract

Objective: The aim of this systematic review was to identify, review, analyze, and summarize available evidence on the accuracy of linear measurements when using maxillofacial cone beam computed tomography (CBCT) specifically in the field of implant dentistry.

Material and methods: The search was undertaken in April 2017 in the National Library of Medicine database (Medline) through its online site (PubMed), followed by searches in the Cochrane, EMBASE, ScienceDirect, and ProQuest Dissertation and Thesis databases. The main inclusion criterion for studies was that linear CBCT measurements were performed for quantitative assessment (e.g., height, width) of the alveolar bone at edentulous sites or measuring distances from anatomical structures related to implant dentistry. The studies should compare these values to clinical data (humans) or ex vivo and/or experimental (animal) findings from a "gold standard."

Results: The initial search yielded 2,516 titles. In total, 22 studies were included in the final analysis. Of those, two were clinical and 20 ex vivo investigations. The major findings of the review indicate that CBCT provides cross-sectional images that demonstrate high accuracy and reliability for bony linear measurements on cross-sectional images related to implant treatment. A wide range of error has been reported when performing linear measurements on CBCT images, with both over- and underestimation of dimensions in comparison with a gold standard. A voxel size of 0.3 to 0.4 mm is adequate to provide CBCT images of acceptable diagnostic quality for implant treatment planning.

Conclusions: CBCT can be considered as an appropriate diagnostic tool for 3D preoperative planning. Nevertheless, a 2 mm safety margin to adjacent anatomic structures should be considered when using CBCT. In clinical practice, the measurement accuracy and reliability of linear measurements on CBCT images are most likely reduced through factors such as patient motion, metallic artefacts, device-specific exposure parameters, the software used, and manual vs. automated procedures.

KEYWORDS

CT imaging, diagnosis/clinical assessment, radiology/imaging

1 | INTRODUCTION

The introduction of cone beam computed tomography (CBCT) in dento-maxillofacial radiology (DMFR) almost two decades ago (Ganguly, Ramesh & Pagni, 2016) has resulted in a paradigm shift from planar, two-dimensional (2D) to volumetric, three-dimensional (3D) radiographic visualization (Visconti, Verner, Assis & Devito, 2013). CBCT imaging is currently considered a well-established adjunctive diagnostic, virtual simulation, and treatment planning tool with various clinical applications in disciplines such as implant dentistry (Bornstein, Al-Nawas, Kuchler & Tahmaseb, 2014; Bornstein, Horner & Jacobs, 2017; Guerrero et al., 2006; Harris et al., 2002, 2012; Kan et al., 2011), orthodontics (Kapila, Conley & Harrell, 2011; Mah, Huang & Choo, 2010; Mamatha et al., 2015; van Vlijmen et al., 2012), endodontics (Janner, Jeger, Lussi & Bornstein, 2011; Lofthag-Hansen, Huumonen, Grondahl & Grondahl, 2007; Patel, 2009), periodontology (Misch, Yi & Sarment, 2006; Vandenberghe, Jacobs & Yang, 2008; Walter, Kaner, Berndt, Weiger & Zitzmann, 2009), oral and maxillofacial surgery (Carter, Stone, Clark & Mercer, 2016; Kaeppler & Mast, 2012; Pohlenz et al., 2007; Popat, Richmond & Drage, 2010; Ren et al., 2016), and forensic dentistry (Ma et al., 2009; Yang, Jacobs & Willems, 2006).

CBCT provides numerous advantages for the depiction of bony structures compared to other dental (Cavalcanti, Haller & Vannier, 1999; Navarro Rde et al., 2013; Oliveira-Santos et al., 2011; Scarfe, Farman & Sukovic, 2006) and medical (Brisco, Fuller, Lee & Andrew, 2014; Kamburoglu, Murat, Yuksel, Cebeci & Paksoy, 2010; Patel, 2009; Suomalainen, Vehmas, Kortesniemi, Robinson & Peltola, 2008) imaging modalities. CBCT is a widely available, technically simple, low-cost, rapid acquisition radiographic procedure providing images with high spatial image resolution at relatively low radiation dose. In dental implant therapy, the use of CBCT facilitates diagnosis and improves treatment planning (Behneke, Burwinkel & Behneke, 2012; Bornstein et al., 2015; Chen, Lundgren, Hallstrom & Cherel, 2008; Worthington, Rubenstein & Hatcher, 2010).

CBCT units operate by directing a collimated cone-shaped X-ray beam through the head onto a flat panel or image intensifier detector and acquiring a series of planar basis images as a gantry connecting the two rotates around a fixed focal plane in a partial or full arc. Multiple planar basis images are reconstructed to generate volumetric data sets, which are processed by software to provide various inter-relational projections of the maxillofacial complex (De Vos, Casselman & Swennen, 2009; Scarfe, Levin, Gane & Farman, 2009). Sequential, contiguous, thin-slice cross-sectional images in multiplanar reconstructions (MPR) are usually created to depict the anatomic structures in flattened curved or linear transaxial planes, enabling linear measurements (Cavalcanti et al., 1999; Wikner et al., 2016). For most clinical applications, CBCT images are considered to enable highly accurate and reliable linear measurements (Raes, Renckens, Aps, Cosyn & De Bruyn, 2013; Scarfe & Farman, 2008; Scarfe et al., 2006; Tyndall et al., 2012; Yim, Ryu, Lee & Kwon, 2011). Nevertheless, the accuracy of reformatted CBCT images is affected by many factors. These include the characteristics of the machine (e.g., nominal resolution, image quality), radiation exposure (kV, mA, and the number of basis images), the software used for image reconstruction and dimensional measurement, patient motion artifacts, and the limitations of the clinician in interpretation (Halperin-Sternfeld, Machtei & Horwitz, 2014; Nikneshan et al., 2014).

The anatomic radiographic fidelity of bone structures and accuracy of linear measurements are crucial for basic preoperative implant planning, and even more so when applied in image-guided implant surgery (Nickenig & Eitner, 2007; Schneider, Marquardt, Zwahlen & Jung, 2009; Vieira, Sotto-Maior, Barros, Reis & Francischone, 2013). All guided surgery systems incorporate some degree of imprecision resulting in horizontal and particularly vertical deviations of the actual position of the implant compared to the presurgical virtual position (Laederach, Mukaddam, Payer, Filippi & Kuhl, 2016; Schneider et al., 2009; Vercruyssen et al., 2014, 2015, 2016).

As CBCT imaging is widely used to ascertain linear dimensions in various clinical dental applications, measurement accuracy must be defined. However, most in vivo clinical studies rarely quantify measurement accuracy, as this would often require an intervention to control the radiographic measurements (Feijo, Lucena, Kurita & Pereira, 2012). Thus, the objective of this systematic review was to identify, review, analyze, and summarize available evidence on the accuracy of linear measurements when using maxillofacial CBCT specifically in the field of implant dentistry.

2 | MATERIALS AND METHODS

2.1 | Search strategies

This systematic literature review was performed using a PICO (Patient or Population, Intervention, Control or Comparison, Outcome and Study design) framework (Table 1). The population was defined as patients or models (in vitro or experimental) specific for, but initially not limited to, implant placement. The intervention and comparison were described as the use of CBCT for the purpose of determining outcomes associated with the accuracy and reliability (repeatability/reproducibility) of linear measurements based on the data and the respective control values in patients or in vitro models/animals. The accuracy as measured in millimeters, kappa values, or correlation factors comparing test (CBCT measurements) with the control (patients, animals, or in vitro) were set as the outcome.

An electronic search without any time or language restrictions was undertaken in April 2017 initially in the National Library of Medicine database (Medline) through its online site (PubMed), followed by searches in the Cochrane, EMBASE, ScienceDirect, and ProQuest Dissertation and Thesis databases. Text terms as well as MeSH keywords specific to each part of the question were used for the searches (Table 1).

Gray literature was also searched and identified. Gray literature includes conference reports, technical reports, and working papers from government agencies, and university and scientific research groups that are not commercially published, and thus, they are usually not identified with conventional search strategies.

TABLE 1 Systematic search strategy for the focused question

Focused question	What is the accuracy of linear measurements using CBCT in daily clinical practice with special emphasis on implant dentistry?	
Search Strategy	Population	• Dental implants • Dentistry • Dental procedures • Dental care • Dental arch • in vivo • ex vivo • edentulous jaw • Mandible • Mandibular • Mandibular alveolar process • Maxillary • Maxilla
	Intervention or exposure	• cone beam computed tomography • tomography, X-ray computed tomography • CT scan • Volumetric CT • Volumetric computed tomography
	Comparison	• Linear measurement* • Measurement*
	Outcome	• Accuracy • Precision • Reproducibility of results • Dimensional measurement accuracy
	Search combinations	**PubMed** (((((linear measurement*) OR measurement*)) AND ((((((((((((dental implants) OR dentistry) OR dental care) OR dental procedures) OR dental arch) OR in vivo[Title/Abstract]) OR ex vivo[Title/Abstract]) OR cadaver) OR edentulous) OR maxillary) OR mandible) OR mandibular) OR mandibular alveolar process)) AND (((((((cone beam computed tomography) OR tomography, x ray computed) OR Computed tomography scan) OR CT Scan) OR volumetric ct) OR volumetric computed tomography) OR linear measurement[Text Word])) AND ((((accuracy) OR precision) OR reproducibility of results) OR dimensional measurement accuracy) **EMBASE** "cone beam computed tomography"/exp OR "cone beam computed tomography" OR "X-ray tomography"/exp OR "X-ray tomography" OR volumetric AND computed AND tomography OR volumetric AND ct AND linear AND measurement* OR measurement* AND "accuracy"/exp OR "accuracy" OR "reproducibility"/exp OR "reproducibility" OR "dimensional measurement accuracy"/exp OR "dimensional measurement accuracy" AND "tooth implant"/exp OR "tooth implant" OR "tooth implantation" OR "dentistry"/exp OR "dentistry" OR "dental procedure"/exp OR "dental procedure" OR "tooth arch"/exp OR "tooth arch" OR "in vitro study" OR "ex vivo study" OR "edentulousness"/exp OR "edentulousness" OR "mandible"/exp OR "mandible" OR mandibular OR "alveolar bone"/exp OR "alveolar bone" OR "maxilla"/exp OR "maxilla" OR dental AND implant* **Cochrane** "dental implants or dentistry or dental care or dental arch or in vivo or ex vivo or edentulous or mandib* or maxill* in Title, Abstract, Keywords and linear measurement* or measurement* in Title, Abstract, Keywords and cone beam computed tomograph* or volumetric computed tomograph* or x-ray computed tomograph* in Title, Abstract, Keywords and precision or accuracy or reproducibility or dimensional meausrement accuracy in Title, Abstract, Keywords in Trials" **Proquest Dissertation & Thesis** (ab(dental implants) OR ab(dentistry) OR ab(dental care) OR ab(dental procedures) OR ab(dental arch) OR ab(in vivo) OR ab(ex vivo) OR ab(edentulous) OR ab(mandib?) OR ab(Maxilla?)) AND (ab(cone beam computed tomography) OR ab(cone beam ct) OR ab(tomography) OR ab(ct scan) OR ab(volumetric ct) OR ab(volumetric computed tomography) OR ab(x-ray computed tomography)) AND (ab(linear measurement?) OR ab(Measurement?)) AND (ab(accuracy) OR ab(precision) OR ab(reproducibility) OR ab(measurement accuracy))
Database search	Electronic	MEDLINE (Pubmed), Cochrane Library, Embase, ProQuest Dissertation & Thesis

2.2 | Inclusion criteria

Eligibility criteria were as follows:

- Studies performing linear CBCT measurements for quantitative assessment (e.g., height, width) of the alveolar bone at edentulous sites or measuring distances from anatomical structures related to implant dentistry. The studies should compare these values to clinical data (humans) or ex vivo and/or experimental (animal) findings from a "gold standard," that is, physical measurements using digital calipers and histomorphometry.
- Clinical studies with a sample size greater than 5.
- Experimental (animal) studies.
- In vitro studies using human cadavers or dry skulls measuring linear distances in alveolar bone or between fiducial placed markers.

The exclusion criteria were defined as:

- Studies with no control method for assessing the accuracy of linear measurements performed using CBCT.
- Studies comparing CBCT with other radiographic tests without an external control as gold standard.
- Case reports and case series with fewer than five patients.
- Linear measurements in disciplines unrelated to dental implant treatment (e.g., orthodontics, maxillofacial surgery, periodontology).
- Linear measurements on teeth or around teeth or implants.
- Review articles.

2.3 | Study selection process

Selection of studies was carried out in accordance with PRISMA guidelines. The initial search was formulated for maximal inclusion and high turnout. Two independent observers (G.F. and W.C.S.) analyzed the titles and abstracts of all identified reports. For the studies that appeared to meet the inclusion criteria or for which there were insufficient data in the titles and the respective abstracts to make a clear decision, the full texts of the articles were retrieved for further analysis. The final inclusion of the relevant full-text articles for evaluation was decided by consensus by the three observers (G.F., W.C.S., and M.B.).

2.4 | Data extraction process

Two reviewers (G.F. and W.C.S.) extracted relevant data according to the PICO framework using standardized data extraction tables. Extracted data included the following: author, title, year of publication, study model, nature of the "gold standard" measure, nature of other comparator measures, study design, CBCT parameters used, inter- and intra-observer reliability/agreement, and other outcome measures related to accuracy.

2.5 | Quality assessment

The quality of clinical studies was assessed using the National Institutes of Health "Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies" (https://www.nhlbi.nih.gov/health-pro/guidelines/in-develop/cardiovascular-risk-reduction/tools/cohort).

3 | RESULTS

3.1 | Study selection

The screening process is illustrated as a flowchart in Figure 1. The initial search yielded 2,516 titles. Of these, 458 were duplicates, resulting in 2,058 titles for further screening. The inclusion and exclusion criteria were applied and a total of 529 abstracts were considered for full-text selection, of which 40 were deemed as eligible. After full-text reading, 18 articles were further excluded for the following reasons (Table 2): (i) the measurements were taken on dentate jaws (Abboud, Guirado, Orentlicher & Wahl, 2013; Egbert, Cagna, Ahuja & Wicks, 2015; Halperin-Sternfeld et al., 2014; Maloney, Bastidas, Freeman, Olson & Kraut, 2011; Sun et al., 2011), (ii) both dentate and edentulous sites were studied, but separate data extraction for the edentulous sites was not possible (Fatemitabar & Nikgoo, 2010; Ganguly et al., 2011; Loubele, Guerrero, Jacobs, Suetens & van Steenberghe, 2007; Pertl, Gashi-Cenkoglu, Reichmann, Jakse & Pertl, 2013; Shokri & Khajeh, 2015; Suomalainen et al., 2008; Tarazona-Alvarez et al., 2014; Tarleton, 2014), (iii) no "gold standard" was used for the comparison as stated in the inclusion criteria (Li, Zhang, Liu, Fu & Zhang, 2016; Ritter et al., 2012; Vandenberghe et al., 2008; Yim et al., 2011), (iv) the measurements were taken using non-implant-related anatomical landmarks (Kamburoglu et al., 2011; Lascala, Panella & Marques, 2004; Tarazona-Alvarez et al., 2014).

In total, 22 studies were included in the final analysis. Of those, two were clinical (Eachempati et al., 2016; Luk, Pow, Li & Chow, 2011) and 20 ex vivo investigations. The ex vivo studies included 14 studies on dry jaws/skulls (Al-Ekrish, 2012; Al-Ekrish & Ekram, 2011; Al-Ekrish, Ekram, Al Faleh, Alkhader & Al-Sadhan, 2013; Alkan, Aral, Aral, Acer & Şişman, 2016; Freire-Maia et al., 2017; Kamburoglu, Kilic, Ozen & Yuksel, 2009; Luangchana, Pornprasertsuk-Damrongsri, Kiattavorncharoen & Jirajariyavej, 2015; Neves, Vasconcelos, Campos, Haiter-Neto & Freitas, 2014; Pena de Andrade, Valerio, de Oliveira Monteiro, de Carvalho Machado & Manzi, 2016; Sheikhi, Dakhil-Alian & Bahreinian, 2015; Torres, Campos, Segundo, Navarro & Crusoe-Rebello, 2012; Vasconcelos, Neves, Moraes & Freitas, 2015; Veyre-Goulet, Fortin & Thierry, 2008; Waltrick et al., 2013) and six cadaver studies (Ganguly et al., 2016; Gerlach et al., 2013, 2014; Kobayashi, Shimoda, Nakagawa & Yamamoto, 2004; Loubele et al., 2008; Santana et al., 2012).

As the methodology of the included studies as well as the extracted data was inhomogeneous, a meta-analysis could not be carried out and thus only a descriptive analysis performed.

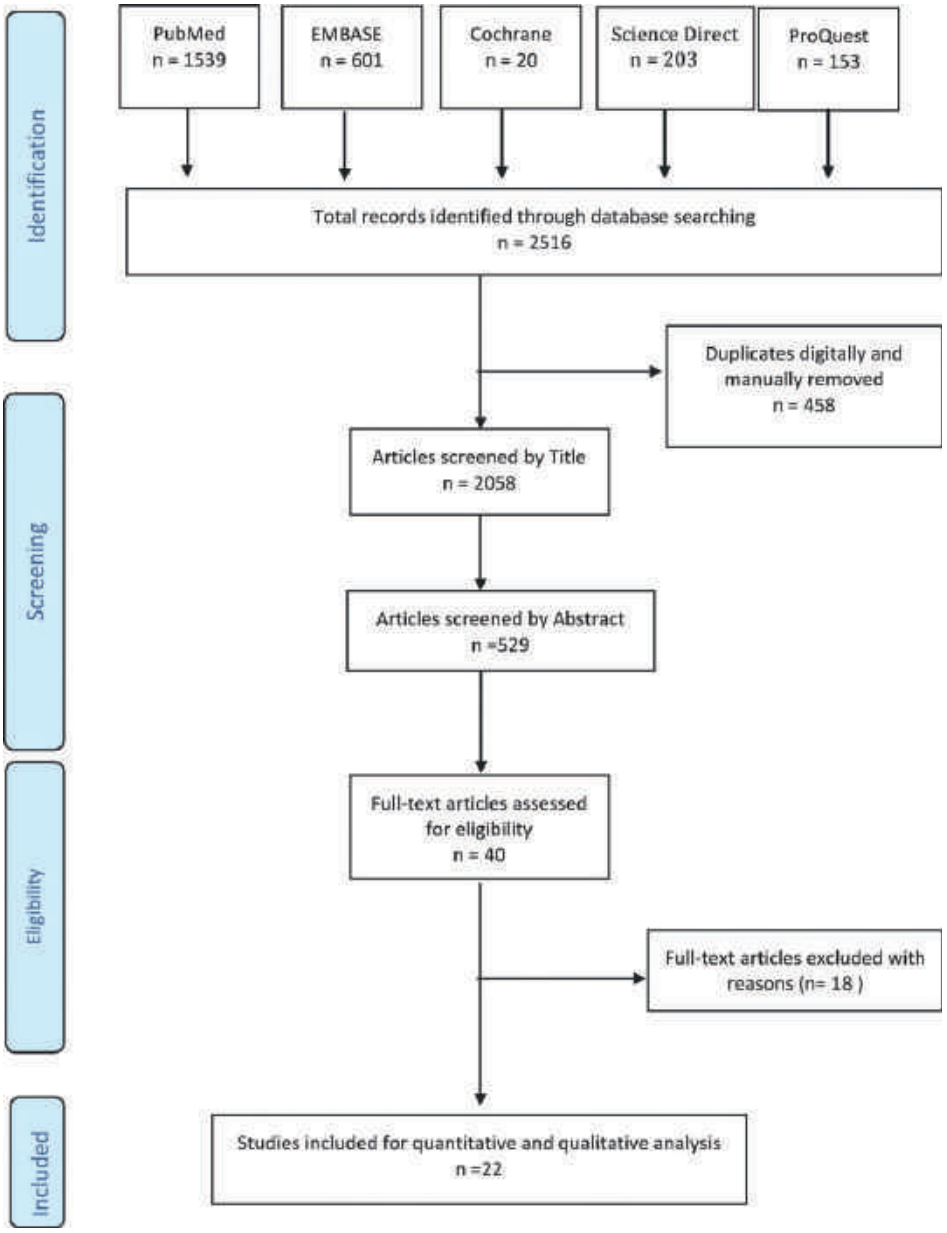

FIGURE 1 Flowchart showing the screening process

3.2 | Study characteristics

The key information of the selected studies such as study design, aim of the study, sample size, reference standards (comparator), methodology of assessment, representative outcomes, and major conclusions is presented in Table 3.

