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REVIEW ARTICLE

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Effects of lateral bone augmentation procedures on peri-implant health or disease: A systematic review and meta-analysis

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Abstract

Objectives: This systematic review evaluated the evidence on the effect of the interventions aimed for lateral ridge augmentation (both simultaneously with implant placement or as a staged procedure) on peri-implant health or disease.

Methods: A protocol was developed to answer the following PICO question: "In patients with horizontal alveolar ridge deficiencies (population), what is the effect of lateral bone augmentation procedures (intervention and comparison) on peri-implant health (outcome)?" Included studies were randomised controlled trials or controlled clinical trials with a follow-up of at least 12 months after implant loading. Meta-analyses were performed whenever possible, including subgroup analysis based on follow-up.

Results: Twelve final publications from eight investigations were included. The results from the meta-analysis indicated that irrespective of the type of intervention, the inflammatory changes, based on bleeding on probing (%) were minimal, both at short- (n = 1; weighted mean difference [WMD] = −1.00; 95% CI [−14.04; 12.04]; p = .881) and long-term (n = 5; WMD = −5.63; 95% CI [−18.42; 7.16]; p = .881). When comparing different treatment modalities, no significant differences were observed (n = 6; WMD = −3.36; 95% CI [−12.49; 5.77]; p < .471). Similarly, changes in probing pocket depth and marginal bone levels were not significantly different among groups. The incidence of peri-implantitis was evaluated in three investigations and varied from 16% to 26% after a follow-up period of 6–8 years.

Conclusions: The results from this systematic review and meta-analysis have shown that lateral ridge augmentation procedures can maintain peri-implant health over time with low mucosal inflammatory changes and a relatively small incidence of peri-implant bone loss.

KEYWORDS

alveolar ridge atrophy, bone regeneration, bone substitutes, dental implant, periodontal index, ridge augmentation

1 | INTRODUCTION

Dental implants have become a highly predictable treatment to rehabilitate, partially or fully, edentulous patients, with resulting cumulative survival rates ranging between 89.5% and 92.7% after 10–27 years of function (Balshi, Wolfinger, Stein, & Balshi, 2015; Chappuis et al., 2013). However, due to the bone resorptive changes occurring in the alveolar process after tooth extraction (Schropp, Wenzel, Kostopoulos, & Karring, 2003; Vignoletti et al., 2012) or due to pathologic bone loss, as a result of periodontitis, trauma or infection, it is frequently the lack of sufficient bone volume to place implants in the ideal prosthetic position, which is a critical factor to attain the appropriate function and aesthetics of the implant-supported restorations.

To reconstruct deficient alveolar ridges to facilitate dental implant placement different bone regenerative techniques have been proposed and evaluated (Donos et al., 2008; Rocchietta, Fontana, & Simion, 2008). Depending on the morphology of the bone defect (Seibert, 1983), these regenerative interventions may have as main objectives, lateral, vertical or combined bone augmentation. Depending whether the implant could be placed with primary stability in the prosthetically driven position, these regenerative interventions could be simultaneous to the regenerative procedure or be staged to the implant installation (staged approach) (Benic & Hammerle, 2014; Hämmerle, Jung, & Feloutzis, 2002; Kuchler & von Arx, 2014; Merli et al., 2016).

While lateral augmentation procedures are highly predictable, with reported implant survival rates of 87%–95% and 99%–100% for the simultaneous and the staged approaches, respectively (Donos et al., 2008), vertical ridge augmentation interventions have a low degree of predictability and a high incidence of complications (Rocchietta et al., 2008). For lateral bone augmentation, two main approaches have been used, either using autogenous bone blocks fixated to the jaw bone by micro screws, or by means of guided bone regeneration (GBR) combining different bone replacement grafts and barrier membranes. A recent systematic review studied the efficacy of both types of interventions in lateral bone augmentation (Sanz-Sanchez, Ortiz-Vigon, Sanz-Martin, Figuero, & Sanz, 2015). The results from the meta-analysis showed that for the simultaneous approach, the combination of bone replacement grafts and barrier membranes were associated with superior outcomes. For the staged approach, however, the combination of bone blocks, particulated grafts and barrier membranes provided the best outcomes, although the morbidity and advent of postoperative complications when using this procedure should be taken into consideration.

Nowadays, with the better understanding on the ethiopathogenesis and the incidence of peri-implant diseases (Berglundh, Zitzmann, & Donati, 2011; Derks & Tomasi, 2015; Lang, Bosshardt, & Lulic, 2011) and the low predictability in the treatment of peri-implantitis (Figuero, Graziani, Sanz, Herrera, & Sanz, 2014), it is important to assess the impact of the different implant surgical protocols on the peri-implant tissue health and the incidence of biological complications, at both short- and long-term. Whereas some cross-sectional retrospective studies have shown that implants placed into regenerated bone exhibit a clinical performance similar to implants placed into native bone with respect to implant survival, marginal bone height and peri-implant soft tissue parameters (Benic, Jung, Siegenthaler, & Hammerle, 2009; Zumstein, Billstrom, & Sennerby, 2012), there is not clear evidence on the possible effect of these bone augmentation procedures on the health of the peri-implant mucosa and on the incidence of peri-implantitis.

It is, therefore, the purpose of this systematic review to answer the following P.I.C.O. question: In patients with horizontal alveolar ridge deficiencies (population), what is the effect of lateral bone augmentation procedures (intervention and comparison) on peri-implant health (outcome)?

Additionally, we would like to answer the following question:

"What lateral bone augmentation procedures are associated with superior short- and long-term outcomes associated with peri-implant health?"

2 | MATERIAL AND METHODS

2.1 | Protocol development and eligibility criteria

A protocol was developed and followed the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analyses) statement (Moher, Liberati, Tetzlaff, & Altman, 2009).

2.1.1 | Inclusion criteria (PICOS)

Population: patients, older than 18 years and in good general health, requiring the placement of one or more implants is sites presenting ridge deficiencies.

