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Title: Effectiveness of vertical ridge augmentation interventions. A systematic review and meta-analysis**.**

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ABSTRACT

Aim: The primary aim of this systematic review was to evaluate the effect of various techniques used for vertical ridge augmentation on clinical vertical bone gain.

Material and Methods: A protocol was developed to answer the following focused question: "In patients with vertical alveolar ridge deficiencies, how effective are different augmentation procedures for clinical alveolar ridge gain?" Randomized and controlled clinical trials and prospective and retrospective case series were included, and meta-analyses were performed to evaluate vertical bone gain based on the type of procedure and to compare bone gains in controlled studies.

Results: Thirty-six publications were included. Results demonstrated a significant vertical bone gain for all treatment approaches [n=33; weighted mean effect = 4.16 mm; 95% CI 3.72-4.61; p<0.001]. Clinical vertical bone gain and complications rate varied among the different procedures, with a weighted mean gain of 8.04 mm and complications rate of 47.3% for distraction osteogenesis, 4.18 mm and 12.1% for guided bone regeneration (GBR) and 3.46

mm and 23.9% for bone blocks. In comparative studies, GBR achieved a significant greater bone gain when compared to bone blocks [n=3; weighted mean difference=1.34 mm; 95% CI 0.76-1.91; p<0.001].

Conclusions: Vertical ridge augmentation is a feasible and effective therapy for the reconstruction of deficient alveolar ridges, although complications are common.

Clinical Relevance

Scientific rationale for study: Bone atrophy often hinders the adequate placement of dental implants. Different techniques have been proposed to augment the ridge vertically in order to improve bone support.

Principal findings: Vertical ridge augmentation (VRA) procedures are effective in treating deficient alveolar ridges irrespective of the technique used. However, the rate of associated complications should not be underestimated.

Practical implications: Clinicians should be aware that VRA is a highly demanding therapy. The decision-making process for the ideal treatment should be made on the basis of site and patient related factors, in combination with surgical experience and skill.

Introduction

Vertical ridge augmentation (VRA) is one of the greatest challenges for bone regeneration in implant dentistry. This is primarily due to technique sensitivity and, consequently, frequent intra- and post-operative complications (Fontana, Maschera, Rocchietta, & Simion, 2011; Rocchietta, Fontana, & Simion, 2008; Tinti & Parma-Benfenati, 1998). VRA aims to achieve bone regeneration without osseous wall containment (i.e., bony walls to support the stability of the clot and the bone graft), and for this reason, it is biologically demanding, as angiogenesis must reach a certain distance from existing bone for new bone to be formed (Wang & Boyapati, 2006; Wikesjo, Kean, & Zimmerman, 1994). In addition, the soft tissue has to be advanced to provide a closed healing environment for the increased dimensions of the

alveolar ridge, requiring a correct flap design and tension-free flap approximation (Urban, Monje, Lozada, & Wang, 2017).

Due to the associated comorbidities of augmentation procedures, such as post-operative infections, wound dehiscences or neurosensory disorders, other approaches besides VRA have been proposed (e.g., short dental implants). These therapeutic modalities have proven to be effective and valid alternative treatments to sinus floor elevation or VRA, with reduced morbidity and high patient satisfaction (Hammerle & Jung, 2003; Nisand, Picard, & Rocchietta, 2015; Salvi, Monje, & Tomasi, 2018; Thoma, Haas, et al., 2015; Thoma, Zeltner, Husler, Hammerle, & Jung, 2015). However, in cases with limited bone availability for placing short implants, or due to restorative considerations, VRA may be the best therapy choice as it offers an opportunity for augmenting lost bony structure and often leads to improved esthetic outcomes (Salvi et al., 2018).

Several therapeutic modalities have been proposed for VRA, namely distraction osteogenesis (DO) (Froum, Rosenberg, Elian, Tarnow, & Cho, 2008), bone blocks (either as onlays or inlays/ interpositional grafts) (Chiapasco, Brusati, & Ronchi, 2007; Chiapasco, Zaniboni, & Rimondini, 2007), and guided bone regeneration (GBR) (Hammerle & Jung, 2003). Even though these therapies have been widely investigated within the last three decades, the most suitable approach remains unclear, in particular regarding the relative effectiveness of these techniques for vertical clinical bone gain (VCBG). While the use of autologous block grafts has been described as the "gold standard" for severe atrophies (Tessier et al., 2005), advances in the field of biomaterials have favored the use of less invasive approaches (i.e., GBR). In an attempt to develop clinical guidelines, systematic reviews have been conducted to assess the outcomes of clinical investigations. The most recent reviews have demonstrated that VRA, regardless of the intervention carried out, can achieve on average ~4mm of vertical bone gain (Elnayef et al., 2017; Milinkovic & Cordaro, 2014). However, these reviews were focused on specific anatomical areas, or were not aimed at assessing relevant secondary outcome variables such as implant-related outcomes, intra- and post-operative complications, or patient-reported outcomes.

Therefore, it seems reasonable to evaluate the effectiveness of vertical bone augmentation, to correlate it with associated complications and to explore peri-implant health outcomes over time. This systematic review was performed as required by group 4 (regeneration of alveolar ridge defects) in preparation for the XV European Worksop in Periodontology held in La Granja de San Ildefonso (Segovia, Spain) between 11 and 14 November, 2018.

Material and methods

Protocol development and focused question

The protocol followed the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analyses) statement (Moher, Liberati, Tetzlaff, & Altman, 2009). The review protocol was registered and allocated the identification number CRD42018088189 in the PROSPERO International Prospective Register of Systematic Reviews hosted by the Centre for Reviews and Dissemination, University of York, National Institute for Health Research (United Kingdom). The protocol aimed at answering the following focused question: "*In patients with vertical alveolar ridge deficiencies (population), how effective are vertical bone augmentation procedures (intervention and comparison) attaining clinical alveolar ridge gain (primary outcome)?"*

Eligibility criteria

Inclusion criteria

- *Population***:** patients older than 18 and in good general health with vertical ridge deficiencies in need of an implant-supported/-retained prosthesis;
- *Interventions*: any given intervention for VRA;
- *Comparisons:* any given intervention for VRA in controlled studies;
- *Outcomes:* changes in the clinical vertical dimension of the ridge;
- *Study design***:** randomized clinical trials (RCTs), controlled clinical trials (CCT's), prospective/ retrospective cohort studies or prospective/ retrospective case series (CS) with a minimum of 10 patients (5 per group in controlled studies).