The two included clinical studies assessed edentulous sites of patients prior to dental implant treatment (Eachempati et al., 2016; Luk et al., 2011). The majority of the selected studies used dry human mandibles as the sample (Al-Ekrish, 2012; Alkan et al., 2016; Freire-Maia et al., 2017; Kamburoglu et al., 2009; Kobayashi et al., 2004; Neves et al., 2014; Pena de Andrade et al., 2016; Sheikhi et al., 2015; Torres et al., 2012; Vasconcelos et al., 2015; Waltrick et al., 2013). Two studies used both the maxilla and mandible of dry skulls (Abboud et al., 2013; Al-Ekrish & Ekram, 2011; Luangchana et al., 2015), and one study used only three dry maxillae (Veyre-Goulet et al., 2008). With regard to cadaver studies, only one study scanned both jaws for the measurements (Ganguly et al., 2016), four studies used mandibles (Gerlach et al., 2013, 2014; Kobayashi et al., 2004; Santana et al., 2012), and one study used a cadaver maxilla only (Loubele et al., 2008).

Seven of the ex vivo studies placed the dry jaws/skulls in a container with water to simulate the effects of soft tissue for CBCT imaging (Alkan et al., 2016; Freire-Maia et al., 2017; Neves et al., 2014; Sheikhi et al., 2015; Torres et al., 2012; Vasconcelos et al., 2015; Veyre-Goulet et al., 2008), while Luangchana et al. covered the jaws entirely in acrylic resin for that purpose (Luangchana et al., 2015).

TABLE 2 Reason for exclusion of full-text articles

Publication (author, year)	Reason for exclusion
Li et al. (2016)	Measurements performed on models printed using a CBCT data
Shokri & Khajeh (2015)	Does not specify or identify, which of the measured areas were edentulous
Egbert et al. (2015)	Uses a single dentate cadaveric mandible
Tarleton (2014) (thesis)	Does not discriminate between samples (dentate and partially dentate hemisected dry mandibles)
Tarazona-Alvarez et al. (2014)	Does not discriminate between dentate and edentulous; uses surgical anatomical landmarks
Halperin-Sternfeld et al. (2014)	Uses dentate fresh pig mandibles
Pertl et al. (2013)	Does not specify or identify which of the measured areas were edentulous
Abboud et al. (2013)	Uses a dentate mandible only; does not specify if edentulous sites are measured
Ritter et al. (2012)	No gold standard used for evaluating accuracy
Yim et al. (2011)	No gold standard used (GP markers of known length and calibration as reference); sites for linear measurements not specified (compares magnification of OPG and CBCT)
Sun et al. (2011)	Uses a dentate porcine maxillae
Maloney et al. (2011)	Uses dentate dry human mandibles
Kamburoglu et al. (2011)	Measures distances between anatomical landmarks. Does not specify implant dentistry-related distances (e.g., mental foramen–mental foramen)
Ganguly et al. (2011)	Uses dentulous and edentulous cadaver heads; does not specify if edentulous areas are measured
Fatemitabar & Nikgoo (2010)	Measurements performed on dentate and edentulous segments; does not specify if edentulous areas are measured
Suomalainen et al. (2008)	Only one partially edentulous human dry mandible used; does not specify which edentulous areas are measured
Loubele et al. (2007)	Uses partially and fully edentulous dry mandibles; does not specify which edentulous areas are measured
Lascala et al. (2004)	Does not specify implant dentistry-related distances (e.g., mental foramen–mental foramen)

A wide spectrum of CBCT units and acquisition parameters were used to acquire volumes (Table 4). Some authors investigated the effect of various exposure, acquisition, or display factors while others compared accuracy of CBCT to MSCT.

3.3 | Aim of the included studies

For many studies, the stated objectives were often at variance from the methodology and results presented. Of the authors that aimed solely to evaluate the accuracy of CBCT, some used one single machine and fixed acquisition parameters (Gerlach et al., 2013, 2014; Kamburoglu et al., 2009; Kobayashi et al., 2004; Veyre-Goulet et al., 2008), while others evaluated the effect of different scan parameters (Al-Ekrish, 2012; Ganguly et al., 2016; Neves et al., 2014; Torres et al., 2012; Waltrick et al., 2013), different reconstruction software (Vasconcelos et al., 2015), or different monitors (Al-Ekrish et al., 2013) on linear accuracy. Furthermore, in several studies the authors' primary objective was to compare the accuracy of CBCT with other radiographic or clinical diagnostic tests (Al-Ekrish & Ekram, 2011; Alkan et al., 2016; Eachempati et al., 2016; Freire-Maia et al., 2017; Loubele et al., 2008; Luangchana et al., 2015; Luk et al., 2011; Pena de Andrade et al., 2016; Santana et al., 2012; Sheikhi et al., 2015).

3.4 | Reference standards (comparators for linear CBCT measurements)

For the ex vivo studies, 17 of the 20 utilized histologic sectioning of the jaws followed by physical measurements with a digital caliper as a reference standard. Santana et al. (2012) used a combination of an analogue and a digital caliper on cadaver dissections to establish to extension of the anterior loop of the mental branch relative to the mental foramen. The accuracy of these measuring instruments was specified in only seven studies: Three studies described a 0.01 mm accuracy of the caliper used (Loubele et al., 2008; Sheikhi et al., 2015; Waltrick et al., 2013) and four described an accuracy of 0.02 mm (Al-Ekrish, 2012; Al-Ekrish & Ekram, 2011; Al-Ekrish et al., 2013; Luangchana et al., 2015). The two studies by Gerlach et al. (2013, 2014) on fresh frozen cadavers used histomorphometry as the gold standard.

TABLE 3 General characteristics of the included studies with focus on comparison of linear measurements using CBCT vs gold standard (n = 22) [In PDF format, this table is best viewed in two-page mode]

Author (year)	Sample	Aim of study	Gold standard	Sample size
Freire-Maia et al. (2017)	Eight dry mandibles (ex vivo)	Compare the accuracy of linear measurements of 64-detector MSCT and CBCT	Sectioning+ digital caliper (DC)	Six sites on each sample (molar, retromolar, ramus); 48 measurements in total
Pena de Andrade et al. (2016)	Six dry mandibles (ex vivo)	Compare the accuracy of linear measurements of 64-detector MSCT and CBCT	Sectioning+ digital caliper	Eight sites on each sample (incisor, canine, premolar, molar); 48 measurements
Ganguly et al. (2016)	Four cadaver heads (maxilla and mandible) (ex vivo)	Compare the effect of FOV and voxel size on the accuracy of linear measurements of CBCT	Sectioning+ digital caliper	Two edentulous sites on each sample in both dental arches (premolar, molar); 28 measurements
Eachempati et al. (2016)	Edentulous sites of 12 patients (in vivo)	Compare ridge mapping and panoramic radiographs with CBCT for implant site assessment	Ridge mapping (RM)	37 edentulous sites (anterior maxilla, posterior maxilla, posterior mandible); 37 measurements
Alkan et al. (2016)	Five dry mandibles/ five dry maxillae (ex vivo)	Compare the linear measurement accuracy of CBCT, panoramic radiography, periapical radiography, and digital photography in evaluating alveolar bone height and extraction socket dimensions	Sectioning+ digital caliper with loupe magnification (3.5×) (DC + L)	Anterior, premolar, and molar sites; buccal–lingual and mesiodistal alveolar extraction socket dimensions; 255 measurements
Vasconcelos et al. (2015)	Eight dry edentulous mandibles (ex vivo)	Comparing the accuracy of linear alveolar bone height measurements of three different commercial dental software packages for CBCT	Sectioning+ digital caliper	Five edentulous sites (incisor canine, premolar, first molar, second molar); 80 measurements
Sheiki et al. (2015)	Three dry edentulous mandibles (ex vivo)	Compare the linear measurement accuracy of tangential projection (TP) and CBCT in evaluating alveolar bone height and width	Sectioning+ digital caliper	Three edentulous sites (midline lateral incisor, canine); 30 measurements
Luangchana et al. (2015)	Six partially or fully edentulous skulls (ex vivo)	Compare the linear measurement accuracy of CBCT and digital panoramic radiographs in evaluating alveolar bone height	Sectioning+ digital caliper	Six edentulous sites (maxillary and mandibular incisor, mandibular canine, maxillary and mandibular premolar and molar); 48 measurements

(Continues)

TABLE 3 (additional columns)

Accuracy Index	Representative outcomes	Key inference
Mean differences of the distance between the mandibular cortical bone and the mandibular canal (MC) between DC/CBCT at the different sites measured	Ramus: −0.16 to 0.11 mm Retromolar: −0.01 to 0.21 mm Molar: −0.16 to 0.19 mm	No significant difference* CBCT and MSCT are highly accurate to measure the location of the mandibular canal in relation to the adjacent cortical bone of the mandible
Mean measurements for height and width of alveolar ridge	Difference caliper/CBCT −0.08 to −0.23 mm (height) −0.18 to −0.22 mm (width)	No significant difference* CBCT and MSCT are accurate to measure the height and width of alveolar bone
Mean measurements and absolute differences with three scan protocols: • large FOV/0.3 mm voxel • large FOV/0.2 mm voxel • small FOV/0.16 mm voxel for height and width of alveolar ridge	Mean absolute difference: 1.10 ± 1.3 mm (0.3 mm voxel) 1.2 ± 1.5 mm (0.2 mm voxel) 1.1 ± 1.4 mm (0.16 mm voxel)	No statistical difference* between the physical measurements and measurements from any of the CBCT protocols applied using different voxel sizes
Absolute difference among the three protocols		No statistical difference among protocols* CBCT measurements are accurate to measure the height and width of alveolar bone. Smaller voxel sizes do not result in greater accuracy of linear measurements
Correlation of width of alveolar crest between RM and CBCT (Pearson's *r*)	0.53	Moderate correlation between RM and CBCT for measurements of width of alveolar crest
Mean/median difference of width of alveolar crest between RM and CBCT	1.2/0.34 mm	CBCT (alveolar crest) measurements overestimate RM
Correlation of alveolar crest measurements between RM and CBCT (Pearson's *r*)	94.6% of measurement within 95% CI	
Correlation (Spearman's)	Extraction socket: Buccolingual: 0.782 ($p < 0.05$) Mesiodistal: 0.983 ($p < 0.01$)	High correlation between CBCT and DC + L for extraction socket dimensions
Mean difference between DC + L/CBCT	Buccolingual (mm) 6.77 ± 1.15/6.63 ± 1.35 ($p < 0.05$) Mesiodistal (mm) 4.72 ± 1.23/4.73 ± 1.12 ($p < 0.001$)	The difference of the buccolingual measurement was significant (CBCT < DC + L)
Mean difference of the distance between the cortical bone and the MC for three software packages S1, OnDemand S2, KDIS 3D S3, XoranCat	S1: −0.11 mm S2: −0.14 mm S3: 0.25 mm	No significant differences between the measurements with the three software packages and the gold standard or among them All tested dental software packages provide accurate linear alveolar bone height measurements
Agreement CBCT/DC (ICC)	Bone height: CBCT 0.89 Bone width: CBCT 0.91	There was a high agreement among physical measurements, CBCT, and TP
Mean error	Height: 0.06 ± 0.05 mm Width: 0.04 ± 0.03 mm	There was a slight underestimation of dimensions in the CBCT results
Correlation CBCT/DC (Paired sample correlation) Mean difference of measurements CBCT/DC for five CBCT scan protocols (voxel size 0.125 mm/0.16 mm/0.25 mm/0.2 mm/0.3 mm) Absolute error (mm) for all five protocols Absolute percentage error for all five protocols	>0.997 Maxilla: −1.06 ± 1.0 to −1.23 ± 0.81 mm Mandible: −0.24 ± 0.46 to −0.55 ± 0.61 mm Maxilla 1.14 ± 0.80 to 1.27 ± 0.89/ Mandible 0.39 ± 0.27 to 0.66 ± 0.47 Maxilla: 10.74% to 11.81% Mandible: 2.77% to 4.84%	The correlation was significant for all voxel sizes CBCT and PR measurements underestimate the actual distance. No significant difference between any protocol and the physical measurements. Machine or voxel size does not affect measurement accuracy

(Continues)

TABLE 3 (Continued) [In PDF format, this table is best viewed in two-page mode]

Author (year)	Sample	Aim of study	Gold standard	Sample size
Neves et al. (2014)	16 dry edentulous hemimandibles (ex vivo)	Evaluate the effect of CBCT scan mode for preoperative dental implant measurements	Sectioning+ digital caliper	Five edentulous sites (incisor, canine, premolar, first molar, second molar); 64 measurements
Gerlach et al. (2014)[a]	One dentate and one edentulous fresh frozen cadaver head (ex vivo)	Evaluate the linear measurement accuracy of CBCT in evaluating the size and position of the MC	Histological sections (HS)	Eight sites (second molar, second premolar); 46 measurements (24 for the edentate cadaver)
Waltrick et al. (2014)	12 dry hemimandibles with edentulous posterior ridges (ex vivo)	Verify the accuracy of linear measurements of alveolar bone and width and analyze the visibility of the MC on CBCT images obtained using different voxel sizes	Sectioning+ digital caliper	Three edentulous sites (second premolar, first molar, and second molar); 108 measurements
Gerlach et al. (2013)[a]	One dentate and one edentulous fresh frozen cadaver head (ex vivo)	Compare the linear measurement accuracy of CBCT in evaluating alveolar bone dimensions and cortical layer thickness	Histological sections	Four sites in the maxilla (second molar, second premolar, canine, lateral incisor), three sites in the mandible (second molar, second premolar, lateral incisor); 46 measurements (24 for the edentate)
Al-Ekrish et al. (2013)	Five edentulated dry human skulls (four maxillae, five mandibles) (ex vivo)	Determine the effect of the use of three LCD monitors on the linear measurement accuracy of CBCT in evaluating alveolar bone dimensions	Sectioning+ digital caliper	Three sites (incisor, canine–premolar, molar); 48 measurements
Torres et al. (2012)	Eight dry fully edentulous human mandibles (ex vivo)	Compare the effect of different voxel size on the linear measurement accuracy of CBCT in evaluating alveolar bone dimensions	Sectioning+ digital caliper	Three sites (incisor, premolar, molar); 96 measurements
Santana et al. (2012)	12 cadavers (six dentate/six edentulous) (ex vivo)	Compare the degree of visibility and linear measurement accuracy of CBCT and STL model in identifying and measuring the anterior loop length of the mental nerve	Anatomic dissection+ Digital and analog caliper	23 mental nerve plexus; 115 measurements

(Continues)

TABLE 3 (additional columns - continued)

Accuracy Index	Representative outcomes	Key inference
Correlation CBCT/DC (Wilcoxon signed-rank test)	Incisor P1/P2: 0.23/0.11 Canine P1/P2: 0.95/0.45 Premolar p1/P2: 0.48/0.64 1st molar P1/P2: 0.06/0.23 1st molar MC height, P1/P2: 0.31/0.51	No statistically significant difference between CBCT and DC for both scan modes except for 2nd molar in full scan (360°) mode
	2nd molar P1/P2: 0.02*/0.36 2nd molar MC height, P1/P2: 0.75/0.15	Half-scan mode (180°) provides same accuracy at 50% dose reduction
Mean difference for measurements between alveolar crest and lower border of mandible or MC for two CBCT scan protocols (P1, 360°; P2, 180°)	Incisor P1/P2, −0.2/−0.2 mm Canine P1/P2, 0.1/0.3 mm PM P1/P2, −0.1/−0.0 mm First molar, P1/P2, −0.2/0.1 mm Second molar, P1/P2, −0.4/−0.2 mm	
Mean differences CBCT/HS for the six different sites	Range: −0.14 ± 0.16 to 0.35 ± 0.25 mm	No statistically significant difference except the distance center of MC to the buccal margin of the mandible ($p = 0.006$)
Mean difference between maximum and minimum diameter of MC	−0.52 ± 0.26 mm to 0.02 ± 0.33 mm	To be clinically safe, an extra 0.74 mm should be added when determining the diameter of the MC
Correlation (Pearson's *r*)	>0.998	Excellent agreement between CBCT and direct measurements
Absolute mean error between three CBCT scan protocols (voxel size 0.2 mm/0.3 mm/0.4 mm)	Overall: 0.23 ± 0.20 mm Overall height: 0.18 ± 0.14 mm Overall width: 0.33 ± 0.25 mm	All measurements are accurate (ME < 1 mm) Underestimation occurs in 60.2% of measurements
Visibility rated on scale of 3 (visible) to 0 (not visible) for three CBCT scan protocols	0.2 mm: 86.1% scored 3 0.3 mm: 70.8% scored 3 0.4 mm: 55.6% scored 3	Increasing voxel resolution increases visibility (but NSD)
		A voxel size of 0.3 mm is a good compromise between image quality and radiation optimization
Absolute and relative (%) mean difference for alveolar height and width and mandibular border cortical thickness	Height edentulous 0.16 ± 0.15 mm Width edentulous 0.31 ± 0.22 mm	The edentate measurements were statistically significant for all distances
	Cortical thickness range edentulous, 0.49 ± 0.19 mm to 0.63 ± 0.1 mm	All measurements overestimate actual dimensions up to 4.4% but are <1 mm
		All measurements overestimate cortical thickness from 32.1% to 82.6%
Absolute mean error of measurement of alveolar height and width (combined) for three CBCT viewing monitors (M1, workstation; M2, laptop 1; M3, laptop 2)	M1: 0.55 ± 0.18 mm; M2: 0.61 ± 0.1 9 mm; M3: 0.68 ± 0.22 mm	The measurement error from all three display monitors was significantly different from the direct measurements ($p < 0.001$)
		No significant difference among the three tested devices
% mean error of measurement of alveolar bone dimensions (V, vertical; H, horizontal) for four CBCT scan protocols (voxel size: 0.2 mm/0.25 mm/0.3 mm/0.4 mm)	Mean/Median: 0.2 mm: 12.65%/8.54% 0.25 mm 12.2%/7.46% 0.3 mm: 12.18%/7.46% 0.4 mm: 13.62%/8.38%	No significant difference among the four protocols. All measurements are accurate (ME < 1 mm)
Mean difference DC/CBCT	Range 0.68–0.72 for the four protocols	Most measurements underestimated the real values
Mean measurement (mm) of the anterior loop length of the mental nerve using two protocols (T, with radiopaque tracer; NT, without radiopaque tracer) for CBCT and STL models	Caliper: 1.64 ± 1.37 mm CBCT NT: 1.6 ± 1.44 mm CBCT T: 1.59 ± 1.38 mm	No significant difference between the anterior loop length of the mental nerve measurements and CBCT with ($p = 0.332$) or without tracer ($p = 0.102$)
		CBCT is a prerequisite in identifying and measuring the anterior loop length

(Continues)

TABLE 3 (Continued) [In PDF format, this table is best viewed in two-page mode]

Author (year)	Sample	Aim of study	Gold standard	Sample size
Al-Ekrish (2012)	Five edentulous dry human skulls (four maxillae, five mandibles) (ex vivo)	Evaluate the effect of reducing number of basis images (low dose) on the linear measurement accuracy of CBCT in evaluating alveolar bone dimensions	Sectioning+ digital caliper	Three sites (incisor, canine–premolar, molar); 83 measurements
Luk et al. (2011)	14 partially dentate patients (in vivo)	Compare the linear measurement accuracy of RM and CBCT in evaluating alveolar crestal bone dimensions	Ridge mapping (RM)	21 alveolar potential implant sites (posterior and anterior maxilla, posterior mandible); 147 measurements
Al-Ekrish & Ekram (2011)	Five edentulous dry human skulls (four maxillae, five mandibles) (ex vivo)	Compare the accuracy of linear measurements of 16-detector MSCT and CBCT	Sectioning+ digital caliper	Three sites (incisor, canine–premolar, molar); 80 measurements
Kamburoglu et al. (2009)	Six dry human hemimandibles (ex vivo)	Compare the accuracy of linear measurements of CBCT in evaluating bone dimensions adjacent to the MC	Sectioning+ digital caliper	Seven sites from the anterior margin of the third molar to the anterior margin of the second premolar; 84 measurements
Veyre-Goulet et al. (2008)	Three dry maxillae (ex vivo)	Compare the accuracy of linear measurements of CBCT in evaluating alveolar bone height and width in maxillary edentulous regions	Sectioning+ digital caliper	14 anatomic sites; 28 measurements
Loubele et al. (2008)	One edentulous cadaver maxilla (ex vivo)	Compare the accuracy of linear measurements of 16-detector, four detector MSCT and CBCT in evaluating alveolar bone width	Holes drilled in the position of the markers+ digital caliper	Eight sites around maxillary arch; eight measurements
Kobayashi et al. (2004)	Five cadaver mandibles (ex vivo)	Compare the accuracy of linear measurements of MSCT and CBCT in evaluating alveolar bone height	Sectioning+ digital caliper	Seven sites (right and left molar, right and left premolar, right and left canine, midline, left canine); 35 measurements

CBCT, cone beam computed tomography; DC, digital caliper; L, loupe; MC, mandibular canal; MSCT, multislice computed tomography; RM, ridge mapping; STL, stereolithography; NSD, no significant difference; ICC, intraclass correlation coefficient.
*$p < 0.05$.
[a]Part of the same study.