Interventions: any procedure aimed for lateral bone augmentation (simultaneous or staged).

Comparisons: any procedure aimed for lateral bone augmentation (simultaneous or staged) or the absence of treatment.

Outcomes: peri-implant health outcomes, such as peri-implant bleeding index.

Study design: randomised controlled clinical trials (RCTs) or controlled clinical trials (CCTs) with a minimum sample size of 10 patients (five per group) and a minimum follow-up time of 12 months after implant loading.

2.1.2 | Exclusion criteria

1. Studies assessing the effectiveness of interventions aimed at vertical bone augmentation (GBR, bone blocks, distraction osteogenesis, orthognathic surgery, inter-positional grafts, maxillary sinus augmentation, etc.).
2. Studies aimed at regenerating extractions sockets with or without implant placement.

3. Preclinical studies in animal models.
4. Articles published in a different language than English.

2.1.3 | Type of interventions and comparisons

Studies were selected when including interventions aimed for lateral ridge augmentation with one of these objectives:

1. To locally augment the bone horizontally around an implant to cover exposed threads in dehiscence or fenestration type defects (simultaneous approach).
2. To locally augment the bone horizontally to enable the placement of a dental implant in a subsequent intervention (staged approach).

The following procedures were considered: (i) GBR; (ii) autogenous bone blocks; (iii) allogeneic or xenogeneic bone blocks; (iv) Ridge expansion techniques.

2.1.4 | Types of outcomes

The primary outcomes to assess the peri-implant health status were the percentage of sites positive to bleeding on probing (BOP) at the end of the study. This outcome was calculated as the average of positive sites only around implants. In the studies where a different bleeding index was used and when the raw data could be obtained, the results were transformed to positive or negative BOP.

The following secondary outcomes were studied:

1. Implant survival rates (%).
2. Probing pocket depth (PPD).
3. Interproximal crestal bone level changes assessed with periapical x-rays (mm).
4. Plaque indexes (PI).
5. Bone level changes assessed with a cone beam computer tomography (CBCT).
6. Patient reported outcome measurements (PROMs), such as pain, discomfort, satisfaction, etc.
7. Occurrence of biological complications (%). Biological complications were defined as the occurrence of mucositis (BOP with or without increased PPD and without radiographic bone loss) and/or peri-implantitis (BOP with or without increased PPD and with radiographic bone loss) (Lang & Berglundh, 2011).

2.1.5 | Search strategy

Three electronic databases were used as sources in the search for studies satisfying the inclusion criteria: (i) The National Library of Medicine (MEDLINE via Pubmed); (ii) Embase and (iii) Cochrane Central Register of Controlled Trials. These databases were searched for studies published until August 2016. The search was limited to humans, English language and articles reporting clinical trials.

All reference lists of the selected studies were checked for cross-references. The following journals were hand searched from year 2006 to *2016: Journal of Clinical Periodontology*, *Journal of Periodontology*, *Clinical Oral Implants Research*, *International Journal of Oral & Maxillofacial Implants*, *European Journal of Oral Implantology*, *Implant Dentistry*, *International Journal of Oral and Maxillofacial Surgery*, *Journal of Dental Implantology*, *Journal of Oral and Maxillofacial Surgery and Clinical Implant Dentistry and Related Research*.

The following search terms were used:

Population

[text words]: "dental implant" OR "dental implants" OR "oral implant" OR "oral implants" OR "implant dehiscence" OR "implant dehiscences" OR "dehiscence defect" OR "dehiscence defects" OR "fenestration defect" OR "fenestration defects" OR "alveolar bone loss" OR "ridge atrophy" OR "ridge deficiency" OR "horizontal ridge deficiency" OR "alveolar ridge atrophy"

OR

[MeSH terms]: alveolar bone loss OR dental implants OR bone resorption

Intervention

[text words]: "bone augmentation" OR "lateral bone augmentation" OR "guided bone regeneration" OR GBR OR "alveolar ridge augmentation" OR "lateral ridge augmentation" OR "bone regeneration"

OR

[MeSH terms]: bone regeneration OR guided tissue regeneration OR alveolar ridge augmentation OR alveolar bone grafting

Population AND Intervention

2.2 | Screening methods

Two reviewers (ISS and AC) did the primary search by screening independently the titles and abstracts. The same reviewers selected for evaluation the full manuscript of those studies meeting the inclusion criteria, or those with insufficient data in the title and abstract to make a clear decision. Any disagreement was resolved by discussion with a third reviewer (MS). The inter-reviewer reliability (percentage of agreement and kappa correlation coefficient) of the screening method was calculated.

2.3 | Data extraction

One reviewer (ISS) extracted the data. Authors of studies were contacted for clarification when data was incomplete or missing. Data were excluded until further clarification could be available if agreement could not be reached. When the results of a study were published more than once or if the results were presented in a number of publications, the data with longest follow-up was included only once. Information regarding tobacco consumption and history of periodontitis was collected.

2.4 | Assessment of risk of bias

Quality of the included RCTs and CCTs was assessed by one reviewer (ISS), following the Cochrane Collaboration recommendations (Higgins & Green, 2011).

The following items were evaluated as low, high or unclear risk of bias:

1. Selection bias (sequence generation and allocation concealment).
2. Performance bias (blinding of participants/personnel).
3. Detection bias (blinding of outcome assessment).
4. Attrition bias (incomplete outcome data).
5. Selective reporting bias (selective reporting outcomes).
6. Other potential risk of bias.

2.5 | Data synthesis

To summarise and compare studies, mean and standard deviation (*SD*) values were directly pooled and analysed with weighted mean differences (WMDs) and 95% confidence intervals (CIs). For comparing the changes on BOP, two types of meta-analyses were performed. The first one compared the final and baseline visits within each arm of the RCT independently, whereas the second evaluated the differences on the changes over time among interventions. This second meta-analysis was also applied to PPD, marginal bone loss and plaque. In the case of studies with more than two arms, each intervention was compared against the control group.

