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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

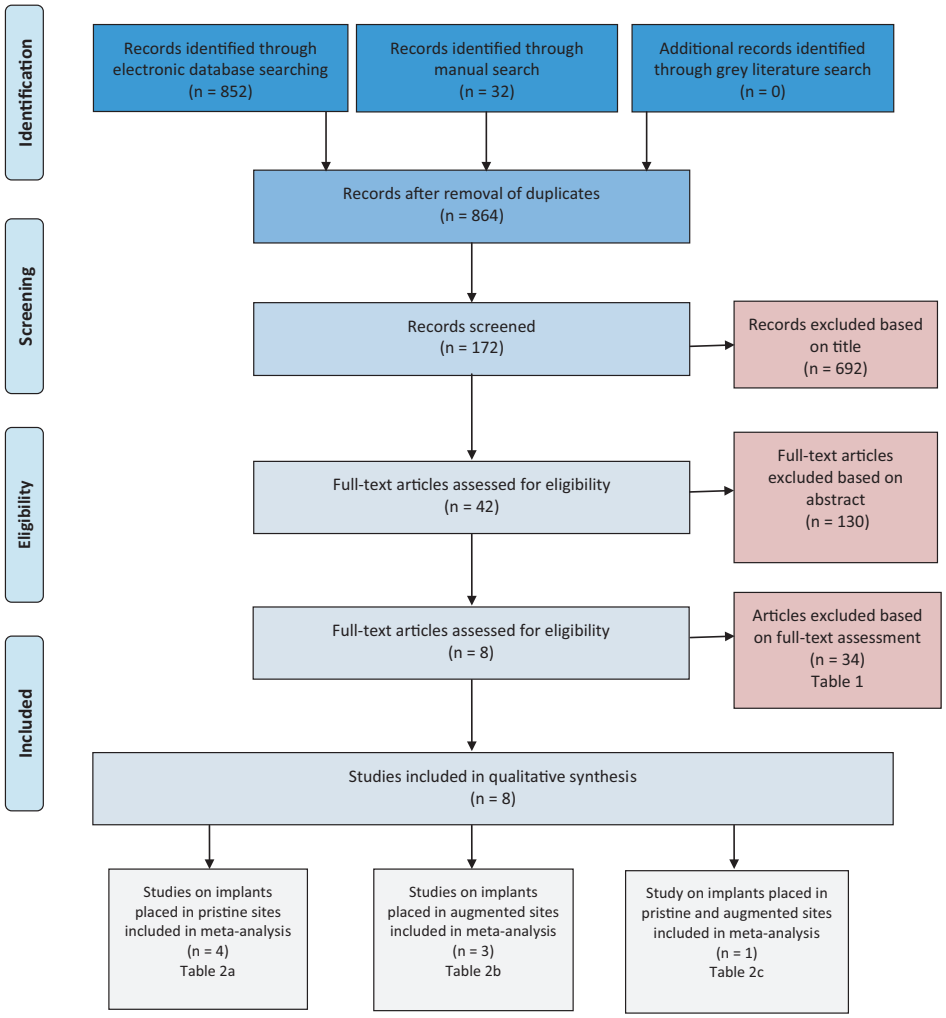

FIGURE 1 Flow diagram of the systematic review

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

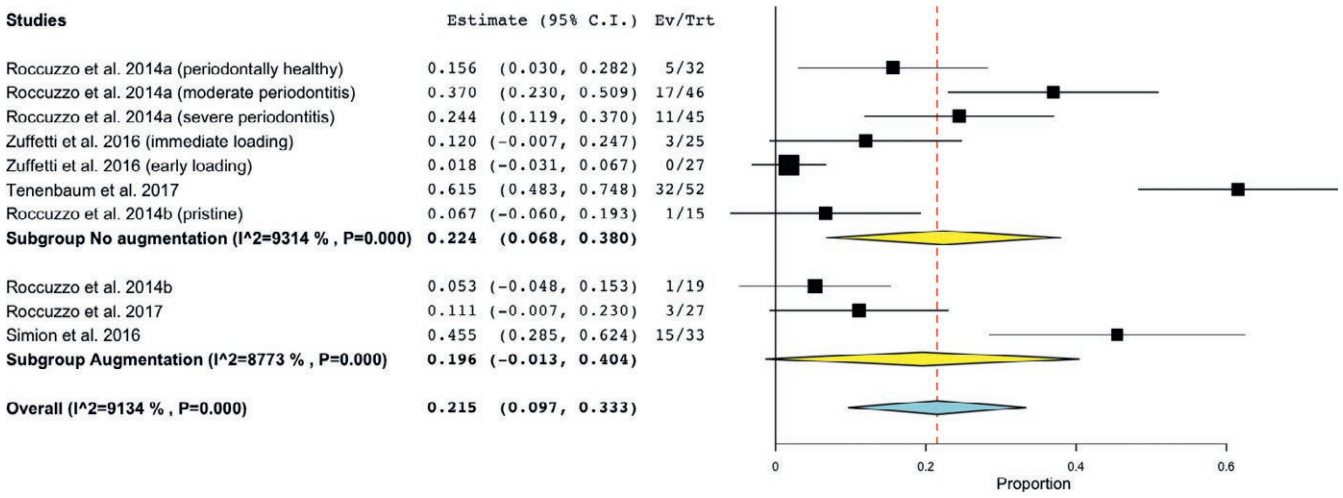