Both clinical studies used alveolar crestal ridge mapping as a reference (Eachempati et al., 2016; Luk et al., 2011). Eachempati et al. (2016) did not specify the instruments used for these measurements, and Luk et al. (2011) mentioned using a steel ruler with 0.5-mm accuracy.

3.5 | Assessment of accuracy

Overall, there was no consistency in the use of an accuracy index between the gold standard and the linear measurements using CBCT in the identified studies (Table 3).

The mean difference was used in 12 studies (Alkan et al., 2016; Eachempati et al., 2016; Freire-Maia et al., 2017; Gerlach et al., 2014; Loubele et al., 2008; Luangchana et al., 2015; Luk et al., 2011; Pena de Andrade et al., 2016; Santana et al., 2012; Torres et al., 2012; Vasconcelos et al., 2015; Veyre-Goulet et al., 2008), two studies presented the mean absolute difference (Ganguly et al., 2016; Gerlach et al., 2013), and one study also presented the mean relative difference as a percentage (Gerlach et al., 2014).

The correlation between CBCT and the reference standard used was presented in six of the included studies (Alkan et al., 2016; Eachempati et al., 2016; Kamburoglu et al., 2009; Luangchana et al., 2015; Neves et al., 2014; Waltrick et al., 2013), and two assessed agreement (Eachempati et al., 2016; Sheikhi et al., 2015). The mean measurement error in millimeters between the two values was calculated in two studies (Kobayashi et al., 2004; Sheikhi et al., 2015), one study presented the absolute error of the measurements in millimeters (Luangchana et al., 2015), four studies evaluated the mean absolute error in millimeters (Al-Ekrish, 2012; Al-Ekrish & Ekram,

TABLE 3 (additional columns - continued)

Accuracy Index	Representative outcomes	Key inference
Absolute mean error CBCT/direct (height and width) for three acquisition protocols (40s, 20s, 7s) overall	40s: 0.50 ± 0.47 mm, 20s: 0.46 ± 0.46 mm 07s: 0.51 ± 0.47 mm	The absolute mean errors were statistically significant for the entire sample size, even though submillimetric
Absolute error of height measurements at sites containing the inferior dental canal	40s: 0.43 ± 0.49 mm 20s: 0.53 ± 0.49 mm 7s: 0.52 ± 0.52 mm	No statistically significant difference among the protocols
Frequency of absolute ME measurements >0.5 and 1.0 mm	Frequency >0.5 mm/>1 mm: 40 s: 36.1%14.5%, 20s: 41%/12.1%, 07s: 36.1%/16.9%	Reducing the CBCT exposure time number of basis images does not affect the measurement accuracy at implant sites
		CBCT significantly (>1 mm) overestimates measurements 12.1% to 16.9% of the time
Difference CBCT/RM	Mean: 0.4 ± 0.5 mm Range: −0.9 to 2.9 mm	CBCT > RM (p = 0.001)
		CBCT overestimates RM by 0.3 to 0.5 mm
Absolute mean error CBCT/direct of measurement of alveolar height and overall (height and width)	Overall: 0.48 ± 0.44 mm	Statistically significant for the entire sample size and separately height/width/maxilla/mandible
Frequency of absolute mean error >0.5 and 1.0 mm	>0.5 mm/>1 mm: 33.3%/12.5%	CBCT significantly (>1 mm) overestimates measurements in 12.5% of the times
Correlation (ICC) Mean difference (mm) of six dimensions (mandibular width; mandibular height; superior/inferior/buccal/lingual to the MC) per site	Observer1: 0.61–0.93 Observer2: 0.4–0.95 (Distance MC-top of ridge ICC>0.9. ICC 0.4&0.61 was only for the distance between the canal and the lingual margin)	The mean/median differences were "clinically insignificant"—but no statistical analysis was performed
Difference in alveolar height and width	Height range: 0.05 to 0.6 mm, Width range: 0.00 to 0.3 mm	No clinically significant difference (however, no statistics performed)
		CBCT provides clinically acceptable data, but in general with an overestimation of bone height and width
Difference CBCT/direct	Accuracy −0.09 ± 1.64 mm	NSD between physical and radiographic measurements or between CBCT/MSCT
Absolute error CBCT/direct	Mean 0.22 ± 0.15 mm Range 0.01 to 0.65 mm/	Maximum error <1 mm
Percentage of absolute error	Mean: 1.4% Range: 0.1%–5.2%	Mean error of CBCT significantly less than spiral CT

2011; Al-Ekrish et al., 2013; Waltrick et al., 2013), and three studies reported on the absolute percentage error (Kobayashi et al., 2004; Luangchana et al., 2015; Torres et al., 2012).

3.6 | Outcomes of assessment of accuracy

The majority of the studies reported submillimeter differences between CBCT and "gold standard" measurements without a statistically significant difference. Nevertheless, the range of differences between these measurements often exceeded the 1-mm threshold. Eachempati et al. (2016) reported a mean difference of 1.2 mm, but no statistical analysis was performed. Similarly, Veyre-Goulet et al. (2008) reported a range of differences from 0.03 to 0.6 mm, indicating that these differences were "not clinically significant," but without further analysis. However, in studies where a similar difference range was reported, these differences were determined to be statistically significant (Gerlach et al., 2013, 2014; Luk et al., 2011).

In studies that assessed absolute error (millimeters) between the two measurements, most authors reported low values ranging from 0.04 mm (Sheikhi et al., 2015) to 0.68 mm (Al-Ekrish et al., 2013) with the exception of Luangchana et al. (2015), who reported errors of 1.14 to 1.27 mm for the maxilla (Luangchana et al., 2015). Al-Ekrish and Ekram (2011) (Al-Ekrish, 2012; Al-Ekrish & Ekram, 2011; Al-Ekrish et al., 2013) reported that absolute errors of this magnitude were statistically significant. Luangchana et al. (2015) and Torres et al. (2012) both reported significant differences between the gold standard and CBCT (Luangchana et al., 2015; Torres et al., 2012),

TABLE 4 Summary of the CBCT units used in the included studies (n = 22) and reported exposure and acquisition parameters

Study/year	Unit (make/model)	Voxel size (mm^3)	FOV (H × W) (cm)	Voltage (kV)	Current (mA)	Scan time (s)	Slice thickness (mm)	Viewing software
Freire-Maia et al. (2017)	i-CAT Next Generation[a]	0.2	13 × 16 (Large)	120	7	20	–	–
Pena de Andrade et al. (2016)	i-CAT[a]	–	–	–	–	–	–	–
Ganguly et al. (2016)	i-CAT Classic[a]	0.2	13 × 16 (Large)	–	–	20	–	XoranCat[b]
		0.3	13 × 16 (Large)	–	–	20	–	XoranCat[b]
	Promax 3D[c]	0.16	5 × 8 (Small)	84	14	12	–	Romexis 3.0[c]
Eachempati et al. (2016)	Promax 3D[c]	0.16	5 × 8 (Small)	90	14	–	–	Romexis 3.0[c]
Alkan et al. (2016)	i-CAT Next Generation[a]	0.3	–	120	5	9.6	0.25	ImageJ[d]
Vasconcelos et al. (2015)	i-CAT Next Genera tion[a]	0.2	–	120	37.07	26.9	–	XoranCat[b] OnDemand3D[e] KDIS3D[f]
Sheikhi et al. (2015)	Galileos Compact[g]	–	–	–	–	14	–	–
Luangchana et al. (2015)	3D Accuit omo 170[h]	0.125	–	–	–	–	–	i-Dixel[h]
		0.16	–	–	–	–	–	i-Dixel[h]
		0.25	–	–	–	–	–	i-Dixel[h]
	CS 9500[f]	0.2	–	–	–	–	–	CS 3D[f]
		0.3	–	–	–	–	–	CS 3D[f]
Neves et al. (2014)	i-CAT Next Genera tion[a]	0.2	–	120	20.27	14.7 (180°)	–	OnDemand3D[e]
		0.2	–	120	37.07	26.9 (360°)	–	OnDemand3D[e]
Gerlach et al. (2014)	i-CAT[a]	0.4	22 × ? (Large)	120	1.2	40	–	Procera[i]
Waltrick et al. (2013)	- i-CAT[a]	0.4	8 × ?	120	3–8	20	1.2	i-CAT Vision[a]
		0.3	8 × ?	120	3–8	20	1.2	i-CAT Vision1
		0.2	8 × ?	120	3–8	40	1.2	i-CAT Vision[a]
Gerlach et al. (2013)	i-CAT[a]	0.4	22 × ?	120	1.2	40	–	Procera[i]
Al-Ekrish et al. (2013)	Iluma[j]	0.29	19 × 24 (Large)	120	3.8	40	–	Vision 3-D[j]
Torres et al. (2012)	i-CAT[a]	0.2	6 × 16	120 kV	46.72	40	–	XoranCat[b]
		0.25	6 × 16	120	46.72	40	–	XoranCat[b]
		0.3	6 × 16	120	23.87	40	–	XoranCat[b]
		0.4	6 × 16	120	23.87	40	–	XoranCat[b]
Santana et al. (2012)	i-CAT[a]	–	–	120	24	20	–	–
Al-Ekrish (2012)	Iluma[j]	0.29	19 × 24 (Large)	120	3.8	7	0.29	Vision 3-D[j]
		0.29	19 × 24 (Large)	120	3.8	20	0.29	Vision 3-D[j]
		0.29	19 × 24 (Large)	120	3.8	40	0.29	Vision 3-D[j]

(Continues)

TABLE 4 (Continued)

Study/year	Unit (make/model)	Voxel size (mm^3)	FOV (H × W) (cm)	Voltage (kV)	Current (mA)	Scan time (s)	Slice thickness (mm)	Viewing software
Luk et al. (2011)	i-CAT Classic[a]	0.4	—	120	3–8	—	—	i-CAT Vision[a]
Al-Ekrish & Ekram (2011)	Iluma[j]	0.29	19 × 24 (Large)	120	3.8	39.9	0.29	Vision 3-D[j]
Kamburoglu et al. (2009)	Iluma Ultra[k]	0.2	—	120	3.8	40	—	Vision 3-D[k]
Veyre-Goulet et al. (2008)	Newtom 9000[l]	—	—	85	7	70	—	EasyGuide[m]
Loubele et al. (2008)	Accuitomo 3D[h]	0.125	—	70	74	17.5	—	SPM[n]
Kobayashi et al. (2004)	Dental 3D-CT[o]	0.117	4.27 × 3 (Small)	—	—	—	0.117	Express Vision[p]

s: seconds; mm: millimeters; kV: kilovoltage; mA: milliamperes; H: height of scan volume; W: maximum diameter of scan volume.
[a]Imaging Sciences International, Hatfield, PA, USA.
[b]Xoran Technologies LLC, Ann Arbor, MI, USA.
[c]Planmeca USA Inc., Roselle, IL, USA.
[d]United States National Institutes of Health, Bethesda, MD, USA.
[e]CyberMed Inc., Seoul, South Korea.
[f]Kodak Dental Systems, Carestream Health, Rochester, NY, USA.
[g]Sirona Dental Systems GMBH, Bensheim, Germany.
[h]J. Morita Manufacturing Corp., Kyoto, Japan.
[i]NobelGuide, Nobel Biocare, Göteborg, Sweden.
[j]Imtek Imaging, 3M Company, St. Paul, MN, USA.
[k]Imtec Imaging, Ardmore, OK, USA.
[l]Quantitative Radiology, Verona, Italy.
[m]Keystone Dental, Inc., Burlington, MA, USA.
[n]Statistical Parametric Mapping, Wellcome Department of Imaging Neuroscience London, UK.
[o]PSR 9,000 prototype, Asahi Roentgen, Kyoto, Japan.
[p]Zio Software, Tokyo, Japan.

TABLE 5 Descriptive analysis of the outcomes regarding assessment of reiliability (repeatability/reproducibility) in the studies included

Study	Method of assessment	Intra-examiner	Interexaminer
Freire-Maia et al. (2017)	ICC	1.0–0.961[p]	0.923–0.997[r]
Pena de Andrade et al. (2016)	NR	—	—
Ganguly et al. (2016)	Bland and Altman/ICC	0.978–0.985[r]	0.961[r]
Eachempati et al. (2016)	NR	—	—
Alkan et al. (2016)	ICC	0.995 (95% CI: 0.991–0.998)[r]	0.989 (95% CI: 0.979–0.995)[r]
Vasconcelos et al. (2015)	ICC	0.98–0.99[r]	1 examiner
Sheikhi et al. (2015)	ICC	0.78–0.8[r]	0.78–0.97[r]
Luangchana et al. (2015)	ICC/Cronbach's alpha	0.996–1.0[r]/NR	0.991–1.0[r]/NR
Neves et al. (2014)	ICC	0.96–0.98[r]	0.98[r]
Gerlach et al. (2014)	ICC	NR	0.93[r]
Waltrick et al. (2013)	Pearson correlation coefficient (*r*)	NR	0.9983–0.9991[r]
Gerlach et al. (2013)	*SD*/Pearson correlation coefficient (*r*)	(0.03–0.11 mm)[p], (0.13–0.21mm)[r]	0.96[r]
Al-Ekrish et al. (2013)	Pearson correlation coefficient (*r*)/ Cronbach's alpha	(1.000)[p], (0.994–0.998/0.997–0.999)[r]	(0.993–0.99/0.993–0.998)[r]
Torres et al. (2012)	Pearson correlation coefficient (*r*)	(0.831 to 0.995)[r], 0.987[p]	1 examiner
Santana et al. (2012)	Cronbach's alpha	NR	1 examiner
Al-Ekrish (2012)	Pearson correlation coefficient (*r*)/ Cronbach's alpha	(0.99)[p], (0.993–0.996/0.996–0.998)[r]	(0.994–0.98/0.997–0.999)[r]
Luk et al. (2011)	Bland and Altman (mm [CI])	(0.0–0.1 [−0.8 to 0.8])[p], (0.0–0.1 [−0.7 to 0.8])[r]	1 examiner
Al-Ekrish & Ekram (2011)	Cronbach's alpha/% > with absolute difference larger than 0.5 mm	(0.997/10%)[r], (0.999/2%)[p]	(0.979/75%)[r]
Kamburoglu et al. (2009)	ICC/range in mm (aka repeatability)	(0.86 to 0.97/0.78 to 2.05)[r] (0.98 to 0.99/0.43 to 1.07)[p]	(0.84 to 0.97/0.76 to 1.99)[r] (0.78 to 0.97/1.22 to 2.59)[p]
Veyre-Goulet et al. (2008)	NR	—	—
Loubele et al. (2008)	2-way ANOVA (p value)	(0.996)[p]	(0.934)[p] (0.20)[r]
Kobayashi et al. (2004)	NR	—	—

ICC, Intraclass correlation coefficient; *SD*, standard deviation; NR, not reported; p, physical measurements; r, radiographic measurements; CI, 95% confidence interval.

whereas others provided no statistical information (Kobayashi et al., 2004; Sheikhi et al., 2015; Waltrick et al., 2013).

The results of several authors show a high correlation between CBCT and the gold standard using different correlation parameters (Alkan et al., 2016; Luangchana et al., 2015; Neves et al., 2014; Waltrick et al., 2013). However, one author showed only moderate correlation (Eachempati et al., 2016). Kamburoglu et al. (2009) reported overall ICC values of 0.61 to 0.93 and 0.4 to 0.95 for two observers. The authors indicated that the low values (0.61 and 0.4) were only for measurements of the distance between the mandibular canal and the surface of the lingual cortical plate. Sheikhi et al. (2015) also reported high ICC values for height (0.89) and width (0.91). Eachempati et al. (2016) also reported high level of agreement among the clinical gold standard, ridge mapping, and CBCT measurements, with 94.6% of the data being within the mean and one standard deviation in a Bland–Altman plot.

No clear trend in measurement error is apparent as authors report both overestimation (Al-Ekrish, 2012; Al-Ekrish & Ekram, 2011; Al-Ekrish et al., 2013; Freire-Maia et al., 2017; Gerlach et al., 2013, 2014; Kobayashi et al., 2004; Loubele et al., 2008; Luk et al., 2011; Pena de Andrade et al., 2016; Vasconcelos et al., 2015; Waltrick et al., 2013) and underestimation (Alkan et al., 2016; Eachempati et al., 2016; Freire-Maia et al., 2017; Ganguly et al., 2016; Luangchana et al., 2015; Pena de Andrade et al., 2016; Santana et al., 2012; Sheikhi et al., 2015; Torres et al., 2012; Vasconcelos et al., 2015; Veyre-Goulet et al., 2008; Waltrick et al., 2013) between CBCT and the "gold standard" measurements.

3.7 | Outcomes of assessment of reiliability (repeatability/reproducibility)

Inter- and intra-observer reliabilities were reported in most of the 22 studies included (Table 5). One study described performing interobserver analysis, but the results were not reported (Santana et al., 2012), and in three studies, data were only provided for one

TABLE 6 Quality assessment of the included clinical studies: blue = Luk et al. (2011); red = Eachempati et al. (2016)

Criteria	Yes	No	Other(CD,NR.NA)
1. Was the research question or objective in this paper clearly stated?	◆◆		
2. Was the study population clearly specified and defined?	◆◆		
3. Was the participation rate of eligible persons at least 50%?			NR NR
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	◆	◆	
5. Was a sample size justification, power description, or variance and effect estimates provided?	◆		CD
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?		◆◆	
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?		◆◆	
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?			NA NA
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants	◆		
10. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants	◆		CD
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	◆◆		
12. Were the outcome assessors blinded to the exposure status of participants?			NA NA
13. Was loss to follow-up after baseline 20% or less?			NA NA
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?	◆◆		

CD, cannot determine; NA, not applicable; NR, not reported.

observer (Luk et al., 2011; Torres et al., 2012; Vasconcelos et al., 2015). A variety of methods were used for to describe reliability including intraclass correlation coefficient alone or together with Cronbach's alpha, range in millimeters or Bland and Altman, Bland and Altman alone, the Pearson correlation coefficient alone or together with Cronbach's alpha or standard deviation, Cronbach's alpha alone or together with percentage of measurements with an absolute difference greater than 0.5 mm and respective *p*-value.

Values for all studies reporting inter- and intra-observer were high (Table 5).

3.8 | CBCT imaging parameters

There was no consistency in the reporting of exposure, acquisition or display protocols used among the included studies (Table 4). In addition, no author reported on the standardization of these parameters with respect to the gold standard. Some authors deliberately modified selected parameters and found no effects on measurement accuracy. This included voxel size (Ganguly et al., 2016; Luangchana et al., 2015; Torres et al., 2012; Waltrick et al., 2013), scan times (Al-Ekrish, 2012; Waltrick et al., 2013), software used for analysis (Vasconcelos et al., 2015), and display monitor (Al-Ekrish et al., 2013). Only one author investigated the use of two different CBCT units and found no difference in measurement accuracy (Luangchana et al., 2015). Torres et al. (2012) recommended a voxel size of 0.3 to 0.4 mm^3 as a good compromise between image quality and reduced radiation exposure.