Study-specific estimates were pooled with both the fixed and random-effect models (DerSimonian & Laird 1986) and the random-effect model results were presented. The use of a particulate xenograft and a collagen resorbable membrane was selected as the control group in most of the studies. In addition, two subgroup analyses were performed based on the type of procedure that was compared against the most common control group (particulate xenograft and collagen resorbable membrane) and the type of follow-up (short-term: up to 3 years, long-term: ≥5 years).

The statistical heterogeneity among studies was assessed using the Q test, according to chi-square statistics and the I^2 index (I^2 = 25%: low; I^2 = 50%: moderate; I^2 = 75%: high heterogeneity).

The publication bias was evaluated using the Begg′s and Egger′s tests for small-study effects for BOP change. A sensitivity analysis of the meta-analysis results was also performed.

Forest plots were created to illustrate the effects of the different studies and the global estimation in the meta-analysis. STATA® (StataCorp LP, Lakeway Drive, College Station, TX, USA) intercooled software was used to perform all analyses. Statistical significance was defined as a *p*-value < .05.

3 | RESULTS

3.1 | Search

Figure 1 depicts the study flow chart. Ten thousand and nine hundred and fifty-one titles were identified by the electronic search before applying the limits and 2,831 after. Once the titles and abstracts were evaluated, 2,661 articles were discarded, resulting in 170 studies, which after including 16 additional ones found on the manual search, resulted in 186 potentially relevant papers that were subjected to full text analysis (agreement = 86.15%; κ = .723; 95% CI [0.487; 0.894]). After this analysis, twelve final publications were included reporting data from eight different studies, as four publications reported long-term data from already included studies. The reasons for excluding of the remaining studies are reported in Appendix S2.

3.2 | Description of studies

Table 1 depicts the methodological characteristics of the selected studies. From the eight selected studies, six investigated the simultaneous approach (three parallel RCTs and three split-mouth RCTs) and two the staged approach (two parallel RCTs). Three groups of papers reported longer follow-ups from the same investigation (Schwarz, Hegewald, Sahm, & Becker, 2014; Schwarz, Schmucker, & Becker, 2016 from Schwarz, Sahm, & Becker, 2012; Jung, Benic, Scherrer, & Hammerle, 2015 from Ramel, Wismeijer, Hammerle, & Jung, 2012; Meijndert et al., 2016 from Meijndert, Raghoebar, Meijer, & Vissink, 2008). When data from more than one experimental or control group were reported, each comparison was considered independently (Amorfini, Migliorati, Signori, Silvestrini-Biavati, & Benedicenti, 2014; Meijndert et al., 2008, 2016). The two comparisons of these four-armed and three-armed studies appeared in the meta-analysis Forest plots with references a and b.

This systematic review pooled data from 256 systemically healthy patients at baseline (200 at the end of the study), with a total of 405 implants placed. The mean follow-up period taking into consideration the longest evaluation from each investigation was of 50.25 months, with a minimum of 12 months (Amorfini et al., 2014; Van Assche, Michels, Naert, & Quirynen, 2013) and a maximum of 120 (Meijndert et al., 2016). Four of eight investigations reported on the tobacco consumption, with two studies including non-smoker patients (Meijndert et al., 2016; Schwarz et al., 2016) and two additional specifying the number of smokers (one to three) per group (Jung et al., 2017; Van

FIGURE 1 Flow-chart depicting the search strategy and selection process

TABLE 1 Methodological characteristics of the selected studies, the regenerative objective (simultaneous, staged or ridge expansion), the types of interventions and the outcomes measured

References	Study design (RCT)	Follow-up (months)	Test patients baseline (final)/ Control patients baseline (final)	Test implants/ Control implants	Smoking test/ Control	Interventions test	Interventions control	Study outcomes mesured	Level of analysis
Simultaneous									
Jung et al. (2009)	RCT (split)	60	11 (10)/11 (10)	18/16	NR	Xenograft + RH-BMP2 + collagen membrane	Xenograft + collagen membrane	IS, BOP, PPD, PI, PROMs, BL	Patient
Van Assche et al. (2013)	RCT (split)	12	14 (14)/14 (14)	14/14	2/2	Particulate autologous bone + HA-60% TCP-40% + collagen membrane	Particulate autologous bone + Xenograft + collagen membrane	IS, BOP, PPD, BL	Implant
Schwarz et al. (2012) Schwarz et al. (2014) Schwarz et al. (2016)	RCT (parallel)	48 72 96	23 (9)/26 (10)	41/37	0/0	Xenograft + cross-link collagen membrane	Xenograft + collagen membrane	IS, BOP, PPD, PI	Implant
Ramel et al. (2012) Jung et al. (2015)	RCT (parallel)	36 60	19 (16)/18 (17)	19/18	NR	Xenograft +polyethylen glycol resorbable membran	Xenograft + collagen membrane	IS, BOP, PPD, PI, BL	Patient
Jung et al. (2017)	RCT (parallel)	18	10 (10)/12 (12)	13/15	1/3	Xenograft + collagen membrane	Spontaneous healing of a dehiscence ≤5 mm	IS, BOP, PPD, PI, BL, CBCT	Patient
Amorfini et al. (2014)	RCT (Split 4-armed)	12	8 (8)/8 (8)	25/25	NR	T1 and T2: Allograft bone block + collagen membrane + rhPDGF-BB or saline	C1 and C2: Xenograft + collagen membrane + rhPDGF-BB or saline	IS, BOP, PPD, PI, BL, CBCT	Implant
Staged									
Cordaro et al. (2011)	RCT (parallel)	24	11 (11)/11 (11)	28/27	NR	Autologous ramus block + collagen membrane	Autologous ramus blocks	IS, BOP, PPD, PI	Implant
Meijndert et al. (2008) Meijndert et al. (2016)	RCT (parallel 3-armed)	12 120	62 (53)/31 (19)	62/31	0/0	T1: Autologous chin block + collagen membrane T2: Autologous chin block	Xenograft + collagen membrane	IS, BOP, PPD, PI, PROMs, BL	Patient

RCT, randomised controlled trial; NR, no reported; rh-BMP2, recombinant human bone morphogenic protein 2; HA, hydroxyapatite; TCP, tri-calcium phosphate; T1, test 1; T2, test 2; C1, control 1; C2, control 2; rhPDGF-BB, recombinant human platelet-derived growth factor-BB; IS, implant survival; BOP, bleeding on probing; PPD, peri-implant probing depth; PI, eri-implant plaque index; PROMs, patient reported outcomes; BL, marginal bone levels assessed radiographically; CBCT, bone levels measured by three-dimensional methods (cone beam computer tomography).