Exclusion criteria

- Studies assessing the effectiveness of interventions aimed only at horizontal bone regeneration;
- Studies assessing the effectiveness of VRA procedures using only radiographs;
- Studies aiming at regenerating extractions sockets before or simultaneous with implant placement;
- Studies evaluating solely maxillary sinus floor elevation;
- Studies including only oncologic and poly-traumatized patients;
- Orthognathic procedures aiming at changing the bone dimensions for different purposes than tooth replacement.

Type of intervention and comparisons

Studies were selected that included interventions for VRA. The following procedures were considered: (1) GBR; (2) bone blocks, either as onlay or inlay grafts; (3) distraction osteogenesis; (4) other approaches. Inlay graft was used as a synonym for interpositional graft. Moreover, the following biomaterials were assessed: (1) autogenous bone grafts; (2) allogeneic bone grafts; (3) xenogeneic bone grafts.

Type of outcomes

The primary outcome for assessing VRA was the change in the clinical vertical alveolar ridge dimension, as determined by direct linear measurements between baseline and re-entry.

The following secondary outcomes were studied:

- Surgical intra- and post-operative complications, including the need for re-grafting, flap dehiscence, graft or membrane exposure, loss of graft integration, local infection, prolonged pain, paresthesia, etc;
- Implant survival and success rates (%);
- Changes in marginal bone levels, defined as the distance between the implant shoulder and the first bone to implant contact measured at both mesial and distal aspects (mm);
- Probing pocket depth (PPD);

- Gingival or bleeding indexes;
- Occurrence of biological complications (%) defined as the occurrence of mucositis (bleeding on probing 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);
- Patient-reported outcome measures (PROMs), such as pain, discomfort, satisfaction, etc.

For the secondary outcome measurements related to implants, only studies with a minimum follow-up of 12-months after definitive loading were considered.

Information sources and search

Electronic search

Three electronic databases were used as sources in the search for studies satisfying the inclusion criteria: (1) The National Library of Medicine (MEDLINE via PubMed); (2) Cochrane Central Register of Controlled Trials; and (3) Embase. These databases were searched for studies published up until January 2018. The search was limited to human subjects.

Manual search

All reference lists of the selected studies and previously published systematic reviews were checked for cross-references. The following journals were hand-searched from year 2008 to 2018: *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 Oral and Maxillofacial Surgery, The International Journal of Periodontics and Restorative Dentistry* and *Clinical Implant Dentistry and Related Research.*

Search strategy

Information on the search strategy can be accessed in the Supplemental Methods.

Screening methods

Two reviewers (ISS and EM) did the primary search by independently screening the titles and abstracts. The same reviewers selected full manuscripts of 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 (AM). The inter-reviewer reliability (percentage of agreement and kappa correlation coefficient) of the full-text analysis was calculated.

Data extraction

The same two reviewers performed duplicate data extraction. When data was incomplete or missing, authors of studies were contacted for clarification. If agreement could not be reached, data was excluded until further clarification was available. When the results of a study were published more than once, only the longest follow-up was included.

Quality assessment (risk of bias in individual studies) 11-12

The Newcastle-Ottawa scale (NOS) for cohort studies and a modification of the scale for cross-sectional studies were used for the assessment of risk of bias in individual observational studies and non-randomized trials (Wells et al. 2011). This scale includes 3 main categories: selection of study groups, comparability of participants, and outcome. Each individual study received a maximum of 6 points in CS and 7 points in CCT's.

A quality assessment of the included RCT's was performed according to the Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (Higgins & Green, updated March 2011,) and the CONSORT statement (Moher et al., 2012). Seven main quality parameters were assessed: sequence generation, allocation concealment, blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective outcome reporting (reporting bias) and other sources of bias. These parameters were rated to be in low risk of bias if all the criteria were met.

Risk of bias across studies

The publication bias was evaluated using a Funnel plot and the Egger´s linear regression method for the clinical vertical ridge dimension changes. A sensitivity analysis of the meta-analysis results was also performed for this outcome (Tobias & Campbell, 1999).

Data analyses

The statistical heterogeneity among studies was assessed using the Q test based on chi-square statistics (Cochrane, 1954) as well as the I^2 index (Higgins, Thompson, Deeks, & Altman, 2003) in order to know the percentage of variation in the global estimate that was attributable to heterogeneity.

To summarize and compare studies, mean values of primary and secondary outcomes were directly pooled and analyzed with weighted mean differences (WMDs) and 95% confidence intervals (CIs). Study specific estimates were pooled with both the fixed and random-effect models (DerSimonian & Laird, 1986). If a significant and high heterogeneity was found, then the random-effect model results were presented. Two groups of meta-analyses were performed based on study design: (1) when comparing different techniques for VRA, only RCTs or CCTs were included; (2) when comparing mean changes of the studied outcomes between final and baseline visits, CS and each test arm of RCTs and the CCTs were included (Sanz-Sanchez, Ortiz-Vigon, Sanz-Martin, Figuero, & Sanz, 2015). In addition, subgroup analyses were performed on the selected main outcome variable using the study design, the unit of analysis, the time of implant placement and the type of intervention as explanatory variables.

A Forest Plot was created to illustrate the effects of the different studies and the global estimation. STATA® (StataCorp LP, Lakeway Drive, College Station, Texas, USA), and OpenMeta[Analyst] intercooled software was used to perform all analyses. Statistical significance was defined as a p value <0.05.

Results

Search

Figure 1 depicts the flow chart summarizing the results of the selection. The electronic and manual search rendered 3925 titles, which, after evaluating their titles and abstracts, resulted in 348 articles for full text analysis. After this analysis, 36 final articles were included for data extraction, which represented 34 independent investigations, since results of the same studies

reported at different time points were excluded (Merli, Lombardini, & Esposito, 2010; Merli, Migani, & Esposito, 2007; Merli et al., 2014) [agreement=87.36%; kappa=0.76; 95% CI (0.64-0.89); p<0.001]. The reasons for excluding the remaining studies are detailed in Supplementary Table 1.