3.9 | Comparison to other radiographic diagnostic methods

CBCT measurement accuracy was compared most often to MSCT with five ex vivo studies (Al-Ekrish & Ekram, 2011; Freire-Maia et al., 2017; Kobayashi et al., 2004; Loubele et al., 2008; Pena de Andrade et al., 2016) and panoramic radiography with three studies (Alkan et al., 2016; Eachempati et al., 2016; Luangchana et al., 2015). One study compared CBCT to digital radiography and digital photography (Alkan et al., 2016), and another compared it to tangential projection (Sheikhi et al., 2015).

Freire-Maia et al. (2017), Pena de Andrade et al. (2016) and Loubele et al. (2008) found no significant differences in accuracy between CBCT imaging and MSCT regarding the accuracy of linear measurements, and reported submillimeter error ranges for both radiographic techniques (Freire-Maia et al., 2017; Loubele et al., 2008; Pena de Andrade et al., 2016). However, Kobayashi et al. (2004) and Al-Ekrish et al. (2013) reported significant differences in measurement error between CBCT and MSCT (Al-Ekrish et al., 2013; Kobayashi et al., 2004), particularly for width measurements (Al-Ekrish et al., 2013), at mandibular sites (Al-Ekrish et al., 2013), and at specific regions (Al-Ekrish et al., 2013; Kobayashi et al., 2004).

Studies comparing measurement accuracy of CBCT and panoramic radiography are limited, and the results are equivocal. Alkan et al. (2016) demonstrated that CBCT and digital radiography measurements were significantly correlated to the gold standard, in contrast to panoramic imaging, where mesiodistal linear measurements differed significantly. Luangchana et al. (2015) reported no difference between CBCT and panoramic radiography in the mean measurement difference of vertical alveolar bone, but absolute and percentage differences were significantly less for CBCT than panoramic radiography, particularly in the mandible. These findings are supported by Eachempati and coworkers (Eachempati et al., 2016), who found a high correlation between height measurement in CBCT and panoramic radiography utilizing metallic ball markers as fiducial markers.

3.10 | Quality assessment of included studies

The majority of the included studies were ex vivo (20 of 22), and thus, a quality assessment for these studies was not performed. For the two remaining clinical studies, the NIH "Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies" was applied (Table 6). Domains on exposure and follow-up of this assessment tool do not apply for the current studies. Only one of the two studies reported a power description of the sample size.

4 | DISCUSSION

Successful dental implant treatment should incorporate a thorough planning phase using an appropriate radiographic examination providing images of diagnostic quality (Freire-Maia et al., 2017; Neves et al., 2014). Three-dimensional presurgical assessment is often necessary to identify vital anatomical structures (e.g., mandibular canal, maxillary sinus floor, mental foramen) and assessing the bone quantity and quality, which will maximize the potential for success of the inserted implants (Molly, 2006; Turkyilmaz & McGlumphy, 2008), and facilitate bone grafting procedures (Verdugo, Simonian, Smith McDonald & Nowzari, 2009). CBCT imaging is now commonplace and has become popular for diagnostic procedures, especially in implant dentistry. Compared to MSCT, CBCT provides cross-sectional and 3D imaging at reduced radiation exposure (Freire-Maia et al., 2017; Patel, 2009) at an overall lower price (Scarfe et al., 2006). The majority of clinicians consider CBCT images to be reliable and distortion free and are unaware of potential inaccuracies or inconsistencies that may exist when performing linear measurements or evaluating bone and anatomic structures prior to implant placement.

Many authors have reported bone measurements made on CBCT images can be considered accurate, when errors less than 1 mm can be tolerated (Kobayashi et al., 2004; Torres et al., 2012; Wyatt & Pharoah, 1998). Most studies in our review showed submillimeter accuracy of CBCT measurements compared to a gold standard. There was no clear trend as to whether measurements are consistently under- or overestimated. However, the range of absolute error in some studies exceeded the clinically considered threshold of 1 mm. This finding may be of clinical importance as it implies that the previously stated submillimeter accuracy of CBCT for preoperative evaluation of implant sites may, in some circumstances, be insufficient and could potentially lead to clinical complications. The higher radiographic contrast of radiopaque markers used in several of the included studies may contribute to increased accuracy of the ex vivo measurements. On the other hand, some have claimed that the embalming fluid associated with cadaver specimens might be partially responsible for reduced accuracy compared to measurements on patients. Several authors

have suggested a 2 mm safety zone for measurements obtained from panoramic radiography (Bartling, Freeman & Kraut, 1999; Buser & von Arx, 2000; Greenstein & Tarnow, 2006). Considering the inhomogeneity of data from our current review and the lack of conclusive evidence from clinical studies, we also recommend a safety margin of 2 mm from vital anatomical structures, when using 3D data from CBCT imaging.

It is possible that specific makes and models of CBCT equipment may have different levels of accuracy in linear measurements of the residual alveolar ridge. This could be potentially because of the many machine-specific, operator-independent variables such as filtration, target-object/object-sensor distances, reconstruction algorithms used, or different designs of head restraining devices that could potentially influence measurement accuracy. However, due to the inhomogeneity of the dependent variables identified (linear measurement indices) in this review, further attempts at identifying these machine-specific conditions for the purposes of comparison would not add to the outcomes of the present analysis as even the metric data from seemingly the same machine by two different investigators are not comparable.

In one study, the maxillary measurements were found to be less accurate than those of the mandible (Luangchana et al., 2015). This may be explained a potential reduction in overall density of the maxilla than the mandible due to the thinner cortical layer and greater cancellous component. On the other hand, Gerlach et al. (2013) found overestimation of mandibular dimensions on CBCT cross-sectional images, especially when assessing the cortical thickness (Gerlach et al., 2013). This finding may result from errors introduced when measuring short distances on CBCT images with limited spatial resolution acquired at relatively large voxel dimensions (Molen, 2010) or to partial volume averaging, which appears when different bone densities appear in the same voxel (Barrett & Keat, 2004; Molen, 2010).

As expected, the majority of studies were in vitro—either on dry skulls or on cadaver samples—with only two clinical studies identified. Clinical studies are inherently difficult to perform as they require accurate, physical measurements of the bone intraoperatively. Due to the nature of the ex vivo studies, a quality assessment of these investigations was not performed. Ex vivo studies are ranked low within the spectrum of strength of evidence within the hierarchical pyramid in a clinical setting (Hujoel, 2009). Nevertheless, the importance and validity of these studies should not be undervalued as they are observational diagnostic studies, where findings can be extrapolated to daily clinical practice. The outcome reports of the two cross-sectional clinical studies were analyzed and the overall risk of potential for bias was considered as limited.

In terms of sample size, the number of measurements for CBCT varied from 8 (Loubele et al., 2008) to 255 (Alkan et al., 2016). It appears that most authors arbitrarily determined sample size without performing power calculations. Without a power analysis, it is difficult to determine the external validity of the reported outcomes. Most authors reported that measurements were carried out by two or more observers, except for one study where the number of observers was unreported (Pena de Andrade et al., 2016) and two studies that had only one examiner (Luk et al., 2011; Santana et al., 2012). Although calibration of the examiners is necessary for optimal diagnostic performance and reliability (de Oliveira et al. 2009), only two authors reported that a measurement calibration procedure was performed, but without details (Eachempati et al., 2016; Vasconcelos et al., 2015). The reported inter- and intra-examiner agreement was very high for all the studies.

There was a large heterogeneity of devices, parameters and software used in the included studies, which made a direct comparison impossible. Several studies reported that smaller voxel sizes did not lead to greater accuracy for the linear measurements at edentulous sites (Ganguly et al., 2016; Luangchana et al., 2015; Torres et al., 2012; Waltrick et al., 2013). This is in agreement with other CBCT studies comparing different voxel sizes (Damstra, Fourie, Huddleston Slater & Ren, 2010; Liedke, da Silveira, da Silveira, Dutra & de Figueiredo, 2009; Patcas, Muller, Ullrich & Peltomaki, 2012). Voxel size plays a significant role in image quality as it defines the spatial resolution of the CBCT images (Patel, Dawood, Ford & Whaites, 2007; Scarfe et al., 2006; Watanabe, Honda, Tetsumura & Kurabayashi, 2011), providing higher degree of detail. High resolution has been reported to influence diagnostic tasks in other applications fields, like endodontics (Kamburoglu & Kursun, 2010; da Silveira et al., 2013), but for implant treatment planning, a voxel size of 0.3 to 0.4 mm seems to be sufficient to provide the necessary accuracy. Similarly, our review indicates that numerous radiation dose reduction settings such as limitation of field of view (Ganguly et al., 2016), reducing scan time (Al-Ekrish, 2012; Waltrick et al., 2013), or scan arc (Neves et al., 2014) can be applied without adversely affecting the accuracy of measurements on cross-sectional CBCT images.

There appear to be no differences between software packages in measuring CBCT images (Vasconcelos et al., 2015). Nevertheless, clinicians should be cautious when using new software as there is little scientific, evidence-based validation of the performance of these algorithms.

Clinical extrapolation of the findings from ex vivo CBCT studies is inherently problematic as CBCT reconstruction algorithms are optimized for in vivo scanning of maxillofacial areas, which are composed of both skeletal and soft tissue elements. In addition, high-density materials such as root canal fillings, composite resins, metallic restorations, and dental implants create beam hardening artifacts (Schulze, Berndt & d'Hoedt, 2010). Therefore, as most experimental conditions using dry skulls or formalin-fixed cadavers are not equivocal to clinical situations, the accuracy of linear measurements obtained ex vivo may not be directly comparable to in vivo situations and may result in over- or underestimation. Soft tissues attenuate the X-ray beam, reducing tissue contrast increasing scatter and contributing to image noise, thus potentially affecting the accuracy of the relative measurements (Ganguly et al., 2016; Gerlach et al., 2013; Patcas et al., 2012). Recent studies though have shown that accuracy outcomes were similar with and without soft tissues (Ganguly et al., 2011; Wood et al., 2013). Wood et al. (2013) showed that the presence of soft tissues had

no effect when a 0.4 mm voxel size was used, and 0.2-mm scans demonstrated a clearly inferior accuracy associated with absence of soft tissues. Even though not directly comparable, all studies in the current review reported high accuracy outcomes for the linear measurements, irrespective of the presence or absence of soft tissues or soft tissue simulation, supporting the assertion that the presence of soft tissues in ex vivo CBCT studies is not a crucial factor for accuracy measurements.

Digital calipers were used in the majority of studies to provide gold standard dimensions on histologic sections to which linear measurements on CBCT images were compared. While an accuracy of 0.01 mm or 0.02 mm accuracy was commonly reported, calipers were tested and calibrated only in three studies (Al-Ekrish, 2012; Al-Ekrish & Ekram, 2011; Al-Ekrish et al., 2013). While the precision with which a repeated point of insertion of the caliper on the sectioned specimens is arguable, the high inter- and intra-observer agreement reported on most studies support the validity of this method. Gerlach et al. performed measurements on digitized histological sections with great accuracy as confirmed by the small standard deviations (Gerlach et al., 2013, 2014). These authors attributed this finding to the use of methyl methacrylate as an embedding medium for the sections, which prevents shrinking artifacts (Wittenburg, Volkel, Mai & Lauer, 2009; Yang, Davies, Archer & Richards, 2003).

The two clinical studies included used ridge mapping for assessing the width of the edentulous alveolar ridge. Although it was not explicitly mentioned in these studies that this method is used as a control for the linear CBCT measurements, it was decided to include them in the present review as they fitted the presented inclusion and exclusion criteria. Despite the high agreement of the reported measurements in these studies, one should acknowledge certain limitations of this method such as the ability to accurately stop the measuring instruments at the first bone contact after penetrating the soft tissues, especially when the mucosa is mobile or the bone density is low, as well as to reproduce the point of entry precisely with the templates used for this purpose.

Finally, it must be mentioned that the current systematic review focused only on the accuracy of linear bone measurements on cross-sectional and therefore multiplanar reformatted, two-dimensional CBCT images. However, CBCT imaging provides three-dimensional depiction of bony structures, making it a crucial diagnostic tool that, in addition to linear measurements, enables evaluation of the morphology, bone quality, and volume of the residual alveolar ridge, which are also important and basic considerations in overall implant site assessment.

5 | CONCLUSIONS

Based on the results of this systematic review, it can be concluded that:

- CBCT provides cross-sectional images that demonstrate high accuracy and reliability for bony linear measurements on cross-sectional images related to implant treatment. Therefore, CBCT is an appropriate diagnostic tool for 3D preoperative planning.
- A wide range of error has been reported when performing linear measurements on CBCT images, with both over- and underestimation of dimensions in comparison with a gold standard. Therefore, a 2 mm safety margin to adjacent anatomic structures should be considered when using CBCT.
- A voxel size of 0.3 to 0.4 mm is adequate to provide CBCT images of acceptable diagnostic quality for implant treatment planning.
- As most studies were ex vivo (i.e., dry skulls or cadavers), the reported results should be considered optimal. In clinical practice, measurement accuracy and reliability are most likely reduced as several factors (e.g., patient motion, device and software used, manual or automated procedures) might influence linear measurements on CBCT images.
- Due to the inhomogeneity of the extracted data from the included studies, it was not possible to conduct a meta-analysis to account for multivariate effect estimates. Thus, further studies that focus on determining which factors specifically influence the accuracy of the measurements in 3D imaging are recommended.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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REVIEW ARTICLE

WILEY CLINICAL ORAL IMPLANTS RESEARCH

The accuracy of static computer-aided implant surgery: A systematic review and meta-analysis

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*[Correction added on 29 October 2018, after publication: second author's forename corrected from 'Viviane' to 'Vivian']

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Abstract

Objectives: To assess the literature on the accuracy of static computer-assisted implant surgery in implant dentistry.

Materials and Methods: Electronic and manual literature searches were conducted to collect information about the accuracy of static computer-assisted implant systems. Meta-regression analysis was performed to summarise the accuracy studies.

Results: From a total of 372 articles. 20 studies, one randomised controlled trial (RCT), eight uncontrolled retrospective studies and 11 uncontrolled prospective studies were selected for inclusion for qualitative synthesis. A total of 2,238 implants in 471 patients that had been placed using static guides were available for review. The meta-analysis of the accuracy (20 clinical) revealed a total mean error of 1.2 mm (1.04 mm to 1.44 mm) at the entry point, 1.4 mm (1.28 mm to 1.58 mm) at the apical point and deviation of 3.5°(3.0° to 3.96°). There was a significant difference in accuracy in favour of partial edentulous comparing to full edentulous cases.

Conclusion: Different levels of quantity and quality of evidence were available for static computer-aided implant surgery (s-CAIS). Based on the present systematic review and its limitations, it can be concluded that the accuracy of static computer-aided implant surgery is within the clinically acceptable range in the majority of clinical situations. However, a safety marge of at least 2 mm should be respected. A lack of homogeneity was found in techniques adopted between the different authors and the general study designs.

1 | INTRODUCTION

Prosthetically driven implant dentistry is the optimal way to treat patients with dental implants (Katsoulis, Pazera & Mericske-Stern, 2009; Tzerbos, Sykaras & Tzoras, 2010; Zitzmann & Marinello, 1999). It requires detailed pretreatment planning to ensure a correct three-dimensional (3-D) implant position is achieved within the alveolar bone, relative to the planned prosthetic restoration (Belser et al., 2007). A 3-D model or digital file of the alveolar bone and related oral anatomy can be generated using either CT (computed tomography) or CBCT (cone beam computed tomography). CBCT offers significant radiation dose reduction with the ability to image restricted fields of view (Bornstein, Scarfe, Vaughn & Jacobs, 2014). In addition, the introduction of surface scanning technology, via either intra-oral or extra-oral scanning approaches, generates a further 3-D model of the patients' oral condition which can be superimposed on the radiographic data set, to create a realistic 3-D virtual patient.

This virtual patient can be viewed on implant planning software where the data on soft and hard dental tissue, proposed prosthetic treatment proposals and bone volume information can be visualised

as different layers (Lee, Betensky, Gianneschi & Gallucci, 2015). Within the implant planning software, clinicians can perform a virtual implant placement in accordance with the future prosthetic needs, whilst respecting the existing anatomical situation. This information can be used to design and fabricate surgical drill guides, which aid the clinician to insert the implants in the planned positions. Static guidance systems are defined as systems which communicate the predetermined virtual implant position to the surgical operating area, using a rigid surgical implant template or guide (Jung et al., 2009). In an increasing manner, such static guidance systems are marketed to dental clinicians under the assumption they can produce high levels of accuracy.

Whilst these developments seem to be promising, questions have been raised about the reliability, accuracy, and the precision of these static surgical drill guides to replicate the planned implant position. Two previous ITI consensus publications on the accuracy of guided surgery were inconclusive (Jung et al., 2009; Tahmaseb, Wismeijer, Coucke & Derksen, 2014). It was recognised that each step, either solely, or in accumulation with other steps in this digital workflow, can result in inaccuracies (Tahmaseb et al., 2014). Failure

TABLE 1 Search strategy and selection criteria

Focused question (PICO)	**"What is the accuracy of static computed guided implant placement in partial and fully edentulous human subjects?"**	
Search Strategy	Population	#1 [Text Words]: ((jaw, edentulous, partially[Mesh Terms]) OR (partially edentulous) OR (partial edentulism))
	Intervention or exposure	# 2 [MeSH terms]: (Surgery, Computer-assisted) AND (Dental Implants) [Text Words]: dental AND (implant OR implants OR implantation OR implantology) AND (guide* OR computer*)
	Comparison	# 3 [Text Words]: ((((((adjusted drills) OR drill handles) OR (printed guide AND milled guide) AND (lab guide OR full guided AND partial guided) OR (depth control OR no depth control)
	Outcome	#4 [Text Words]: (1) Accuracy of placement, (2) Implant survival
	Search combination	#1 AND #2 AND #3 AND #4 #2
Database search	Language	English
	Electronic	PubMed, Cochrane
	Journals	Clinical Implant Dentistry and Related Research, Clinical Oral Implants Research, The International Journal of Oral Maxillofacial Surgery, Journal of Periodontology, Journal of Prosthetic Dentistry, Implant Dentistry, and The International Journal of Periodontics and Restorative Dentistry.
Selection criteria	Inclusion criteria	• Randomised and nonrandomised clinical studies • Case reports including at least 10 patients • Computer-guided (static) surgery in which a CT/CBCT scan was conducted for computerised planning prior to the actual implant insertion. • Studies with a primary outcome of • accuracy of computer-guided implant surgery • Clear description on accuracy measurements: distances between the • planned and actual position of the implants and/or implant angle deviations. Data on the position of actual inserted implants
	Exclusion criteria	• Cadaver, model, animal studies • Expert opinions • Dynamic computer-navigated surgery and 2D radiographic stents • Zygomatic, pterygoid and orthodontic implants • Studies with primary outcomes other than accuracy of computer-guided implant surgery • No actual insertion of the implants • Unclear description on accuracy measurements • Insufficient information on timing of implant placement after tooth extraction • Absence of objective parameters—aesthetic indices, soft tissue measurements • Multiple publications on the same patient population. • No author response to inquiry email for data clarification

of the final implant position to accurately match the virtual planned implant position can compromise the outcome.

This article aimed to review the literature in respect to the positional accuracy of implants placed using static guided implant surgery techniques in both partially and fully edentulous patients, and to assess survival rates for implants placed using static guidance systems.

2 | MATERIALS AND METHODS

2.1 | Search strategy

In accordance with PRISMA guidelines, this systematic review reports on the accuracy of implant placement and the subsequent implant survival of dental implants placed using static computer-aided guided implant surgery for partially and fully edentulous patients. The term partially edentulous patient was used to define any patient that is missing one, or more teeth, but not all teeth. A patient that is missing all teeth is defined as fully edentulous. The focused question was as follows: "What is the accuracy of static computed guided implant placement in partial and fully edentulous human subjects?"

2.2 | PICO question

Table 1 summarises the PICO question where data were sought for:

- (P) Edentulous or partially edentulous jaws,
- (I) Dental implants and computer guides,
- (C) Drill guides; printed and milled for both partially or fully guided surgery and
- (O) Accuracy of implant position and subsequent survival rate.