Assche et al., 2013). Periodontally healthy patients were recruited in two studies (Cordaro, Torsello, Morcavallo, & di Torresanto, 2011; Meijndert et al., 2016), whereas no information on the periodontal diagnosis was given in the remaining articles. When stratified by treatment group, 141 patients were treated with the simultaneous approach (106 completed the follow-up) and 115 patients with the staged approach (94 completed the follow-up). No single study was identified matching the inclusion criteria for the ridge expansion approach. The most common regenerative intervention was the use of a particulated xenogeneic bone replacement graft (de-proteinized bovine bone mineral DBBM) combined with a bioabsorbable native collagen barrier membrane, which was considered the control group in six of eight from the investigations included in the systematic review (Amorfini et al., 2014 [C: 2]; Jung et al., 2009, 2015, 2017; Meijndert et al., 2016; Schwarz et al., 2016).

3.3 | Assessment of risk of bias

Table 2 depicts the risk of bias for RCTs. Only three publications showed a low-risk of bias in all the fields (Jung et al., 2017; Schwarz et al., 2014, 2016) and one in all except for one (Jung et al., 2015). In general, most of the RCTs showed a low-risk of bias in the majority of the categories.

No publication bias for BOP changes was detected by Begg (p = .851) or Egger tests (p = .663). The sensitivity analyses for this outcome showed that the exclusion of a single study did not substantially alter any estimate.

3.4 | Effects of interventions

3.4.1 | Main outcome: Inflammation of the Peri-implant Mucosa

In case of incomplete data, the authors were contacted and the bleeding or gingival indexes could be transformed to BOP values. One investigation was not included in the meta-analysis as only the final values were reported (Cordaro et al., 2011). The longest follow-up from the same study was included in the meta-analysis. Changes in BOP percentages for all treatment modalities were not significant when comparing test to control treatment protocols (n = 6; weighted mean difference [WMD] = −3.36; 95% CI [−12.49; 5.77]; p < .471) and there was a low heterogeneity (I^2 = 0%; p = .891). Additionaly, no significant differences could be observed between groups when comparing the use of a xenograft plus a native collagen membrane to different types of membranes, to the addition of biological factors, such as bone morphogentic proteins (BMP's) or recombinant human platelet-derived growth factor-BB (rh PDGF-BB). Similarly, the use of autogenous bone blocks plus bioabsorbable collagen membrane resulted in similar outcomes when compared to the use of the bone block alone (Table 3) (Figure 2). When evaluating the differences between groups depending on the follow-up (1–3 years or >3 years), no significant differences were detected (Table 3) (Figure 3).

A meta-analysis was conducted to evaluate the changes on BOP values within each treatment modality (final minus baseline). For the overall procedures, there was no significant change over time (n = 10; WMD = −10.02; 95% CI [−22.23; 2.20]; p = .108) and there was a medium heterogeneity (i^2 = 59.3%; p < .009). When evaluating each treatment modality independently, there was a statistically significant reduction in BOP values when a cross-linked membrane plus a particulate xenograft was used (n = 1; WMD = −41.6; 95% CI [−63.51; −19.68]; p < .001). Some procedures were excluded from this meta-analyses due to an imputed weight of 0% (Particulate xenograft + collagen membrane [n = 2], rhPDGF-BB+ particulate xenograft + collagen membrane [n = 1], chin blocks [n = 1], spontaneous healing [dehiscence] [n = 1]; allografts blocks + collagen membrane + rhPDGF-BB [n = 1], allograft blocks + collagen membrane [n = 1]) (Table 4).

3.4.2 | Effects of interventions: Secondary outcomes

Data on implant survival was provided in all the studies except two (Schwarz et al. 2014, 2016). The mean implant survival rate was 99.24% (min: 93.5%; max: 100%), and there were no differences between the test and control groups (98.56% and 100%, respectively).

Data on PPD were reported in all the studies except one (Ramel et al., 2012). Two additional studies only reported the final values, so they were not included in the meta-analysis (Cordaro et al., 2011; Jung et al., 2015) and a total of six investigations were considered. The results revealed no significant differences between the test and control groups neither for the overall analysis (n = 6; WMD = −0.051; 95% [−0.333; 0.232]; p = .726) nor for any of the comparisons between xenograft plus a native collagen membrane and different membranes, biological factors (BMP's, PDGF), bone blocks or the spontaneous healing of the dehiscence. When evaluating the results depending on the follow-up, no significant differences were observed (Table 5).

Radiographic changes in crestal bone levels were assessed in all the investigations except two (Cordaro et al., 2011; Schwarz et al., 2016), both as mesial and distal values, or as its average. The meta-analysis revealed no significant differences between the test and control treatment approaches when compared all together (n = 6; WMD = 0.062; 95% CI [−0.130; 0.253]; p = .527). The only significant differences were observed in the study in which a xenograft plus a native collagen membrane was compared to the spontaneous healing in the treatment of dehiscence defects, with a statistical significant greater amount of bone loss for the group with no treatment (n = 1; WMD = 0.41; 95% CI [0.003; 0.817]; p = .048) (Table 5).