Description of selected studies

Table 1 depicts the methodological characteristics of the selected studies. Out of the 34 investigations, 16 were prospective CS, 8 retrospective CS, 4 CCT's and 6 RCT's (5 had a parallel design and 1 a split-mouth design). All the controlled studies compared two arms, whereas only one study among the CS evaluated three different treatment approaches, so data from each experimental group was analyzed independently (Simion, Jovanovic, Tinti, & Benfenati, 2001). Moreover, in one study three different particulate grafts were used, although the results were pooled together (Fontana, Grossi, Fimano, & Maiorana, 2015). Simultaneous implant placement was performed in 11 studies, whereas the stage approach was used in 20 investigations. Additionally, there were 3 investigations in which staged and simultaneous approaches were combined together (Beitlitum, Artzi, & Nemcovsky, 2010; Fontana et al., 2015; Urban, Jovanovic, & Lozada, 2009), with only one study giving the results separately (Fontana et al., 2015). One of the included CS evaluated both horizontal and vertical bone augmentation and met the inclusion criteria (Anitua, Alkhraisat, & Orive, 2013). However, the authors did not report the number of patients/implants within each group and; therefore, relevant data could not be used for most of the analyses. Among the controlled studies, 3 compared GBR procedures using different grafts, 3 compared GBR procedures using different membranes, and 4 compared onlay grafts to GBR procedures.

The resulting systematic review pooled data from 678 patients at baseline, with a total of 1,392 implants. Six studies did not report the number of implants placed (Anitua et al., 2013; Funato, Ishikawa, Kitajima, Yamada, & Moroi, 2013; Leong et al., 2015; Rocchietta et al., 2016; Roccuzzo, Ramieri, Bunino, & Berrone, 2007; Urban, Lozada, Jovanovic, Nagursky, & Nagy, 2014). Among the 34 included investigations, 14 reported the results up until re-entry surgery only, which was carried out between 4.6 and 10.41 months. The remaining 20 clinical studies followed the implants for a mean period of 36.80 ± 9.35 months, with a range between 12-73 months. At the end of the follow-up period, among the studies included in this systematic

review, 668 patients and a total of 1,309 implants were analyzed. Additionally, 13 investigations reported on tobacco consumption.

Risk of bias in individual studies

A total of 26 non-randomized studies were evaluated using the NOS Scale. A mean value of 2.6 (min: 2, max: 3) was achieved for the section "Selection." Five trials were appropriate for "Comparability," where a mean value of 1 (min = 1, max = 1) was obtained. For the section "Exposure/Outcome," a mean value of 2.14 (min = 2, max = 3) was obtained (Supplementary Table 2).

The Cochrane tool was used to score the randomized clinical trials. A total of 6 studies could be scored. All the studies were scored with 2 stars in the sections concerning the randomization and allocation. For the sections that concerned "bias," a total of 12 stars were achieved, giving a mean of 2.00 (min = 1, max = 4). Two studies achieved a low risk of bias in the main 6 criteria (Supplementary Table 3).

Risk of bias across studies

No significant publication bias was observed when combining all controlled studies for the primary outcome measure (p = 0.746). However, a statistically significant publication bias was observed for the same outcome when combining *all* studies, both controlled and not controlled (p < 0.001). The sensitivity analyses showed that the exclusion of a single study did not substantially alter any estimate.

Effects of Interventions

Primary outcome: changes in the clinical alveolar ridge vertical dimension

Table 2 depicts the meta-analysis evaluating clinical vertical bone gain. For all studies, there was a statistically significant vertical bone gain (n=33; WME=4.16 mm; 95% CI 3.72-4.61; p<0.001). Based on the type of intervention, the maximum vertical bone augmentation was reported for distraction osteogenesis (n=3; WME=8.04 mm; 95% CI 5.68-10.41; p<0.001), whereas the minimum gain was reported for particulate, synthetic graft alone (n=1; WME=2.05 mm; 95% CI 1.44-2.66; p<0.001 - Figure 2). GBR was the most frequently reported

procedure (n=20), with the majority of studies employing non-resorbable membranes (n=13). Case series demonstrated greater vertical bone gain than RCT's or CCT's. In regard to the time of implant placement, the staged approach achieved a weighted mean gain of 4.39 mm (n=21; WME=4.39 mm; 95% CI 53.71-5.06; *p*<0.001) and the simultaneous approach of 3.81 mm (n=12; WME=3.81mm; 95% CI 53.31-4.30; *p*<0.001).

Distraction osteogenesis for vertical alveolar ridge augmentation

Owing to the small sample size (n=3) and to the nature of this approach (graftless procedure), no variables could be sub-analyzed.

Guided bone regeneration for vertical alveolar ridge augmentation: effect of type of particulate grafting material and barrier membrane upon the primary outcome

Within non-resorbable membranes, the most commonly used graft was particulate autologous bone (n=6). There were more studies evaluating expanded PTFE (PTFE-e) (n=11; WME=4.31 mm; 95% CI 3.80-4.82; p<0.001) than dense PTFE (PTFE-d) membranes (n=3; WME=4.99 mm; 95% CI 4.03-5.95; *p*<0.001). Moreover, the type of graft used underneath influenced the clinical bone gain (Table 2).

When using a resorbable membrane, the vertical bone gain was 3.51 mm; (n=7; 95% CI 2.80-4.22; *p*<0.001), while for non-resorbable membranes it was 4.42 mm; (n=13; 95% CI 3.97-4.87; *p*<0.001). Cross-linked membranes achieve a bone gain of 4.19 (n=4; WME=4.19 mm; 95% CI 3.18-5.21; *p*<0.001) and native collagen membranes 2.66 mm (n=3; WME= 2.66 mm; 95% CI 1.49-3.82; p<0.001). Again, the type of graft used underneath influenced the outcome, so as providing a space maintainer by means of a titanium mesh or plate (Table 2).

Block grafts for vertical alveolar ridge augmentation: effect of type of block grafting material upon the primary outcome

The second most frequently reported procedure was block grafts (n=12; WME=3.46 mm; 95% CI 2.71-4.22; *p*< 0.001). Based on the nature of the graft, the results were heterogeneous and the vertical bone gain ranged from 4.12 mm for autologous bone (n=7; WME=4.12 mm; 95% CI 3.11-5.13; *p*< 0.001), to 2.03 mm for allograf bone (n=4; WME=2.03 mm; 95% CI 1.88-2.18 *p*< 0.001). The impact of the technique used with autologous bone influenced the outcome (Table 2). Due to the heterogeneity of the type of membrane/ barrier used, no sub-analysis was performed regarding covering or not covering the block.

Table 3 depicts the meta-analysis comparing vertical bone gain among interventions (RCTs or CCTs). Within the five possible comparisons, two were based on three studies, one was based on two studies and two on single trials. When comparing GBR procedures to onlay blocks, significantly better results were yielded for GBR (n=3; WMD= 1.34 mm; 95% CI 0.76-1.91; *p*<0.001). Also, adding a Titanium mesh to an autogenous onlay block led to higher vertical bone gain (n=1; WMD=1.20 mm; 95% CI 0.04-2.36; *p*<0.001). No significant differences between the test and control groups were found for other comparisons.