All electronic data resources of PubMed and Cochrane were searched as well as hand searches of the following relevant journals: Clinical Implant Dentistry and Related Research, Clinical Oral Implants Research, The International Journal of Oral Maxillofacial Surgery, Journal of Periodontology, Journal of Prosthetic Dentistry, Implant Dentistry and The International Journal of Periodontics and Restorative Dentistry.

The following terms were used for the search strategy:

MeSH terms: (Surgery, Computer-Assisted) AND (Dental Implants).

Text words: Computer Aided Surgery AND (implant OR implants) AND (dental OR oral) AND (guided surgery OR guided implant placement OR computer guided OR ((drill guide OR template) AND computer) OR surgical template OR simplant OR codiagnostix OR SMOP OR nobelguide).

The results were limited to studies written in English.

The search, electronic and manual, was limited to studies published between January 1, 2008, and December 31, 2016. Previous systematic reviews have shown that publications prior to 2008 report varying degrees of inaccuracy, possibly as a result of the limited technology available at the time (Tahmaseb et al., 2014). Therefore, the authors decided to limit the search to only include publications after 2008.

This review was registered in PROSPERO with ID number: 91834.

2.3 | Study selection

Two reviewers (A.T. and V.W.) screened all titles and abstracts independently. The reference lists of the subsequently selected abstracts and the bibliographies of the systematic reviews were searched manually. Disagreements were solved through discussion. No kappa score was calculated. Studies were screened and eliminated when either (a) group size was not clear or (b) no statistical analysis was performed. Full-text evaluation of the remaining publications was performed using the inclusion and exclusion criteria listed below:

Randomised and nonrandomised clinical studies were included for the review. Case reports were considered eligible for inclusion but must document a minimum of 10 patients. This review included only computer-guided (static) surgery in which a CT or CBCT scan was conducted for computerised planning prior to actual implant insertion in a human.

Publications containing expert opinions were excluded. Articles regarding dynamic computer-navigated surgery and 2D radiographic stents were excluded. Studies with zygomatic, pterygoid and orthodontic implants were also excluded. Data were excluded if the position of the osteotomy following computer-guided surgery was provided, but no actual implant insertion was performed. Articles were excluded if there was insufficient information on timing of implant placement.

2.4 | Data extraction

Two reviewers, A.T and V.W, independently extracted data from the included studies. Disagreements were again resolved through discussion until a consensus was reached between both reviewers. Where data were unclear or incomplete, the authors of the publication were contacted for further explanation.

The data were further analysed based on the following subgroups:

- Flapless vs. open-flap surgical procedure
- Implanted jaw: maxilla vs. mandible
- Type of edentulism: partial vs. Full
- Static Guide support: (a) mucosa, (b) tooth, (c) bone, (d) mini-pins

2.5 | Quality of the studies

A quality assessment of the included RCT was performed according to the Cochrane Handbook for Systematic Reviews of Interventions (version 5.1.0; updated March 2011 by Higgins, Altman & Sterne,

2011). Six main quality criteria were evaluated: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data and selective reporting. Depending on the descriptions given for each individual criteria, it was rated as low, unclear or high risk of bias.

The Newcastle–Ottawa Scale (NOS) adapted by Chambrone, Chambrone, Lima and Chambrone (2010), Chambrone, Shibli, Mercurio, Cardoso and Preshaw (2015) was used to assess the risk of bias in the prospective and retrospective included studies. Thus, the following topics were used: (a) selection of study groups: sample size calculation, representativeness of the patients, description of clear selection criteria of the patients, detailed description of the surgical steps, calibration of the surgeons and assessors of outcomes (b) comparability: comparability of patients on the basis of the study design or analysis and management of potential confounders; (c) outcomes: evaluation of results; and (d) statistical analysis: validity of statistical analysis. Each included study could receive a maximum of nine stars indicating methodological quality, and therefore indicating the risk of bias. Studies with 7–9 points were arbitrarily considered as being of low risk of bias, with 5–6 points indicating medium-level risk of bias and with fewer than five points indicating high risk of bias. Table S1 in the Supporting information section shows the risk of bias per individual study.

2.6 | Statistical analysis

Statistical analysis was performed using the meta library from R, version 3.4.3. The data provided from the selected articles did not allow for the evaluation of the accuracy of different tools. Therefore, the overall accuracy of static guided implant insertion was evaluated. Differences between edentulism type were assessed by means of a random-effects meta-regression with a binary predictor, also known as a dummy variable used to investigate the difference between edentulism status (Hedges & Vevea, 1998). A separate analysis was performed for error at the entry point, error at the apex and angular deviation (Figure 1).

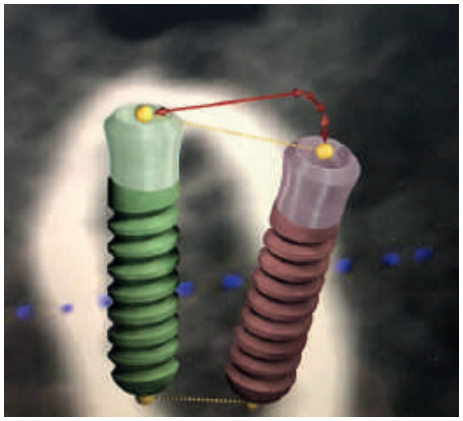

FIGURE 1 The following six outcome variables were evaluated for each selected study: 1. Deviation in entry point measured from the centre of the implant (mm). 2. Deviation in apex location measured at the centre of the implant (mm). 3. Angulation deviation. 4. Error in implant height at the entry point (mm). 5. Error in implant height at the apex (mm)

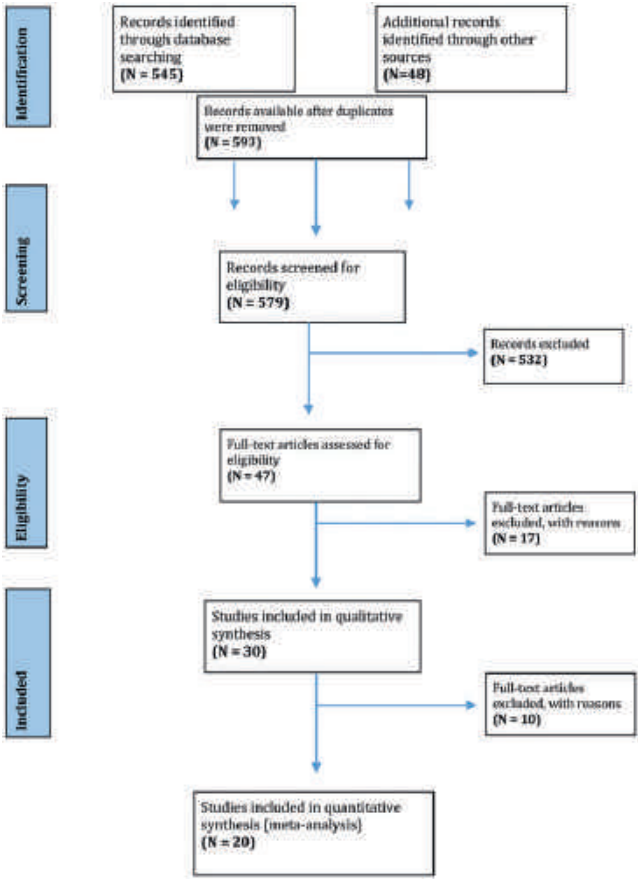

FIGURE 2 Outline of the PRISMA flow diagram for data selection and screening for eligible inclusion in the systematic review. A total of 20 articles were included for qualitative synthesis and assessment

In addition, forest plots were drawn to visualise the magnitude of errors and the difference between groups. As there was evidence of heterogeneity between the articles, totals were calculated using random-effects meta-analysis for continuous variables. The significance level of the tests was 0.05. The funnel plots are demonstrated in the Supporting information Figures S1–S4.

3 | RESULTS

3.1 | Study selection

The initial electronic database search on PubMed and Cochrane database resulted in 545 articles. An additional 48 articles were identified with manual searches yielding a total of 593 articles for review. After removing duplicates, 579 were available for screening. 47 articles were selected for full-text review by two reviewers (AT, VW) independently. After prescreening, application of the inclusion and exclusion criteria and handling of the PICO question, 30 studies remained. A further 10 studies were excluded, resulting in 20 studies selected for inclusion

TABLE 2 Selected publication for meta-analysis

Authors (year)	Study design	Comparison	Software/guide system	No. of patients	No. of implants
Arisan et al. (2013)	Uncontrolled prospective clinical trial	CBCT/CT	Simplant	11	102
Cassetta et al. (2012)	Uncontrolled retrospective study	CT	Simplant/External Hex Safe	11	95
Cassetta, DiMambro et al. (2013), Cassetta, Giansanti et al. (2013) and Cassetta, Stefanelli et al. (2013)	Uncontrolled retrospective study	CT	Simplant/ SurgiGuide, External Hex Safe	20	227
Cassetta, Giansanti, Di Mambro and Stefanelli (2014)	Uncontrolled retrospective study	CT	Simplant/External Hex Safe	28	225
D'haese et al. (2012)	Uncontrolled prospective clinical trial	CT	Facilitate	13	78
Ersoy et al. (2008)	Uncontrolled prospective clinical trial	CT	Stent Cad/swissplus	21	94
Fürhauser et al. (2015)	Uncontrolled retrospective study	CBCT	NobelGuide	27	27
Geng et al. (2015)	Uncontrolled prospective clinical trial	CBCT	Simplant	24	111
Lee et al. (2013a,b)	Uncontrolled retrospective study	CT	OnDemand3D	48	102
Ozan et al. (2009)	Uncontrolled retrospective study	CT	StentCAD	30	110
Pettersson et al. (2012)	Uncontrolled prospective clinical trial	CBCT	NobelGuide	30	139
Schnutenhaus et al. (2016)	Uncontrolled retrospective study	CBCT	Swiss Media Online Planning/Camlog Guide system	24	24
Stübinger et al. (2014)	Uncontrolled prospective clinical trial	MSCT	Facilitate	10	44
Van de Wiele et al. (2015)	Uncontrolled prospective clinical trial	CBCT	Simplant	16	75
Vasak et al. (2011)	Uncontrolled prospective clinical trial	CT	Procera/ NobelGuide	18	86
Vercruyssen et al. (2014, 2015)	(RCT) randomised controlled trial	CBCT (note patients had CTs prior to CBCT to confirm eligibility)	Simplant/ Materialise Universal, Facilitate	48	209
Vercruyssen et al. (2015)	Uncontrolled prospective clinical trial	CBCT	Procera/ NobelGuide	25	150
Vercruyssen et al. (2015)	Uncontrolled prospective clinical trial	CBCT	Procera/ NobelGuide	30	104
Verhamme et al. (2017)	Uncontrolled prospective clinical trial	CBCT	Maxilim/ NobelGuide	12	72
Vieira, Sotto-Maior, Barros, Reis and Francischone (2013)	Uncontrolled retrospective study	CBCT	NobelGuide	14	62

for qualitative synthesis (Figure 2). Complete data extraction and statistical analysis were performed. From the 20 studies, one was a randomised controlled trial (RCT), eight were uncontrolled retrospective studies, and 11 were uncontrolled prospective studies. Table 2 details the article selected for inclusion and Table 3 the articles excluded from the analysis with the reasons for exclusion.

TABLE 3 The excluded papers and the reason for their exclusion

Cassetta et al.	The Influence of the Tolerance between Mechanical Components on the Accuracy of Implants Inserted with a Stereolithographic Surgical Guide: A Retrospective Clinical Study	2015	Only results on angle deviation reported
Al-Harbi and Sun	Implant placement accuracy when using stereolithographic template as a surgical guide: preliminary results	2009	Less than 10 patients included
Behneke, Burwinkel, & Behneke	Factors influencing transfer accuracy of cone beam CT-derived template-based implant placement	2012	Same cohort as Behneke et al. 2011
Behneke, Burwinkel, Knierim et al.	Accuracy assessment of cone beam computed tomography-derived laboratory-based surgical templates on partially edentulous patients	2012	Radical deviation measured instead of 3D
Cassetta, Stefanelli et al.	Accuracy of implant placement with a stereolithographic surgical template	2013	Same as Accuracy of two Stereolithographic
Cassetta, Stefanelli et al.	Accuracy of a computer-aided implant surgical technique	2013	Same as Accuracy of two stereo-lithographic 2013
Cassetta, Di Mambro et al.	Is it possible to improve the accuracy of implants inserted with a stereolithographic surgical guide by reducing the tolerance between mechanical components?	2013	Less than 10 patients included
Cassetta, Di Mambro et al.	How does an error in positioning the template affect the accuracy of implants inserted using a single fixed mucosa-supported stereolithographic surgical guide?	2013	No data error at the apex
Cassetta et al.	The influence of the tolerance between mechanical components on the accuracy of implants inserted with a stereo-lithographic surgical guide: A retrospective clinical study	2015	No data error at the entry and apex
Di Giacomo et al.	Accuracy and complications of computer-designed selective laser sintering surgical guides for flapless dental implant placement and immediate definitive prosthesis installation	2012	Only lateral deviation reported not three Dimension measurements
Farley et al.	Split-mouth comparison of the accuracy of computer-generated and conventional surgical guides	2013	No clear description on material and methods
Lee et al.	Accuracy of a direct drill-guiding system with minimal tolerance of surgical instruments used for implant surgery: a prospective clinical study	2016	No data error at the apex and angulation
Cassetta, Di Mambro et al.	The intrinsic error of a stereolithographic surgical template in implant guided surgery	2013	Same as Accuracy of two stereo-lithographic 2013
Cassetta, Stefanelli et al.	Depth deviation and occurrence of early surgical complications or unexpected events using a single stereolithographic surgi-guide	2013	Different research question
Moon et al.	Clinical problems of computer-guided implant surgery	2016	Less than 10 patients included
Naziri et al.	Accuracy of computer-assisted implant placement with insertion templates	2016	Results reported median instead of mean
Nickenig et al.	Evaluation of the difference in accuracy between implant placement by virtual planning data and surgical guide templates versus the conventional free-hand method—a combined in vivo—in vitro technique using cone-beam CT (Part II)	2010	No results reported on entry or apex in three Dimensions
Ochi et al.	Factors affecting accuracy of implant placement with mucosa-supported stereolithographic surgical guides in edentulous mandibles	2013	No results on angulation reported
Ozan et al.	Correlation between bone density and angular deviation of implants placed using CT-generated surgical guides	2011	No results reported on entry or apex in three Dimensions
Platzer et al.	Three-dimensional accuracy of guided implant placement: indirect assessment of clinical outcomes	2013	Less than 10 patients included
Shen et al.	Accuracy evaluation of computer-designed surgical guide template in oral implantology	2015	Not clear flapless? Edentulous/dentate/fully guided?
Sun, Luebbers, Agbaje, Kong et al.	Accuracy of a Dedicated Bone-Supported Surgical Template for Dental Implant Placement with Direct Visual Control.	2015	Less than 10 patients included

(Continues)

TABLE 3 (Continued)

Sun, Luebbers, Agbaje, Schepers et al.	Accuracy of Dental Implant Placement Using CBCT-Derived Mucosa-Supported Stereolithographic Template	2015	No apex results
Testori et al.	Evaluation of accuracy and precision of a new guided surgery system: A multicenter clinical study	2014	No SD
Van Assche et al.	Accuracy assessment of computer-assisted flapless implant placement in partial edentulism	2010	Less than 10 patients included
Vercruyssen et al.	Depth and lateral deviations in guided implant surgery: an RCT comparing guided surgery with mental navigation or the use of a pilot-drill template	2015	Same patient group as Vercruyssen 2014
Zhao et al.	Accuracy of computer-guided implant surgery by a CAD/CAM and laser scanning technique	2014	No results reported on entry, angulation or apex in three Dimensions

3.2 | Study characteristics

All patients in all studies were assessed prior to inclusion and reported to be suitable candidates for implant-supported prostheses. All patients were in good health at the time of implantation. Eight studies assessed the outcome of guided surgery in edentulous patients, while 12 studies reviewed the outcome for fully edentulous patients. CBCT was used for pretreatment assessment in 11 of 20 studies, whilst 9 of 20 used a medical CT device. One study used both CT and CBCT technology. The support mechanism for the surgical guides was mixed in all but one study to include, mucosa, mucosa with fixation pins, bone and tooth. Only one study evaluated tooth-supported static surgical guides (Fürhauser et al., 2015).

3.3 | Results of the individual studies

A total of 20 studies met the selection criteria for review (Table 2). This provided a total of 2,136 implants, in 460 patients which were available for review (Table 4). All studies employed a fully guided drilling sequence; however, four studies sought to compare the accuracy of fully guided implant placement with freehand implant placement following a fully guided drilling sequence and contained a cohort of implants (n = 355) which were not fully guided. A total of 1,883 implants had been placed with a static surgical guide that remained in situ following osteotomy preparation. Stabilisation of the surgical guide varied across all studies. Partially edentulous cases were completed with a mix of tooth support and tooth/mucosa support when distal extension cases were treated. Fully edentulous cases were treated with either mucosa-supported guides (9/20 studies), mucosa-supported guides stabilised with fixation pins (12/20 studies) or bone-supported guides fixed in place with stabilisation screws (7/20 studies).

A total of seven different software systems were used for pretreatment planning of the cases:(a) Simplant (7/20) (b) Facilitate (2/20) (c) Stent Cad (2/20) (d) NobelGuide (3/20) (e) OnDemand3D (1/20) (f) Swiss Media Online Planning (1/20) (g) Procera (3/20) (h) Maxilim (1/20) (Table 2). A total of 10 different guide systems were used for implant placement:(a) External Hex Safe (3/20) (b) Simplant (3/20) (c) Surgiguide (1/20) (d) Facilitate (3/20) (e) Swissplus (1/20) (f) NobelGuide (7/20) (g) OnDemand3D (1/20) (h) StentCAD (1/20) (i) CamlogGuide system (1/20) (j) Materialise Universal (Table 2). Regarding implant surgery, 12/20 studies reported on flapless surgical implant placement protocols, and 8/20 studies completed surgery with both flapless and open-flap techniques. Only one study considered the aesthetic outcomes of implant placed with static guided surgery (Fürhauser et al., 2015), demonstrating that flapless guided surgery can produce aesthetic outcomes assuming the planned implant position is realised accurately. Comparison of the planned and final implant position was performed using radiographic comparison with CT or CBCT in 19/20 studies with five different software systems being utilised. Only one study (Schnutenhaus,

TABLE 4 All publication (fully and partially edentulous) reporting on error at the entry point

Study	No of patients	No of implants
Arisan (2013)	11	102
Cassetta (2012)	11	95
Cassetta (2013)	20	227
Cassetta (2014)	28	225
D'haese (2012)	13	78
Ersoy (2008)	21	94
Fürhauser (2015)	27	27
Geng (2015)	24	111
Lee (2013)	48	102
Ozan (2009)	30	110
Pettersson (2012)	30	139
Schnutenhaus (2016)	24	24
Van de Wiele (2015)	16	75
Vasak (2011)	18	86
Vercruyssen (2014/2015)	59	311
Verhamme (2015-1)	25	150
Verhamme (2015-2)	30	104
Verhamme (2016)	12	72
Vieira (2013)	14	62
Total	461	2,194

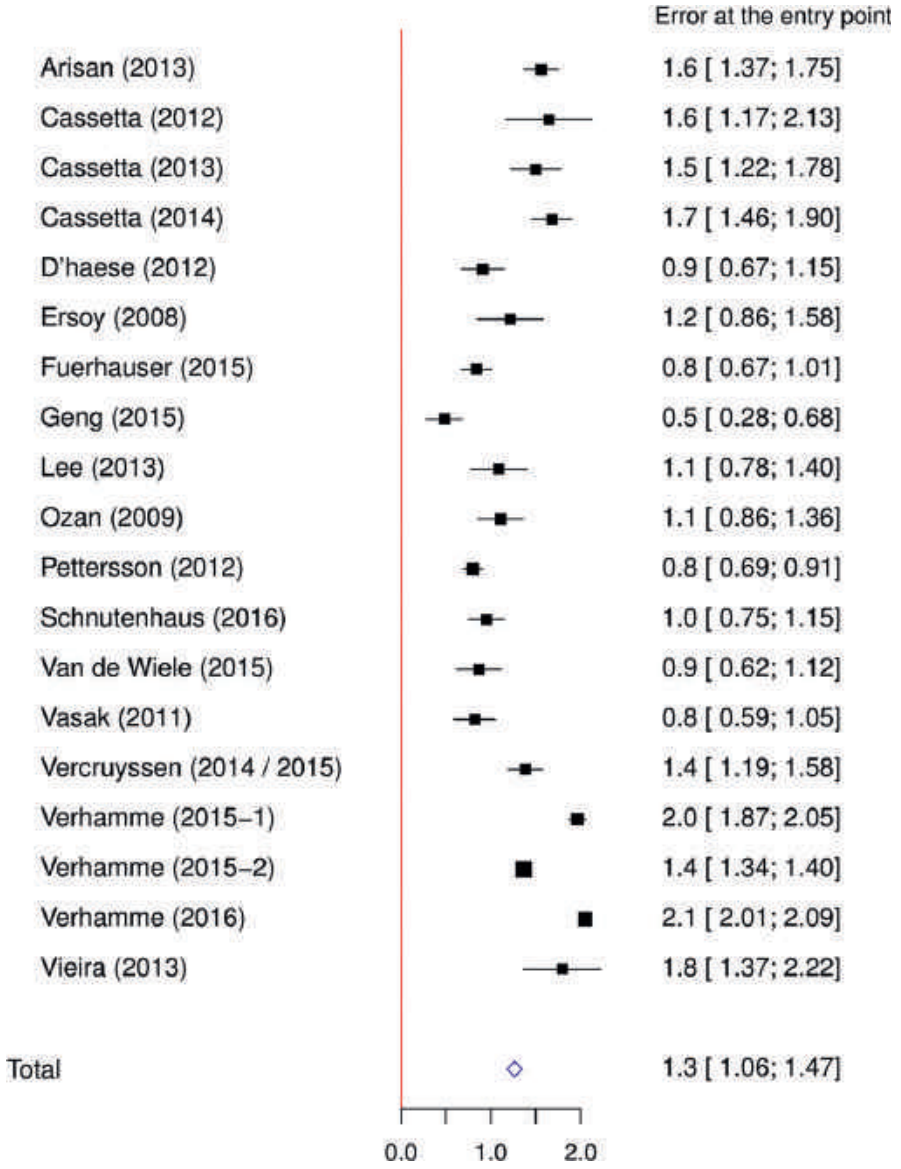

FIGURE 3 Forest plot demonstrating difference in error (mm) at the entry point between full edentulous and partial edentulous groups

Edelmann, Rudolph & Luthardt, 2016) made comparisons of the implant positions using a final impression of the actual implant location. The impression was poured in stone and the implant locations digitised and compared to the pre-treatment position using Geomagic software. In three studies, the software used for comparison of implant locations was not specified.