FIGURE 2 Forest plot of the weighted mean prevalence of peri-implant mucositis at patient level of implants placed in pristine vs. augmented sites

[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).

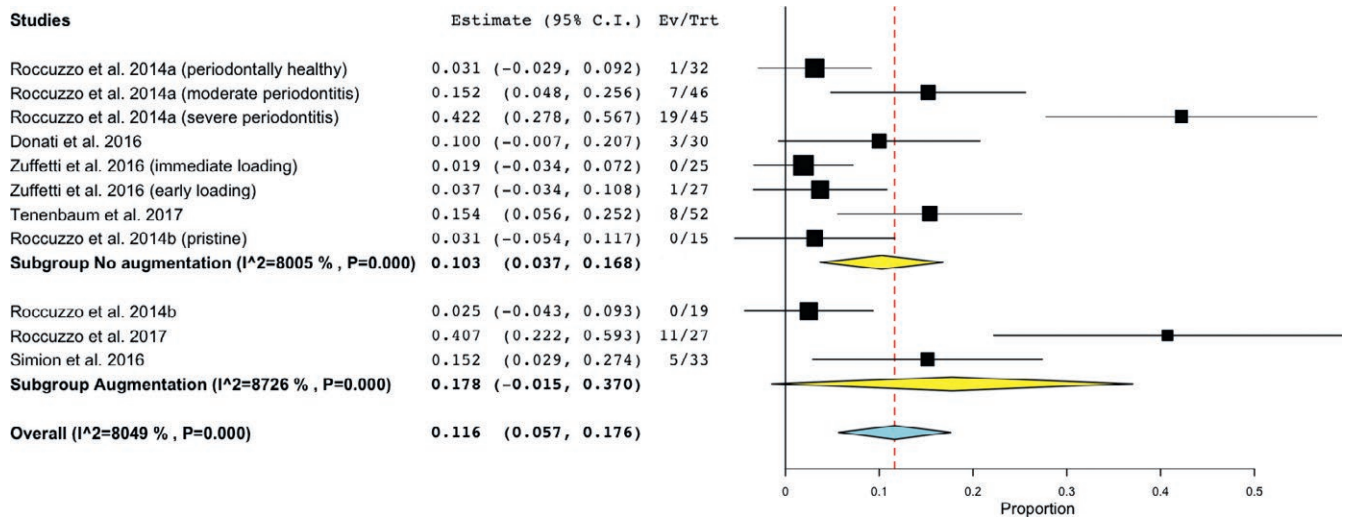

FIGURE 3 Forest plot of the weighted mean prevalence of peri-implantitis at patient level of implants placed in pristine vs. augmented sites