Secondary outcomes

Surgical intra- and post-operative complications

The incidence of complications was assessed in all the studies except one (Jensen, Kuhlke, Bedard, & White, 2006). Seven publications reported no complications. The most common complications were membrane and graft exposures with or without infection. The incidence and description of complications in each individual study is depicted in Table 4.

The meta-analysis was performed on all studies except five, since three studies combined the complication rates for vertical and horizontal bone augmentation (Anitua et al., 2013; Nissan, Gross, et al., 2011; Nissan, Mardinger, Calderon, Romanos, & Chaushu, 2011), one study combined different approaches within the same surgical site (Rocchietta et al., 2016), and one study reported a range of complications (Jensen, Cockrell, Kuhike, & Reed, 2002). The overall complication rate was 16.9% (n=29; Weighted mean incidence (WMI) =16.9%; 95% CI 12.5-21.2; *p*< 0.001), with higher values for controlled studies than for case series. In regard of the time of implant placement the complication rate was 22.3% for the staged approach (n=15; WMI=22.3%; 95% CI 13.4-31.3; p< 0.001) and 11.8% for the simultaneous approach (n=11; WMI=11.8%; 95% CI 6.7-17; p< 0.001). The type of procedure also influenced the rate of complications with a 47.3% rate for distraction osteogenesis (n=2; WMI=47.3%; 95% CI 0.0-98; *p*< 0.001), 12.1% for GBR (n=20; WMI=12.1%; 95% CI 8.2-15.9; p< 0.001) and 23.9% for the use of blocks (n=9; WMI=23.9%; 95% CI 11.3-36.6; *p*< 0.001). Within GBR, non-resorbable membranes have a complication rate of 6.9% (n=13; WMI=6.9%; 95% CI 4.1-9.7; *p*< 0.001) and resorbable membranes of 22.7% (n=8; WMI=22.7%; 95% CI 11.5-33.9; *p*< 0.001) (Table 5).

Implant survival and success

Implant survival was reported in 27 studies. The aggregated mean implant survival rate was 98.95% (range 90.5-100%). For controlled studies, implant survival was 100% in both groups, whereas for the CS, the mean implant survival was 98.35%. Implant success using specific criteria was reported in 7 studies. In 6 studies the Albrektsson & Zarb criteria (Albrektsson & Zarb, 1998) were used, reporting an implant success rate between 85.33 and 100% (Fontana et al., 2015; Froum et al., 2008; Llambes, Silvestre, & Caffesse, 2007; Mangano et al., 2014; Simion et al., 2001; Urban et al., 2009). One study used a modification of the Albrektsson & Zarb criteria, reporting implant success rates of 94.2% (Chiapasco, Consolo, Bianchi, & Ronchi, 2004).

Changes in marginal bone levels

Marginal bone levels with at least 12-months follow-up were evaluated in 11 investigations. The values were reported either as the mean of the mesial and distal scores at the end of the follow-up (Canullo & Malagnino, 2008; Llambes et al., 2007) or as the mean change in bone levels (bone loss) by comparing the final and baseline evaluations (Canullo & Sisti, 2010; Chiapasco et al., 2004; Fontana et al., 2015; Fontana et al., 2008; Merli et al., 2014; Todisco, 2010; Urban et al., 2009). The meta-analysis revealed that there was a significant bone loss over time (n=9; WMD=1.01 mm; 95% CI 0.78-1.24; $p< 0.001$). The type of procedure also influenced the outcome and bone loss ranged from 1.40 mm for distraction osteogenesis (n=1; WMD=1.40 mm; 95% CI 1.33-1.47; $p< 0.001$) to 0.58 mm for GBR with resorbable membranes (n=1; WMD=0.58 mm; 95% CI 0.19-0.97; $p< 0.001$ - Supplementary Table 4).

Probing depth

Probing depth (PD) was assessed in 4 out of the 34 investigations. In one study the mean PD at the end of the follow-up was reported only for the test group (Fontana et al., 2008), whereas in two other studies the final scores for each arm were reported (Simion et al., 2001; Urban et al., 2009), and one study reported only the initial values at prosthesis delivery (Roccuzzo, Ramieri, Spada, Bianchi, & Berrone, 2004). Due to the scarcity and the inconsistency of this outcome, no meta-analysis was performed.

Gingival or bleeding indexes

Inflammation of the peri-implant soft tissues was assessed in 3 out of the 34 investigations, either as bleeding on probing or as the modified sulcus bleeding index. One study reported 8% of bleeding on probing (BOP) at the end of the study, pooling the data for implants receiving horizontal and vertical augmentation (Nissan, Gross, et al., 2011), whereas another revealed 18.2% at prosthesis delivery (Roccuzzo et al., 2004). In the study by Simion et al., 2001, the modified sulcus bleeding varied from 0.16 to 0.39 among the three study arms. No meta-analysis was performed for this outcome.

Biological complications

The occurrence of biological complications based on case definitions was only evaluated in two investigations. One study reported that 3.73% of the implants had progressive bone loss >2 mm plus BOP (Urban et al., 2009), and the other that 0% of the implants had progressive bone loss >3 mm plus BOP (Merli et al., 2014). Additionally, three studies reported that 5.8-20% of the implants had bone loss above the criteria defined by Albrektsson & Zarb (Chiapasco et al., 2004; Fontana et al., 2015; Llambes et al., 2007).

Patient reported outcomes (PROM's)

Finally, PROM's were reported only in one investigation, showing that patient esthetic perception was less than optimal in 8 out of 10 cases (Jensen et al., 2002).

Discussion

Primary findings

The results from this systematic review, based on 36 publications reporting data from 34 investigations, indicate a high variability in terms of VRA interventions. Furthermore, the available evidence is derived mostly from case series (24 investigations) and a small number of comparative studies (10 investigations), showing that VRA studies have provided primarily low levels of evidence (Richards 2009). For this reason, the results presented in the systematic review should be interpreted with caution.

The main findings of the meta-analysis, based on the changes between final and baseline values, show that these interventions significantly augment the clinical vertical ridge dimension, which was influenced by the type of intervention.

GBR was identified as the most frequently used intervention for VRA ($n_{studies}$=18). The concept of GBR is based on the creation of a secluded space to allow the protected migration of osteoblasts (Melcher, 1976). Accordingly, form-stable devices (i.e., titanium reinforced non-resorbable membranes, or resorbable membranes plus space maintainers such as titanium meshes or osteosynthesis plates) may enhance vertical bone gain. On the other hand, resorbable barrier membranes without any space maintenance features apart from the graft may collapse and achieve less bone gain. Among the types of resorbable membranes, the chemical process of cross-linking affects enzymatic degradation leading to prolonged biodegradation of these membranes, which could influence the final result (Melcher, 1976).