The majority of implants were placed using static guides, fabricated using a Rapid Prototyping SLA (stereolithography) method (2,175/2,136). A total of 63 implants were placed using acrylic guides in one study as part of a prelaunch protocol (Pettersson, Komiyama, Hultin, Näsström & Klinge, 2012).

Implant length did not seem to be correlated to positional accuracy in one RCT (Vercruyssen et al., 2015); however, one study did find larger apical deviations for longer implants placed using static guidance (D'haese, Van De Velde, Elaut & De Bruyn, 2012). Longer implants were found to have greater variation in mesio-distal angulation by one group (Verhamme, Meijer, Bergé et al., 2015; Verhamme, Meijer, Boumans et al., 2015). They recommended the use of fixation screws to reduce bucco-lingual errors. Several studies reported that right-handed surgeons had lower accuracy when treating the left side of the patient compared to the right side (Van de Wiele et al., 2015 and Vercruyssen et al., 2014). Implant placement in the anterior region was reported to be more accurate than placement in the posterior by one group (D'haese et al., 2012) which was in contrast to Verhamme et al., who found no differences (Verhamme, Meijer, Bergé et al., 2015; Verhamme, Meijer, Boumans et al., 2015).

3.4 | Quality of the studies

The 20 included studies were assessed for methodological risks analysis. Two different methods, Higgins et al. (2011) for one RCT and the Newcastle–Ottawa Scale (NOS) adapted by Chambrone

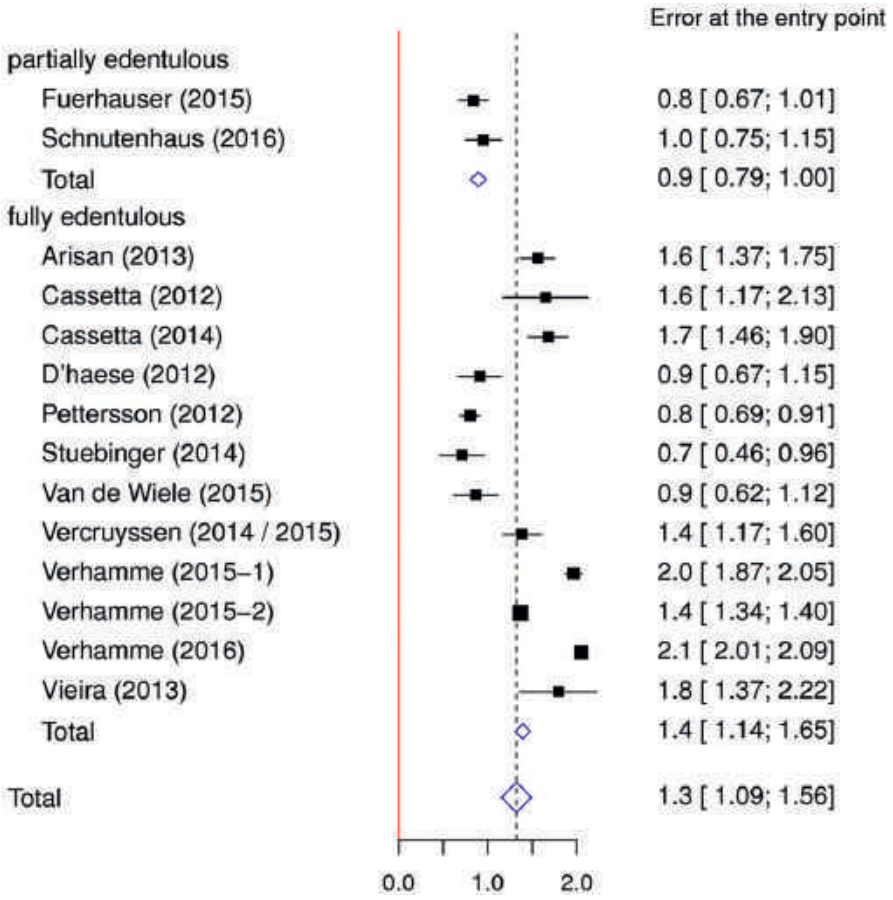

FIGURE 4 Forest plot demonstrating error (mm) at the entry point measured for all selected articles

et al. (2010, 2015) for the remaining 19 included studies, were used (Table risk of bias in the Table S1). All the included studies except the selected RCT met between 55% and 77% of the selected criteria, being considered to have a low-to-moderate level of risk of bias. The only RCT (Vercruyssen et al., 2014) met 83% of the criteria, demonstrating a low risk of bias. However, the level of the data heterogenicity and the nonstandardised measuring methods can be considered as the major limitations of this current meta-analysis.

3.5 | Synthesis of results

Only two papers reported on implant survival rate. Both studies showed 100% survival rate after at least 1 year of observation (Lee et al., 2013a,b; Pettersson et al., 2012). As not all studies reported the full detailed measurements for all outcome variables, even after authors were emailed, it was necessary to make some calculations based on only the studies which clearly demonstrated the data. Table 3 details which studies were able to be used for calculation of the outcome variables.

3.6 | Error at entry point

The mean error for entry point measured at the centre of the implant for fully edentulous cases was 1.3 mm CI:95% [1.09–1.56 mm] and 0.9 mm CI: 95% [0.79–1.00] for partially edentulous cases (Figure 3). Average error for all (partially and fully edentulous) guided surgeries was 1.2 mm, CI: 95% [1.04–1.44] (Figure 4). A significant difference was found between edentulous and fully edentulous cases treated with guided surgery with a smaller error and less deviation found in partially edentulous patients (Figure 3). Table 4 contains all publications that measured the errors at entry point. Table 5 contains all publications where a comparison between fully edentulous and partially edentulous was possible.

3.7 | Error at the apex

The mean error of apical position for partially edentulous cases was 1.2 mm CI:95% [1.11–1.20 mm] and 1.5 mm C:95% [1.29–1.62] for fully edentulous cases (Figure 5). A strongly significant difference between fully and partially edentulous was found. The average error for all cases was 1.4 mm, CI:95% CI [1.28–1.58] (Figure 6). Table 6 contains all publications that measured the errors at apical point. Table 7 contains all publications where a comparison between fully edentulous and partially edentulous was possible.

3.8 | Angular deviation

The angular deviation for partially edentulous cases was 3.3 degrees CI:95% [2.07–4.63] and 3.3 degrees for fully edentulous cases

TABLE 5 Publications specifically reporting on error at the entry point in separate groups, partial edentulous, full edentulous

Edentulism status	Study	No of patients	No of implants
Partially edentulous	Fürhauser (2015)	27	27
Partially edentulous	Schnutenhaus (2016)	24	24
Partially edentulous	Total	51	51
Fully edentulous	Arisan (2013)	11	102
Fully edentulous	Cassetta (2012)	11	95
Fully edentulous	Cassetta (2014)	28	225
Fully edentulous	D'haese (2012)	13	78
Fully edentulous	Pettersson (2012)	30	139
Fully edentulous	Van de Wiele (2015)	16	75
Fully edentulous	Vercruyssen (2014/2015)	59	311
Fully edentulous	Verhamme (2015-1)	25	150
Fully edentulous	Verhamme (2015-2)	30	104
Fully edentulous	Verhamme (2016)	12	72
Fully edentulous	Vieira (2013)	14	62
Fully edentulous	Total	249	1,413
Grand Total		300	1,464

CI:95% [2.71–3.88] (Figure 7). No significant difference between edentulous and fully edentulous. Average angular deviation for both fully and partially edentulous cases was 3.5 degrees CI: 95% [3.00–3.96] (Figure 8). Table 7 contains all publications that measured angular deviations. Table 8 contains all publications where a comparison between fully edentulous and partially edentulous was possible.

3.9 | Error in implant height at the entry point

The average error in height of the entry point is 0.2 mm, CI 95%, [−0.25 to 0.57 mm] (Figure 9).

3.10 | Error in implant height at the apex

The average error is 0.5 mm, CI:95% [−0.08 to 1.13 mm] (Figure 10).

4 | DISCUSSION

This review systematically evaluated the literature, regarding accuracy and clinical outcome of static computer-assisted implant dentistry. Static guidance systems have been previously reported to be more accurate than dynamic guidance systems, which allow the surgeon to vary the implant position in real time (Jung et al., 2009). The current systematic reviewed only implants placed in patients and not implants placed in a preclinical or cadaver studies. The average errors in entry and apex point positions were similar to the results published in a previous systematic review (Tahmaseb et al., 2014). When the 3D measurements were conducted, the vertical errors were found be statically significant inaccuracies when compared to the horizontal and angulation deviations in this present review.

Although the mean deviations seem to be in a clinically acceptable range, still some significant outliners were reported. Verhamme, Meijer, Bergé et al. (2015) and Verhamme, Meijer, Boumans et al. (2015) reported errors up to 7.8 mm at the entry point and 8.7 mm at the apical point. Verhamme et al. (2017), Verhamme, Meijer, Bergé et al. (2015) and Verhamme, Meijer, Boumans et al. (2015)reported errors up to 4.0 mm and 4.2 mm at the entry point and 3.6 mm and 4.3 mm at the apex, respectively. These results were achieved when treating fully edentulous upper jaws. The confidence interval (CI) of 95% was used to report data, in this study; therefore, the outliners were limited to a few studies. These authors also reported that the majority of the errors occurred with the implants being placed too superficially.

When considering height deviations of guided implant surgery, in this systematic review, the error in implant height was considered to be a positive valued error for implants that were not deep enough and a negative value for implants inserted below the reference line.

While the data presented in the current systematic review indicate that static guided surgery can be used to realise virtual implant planning position with reasonable accuracy, considerable errors may still occur when using static drill guides. These errors can be of a magnitude which could jeopardise the aesthetic outcome, the safety of surrounding anatomical structures or prevent the final prosthetic treatment plan from being executed as planned. Implants placed using a free-hand approach do not easily allow the clinician to make a pre- and post-treatment comparison as there is no preplanned implant position available. Vercruyssen and coworkers did seek to compare mental navigation with guided surgical approaches, where a presurgical plan was made and the operator then placed implants

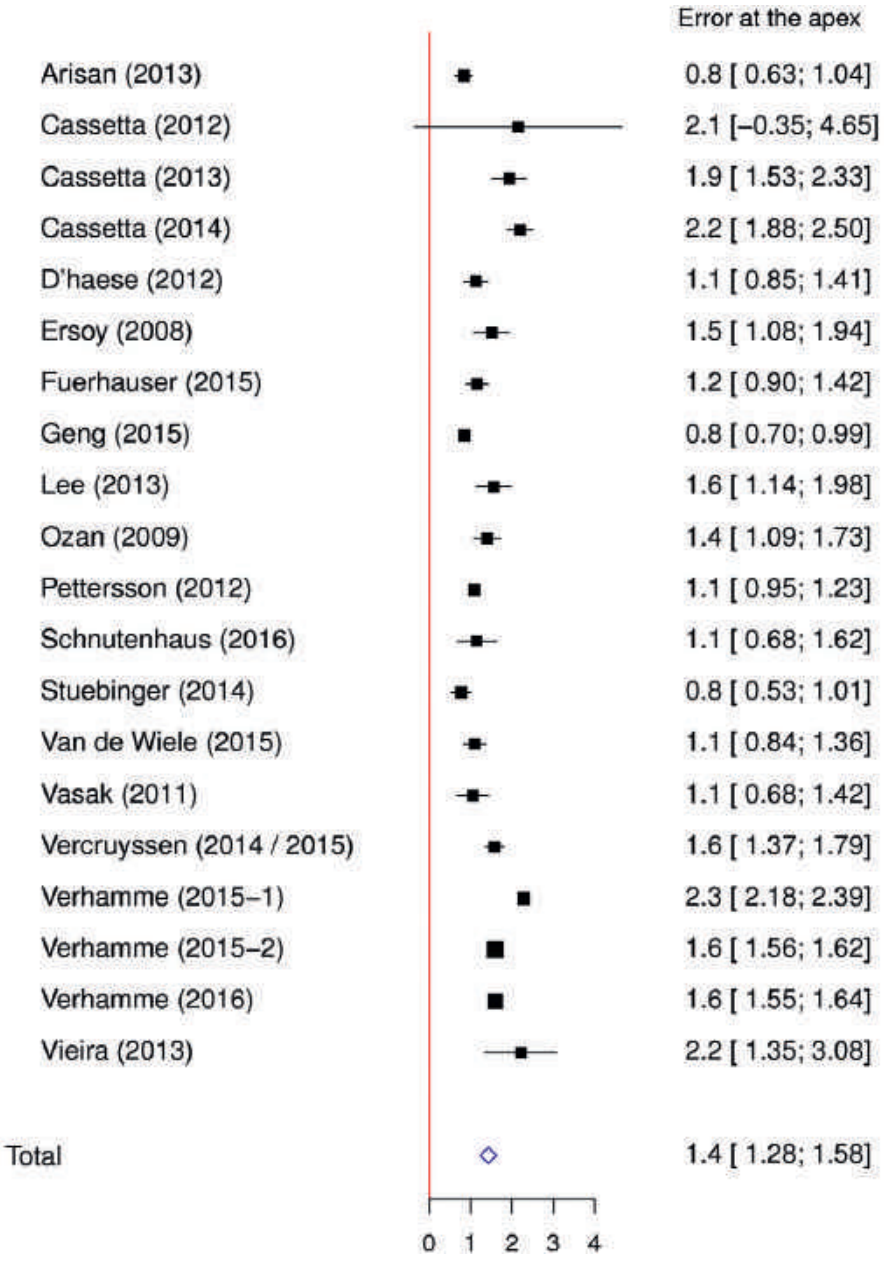

FIGURE 5 Forest plot demonstrating difference in error (mm) at the apical point between partially and fully edentulous patients

based on the mental memory or visualisation of the proposed position (Vercruyssen et al., 2014, 2015). Significantly greater variability in positional outcome was noted with this approach compared to both semiguided and guided placement.

A range of time intervals were reported from pre- to postimplant positional outcome analysis. One study performed comparison immediately after placement (Ozan, Turkyilmaz, Ersoy, McGlumphy & Rosenstiel, 2009) a further study performed analysis 10 days after implant placement (Vercruyssen et al., 2014, 2015) whilst another waited until 12 months after loading (Pettersson et al., 2012). It is quite possible that either implant abutment, or prosthesis connection, as part of immediate loading protocols, result in implant movement which is not yet osseointegrated. This effect on implant accuracy relative to the planned position has been acknowledged by D'haese et al. (2012). Future studies should seek to control this potential error more carefully.

The steps within the digital workflow sequence for guided surgery are summarised as follows: volumetric data acquisition, surface scanning procedures via intra-oral scanning or extra-oral model scanning, computer planning software, surgical guide fabrication via computer assisted milling (CAM) or 3-D printing.

In order to understand why positional errors occur for implants placed using a static guided surgical approach, the clinician must both recognise and understand the limitations within each step of the digital sequence.

From the outset, CT and CBCT volumetric data acquisition is the first potential source of error. The lower radiation dose and cost reported for CBCT compared to multislice computed tomography

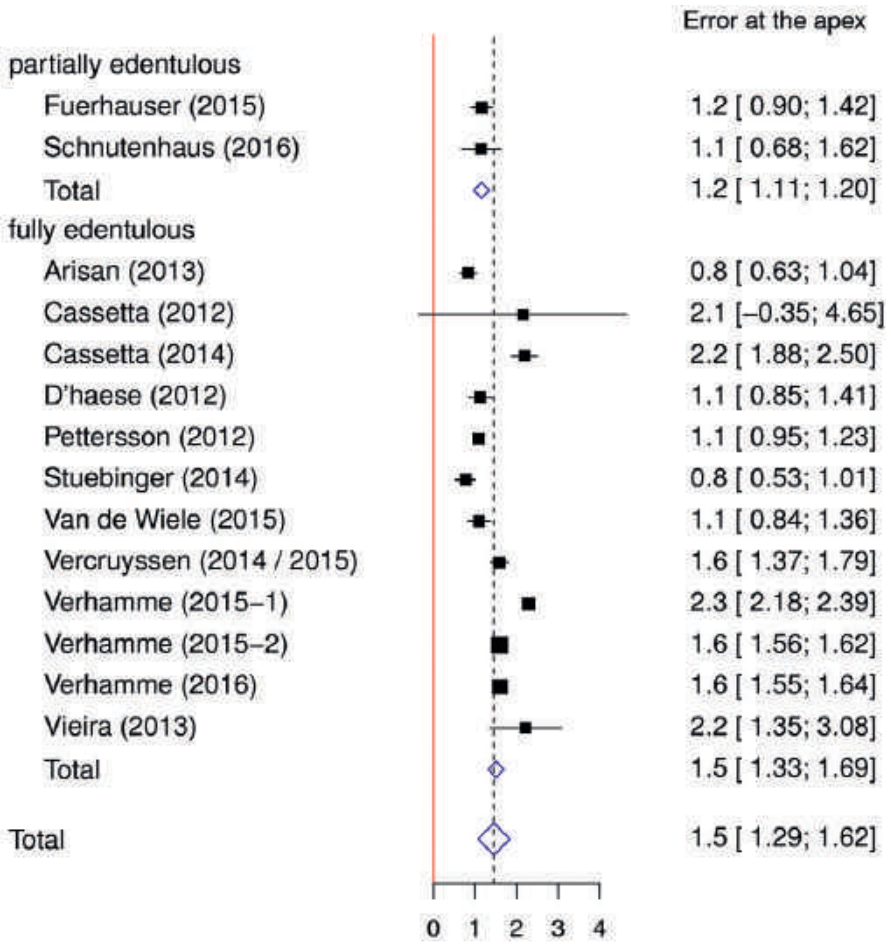

FIGURE 6 Forest plot demonstrating error (mm) at the apical point measured for all selected articles

(MSCT) are often thought to outweigh the reported disadvantages of poor soft tissue contrast with CBCT for imaging the maxillofacial region (Suomalainen, Esmaeili & Robinson, 2015). Although the linear measurements on CBCT images seem to be accurate, different parameters can influence the final results. Arisan and coworkers could not find statistically different outcomes comparing the use of CT and CBCT for planning (Arisan, Karabuda, Pişkin & Özdemir, 2013). Patient movements during the CBCT imaging process can cause image distortion and image quality degradation. Pettersson et al. showed that greater errors were found when patients moved during the CT scans compared to those that did not move (Pettersson et al., 2012). Their results demonstrated that movement resulted in a significant divergence at the level of the implant shoulder and apex. The presence of metallic restorations produces artefacts in CBCT which negatively effects image quality. Tadinada and coworkers concluded that these artefacts cause significant image degradation and often misrepresent the region of interest (Tadinada, Jalali, Jadhav, Schincaglia & Yadav, 2015). They recommend clinicians should be aware of the above limitations and understand these limitations along with normal CBCT anatomy to facilitate accurate evaluation.