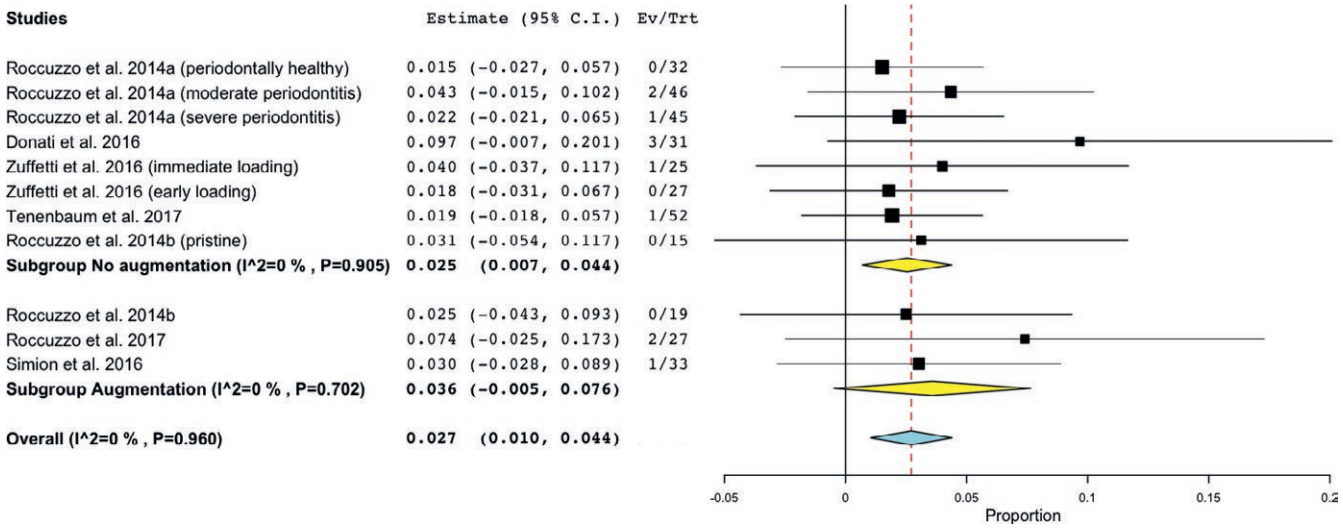

FIGURE 4 Forest plot of the weighted mean prevalence of failure at patient level of implants placed in pristine vs. augmented sites

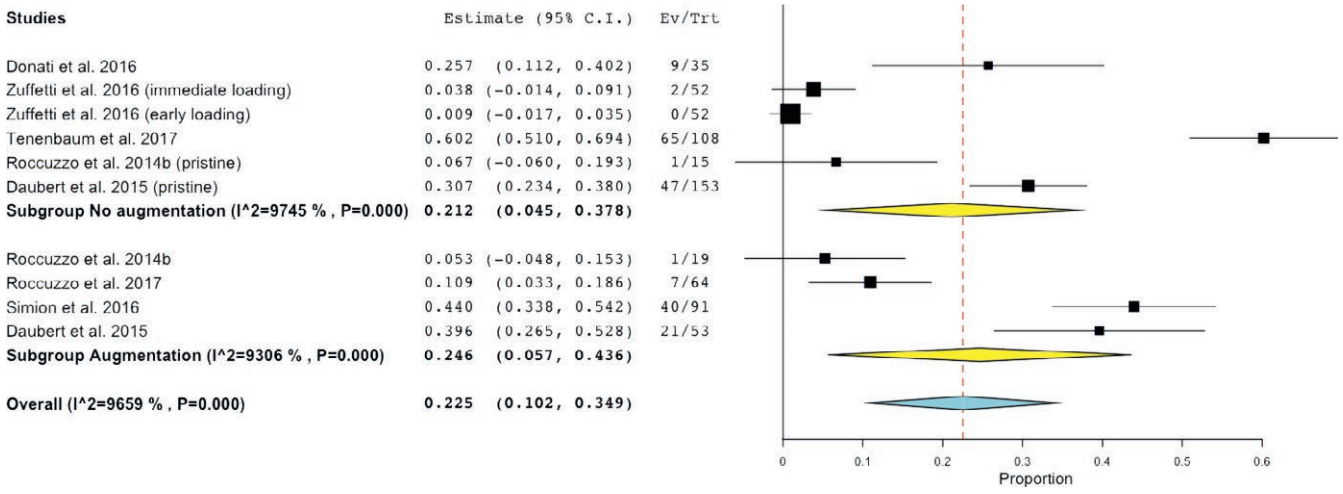

FIGURE 5 Forest plot of the weighted mean prevalence of peri-implant mucositis at implant level of implants placed in pristine vs. augmented sites