Block grafts ($n_{studies}$=14) were shown to be a feasible option for VRA, achieving a clinical bone gain of ~3.5mm. Nevertheless, it should be stressed that vertical bone gain was influenced by the type of technique used with autologous grafts and by the nature of the graft. The meta-analysis for comparative clinical trials showed the superiority of GBR in terms of vertical bone gain compared to onlay block grafts based on 3 studies (WMD ~1.4 mm).

Secondary findings

Based on no direct comparisons, distraction osteogenesis reported the highest complication rate (47.3%), followed by blocks (23.9%) and GBR (12.1%). Interestingly, resorbable membranes were more prone to complications than non-resorbable membranes (~23% versus ~7%), which is in line with previous systematic reviews (Elnayef et al., 2017; Lim, Lin, Monje, Chan, & Wang, 2018; Milinkovic & Cordaro, 2014). Since complication rates were high irrespective of the time of implant placement and taking into consideration that graft/membrane exposures were frequent and that postoperative infections may lead to a bacterial contamination of adjacent implant surfaces, it is speculated that staged VRA might be exposed to less severe complications.

It could be hypothesized that more caution is used when applying non-resorbable barriers, as post-operative complications derived from membrane exposure are more difficult to manage. PTFE-d membranes were less prone to complications than PTFE-e membranes (~4% vs. ~8%). This observation could be related to PTFE-e's lower cell occlusivity (larger pore size), which might lead to easier penetration of putative bacteria that could compromise graft healing outcomes (De Sanctis, Zucchelli, & Clauser, 1996).

The aggregated mean implant survival rate ($n_{studies}$=27) was comparable to previous studies reporting implants placed in pristine sites (Pjetursson, Asgeirsson, Zwahlen, & Sailer, 2014; Pjetursson, Thoma, Jung, Zwahlen, & Zembic, 2012; Salvi et al., 2018). However, bone level changes were seldom reported ($n_{studies}$=9). In addition, only 2 studies with long-term follow-up reported on biological complications based on specific case definitions (Merli et al., 2014; Urban et al., 2009). Hence, considering the limited data and the confounder effect of implant time in function, no conclusions could be drawn regarding the stability of peri-implant tissues around implants placed in VRA bone.

Agreements and disagreements with previous systematic reviews

The effectiveness of the different interventions described for VRA has been a subject of debate for years. As such, diverse systematic reviews have been published within the last decade to assess different techniques. The first review was published as part of the 6th European Workshop on Periodontology (Rocchietta et al., 2008). At that time the variability within the studies considered for the review did not allow a meta-analysis to be performed. Later and based on 8 trials, Esposito and co-workers demonstrated that more vertical bone gain could be achieved with distraction osteogenesis than with interpositional grafts (mean difference: 3.25mm) and with bone substitutes rather than with autogenous bone for GBR (mean difference: 0.6mm) (Esposito et al., 2009). However, insufficient data provided unclear conclusions regarding the most effective technique.

The results reported in the present systematic review are in agreement with a previously published review, which concluded that vertical defects can be successfully treated with GBR or bone block grafts, with a high complication rate for distraction osteogenesis (Milinkovic &

Cordaro, 2014). Moreover, Elnayef et al demonstrated the plausibility of VRA in the posterior mandible regardless of technique (mean vertical bone gain ~4.5mm), with less complications for GBR procedures (Elnayef et al., 2017).

Limitations and recommendations for future research

In the present review, caution is required before interpreting the principal findings due to the high heterogeneity between studies, conflicting inter-study outcomes, uncontrolled confounders inherent in each study design and to the multiple sub-types of interventions. Further, it must be noted that the different interventions were performed by a wide array of clinicians in different environments, with different levels of surgical training and using different biomaterials and instruments.

While evidence may indicate that bone gain occurs using VRA in severely resorbed distal extensions or fully edentulous cases, the same may not true for vertical ridge deficiencies around single implants with mesial and distal bone peaks. However, none of the RCTs included in the present systematic review evaluated a negative control to better understand this issue. As a result, some factors potentially affecting implant outcomes, particularly implant supported single crowns in resorbed ridges (i.e., crown-to-implant ratio or abutment length), could not be evaluated. Moreover, most of the included studies mixed different clinical conditions without sub-analyzing the data, which could have an impact on outcomes.

The method used for VRA measurement, including pre- (baseline defect extension) and post-operative (vertical bone gain) evaluation, was not homogeneous across the included studies. The vast majority of studies used a periodontal probe to evaluate defect depth and bone obtained after VRA, but the placement of the probe in relation to the adjacent dentition, the type of probe and its placement along the augmented bone were inconsistent across the studies. Along these lines, it is important to emphasize that trials assessing vertical bone gain via radiographs (two- or three-dimensional) were excluded from the systematic review because of inaccuracies assessing hard tissue gain and considering the heterogeneity of scattering, energy settings, exposure time, field of view and beam hardening artifacts (Rios, Borgnakke, & Benavides, 2017). Moreover, the long-term fate of the augmented bone and the

implant outcomes (including biological, technical complications and survival rates) are unclear, as only isolated, low level evidence reports containing disparate findings were available.

It must be emphasized that the aforementioned shortcomings should be overcome in future studies. As such, the authors encourage future researchers to conduct double-blind, randomized and controlled trials with long-term follow-up (≥5 years after implant loading) in different clinical environments and with multiple investigators. It would be beneficial if such future studies included incidence of biological complications and PROM's for different VRA techniques so they might also be compared with minimally invasive approaches (e.g., short dental implants).

Within the limitations of the present systematic review, it can be concluded that VRA is a reasonable therapy for the reconstruction of deficient alveolar ridges. Given the body of scientific evidence from the eligible studies included in the present systematic review, no clear conclusions can be drawn regarding the superiority of any particular VRA technique. Nonetheless, it seems that GBR, especially when combined with non-resorbable barrier membranes, offers effective VRA with low post-operative complication rates.

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(Abrahamsson, Walivaara, Isaksson, & Andersson, 2012; Artzi, Dayan, Alpern, & Nemcovsky, 2003; Cardaropoli, Gaveglio, & Cardaropoli, 2013; Corrente, Abundo, Cardaropoli, Martuscelli, & Trisi, 1997; Cucchi, Vignudelli, Napolitano, Marchetti, & Corinaldesi, 2017; De Stavola & Tunkel, 2013; Fontana et al., 2015; Peleg et al., 2010; Ronda, Rebaudi, Torelli, & Stacchi, 2014; Simion, Jovanovic, Trisi, Scarano, & Piattelli, 1998; Yu, Chen, Zhu, & Qiu, 2016)

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Figure Legends

Figure 1. Flow chart depicting the article selection process.