Makins has also made similar statements based on their systematic review (Makins, 2014). The large number of papers included in this systematic review chose MSCT for both pre- and post-treatment implant position evaluation. The use of post-treatment imaging to precisely locate the implant position following static guided surgical placement itself represents a potential source of error, as data set segmentation and image cleaning must be performed carefully to achieve an image quality suitable enough to use for comparison. In addition, CBCT is often considered superior for producing high contrast resolution and allowing submillimetre resolution, allowing for a more accurate post-treatment implant position to be determined. Whilst these facts are known to affect imaging quality, there was insufficient data available within the current review to be able to make comparisons on the effect of the radiographic capturing technique on the outcome of guided surgery.

Surface scanning procedures allow for the capturing of soft and hard tissue intra-oral morphology. There has been a significant increase in the number of intraoral scanners (IOS) available to the clinician. Variability in IOS accuracy has been reported depending on the type of scanner used, the need to use powder application to coat the oral cavity surface and the scan acquisition sequence. Giménez et al. concluded in their study that the IOS operator affected the accuracy of measurements; however, the performance of the operator was not necessarily dependent on experience. The scanned distance affected the predictability of the scanner accuracy, and the error increased with the increased size of the scanned section (Giménez,

TABLE 6 All publication reporting on error at the apical point

Study	No of patients	No of implants
Arisan (2013)	11	102
Cassetta (2012)	11	95
Cassetta (2013)	20	227
Cassetta (2014)	28	225
D'haese (2012)	13	78
Ersoy (2008)	21	94
Fürhauser (2015)	27	27
Geng (2015)	24	111
Lee (2013)	48	102
Ozan (2009)	30	110
Pettersson (2012)	30	139
Schnutenhaus (2016)	24	24
Van de Wiele (2015)	16	75
Vasak (2011)	18	86
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Verhamme (2015-1)	25	150
Verhamme (2015-2)	30	104
Verhamme (2016)	12	72
Vieira (2013)	14	62
Total	461	2,194

Özcan, Martínez-Rus & Pradíes, 2015; Giménez, Pradíes, Martínez-Rus & Özcan, 2015).

In an unfortunate manner, IOS devices do not capture moveable soft tissue well. Extended edentulous or completely edentulous sites may, therefore, still require a conventional analog impression of the clinical situation which subsequently needs to be digitised. Errors can occur in the analog-to-digital conversion of a model. Whilst IOS devices are reported to be clinically efficient and highly accepted by clinicians, their precision decreases with an increasing distance between anatomical structures or implant scan bodies (Joda et al., 2017). The precision of desktop laboratory scanners is unaffected by increased distances between scan bodies, so their use is preferred for long span edentulous sites (Flügge, Att, Metzger & Nelson, 2016).

Implant planning software is used to merge the digital data sets from the radiographic and surface scanning procedures by aligning common regions on both data sets. Misalignment of the data sets may occur when there is an insufficient number of clearly identifiable common features. This can occur with metallic restorations which create artefacts or when CBCT or CT radiographs are performed with the teeth occluding. Segmentation of such radiographic data set can be complicated and compromised when such artefacts are present. Flügge and coworkers demonstrated that the mode of radiographic segmentation is highly significant for the accuracy of aligning and registering surface scan data when using a commercially available planning software (Flügge et al., 2017). They found manual segmentation of CBCT data sets was preferred to default segmentation, and the accuracy of the registration between the radiographic and surfaces scans is influenced by the presence of restorations and operator experience.

Implant manufacturers have designed the instrumentation for guided surgery such that prefabricated sleeves need to be inserted into the surgical guides. A drilling handle fits into these sleeves, ensuring that consecutive drills, with increasing diameter, can be used to prepare the surgical osteotomy. The level of tolerance between both the sleeves and drill handles, and the drill handles and drills, can cause additional inaccuracies (Cassetta, Di Mambro, Giansanti, Stefanelli & Cavallini, 2013; Cassetta, Giansanti, Di

TABLE 7 Publications specifically reporting on error at the apical point in separate groups, partial edentulous, full edentulous

Edentulism status	Study	No of patients	No of implants
Partially edentulous	Fürhauser (2015)	27	27
Partially edentulous	Schnutenhaus (2016)	24	24
Partially edentulous	Total	51	51
Fully edentulous	Arisan (2013)	11	102
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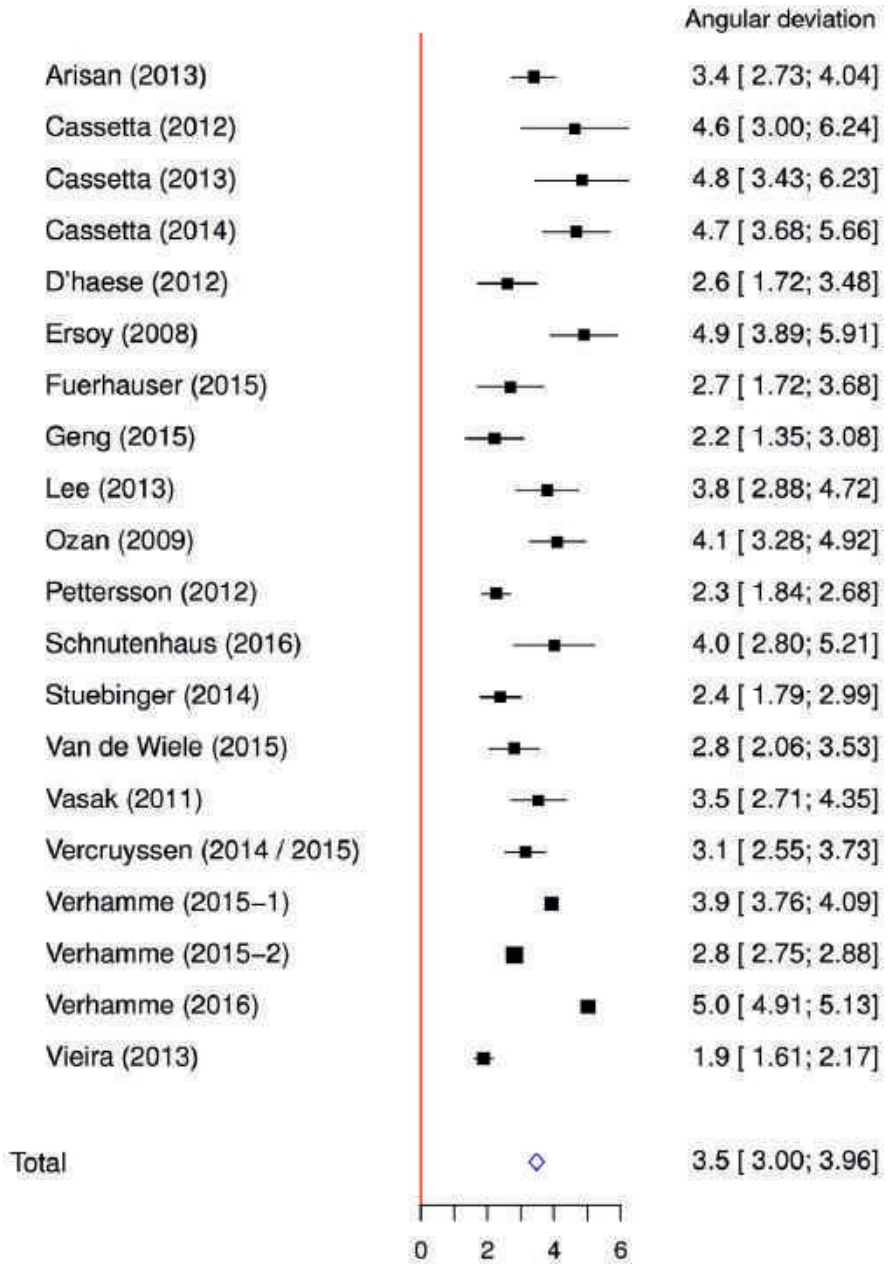

FIGURE 7 Forest plot demonstrating difference in angular error (°) between partially and fully edentulous patients

Mambro, Calasso & Barbato, 2013; Cassetta, Stefanelli, Giansanti, Di Mambro & Calasso, 2013). Schneider and coworkers, in their in vitro study, reported that the tolerance of surgical instruments and the lateral movements of the drills was significantly reduced by the use of 3-D printing with a reduced sleeve diameter (Schneider, Schober, Grohmann, Hammerle & Jung, 2015). This reduction could improve the overall accuracy in computer-assisted template-guided implant dentistry. The lateral movement of the drill can be further reduced using a shorter drill and a higher drill handle. The height and location of the sleeve must be carefully considered during implant planning and design of the surgical guide to reduce this error. One significant feature that is repeatedly highlighted was the need for adequate drill guide stabilisation during guided implant placement (Arisan et al., 2013; Cassetta et al., 2012; Cassetta, DiMambro et al., 2013; Cassetta, Giansanti et al., 2013; Cassetta, Stefanelli et al., 2013; D'haese et al., 2012; Geng, Liu, Su, Li & Zhou, 2015; Vercruyssen et al., 2015). Mucosa-supported guides were found in these studies to show micro-movement, even when multiple fixation pins were used. These authors suggested this could have contributed to inaccuracy (Cassetta, DiMambro et al., 2013; Cassetta, Giansanti et al., 2013; Cassetta, Stefanelli et al., 2013; D'haese et al., 2012).

This is in agreement with the results from a previous review by Tahmaseb and coworkers (Tahmaseb et al., 2014). The flexibility of the drill guides and lack of a physical control could be the cause of these irregularities. Tahmaseb et al. showed in a clinical trial that

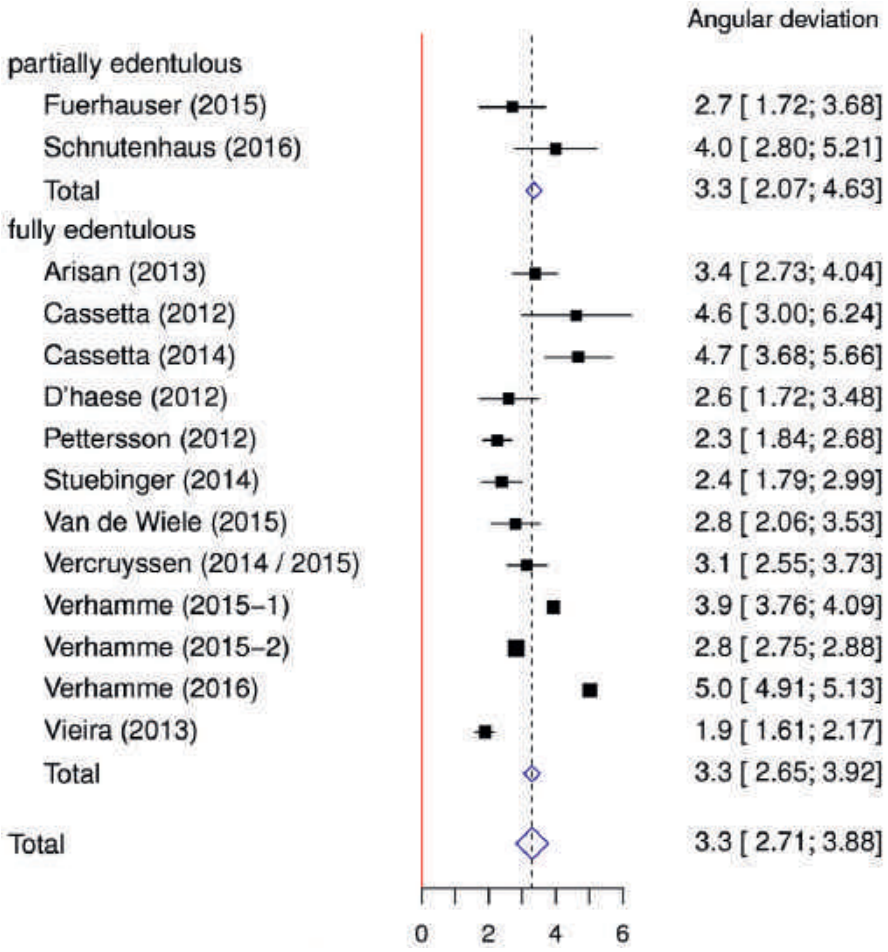

FIGURE 8 Forest plot demonstrating angular deviation (°) for all selected articles

using a novel pin device to control the vertical positioning of the implant can improve the accuracy to a level where prefabricated restoration could be inserted with an overall misfit which did not exceed 40 μm (Tahmaseb, De Clerck, Aartman & Wismeijer, 2012). Therefore, the final static drill guide design will have a significant effect on the final outcome accuracy.

Risk of bias is present in all studies where the follow-up implant position was assessed by CT or CBCT after actual implant placement. Beam hardening and radiographic artefacts create a potential source of error in comparing implant position. Arisan and coworkers noted that the CBCT images often required a manual tuning of greyscale and scatter noise deletion to allow accurate pre- and post-treatment assessment (Arisan et al., 2013). In addition, patient-related movement during scanning may also create errors in pre- and postimplant positional discrepancy. Pettersson et al. found that a large number of implants in their study needed to be removed from analysis as the rendering of the implant form in the postoperative CBCT was geometrically incorrect due to patient movements (Pettersson et al., 2012). Therefore, accurate comparisons could not be made. The number of fixation points for static guides varied between studies; some utilised three fixations screws, whilst others preferred to use 4.

The effect of smoking on mucosal thickness was evaluated by one group who found increases in tissue thickness had an effect on the accuracy (Cassetta, Stefanelli, Giansanti, Di Mambro & Calasso, 2011). Schnutenhaus et al. specified that if tissue thickness was greater than 3.5 mm a flap was raised to reduce the effect of flap thickness on the accuracy of outcome. Smoking habits were not exclusion criteria for patient enrolment within the studies (Schnutenhaus et al., 2016). In an interesting manner, some implants that were placed using a flap-less surgery protocol did not have a tissue punch procedure prior to drilling sequences (D'haese et al., 2012) As the early part of implant placement during guided surgery is unguided, the presence of thick dense tissue, which is not removed by tissue punches in a flapless approach, may alter the accuracy. Mucosal-supported guides also varied in the extent of tissue coverage. Local anaesthesia does also cause tissue swelling, which can affect the fitting and seating of a drilling guide, particularly if it is completely mucosally supported. Instability of the guides during early planning processes is also a further cause of inaccuracy (D'haese et al., 2012). Furthermore, implant abutment connection and tightening at the time of surgery for immediate loading may contribute to positional errors due to a lack of implant rotation stability.

TABLE 8 All publication reporting on angular deviation

Study	No of patients	No of implants
Arisan (2013)	11	102
Cassetta (2012)	11	95
Cassetta (2013)	20	227
Cassetta (2014)	28	225
D'haese (2012)	13	78
Ersoy (2008)	21	94
Fürhauser (2015)	27	27
Geng (2015)	24	111
Lee (2013)	48	102
Ozan (2009)	30	110
Pettersson (2012)	30	139
Schnutenhaus (2016)	24	24
Van de Wiele (2015)	16	75
Vasak (2011)	18	86
Vercruyssen (2014/2015)	59	311
Verhamme (2015-1)	25	150
Verhamme (2015-2)	30	104
Verhamme (2016)	12	72
Vieira (2013)	14	62
Total	461	2,194

The technique for radiographic data set segmentation varied considerably and was not reported in one study (D'haese et al., 2012). In addition, standardisation of the gantry angle is not known for many studies (Ersoy, Turkyilmaz, Ozan & McGlumphy, 2008). Few studies also specified the height of the guiding sleeves creating a possible error for alignment (Schnutenhaus et al., 2016). No studies prescribed an evaluation method of template fit prior to surgery nor an assessment of guide sleeve fit into the SLA produced guide. Implant diameter and length was not specified for every study.

The authors acknowledge that this systematic review is limited by the lack of homogeneity of study designs within the publications included for review. Many different surgical factors and techniques were not standardised between the studies, which serves to confound the true accuracy of guided surgery. In addition, there are many steps within the digital workflow itself, where there is a possibility of accumulating error, which also serves to mask the real accuracy of the technique. The reliance on radiographic techniques alone for comparing pre- and post-treatment positions is also considered another source of potential error and future investigations should seek to use alternative comparison methods. Furthermore, very few of the studies have focussed on the value of guided surgery in realising the intended prosthetic plan or the outcome of the final aesthetics. Whilst these limitations are acknowledged, there is a trend towards greater accuracy with a digital workflow. Also the

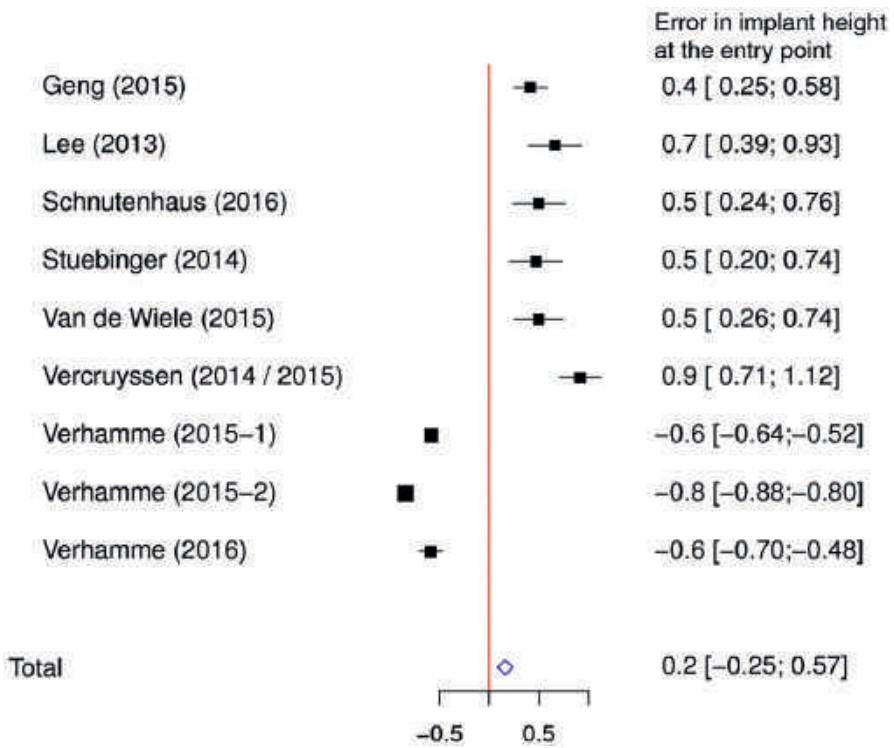

FIGURE 9 The forest plot demonstrating error (mm) in implant height at the entry point in all selected publications

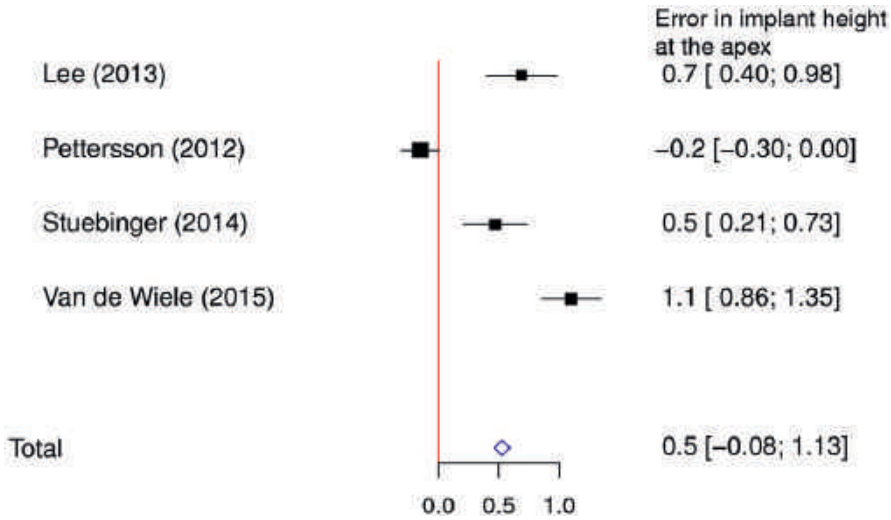

FIGURE 10 The forest plot demonstrating error in implant height (mm) at the apical point in all selected publications

TABLE 9 Publications specifically reporting on angular deviation in separate groups, partial edentulous, full edentulous

Edentulism status	Study	No of patients	No of implants
Partially edentulous	Füerhauser (2015)	27	27
Partially edentulous	Schnutenhaus (2016)	24	24
Partially edentulous	Total	51	51
Fully edentulous	Arisan (2013)	11	102
Fully edentulous	Cassetta (2012)	11	95
Fully edentulous	Cassetta (2014)	28	225
Fully edentulous	D'haese (2012)	13	78
Fully edentulous	Pettersson (2012)	30	139
Fully edentulous	Van de Wiele (2015)	16	75
Fully edentulous	Vercruyssen (2014/2015)	59	311
Fully edentulous	Verhamme (2015-1)	25	150
Fully edentulous	Verhamme (2015-2)	30	104
Fully edentulous	Verhamme (2016)	12	72
Fully edentulous	Vieira (2013)	14	62
Fully edentulous	Total	249	1,413
Grand Total		300	1,464

authors decided to review only the publications in the English language, which might result in missing information published in other languages.