Plaque accumulation was evaluated in all the investigations except two (Cordaro et al., 2011; Van Assche et al., 2013). The meta-analysis revealed no significant differences between the test and treatment approaches for plaque changes over time (n = 6; WMD = −5.12; 95% CI [−15.54; 5.31]; p = .337). The only significant difference when evaluating the type of comparison or the follow-up was observed for the group using autogenous bone blocks, with a statistically significant greater reduction in plaque levels compared to the group using particulate xenografts plus a native collagen membrane (n = 1; WMD = −28.81; 95% CI [−56.25; −1.37]; p = .04) (Table 5).

TABLE 2 Risk of bias assessment according to the Cochrane Collaboration recommendations (Higgins & Green, 2011)

References	Selection bias Sequence generation	Selection bias Allocation concealment	Performance bias Blinding of participants/researchers	Detection bias Blinding of assessments	Attrition bias Incomplete outcome data	Selective reporting bias	Other potential risk of bias
Cordaro et al. (2011)	Low risk	Low risk	High risk	High risk	High risk	Low risk	Low risk
Van Assche et al. (2013)	Unclear	Low risk	High risk	High risk	Low risk	High risk	Low risk
Schwarz et al. (2012)	High risk	High risk	Low risk	Low risk	High risk	Low risk	Low risk
Schwarz et al. (2014)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Schwarz et al. (2016)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Jung et al. (2009)	Low risk	High risk	Low risk	High risk	Low risk	Low risk	Low risk
Ramel et al. (2012)	Low risk	Low risk	High risk	Low risk	Low risk	High risk	High risk
Jung et al. (2015)	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	Low risk
Jung et al. (2017)	Low risk	Low risk	High risk	High risk	Low risk	Low risk	High risk
Meijndert et al. (2008)	Low risk	High risk	High risk	Low risk	Low risk	Low risk	High risk
Meijndert et al. (2016)	Low risk	High risk	High risk	Unclear	Low risk	Low risk	Low risk
Amorfini et al. (2014)	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	High risk

TABLE 3 Meta-analyses on the change between final and baseline values of BOP the studies comparing particulate xenograft (DBBM) and collagen resorbable membrane as control groups compared to different interventions: test vs. control

				Weighted mean difference				Heterogeneity	
					95% CI				
Index	Subgroup		*n*	DL	Upper	Lower	*p*-Value	I^2 (%)	*p*-Value
BOP change	All		6	−3.362	−12.495	5.771	.471	0	.891
	Type of comparison	Membrane (PEG; cross-linked)	2	−8.393	−27.468	10.683	.389	0	.453
		BMPs, PDGF	1	−0.610	−44.191	42.971	.978		
		Spontaneous healing	1	−1.000	−14.044	12.044	.881		
		Chin bone+resorbable membrane	1	3.940	22.160	30.040	.767		
		Chin bone	1	−12.290	−39.313	14.733	.373		
	Follow-up	≥5 years	5	−5.634	−18.425	7.157	.388	0	.836
		Up to 3 years	1	−1.000	−14.044	12.044	.881		

BMP, bone morphogentic proteins; BOP, bleeding on probing; PDGF, platelet-derived growth factor.

Bone level changes assessed with a CBCT were monitored in two studies. In one investigation, the defect height reduction at the buccal aspect was evaluated at baseline and 5 years with similar results when comparing two types of membranes (Jung et al., 2015). Additionally, the buccal bone width at different apico-coronal levels and the distance between the mucosal margin and the implant shoulder were assessed. In another study, the bone volume changes (cm^3) were compared between the baseline preoperative situation and the 1 year follow-up, with similar changes when comparing the GBR procedure to the use of an allograft block, although there was higher bone resorption when the blocks were immersed in saline compared to those immersed in rh PDGF-BB (Amorfini et al., 2014).

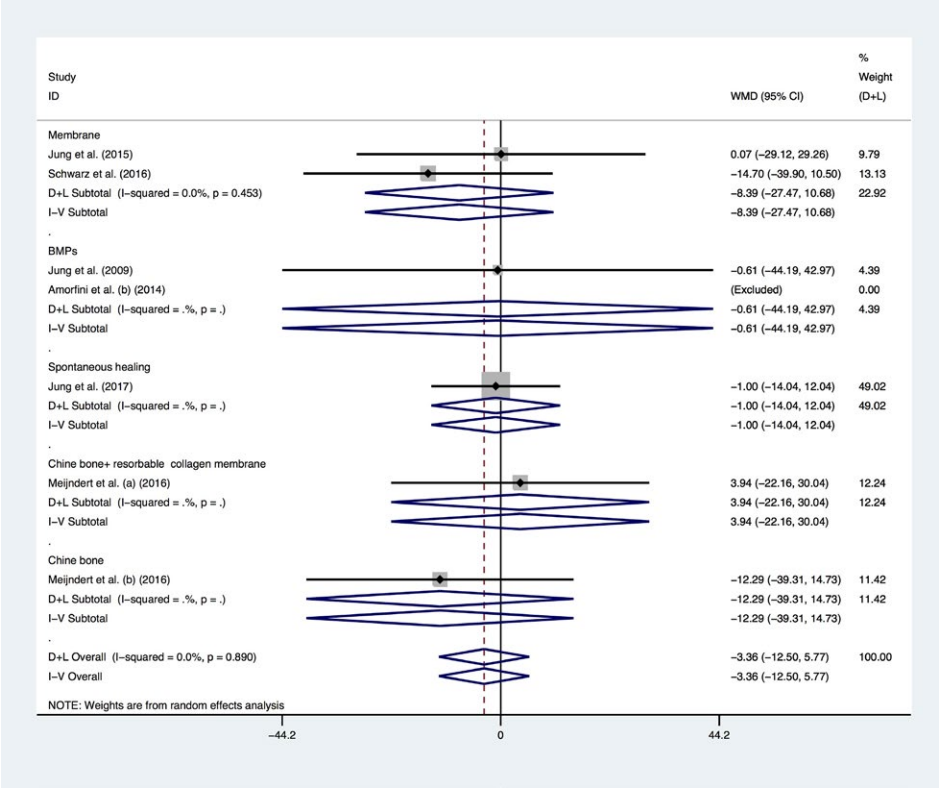

FIGURE 2 Forest-plots for the bleeding on probing meta-analysis for studies comparing particulate xenograft (DBBM) and collagen resorbable membrane as control groups compared to different interventions: type of intervention