Figure 2. Forrest-plots for clinical vertical bone gain based on the type of procedure.

Table 1. Methodological characteristics of the included studies.

Authors/ Year	Study design	Type of procedure Test (graft presentation)	Type of procedure Control (graft presentation)	Treatment Definition Test (Staged, Simultanous)	Treatment Definition Control (Staged, Simultaneous)	Graft origin and Test (T) Control (C)	Number of patients baseline (final)/sites baseline (final)	Number of Implants baseline (final)	Follow-up of implants. Mean (range)	Study outcomes measured	Type of measure to assess vertical bone gain	Condition evaluated and Mean CBG (mm)
Artzi et al. 2003	Case series (prosp)	Titanium mesh only (Particulate)	NC	Titanium mesh + xenograft (Staged)	NC	Xenograft	10 (10)/10(10)	20(20)	Only re-entry	CBG, COM, IS	Probe to record the depth between the supporting screw head base and the current crestal augmented area.	Posterior maxilla and mandible involving more than one tooth 5.2±0.79
Canullo & Sisti 2010	Case series (prosp)	GBR (Particulate)	NC	PTFE-e titanium reinforced membrane + magnesium-enriched hydroxyapatite (Simultaneous)	NC	Synthetic graft	20 (20)/20(20)	42(42)	24	CBG, COM, IS, BL	Periodontal probe to measure exposed implant surface	Single or partial anterior or posterior maxilla or mandible 5.85±1.48
Cardaropoli et al. 2013	Case series (prosp)	GBR (Particulate)	NC	Xenograft + fibrin-fibronectin sealing + native collagen resorbable membrane (Simultaneous)	NC	Xenograft	20 (20)/20(20)	35(35)	Only re-entry	CBG, COM, IS	Periodontal probe to measure exposed implant surface	Single or partial anterior or posterior maxilla or mandible 3.94±1.47

Chiapasco et al. 2004	Case series (prosp)	Distraction (No graft)	NC	Intra-osseous distactor (Staged)	NC	No graft	37(37)/37(37)	138(138)	34 (15-55)	CBG, COM, IS, ISUC, BL	Number of rotations od the distraction device	Full or partial anterior or posterior maxilla or mandible 9.9±3.4
Corrente et al. 1997	Case series (prosp)	Particulate graft only	NC	Calcium carbonate+fibrin-fibronectin sealing (no membrane) (Simultanous)	NC	Synthetic graft	11(11)/11(11)	22(22)	Only re-entry	CBG, COM, IS	Periodontal probe to measure exposed implant surface	Single or partial anterior or posterior maxilla or mandible 2.05±1.47
De Stavola & Tunkel 2013	Case series (prosp)	Onlay (Particulate and block)	NC	Autologous bone using the shell technique (Staged)	NC	Autologous	10(10)/10(10)	18(18)	12	CBG, COM, IS	One periodontal probe placed horizontally al the bone picks and another placer vertically to the base of the bone	Single or partial anterior or posterior maxilla or mandible 6±1.29
Llambés et al. 2007	Case series (prosp)	GBR (Particulate)	NC	Autologous + xenograft +cross-linked resorbable membrane (Simultaneous)	NC	Autologous + xenograft	11 (11)/13(13)	32 (30)	12	CBG, COM, IS, ISUC, BL,	Periodontal probe to measure exposed implant surface	Partial posterior mandible 2.89±1.25

Mangano et al. 2014	Case series (prosp)	Onlay	NC	Custom made Hydroxyapatite (milling from a block) (Staged)	NC	Synthetic graft	10(10)/10(10)	10(10)	12	CBG, COM, IS, ISUC	One periodontal probe placed horizontally al the bone picks and another placer vertically to the base of the bone	Single anterior or posterior maxilla or mandible 3.7±0.82
Nissan et al. 2011a	Case series (prosp)	Onlay	NC	Freeze-dried cancellous allograft (Staged)	NC	Allograft	20(20)/NR	31(30)	42 (12-65)	CBG, COM, IS BOP	Periodontal probe to the base of the bone	Single or partial anterior maxilla 2±0.5
Nissan et al. 2011b	Case series (prosp)	Onlay	NC	Freeze-dried cancellous allograft (Staged)	NC	Allograft	34(31)/NR	63(62)	34 (6-59)	CBG, COM, IS BOP	Periodontal probe to the base of the bone	Single or partial anterior maxilla 2±0.5
Peleg et al. 2010	Case series (prosp)	Onlay	NC	Allogenic cortico-cancellous iliac graft (Staged)	NC	Allograft	13(13)/16(16)	26(26)	26	CBG, COM, IS	Distance between the screw head and the cortical aspect of the graft	Single or partial anterior or posterior maxilla or mandible 2.4±1.09
Roccuzzo et al. 2004	Case Series (prosp)	Onlay + Titanium mesh	NC	Autologous block from ramus/symphysis + Titanium mesh (Staged)	NC	Autologous	18(18)/18(18)	37(37)	Only re-entry	CBG, COM, IS, PPD, BOP	One periodontal probe placed horizontally at the CEJ of the neighbour tooth and another placer vertically to the base of the bone	Single or partial anterior or posterior maxilla or mandible 4.8±1
Todisco 2010	Case Series (prosp	GBR (Particulate)	NC	PTFE-e titanium reinforced membrane + xenograft	NC	Xenograft	20(20)/25(25)	64(64)	12	VBG, COM, IS,	One periodontal probe placed horizontally al the	Single or partial anterior or posterior maxilla