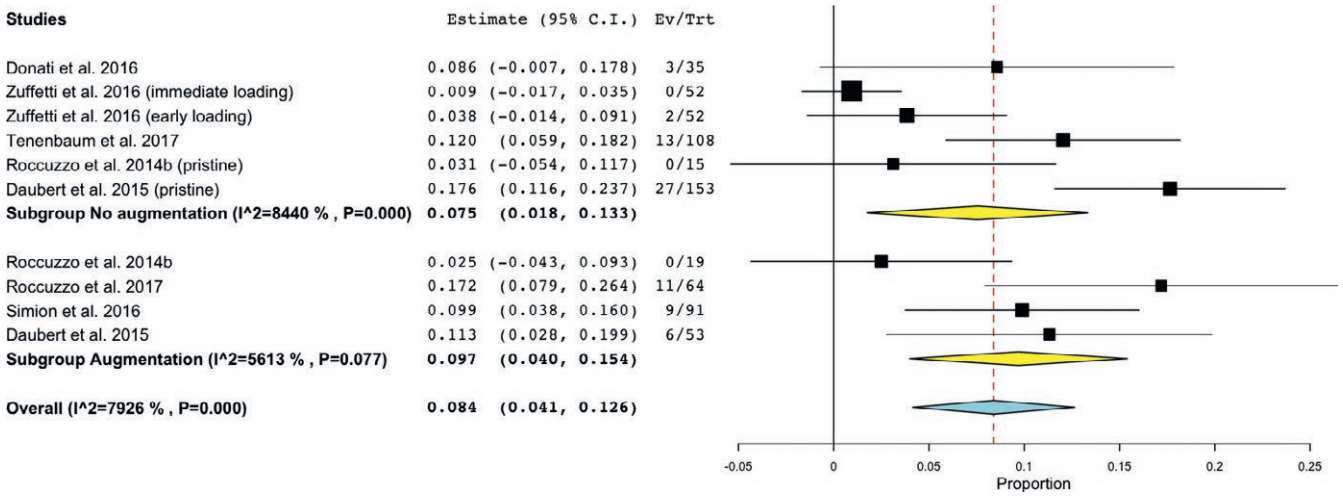

FIGURE 6 Forest plot of the weighted mean prevalence of peri-implantitis at implant level of implants placed in pristine vs. augmented sites

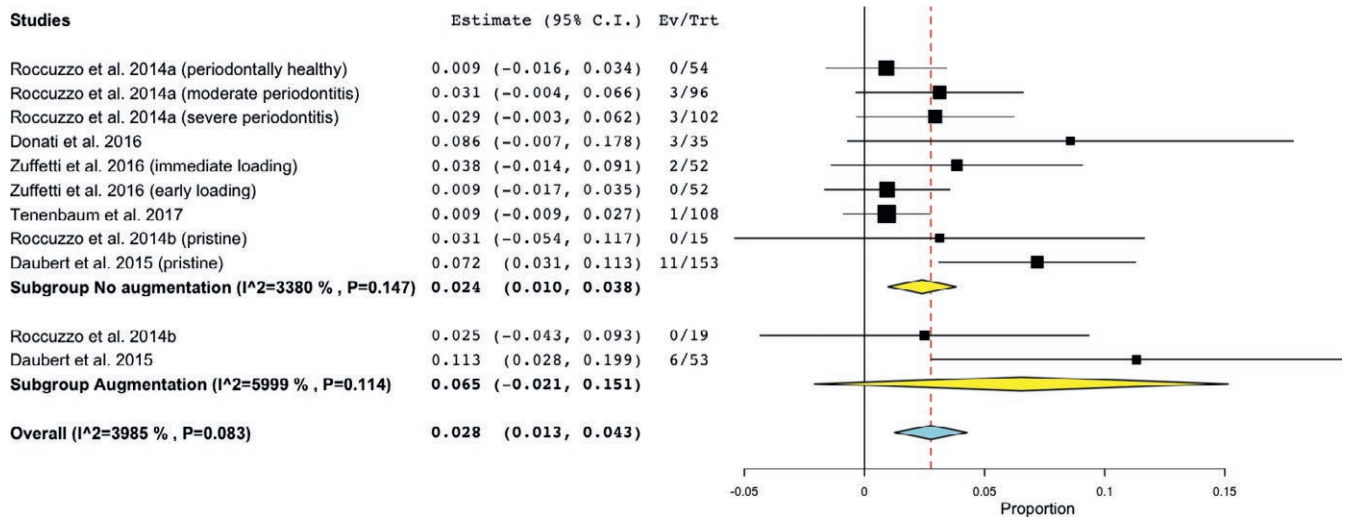

FIGURE 7 Forest plot of the weighted mean prevalence of failure at implant level of implants placed in pristine vs. augmented sites

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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