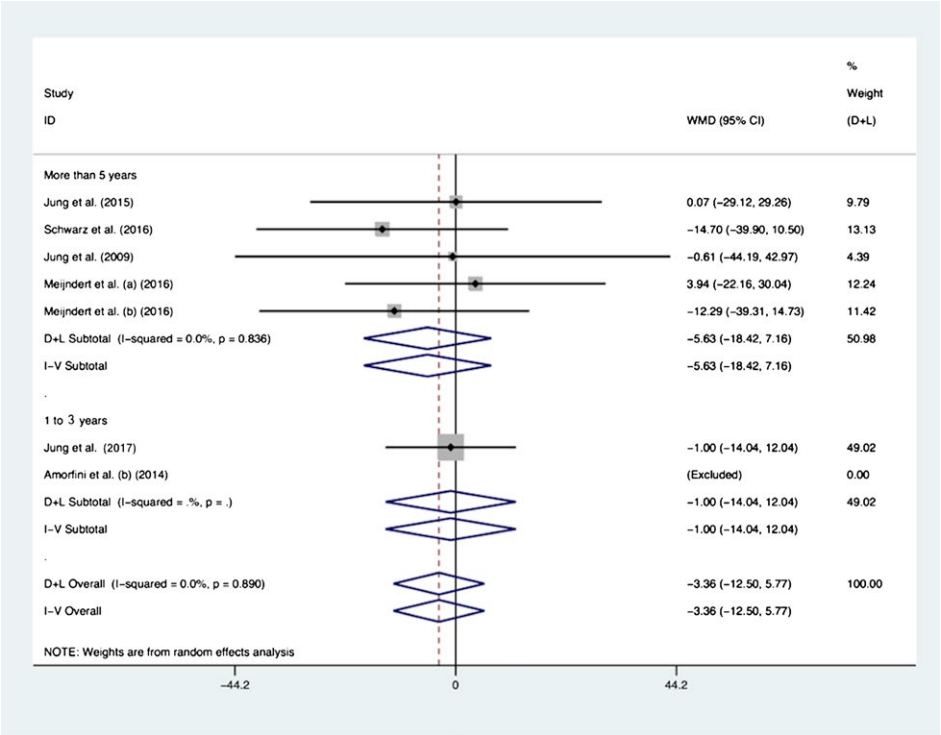

FIGURE 3 Forest-plots for the bleeding on probing meta-analysis for studies comparing particulate xenograft (DBBM) and collagen resorbable membrane as control groups compared to different interventions: follow-up

TABLE 4 Meta-analysis on the increment on BOP values when comparing final-baseline data: final vs. baseline

		WMD				Heterogeneity	
			95% CI				
Subgroup	*n*	DL	Upper	Lower	*p*-Value	I^2 (%)	*p*-Value
All	10	−10.016	−22.232	2.200	.108	59.3	.009
Particulate xenograft + PGE membrane	1	19.790	−8.893	48.473	.176		
Procedure							
Particulate xenograft + cross-link membrane	1	−41.600	−63.515	−19.685	<.001		
rh_BMP2 + particulate xeno-graft + collagen membrane	1	11.970	−31.365	55.305	.588		
Chin blocks + collagen membrane	1	−19.490	−41.617	2.637	.084		
Particulate autologous bone + particulate HA (60%)_TCP (40%) bone+ collagen membrane	1	−14.000	−31.038	3.038	.107		
Particulate xenograft + collagen membrane	4	−6.729	−31.269	17.810	.591	63.4	.042
Particulate xenograft + particulate autologous bone + collagen membrane	1	−7.000	−22.191	8.191	.366		

BMP, bone morphogentic proteins; BOP, bleeding on probing; PDGF, platelet-derived growth factor; WMD, weighted mean difference.
WMD represents the change on BOP between final and baseline visit. Negative symbol means a reduction in BOP values over time. Positive symbol means an increment in BOP values over time. Some procedures were excluded from the meta-analyses due to an imputed weight of 0% (Particulate xeno-graft + collagen membrane [*n* = 2] rhPDGF-BB+ particulate xenograft + collagen membrane [*n* = 1], chin blocks [*n* = 1], spontaneous healing [dehiscence] [*n* = 1]; allografts blocks + collagen membrane + rhPDGF-BB [*n* = 1], allograft blocks + collagen membrane [*n* = 1]).

TABLE 5 Meta-analyses on the change between final and baseline values of PPD, PI and bone loss on the studies comparing particulate xenograft (DBBM) and collagen resorbable membrane as control groups compared to different interventions: test vs. control