	)			(Staged)						BL	CEJ /bone picks of the neighbour tooth and another placer vertically to the base of the bone	or mandible 5.24±1.5
Urban et al. 2014	Case series (prosp)	GBR (Particulate)	NC	PTFE-d titanium reinforced membrane + autologous bone chips+ xenograft(1:1) (Staged)	NC	Autologous + xenograft (1:1)	19(19)/20(20)	NR	Only re-entry	VBG, COM	One periodontal probe placed horizontally al the bone picks and another placer vertically to the base of the bone	Partial anterior or posterior maxilla or mandible 5.45±1.93
Yu et al. 2016	Case series (prosp)	Onlay (Particualte+ Block)		Autologous bone using the shell technique (Staged)		Autologous	21(21)/21(21)	21(21)	73 (48-96)	VBG, COM	One periodontal probe placed horizontally al the CEJ /bone picks of the neighbour tooth and a calliper placer vertically to the base of the bone	Single or partial anterior maxilla 5.12±1.05
Jensen et al. 2002	Case series (prosp)	Distraction (no graft)	NC	Distraction implant or an orthodontic screw device (Staged)	NC	No graft	28(28)/30(30)	48(40)	60	CBG, IS, PROM's, COM	Measuring the length of the distraction implant	Partial anterior maxilla 6.5±1.4
Anitua et al. 2013	Case series (ret)	Particulate graft only	NC	Autologous + xenograft (when needed) + PRGF (Simultaneous)	NC	Autologous + xenograft	NR	80 (NR)	26	CBG, COM, IS BL	Periodontal probe to measure exposed implant surface	Partial posterior mandible 1-3 (range)
Canullo & Malagnino 2008	Case series (ret)	GBR (Particulate)	NC	PTFE-e titanium reinforced membrane + xenograft	NC	Xenograft	10(10)/10(10)	24(24)	36 (24-54)	CBG, COM, IS, BL	Periodontal probe to measure exposed implant surface	Partial anterior or posterior maxilla or mandible

				(Simultaneous)								5.37±1.5
Fontana et al. 2015	Case series (ret)	GBR (Particulate)	NC	Autologous only, allograft only or xenograft+auto-logous 1:1 + PTFE-e titanium rein-forced membrane (Staged or Simultaneous)	NC	Autologous (n=7); Allograft (n=5) Autologous + xenograft (n=17)	21(21)/29(29)	75(73)	42 (12-72)	CBG, COM, IS, ISUC, BL	Distance between the top of the tenting screw or implant shoulder and the first visible bone-screw contact	Partial posterior mandible 4.14±1.33
Froum et al. 2008	Case series (ret)	Distraction (No graft)	NC	Distraction with intra-osseous or extra-osseous distractors (Staged)	NC	No graft	30(30)/30(30)	55(50)	(34-60)	CBG, COM, IS, ISUC	Periodontal probe to measure from one hole of the upper distractor to a hole in the lower	Partial anterior or posterior maxilla or mandible 7.8±4.9
Funato et al. 2013	Case series (ret)	GBR (Particulate)	NC	Autologous + xenograft + cross-linked resorbable membrane + rhPDGF+ Titanium mesh (Staged)	NC	Autologous + xenograft	19(19)/19(19)	NR	Only re-entry	CBG, COM	Periodontal probe to measure from the base of the defect to the most coronal hole of the titanium mesh	Partial anterior or posterior maxilla or mandible 8.6±4
Jensen et al. 2006	Case series (ret)	Inter-positional graft (Inlay)	NC	Interpositional graft using a cortical wedge obtained from the ramus	NC	Autologous	10(10)/10(10)	15(15)	60	CBG, COM, IS	One periodontal probe placed horizontally al the CEJ /bone picks of the neighbour tooth and a calliper placer vertically to the base	Partial anterior maxilla 4.2±0.92

				(Staged)							of the bone	
Simion et al. 2001	Case Series (ret) 3 arms	GBR (Particulate)	NC	PTFE-e titanium reinforced membrane + T1: blood clot T2: DFDBA T3:Autologous (Simultaneous)	NC	T1: Blood clot T2: Allograft T3: Autologous	49(49)/54(54) T1: 6 (6)/7(7) T2: 11 (11)/11(11) T3: 32 (32)/36(36)	123 (122) T1: 17 (16) T2: 24 (24) T3: 82 (82)	(16-69)	CBG, COM, IS, ISUC, BL, PPD BOP	Periodontal probe to measure exposed implant surface	Partial anterior or posterior maxilla or mandible T1: 2.89±1.22 T2: 3.26±0.88 T3: 3.79±1.7
Urban et al. 2009	Case Series (ret)	GBR (Particulate)	NC	PTFE-e titanium reinforced membrane + autologous bone (Staged or Simultaneous)	NC	Autologous	35(35)/36(36)	82(82)	40.3 (12-72)	CBG, COM, IS, ISUC, BL, PPD BIC	One periodontal probe placed horizontally al the bone picks and another placer vertically to the base of the bone or periodontal probe to measure exposed implant surface	Full, single or partial anterior or posterior maxilla or mandible 5.5±2.29
Beitlitum et al. 2010	CCT	GBR (Particulate)	GBR (Particulate)	Autologous bone + FDBA+cross-linked resorbable membrane (Staged or Simultaneous)	FDBA+cross-linked resorbable membrane (Staged or Simultaneous)	Autologous + allograft (T) Allograft (C)	23(23)/23(23)	51(51)	Only re-entry	CBG, COM, IS	Periodontal probe to measure exposed implant surface	Single or partial anterior or posterior maxilla or mandible T: 3.5±1.2 C: 3.47±1.25
Rocchietta et al. 2016	CCT	Onlay + membrane	GBR	Autologous + PTFE-e titanium reinforced	Autologous+ PTFE-e titanium	Autologous (T & C)	10(10)/12(12)	NR	Only re-	CBG, COM	Distance from the base of the bone to the head of the	Partial posterior mandible

			(Particluate)	membrane (Staged)	reinforced membrane (Staged)				entry		titanium screw	T: 2.91±0.92 C: 4.45±0.85
Roccuzzo et al. 2007	CCT	Onlay + Titanium mesh	Onlay	Autologous from ramus/symphysis + Titanium-mesh (Staged)	Autologous from ramus/symphysis (Staged)	Autologous (T & C)	23(23)/24(24)	NR	Only re-entry	CBG, COM,	One periodontal probe placed horizontally al the CEJ of the neighbour tooth and another placer vertically to the base of the bone	Single or partial anterior or posterior maxilla or mandible T: 4.8±1.5 C: 3.6±1.4
Simion et al. 1998	CCT	GBR (Particulate)	GBR (Particulate)	PTFE-e titanium reinforced membrane + DFDBA (Simultaneous)	PTFE-e titanium reinforced membrane + autologous bone (Simultaneous)	Allograft (T) Autologous (C)	20 (20)/22(22)	26 (26)	Only re-entry	CBG, COM, IS	Periodontal probe to measure exposed implant surface	Partial anterior or posterior maxilla or mandible T: 3.14±0.9 C: 5.02±2.3
Abrahamsson et al. 2012	RCT (parallel)	GBR (Particulate)	Onlay	Soft tissue expander + autologous + titanium mesh + native collagen resorbable membrane (Staged)	Autologous graft (Staged)	Autologous (T & C)	20 (20)/20(20)	23(23)	Only re-entry	CBG, COM, IS	T: probe from the crest to the mesh. C: probe to measured graft resoption at the screws	Single or partial anterior maxilla T: 3±1.4 C: 1.6±0.8
Merli et al. 2014, 2010,	RCT (parall	GBR	GBR	Native collagen resorbable membrane	e-PTFE titanium	Autologous	22(21)/22(2	77(74)	72	CBG,	Periodontal probe to measure exposed	Single or partial anterior or