5 | CONCLUSIONS

Based on the present systematic review, it can be concluded that the accuracy of static computer-aided implant surgery (s-CAIS) is within the clinical acceptable range in the majority of clinical situations. However, a safety marge of at least 2 mm should be respected. A lack of homogeneity was found in techniques adopted between the different authors and the general study designs. Better accuracy was found when partially edentulous patients were treated compared to fully edentulous patients. As a large number of factors can contribute to deviations of the actual implant position from the planned, further studies are required to investigate these factors.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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CONSENSUS REPORT

WILEY CLINICAL ORAL IMPLANTS RESEARCH

Group 5 ITI Consensus Report: Digital technologies

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*[Corrections added November 2018, after publication: author's forename changed from 'Aljeandro' to 'Alejandro' and affiliation changed from 'San Sebastian University' to 'Pontificia Universidad Católica de Chile']

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Abstract

Objectives: Working Group 5 was assigned the task to review the current knowledge in the area of digital technologies. Focused questions on accuracy of linear measurements when using CBCT, digital vs. conventional implant planning, using digital vs. conventional impressions and assessing the accuracy of static computer-aided implant surgery (s-CAIS) and patient-related outcome measurements when using s-CAIS were addressed.

Materials and methods: The literature was systematically searched, and in total, 232 articles were selected and critically reviewed following PRISMA guidelines. Four systematic reviews were produced in the four subject areas and amply discussed in the group. After emendation, they were presented to the plenary where after further modification, they were accepted.

Results: Static computer-aided surgery (s-CAIS), in terms of pain & discomfort, economics and intraoperative complications, is beneficial compared with conventional implant surgery. When using s-CAIS in partially edentulous cases, a higher level of accuracy can be achieved when compared to fully edentulous cases. When using an intraoral scanner in edentulous cases, the results are dependent on the protocol that has been followed. The accuracy of measurements on CBCT scans is software dependent.

Conclusions: Because the precision intraoral scans and of measurements on CBCT scans and is not high enough to allow for the required accuracy, s-CAIS should be considered as an additional tool for comprehensive diagnosis, treatment planning, and surgical procedures. Flapless s-CAIS can lead to implant placement outside of the zone of keratinized mucosa and thus must be executed with utmost care.

KEYWORDS
accuracy, computer-aided surgery, cone beam computed tomography, intraoral scans, oral implantology, patient-reported outcome measures

1 | INTRODUCTION

Digital technologies are gaining a predominant position in implant dentistry. Cone beam computed tomography (CBCT) scans provide clinicians with Digital Imaging and Communications In Medicine (DICOM) data which can be aligned with Standard Tessellation Language (STL) files obtained from intraoral scanners in computer-aided design (CAD) software to plan implant treatment and design drill guides. However, the accuracy of these separate technologies, the drill guides as well as the patients' perception of the treatment when using these technologies are still subject of debate.

Group 5 of the 6th ITI consensus conference was assigned the task to review the current knowledge in the area of digital technologies with a special focus on accuracy of linear measurements when using CBCT, using digital vs. conventional implant planning, using digital vs. conventional impressions and assessing the accuracy of static computer-aided implant surgery (s-CAIS).

They were asked to provide statements and recommendations based on their findings. Four systematic reviews which were prepared and reviewed prior to the consensus conference formed the basis for discussion within the working group. Minor modifications were made as required. Consensus statements and clinical

recommendations were formed which were then presented and accepted following further discussion and modifications when required by the plenary. The working group also prepared recommendations for future research. The four systematic reviews are listed below.

2 | PAPER 1

Static computer-aided implant surgery (s-CAIS) analysing patient-reported outcome measures (PROMs), economics, and complications: A systematic review.

Tim Joda, Wiebe Derksen, Julia Gabriela Wittneben, Sebastian Kuehl.

2.1 | Preamble

The objective of this study was to systematically evaluate the scientific literature for patient-reported outcome measures (PROMs) in static computer-aided implant surgery (s-CAIS). A PICO strategy was executed using an electronic (MEDLINE, EMBASE, CENTRAL) plus manual search up to 06-15-2017 focusing on clinical studies investigating s-CAIS with regard to patients' pain & discomfort, economics and/or intraoperative complications. Search strategy was assembled from multiple conjunctions of MeSH-Terms and unspecific free-text words. Assessment of risk of bias in selected studies was made at a trial level applying the Cochrane Collaboration Tool and the Newcastle–Ottawa Assessment Scale, respectively. The systematic search identified 112 titles. Seventy abstracts were screened, and 14 full texts were included for analysis. A total of 484 patients were treated with s-CAIS for placement of 2,510 implants. Due to the heterogeneity of the included studies, meta-analyses could not be performed.

2.2 | Consensus statement 1

It cannot be stated that s-CAIS, in terms of pain & discomfort, economics, and intraoperative complications, is beneficial compared with conventional implant surgery.

Consensus statement 1 is based on four RCTs, four prospective Cohort Studies, five retrospective Cohort Studies, and one Case Series.

2.3 | Clinical recommendations

2.3.1 | However

1. Based on PROMs, economics, and complications, there is no contraindication to use s-CAIS instead of conventional implant surgery.
2. Flapless s-CAIS may be beneficial in fully edentulous cases in relation to postoperative pain intensity compared with open-flap procedures.
3. Flapless s-CAIS may lead to implant placement outside the zone of keratinized mucosa; therefore, the quality and quantity of the keratinized mucosa must be assessed before planning s-CAIS.

2.4 | Recommendations for future research

Based on this systematic review and considering the different clinical indications, such as fully vs. partially edentulous, using flap vs. flapless techniques, the group recommended that there is a clear need for:

RCTs with appropriate power analysis investigating s-CAIS related to PROMs with standardized protocols, which allow reliable and reproducible assessments of:

- Oral health impact profile (OHIP);
- Standardized use of Visual Analog Scales (VAS) for pain & discomfort;
- Cost-benefit-analysis considering virtual planning, surgery, laboratory, and prosthetic work, including required equipment and materials;
- Time efficiency factor analyzing virtual planning, surgery, and the respective prosthetic phase;
- Complication rates.

3 | PAPER 2

The accuracy of different dental impression techniques for implant-supported dental prostheses: A systematic review and meta-analysis.

Tabea Flügge, Wicher Joerd van der Meer, Beatriz Gimenez Gonzalez, Kirstin Vach, Daniel Wismeijer, Ping Wang.

3.1 | Preamble

Digital impression technology is increasingly used in clinical practice as it is said to have many advantages above, and the potential to substitute for, conventional impression techniques.

Intraoral scanners use surface capturing technologies to acquire data. Scan bodies are captured by intraoral scanners and can be used to locate the implant positions in a virtual model.

The accurate transfer of implant positions in relation to neighboring implants or teeth is paramount for the design and the fit of implant-supported prosthesis.

Therefore, this systematic review has evaluated the scientific evidence for the accuracy of optical implant scans compared with scans of stone cast made from conventional implant impressions.

The term accuracy refers to trueness, describing the closeness of a measurement to the actual value, and to precision, describing the closeness of multiple measurement results (ISO 12836: 2015).

The present systematic review includes 79 studies consisting of one RCT, one retrospective study, two clinical studies, and 75 bench studies. A meta-analysis of 63 studies was performed after dividing the data into subgroups; however, a high heterogeneity of reported data was detected.

One of the reasons for the lack of clinical studies is related to the difficulty of assessing the trueness of intraoral impressions, as the actual implant positions can only be approximated as there is no control.

Currently, there is limited clinical evidence on the accuracy of intraoral digital impressions of dental implants compared with conventional implant impressions. The data were based on bench studies and one clinical study.

3.2 | Consensus statement 1

The accuracy of digital impressions with intraoral scanners of single or adjacent implants in partially dentate jaws and multiple implants in edentulous jaws is comparable to the accuracy of conventional implant impressions under laboratory conditions.

Consensus statement 1 is based on six bench studies.

3.3 | Consensus statement 2

The accuracy of digital impressions is negatively influenced with an increase in the interimplant span between multiple implants in partially dentate and edentulous situations.

Consensus statement 2 is based on three bench studies

3.4 | Consensus statement 3

The scan protocol using intraoral scanners has a significant influence on digital implant impression accuracy in the edentulous jaw.

Consensus statement 3 is based on four bench studies using the same control

3.5 | Consensus statement 4

The accuracy of digital implant impressions of edentulous jaws varies when using different intraoral scanners.

Consensus statement 4 is based on four bench studies.

3.6 | Clinical recommendations

1. The use of digital impressions for single implant restorations can be recommended.
2. To optimize digital implant impressions for each clinical situation, device-specific intraoral scanning protocols must be followed.
3. The use of scan bodies is recommended for accurate digital implant impressions.
4. Digital impressions of large interimplant spans are not yet recommended for routine clinical use.
5. For routine clinical use, intraoral digital implant impressions of edentulous jaws cannot yet be recommended.

3.7 | Recommendations for future research

The evolution of software versions goes faster than the process of conducting a study. Major software upgrades may lead to changes in the scanning protocol and the resulting virtual model. The same hardware can produce different results when using the latest software release compared to the previous one.

Therefore, (a) there is a need for established study designs considering standardized conditions, and (b) it is crucial to address the software version and used scan protocol for further studies to create a reliable database for accurate statistical analyses.

Although in clinical practice, single unit restorations are being performed using a digital workflow, there is a need for further research to conclude if it is a predictable and reliable procedure when compared to the conventional workflow.

- There is a lack of literature about the accuracy of different intraoral scan bodies in terms of geometry, dimension, material, and surface characteristics. More studies regarding these aspects should be conducted.
- In studies using scan bodies, design, and characteristics should be defined to make studies comparable.
- Regarding multiple implant-supported restorations for partially dentate or edentulous cases, different scanning protocols should be developed and compared.

The influence of distance between scan bodies, length and geometry of the edentulous span, mucosal morphology, and on the accuracy of digital impressions should be studied.

4 | PAPER 3

Accuracy of linear measurements on CBCT images related to presurgical implant treatment planning: A systematic review.

George Fokas, Vida M. Vaughn, William C. Scarfe, Michael M. Bornstein.

4.1 | Preamble

The aim of this systematic review was to identify studies that assessed the accuracy of linear measurements of bone dimensions related to implant dentistry using CBCT. For inclusion, the studies could be designed as ex vivo or in vivo investigations, but were only included when the linear values from CBCTs were also compared to a control, which could be considered as the gold standard. The review was performed using the PICOs framework, where intervention was described as the use of CBCT for the purpose of determining outcomes associated with

the accuracy and reliability (repeatability/reproducibility) of linear measurements.

There was great variability in the methodology of the included studies as well as the extracted data; thus, a direct comparison of the available evidence was not possible. The data were therefore compared using descriptive modalities, and no meta-analysis was performed.

The present systematic review identifies, reviews, analyses, and summarizes available evidence on the accuracy of linear measurements when using CBCT imaging specifically in the field of implant dentistry.

The primary outcome of this systematic review was demonstration of the accuracy of linear CBCT measurements of alveolar bone at edentulous sites or anatomical structures related to implant dentistry.

The secondary outcomes of this review were as follows:

- Demonstration of reliability (repeatability within one observer / reproducibility between different observers) of linear measurements from CBCTs.
- Assessing the potential impact of imaging factors such as voxel size, FOV, rotational arc, and software package used on the accuracy of linear measurements in CBCTs.

From 2516 titles retrieved initially, a total of 22 studies were included for the final analysis. Of those, two were clinical and 20 were ex vivo investigations.

4.2 | Consensus statement 1

With regard to implant treatment planning, CBCT provides cross-sectional images that demonstrate high accuracy and reliability for linear bone measurements with a relatively low radiation dose according to As Low As Diagnostically Acceptable (ALADA) guidelines.

This statement is based on a total of 19 studies: one clinical, five cadavers, and 13 dry jaws/skulls studies.

4.3 | Consensus statement 2

The actual linear dimensions taken from CBCT scans can be over- or underestimated, and the range of error can exceed 1 mm in selected cases.

This statement is based on a total of six studies: two clinical, two cadavers, and two dry skull studies.

4.4 | Consensus statement 3

A smaller voxel size resulting in a higher resolution does not lead to a higher accuracy of linear measurements on CBCTs for bone dimensions at edentulous sites.

This statement is based on a total of four studies: one cadaver, and three dry skull/jaws studies.

4.5 | Consensus statement 4

The size of the field of view and partial rotations (180° vs. 360°) do not adversely affect linear measurements.

This statement is based on one cadaver study (addressing the FOV) and one dry mandibles' study (addressing the impact of rotation).

4.6 | Consensus statement 5

Reported accuracy is independent of the software package used.

This statement is based on one study (dry mandibles).

4.7 | Clinical recommendations

1. CBCTs should be considered the imaging tool of choice for three-dimensional (3D) dental implant site assessment.
2. Based on consensus statement 2, a minimal safety margin of 2 mm to relevant adjacent anatomic structures should be considered.
3. Smaller voxel sizes do not result in increased accuracy of linear measurements on CBCT scans. A voxel size of 0.3–0.4 mm^3, the smallest FOV, and if possible partial rotations should be used for preoperative implant treatment planning in order to reduce radiation dose exposure: this should result in similar image quality as scans comprised of smaller voxel size or larger FOV.

4.8 | Recommendations for future research

- Due to the inhomogeneity of the extracted data from the included studies, it was not possible to conduct a multivariate analysis. Further studies should focus on identifying specific exposure and acquisition parameters that influence the accuracy of linear measurements. Moreover, it is of interest to know the mechanics of how these parameters influence linear accuracy, how they may interact, and develop dose reduction imaging protocol strategies.
- Additional In vivo studies to assess the linear accuracy of CBCT for implant site assessment are suggested comparing radiographic data with true clinical values and to determine the validity of currently used in vitro models.
- Additional investigations should focus on determining the influence of the choice of software and specific display protocols (e.g. volumetric orientation and image enhancements) on the accuracy of linear measurements at implant sites.

5 | PAPER 4

The accuracy of static computer-aided implant surgery: A systematic review and meta-analysis.

Ali Tahmaseb, Vivian Wu, Daniel Wismeijer, Wim Coucke, Christopher Evans.

5.1 | Preamble

Prosthetically driven implant placement is considered the optimal approach when treating patients with dental implants. Detailed pretreatment planning is necessary to ensure a correct three-dimensional (3D) implant position within the alveolar bone relative to surrounding anatomical structures and the future prosthetic restorations.

The virtual model of the area of interest in static computer-aided implant surgery (s-CAIS) can be created by aligning the 3D volumetric data scan (DICOM file) with the surface scans (STL file) of the patient in the appropriate planning software. In addition, design and production software (CAD/CAM) and associated hardware are necessary to design and produce the surgical guide to perform static computer-guided implant surgery.

The findings of previous systematic reviews have highlighted a clinically unacceptable range of deviations in accuracy between the planned and final implant position. Due to developments in the technology used in computer-aided implant surgery, the authors of the current systematic review decided to search the literature staring form 2008 to find out if these developments do lead to improved accuracy of treatment.

The primary aim of this study was to assess the literature on the accuracy of static computer-aided implant surgery. In addition, factors such as guide support, implanted jaw, and degree of edentulism were assessed for their effect on accuracy.

Electronic and manual literature searches were applied to collect information about the accuracy of static computer-assisted implant systems. Meta-regression analysis was performed to summarize the accuracy studies. From a total of 372 articles, 19 studies were selected for inclusion for qualitative synthesis. A total of 2,238 implants in 471 patients that had been placed using static guides which were available for review.

There was a wide variation in levels of evidence in the studies included on static computer-assisted implant placement.

Sufficient data were available to perform meta-analysis on the primary outcome of 3-D implant position. The only factor found to influence the accuracy was the state of edentulism.

5.2 | Consensus statement 1

The number of included clinical studies was limited to 20 with a heterogeneous mix of study designs.

5.3 | Consensus statement 2

The mean 3-D deviation for static computer-aided implant surgery (s-CAIS) at the entry point was 1.2 mm [1.04, 1.44, 95% CL], at the apical position was 1.5 mm [1.29, 1.62 mm, 95% CL], and for angular deviation was 3.5 [3.00, 3.96, 95% CL].

Consensus Statement 1 is based on 20 clinical trials (one RCT, 11 UPCS's, and eight URCS 's).

5.4 | Consensus statement 3

With s-CAIS, there is a vertical discrepancy in the apical point of the implant between the planned and actual positions of −0.25 and −0.57 mm, 95% CL.

Consensus statement 2 is based on eight publications (one RCT, five UPCS's, and two URCS 's).

5.5 | Consensus statement 4

With s-CAIS, there is a vertical discrepancy in the apical point of the implant between the planned and actual positions of −0.08 and 1.13 mm, 95% CL.

Consensus statement 3 is based on four publications (three UPCS's and one URCS's).

5.6 | Consensus statement 5

Partially edentulous cases show better accuracy using s-CAIS compared to fully edentulous cases.

Consensus statement 4 is based on eight publications (one RCT, five UPCS's, and two URCS 's).

5.7 | Clinical recommendations

1. Static computer-aided implant surgery (s-CAIS) should be considered as an additional tool for comprehensive diagnosis, treatment planning and surgical procedures.
2. s-CAIS should be prosthetically driven.
3. Surgical experience and general comprehensive training are desirable to achieve an accurate and favorable outcome for implants placed using s-CAIS.
4. While recent studies indicate improved accuracy when using s-CAIS in partially edentulous cases, a safety margin of 2mm from critical anatomical structures should be maintained.
5. The alignment of surface scans, including the prosthetic planning, with 3D volumetric imaging data is recommended to improve the accuracy of the anatomical position of the implant.
6. Surgical guides should be digitally designed on surface scan files which have been aligned with DICOM data, which is more accurate than using DICOM data alone.
7. Manufacturer's guidelines should be followed with respect to calibration protocols, for all hardware to maintain optimal accuracy.

5.8 | Recommendations for future research

- Future research should not use CBCT/CT for pre- and postimplant position evaluation.
- Future research should focus on evaluating implant position accuracy using surface scans of the final implant positions. This will reduce patient radiation exposure and improve evaluation accuracy data.

- Future research should more precisely define the degree of edentulism and the treatment protocols that are followed.
- Future research should quantify the effect of every step in the digital workflow.
- A number of factors within the digital workflow contribute to deviations in the actual implant position from the initially planned positions, and these should be investigated separately.

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