				Weighted mean difference				Heterogeneity	
					95% CI				
Index	Subgroup		*n*	DL	Upper	Lower	*p*-Value	I^2 (%)	*p*-Value
PPD change	All		6	−0.051	0	0	.726	0	.71
	Type of comparison	Membrane (PGE. cross-linked)	1	0	−0.547	0.547	1		
		BMPs/PDGF	2	0.109	−0.33	0.547	.626	0	.732
		Spontaneous healing	1	0.17	−0.797	1.137	.73		
		Chin bone+resorbable membrane	1	−0.54	−1.377	0.297	.206		
		Chin bone	1	−0.42	−1.251	0.411	.322		
	Follow-up	≥5 years	4	−0.151	−0.522	0.219	.423	0	.528
		Up to 3 years	2	0.091	−0.348	0.529	.685	0	.857
Bone loss	All		6	0.062		0	.527	19.8	.284
	Type of comparison	Membrane (PGE. cross-linked)	1	0.11	−0.269	0.489	.57		
		BMPs/PDGF	2	−0.04	−0.328	0.248	.785	44.5	.18
		Spontaneous healing	1	0.41	0.003	0.817	**.048**		
		Chin bone+resorbable membrane	1	−0.13	−1.141	0.881	.801		
		Chin bone	1	−0.02	−1.008	0.968	.968		
	Follow-up	≥5 years	4	0.102	−0.144	0.347	.417	0	.959
		Up to 3 years	2	0.101	−0.455	0.658	.722	81.8	.019
Plaque change	All		6	−5.122	−15.538	5.314	.337	11.7	.34
	Type of comparison	Membrane (PGE. cross-linked)	1	8.28	−10.694	27.254	.392		
		BMPs/PDGF	2	0.524	−23.092	24.141	.965	0	.936
		Spontaneous healing	1	−11.01	−27.105	5.085	.18		
		Chin bone+resorbable membrane	1	0.47	−28.592	29.532	.975		
		Chin bone	1	−28.81	−56.247	−1.373	.04		
	Follow-up	≥5 years	4	−4.059	−21.23	13.112	.643	37.8	.185
		Up to 3 years	2	−8.306	−22.523	5.912	.252	0	.482

BMP, bone morphogentic proteins; PDGF, platelet-derived growth factor;PI, Plaque indexes; PPD, probing pocket depth.
The bold p-value means a statistical significant difference

PROMs were evaluated in two studies. In one of them patients were asked to grade the condition of their gums and their ability for a proper hygiene using a visual analogue scale (Jung et al., 2009). In the other, the overall patient satisfaction, and specifically in relation to the final restoration, the peri-implant tissues and the overall percentage of acceptable results were recorded (Meijndert et al., 2016). For none of the comparisons, significant differences were detected between groups.

The occurrence of biological complications based on case definitions was only reported in one investigation including three articles (Schwarz et al., 2012, 2014, 2016). After 6–8 years of follow-up, the incidence of peri-implant mucositis varied from 37% to 47% and for peri-implantitis from 16% to 26%, without significant differences between groups. Additionally, two studies reported the percentage of cases with bone loss ≥1.5–2 mm (Ramel et al., 2012; Van Assche et al., 2013) and four studies reported co-existence of healthy peri-implant tissues with minimal bone loss (Amorfini et al., 2014; Cordaro et al., 2011; Jung et al., 2009, 2017). In one study implants had to be extracted due to buccal bone resorption with altered aesthetics (Meijndert et al., 2016).

4 | DISCUSSION

Based on 12 publications reporting data from eight different investigations, the results from this systematic review indicated that the

interventions aimed for lateral bone augmentation and the different combinations of bone replacement grafts and barrier membranes could maintain stable results over time in terms of peri-implant mucosal inflammation and maintenance of crestal bone levels. When evaluating each treatment approach independently, the meta-analysis showed that these interventions resulted in low BOP values over time, without significant differences among interventions. When evaluating other peri-implant health outcomes, such as marginal bone level, PPD and plaque level changes, similar results were reported among the different surgical interventions, both at short- (up to 3 years) and long-term (≥5 years) follow-ups.

These results are in agreement with long-term studies in which implants receiving GBR procedures have been compared to implants placed in native bone without any augmentation (Benic et al., 2009; Jung, Fenner, Hammerle, & Zitzmann, 2013). As it is impossible to randomise which implant is going or not to receive bone augmentation, cohort studies are needed to compare both treatment modalities. In a recent publication (Benic, Bernasconi, Jung, & Hammerle, 2017), machined implants receiving simultaneous bone regeneration with a particulate xenograft or autologous bone plus, a native collagen membrane were compared to standard implant placement without GBR. At 15 years, interproximal marginal bone levels (MBL) averaged 1.44 ± 0.84 mm for the GBR group and 1.69 ± 0.84 mm for the control group and from the 5- to the 15-year examination, the loss of interproximal MBL averaged 0.23 ± 0.70 mm for the GBR group and 0.28 ± 0.63 mm for the control group. Similarly, no significant differences were observed for BOP (46.2 ± 27.7 GBR vs. 38.3 ± 28.8 control), plaque scores (36.3 ± 30.7 GBR vs. 30.4 ± 36.2 control) or PPD (3.12 ± 0.71 GBR vs. 3.05 ± 0.67 control).

One criticism to all these studies assessing the long-term outcome of horizontal bone regeneration is the fact that crestal bone levels were mainly assessed through conventional periapical radiography, which only evaluates by dimensionally mesial and distal sites, instead of buccal sites, which is precisely the area where bone augmentation was carried out. Although three-dimensional tomography is available for evaluating the outcome of regenerated bone, the resulting higher radiation burden does not justify this evaluation, as there is no direct benefit to the patient (Harris et al., 2012).

At the eighth European Workshop of Periodontology (EWP), the occurrence of biological complications was identified as a main outcome domain when evaluating the long-term efficacy of implant therapy (Tonetti & Palmer, 2012). Identification of peri-implant diseases has been hampered by the use of diverse diagnostic criteria and case definitions (Tomasi & Derks, 2012). The following case definitions were recommended for peri-implant mucositis and peri-implantitis at a European Workshop (Sanz and Chapple (2012). For prevalence studies, in the absence of baseline radiographs, a bone level of 2 mm from the expected level together with clinical inflammation was set as a threshold to define peri-implantitis in the presence of peri-implant mucosal inflammation. For incidence studies with existing baseline radiological measures, a bone loss of 1–1.5 mm in combination with inflammation was established as the minimum threshold. In this systematic review, however, only one investigation use well established case definitions for peri-implant diseases (Schwarz et al., 2012, 2014, 2016) and in two other studies, only those cases with bone loss ≥1.5–2 mm was diagnosed (Ramel et al., 2012; Van Assche et al., 2013). Another difficulty when analysing the data was that each investigation considered a different time point for the baseline evaluation. It was, therefore, impossible to homogenise the data and to obtain a clear conclusion in regards to the change in peri-implant health over time.

To answer the question "Which hard tissue augmentation procedures better maintain peri-implant health?" the results from this systematic review clearly demonstrated that there were no differences between the assessed treatment modalities. A previous systematic review reported on the effectiveness of the interventions aimed for lateral ridge augmentation and the most suitable biomaterials used as bone replacement grafts and barrier membranes (Sanz-Sanchez et al., 2015). It was shown that the type of membrane or bone graft could have a significant impact on the outcome of the regeneration (peri-implant defect height reduction). This systematic review did not study the possible influence of the different interventions on the peri-implant tissue health. It was interesting that the use of a particulate xenograft (DBBM) plus a native collagen membrane was selected in six of eight investigations as the standard of care or positive control for studying new regenerative interventions aiming for horizontal bone augmentation. The comparisons resulted in similar outcomes in regards to peri-implant health, irrespective of the addition of biological factors or different absorbable membranes or bone replacement grafts.

The lack of differences in some of the comparisons analysed may be due to the questioned reliability of periodontal parameters to assess peri-implant health (Coli, Christiaens, Sennerby, & Bruyn, 2017). BOP was selected as the primary outcome to be compliant with the conclusions from the seventh European Workshop on Periodontology, where it was agreed that inflammation disclosed by BOP was the most objective parameter to assess peri-implant tissue inflammation (mucositis) and the combination of BOP and bone loss the two key parameters in the case definition for peri-implantitis (Lang & Berglundh, 2011). However, it is important to bear in mind that BOP is a poor predictor of peri-implant health, while its absence is a much more valuable indicator (Coli et al., 2017). Furthermore, the dichotomous nature of BOP makes it very challenging to ascertain the correlation that it may have with disease status and severity. It has been shown that several factors such as gender or implant position can influence BOP values around implants (Farina, Filippi, Brazzioli, Tomasi, & Trombelli, 2017). Moreover, excessive probing forces may induce false positive BOP readings (Gerber, Tan, Balmer, Salvi, & Lang, 2009). Additionally, the access to insert the periodontal probe in cases of overhanging restorations may underestimate PPD values (Serino, Turri, & Lang, 2013) and may induce trauma in the soft tissues, increasing false positive BOP.

To answer the question "are these horizontal bone augmentation procedures justified?" the present systematic review only found one RCT aimed to study whether to treat or not small dehiscence type defects (≤5 mm) (Jung et al., 2017). After 18 months of follow-up, it

was demonstrated that although both groups had similar values for BOP, PPD and plaque levels, therefore compatible with peri-implant health, dehiscence defects without regenerative treatment experienced significant greater crestal bone loss (mean: 0.41 mm; 95% CI: 0.003–0.817). It has also been suggested that residual defect areas with exposed implant rough surfaces may be at a higher risk of accumulating bacterial biofilms and subsequently developing peri-implant diseases, although there are no prospective cohort studies available to answer this question. Indirect evidence comes from a cross-sectional study studying the impact of the residual dehiscence defects on the development of peri-implant diseases 4 years after lateral bone regeneration procedures comparing two absorbable membranes (Schwarz et al., 2012). It was concluded that implants exhibiting residual defect height values >1 mm were at higher risk of developing peri-implant diseases and these residual defects might be associated with increased mucosal recession, which may compromise the aesthetic outcomes. Based on these data it does not seem reasonable to leave exposed implant surfaces without further treatment.

The fact that most of the selected studies from this systematic review have shown good results in terms of the maintenance of peri-implant health may be explained by the ideal circumstances in which these studies have been performed. In most of the cases, the patients were followed closely and if inflammation was detected, prompt treatment was carried out. Despite our efforts to study the impact of lateral bone augmentation in peri-implant health or disease, very few investigations have evaluated the incidence of peri-implant disease. Although the onset of peri-implantitis has been reported to occur as soon as 3 years after loading (Derks et al., 2016), there is a need of longer follow-up evaluations, as the shift from mucositis to peri-implantitis requires the detection of early signs of bone loss, which demands a long-term longitudinal evaluation.

When evaluating peri-implant health or disease is important to bear in mind that different factors can contribute to an increase risk for mucosal inflammation, such as residual increased PPD in the remaining dentition, smoking, implant position, access to oral hygiene, excess of cement or the type of prosthetic rehabilitation (Jepsen et al., 2015).

This systematic review has some limitations. First of all, the limited number of included studies in the meta-analyses. This was evident with BOP data, as several studies had to be excluded from the anlyses and therefore, no subgroup analysis could be performed for the confounding factors (tobacco consumption and periodontal diagnosis) or the level of analysis (implant or patient level). This fact determined that implant level and patient level data were pooled together in the meta-analysis, which might underestimate the CIs for the pooled estimate, hence rising the type-I error. Despite our efforts to perform a meta-analysis for all the variables evaluated, we could not do it for either the biological complications or the PROMs due to the scarcity of studies reporting these outcomes. Another limitation was due to the fact that the included studies were not primarily designed to detect differences on peri-implant health (gingival or bleeding index) indices. Due to these limitations, care should be applied when interpreting the results, as the included data were probably not powered for the analysed outcomes.

The decision to limit the search to controlled studies written in English and to dismiss the case series, cohort studies or the grey literature may have induced a high-risk of misrepresentation of the pertinent evidence, as the amount of potentially relevant articles that were automatically excluded could be high. In accordance with PRISMA guidelines, the protocol development of the PICO question were strictly followed. Furthermore, due to the limited number of controlled studies, we aimed to be inclusive and we established a very low threshold on subjects per group.

The results from this systematic review and meta-analysis have shown that lateral ridge augmentation procedures are associated with a high implant survival rate and adequate peri-implant health over time with small changes on BOP values and a low incidence of cases presenting peri-implant bone loss.

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SUPPORTING INFORMATION

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