2007	el)	(Particulate)	(Particulate)	supported by osteosynthesis plates + autologous (Simultaneous)	reinforced membrane + autologous (Simultaneous)	(T & C)	1)			COM, BL BIC	implant surface	posterior maxilla or mandible T: 2.16±1.51 C: 2.48±1.13
Ronda et al. 2014	RCT (parallel)	GBR (Particulate)	GBR (Particulate)	d-PTFE titanium reinforced membrane + autologous + allograft 50:50 (Simultaneous)	e-PTFE titanium reinforced membrane + autologous + allograft 50:50 (Simultaneous)	Autologous + allograft (T & C)	23(23)/26(26)	38(38)	(15-37)	CBG, COM, IS	Periodontal probe to measure exposed implant surface	Partial posterior mandible T: 5.49±1.58 C: 4.91±1.78
Cucchi et al. 2017	RCT (parallel)	GBR (Particulate)	GBR (Particulate)	Allograft+ autologous (50:50)+ titanium mesh+ cross-linked collagen membrane (Simultaneous)	Allograft+ autologous (50:50)+ PTFE-d titanium reinforced membrane (Simultaneous)	Autologous + allograft (T & C)	40(35)/40(35)	99 (99)	Only re-entry	CBG, COM, IS	Periodontal probe to measure exposed implant surface	Partial posterior mandible T: 4.1±1 C: 4.2±1
Leong et al. 2015	RCT (parallel)	Onlay+Membrane	GBR (Particulate)	Allograft + native collagen resorbable membrane (Staged)	Cancellous and cortical allograft + native collagen resorbable membrane	Allograft (T & C)	16(16)/19(19)	NR	Only re-entry	CBG, COM	Periodontal probe with a surgical stent	Partial posterior mandible T: 1.78±2.3 C: 1±2.2

					(Staged)							
Fontana et al. 2008	RCT (split)	GBR (Particulate)	GBR (Particulate)	Allograft +PTFE-e titanium reinforced membrane) (Staged)	Autologous +PTFE-e titanium reinforced membrane) (Staged)	Allograft (T) Autologous (C)	5(5)/10(10)	25(25)	24 (12-36)	CBG, COM, IS, BL, PPD	Distance from the base of the bone to the head of the titanium screw	Partial posterior mandible T: 4.7±0.48 C: 4.1±0.88

prosp: prospective; NC: no control; T: test; C: control; GBR: guided bone regeneration; PTFE-e: expandend Polytetrafluoroethylene; PTFE-d: dense Polytetrafluoroethylene; ret: retrospective; DFDBA: demineralized freeze dried bone allograft; FDBA: freeze dried bone allograft; rh-PDGF: recombinant human platelet derived growth factor; CCT: controlled clinica trial; PRGF: platelet rich growth factors; RCT: randomized clinical trial; CBG: Clinical Bone Gain; COM: Complication IS: Implant survival, ISUC: Implant success, BL: Marginal bone levels assessed radiograohically; PPD: Peri-implant probing depth; BOP: Bleeding on Probing; BIC: Biological implant complication; PROMs: patient reported outcomes.; CEJ: cement-enamel junction; NR: Not reported

Table 2. Meta-analysis for vertical bone augmentation: Final vs. Baseline (mm)

Group:Subgroup	n	Weighted Mean Effect					Heterogeneity	
		IV	DL	95% CI		P value	I^2	P value
All	33		4.164	3.716	4.612	<0.001	96.5	<0.001
Study design								
RCT (all)	6		3.358	2.599	4.117	<0.001	93.3	<0.001
RCT (split)	1	4.562		4.193	4.932	<0.001	-	-
RCT (parallel)	5		3.128	2.260	3.997	<0.001	93.0	<0.001
CCT	4		3.826	3.287	4.365	<0.001	83.4	<0.001
Case Series	23		4.670	3.978	5.362	<0.001	97.7	<0.001
Unit of analysis								
Patient	23		4.401	3.904	4.897	<0.001	94.5	<0.001
Implant/Site	10		3.582	2.920	4.244	<0.001	96.4	<0.001
Time of implant placement								
Staged	21		4.386	3.707	5.065	<0.001	97.6	<0.001
Simultaneous	12		3.808	3.312	4.303	<0.001	90.3	<0.001
Intervention								
1. Distraction osteogenesis	3		8.044	5.678	10.409	<0.001	93.6	<0.001
2. Guided Bone Regeneration	20		4.179	3.797	4.560	<0.001	89.7	<0.001

2.1. Non resorbable membrane	13		4.422	3.974	4.870	<0.001	89.4	<0.001
2.1.1. Non resorbable membrane (PTFE-e)	11		4.310	3.801	4.818	<0.001	90.2	<0.001
2.1.2. Non resorbable membrane (PTFE-d)	3		4.986	4.027	5.946	<0.001	81.3	0.005
2.1.3. Non resorbable + particulate autologous	6		4.210	3.408	5.011	<0.001	88.5	<0.001
2.1.4. Non resorbable membrane + particulate allograft	3		3.702	2.683	4.722	<0.001	93.9	<0.001
2.1.5. Non resorbable membrane + particulate xenograft	2	5.277		4.780	5.774	<0.001	0.0	0.817
2.1.6. Non resorbable membrane + particulate synthetic graft	1	5.850		5.201	6.499	<0.001	-	-
2.1.7. Non resorbable membrane + particulate autologous + particulate allograft	2		4.793	3.949	5.637	<0.001	71.4	0.030
2.1.8. Non resorbable membrane + particulate autologous + particulate xenograft	1	5.450		4.604	6.296	<0.001	-	-
2.2. Resorbable membrane	8		3.513	2.801	4.225	<0.001	87.2	<0.001
2.2.1. Resorbable membrane + space maintainer (Ti-mesh/plate)	4		4.263	2.588	5.938	<0.001	93.4	<0.001
2.2.2. Resorbable membrane without space maintainer	4		3.185	2.510	3.861	<0.001	75.3	0.001

2.2.3. Native collagen resorbable membrane	4		2.659	1.493	3.825	<0.001	86.6	<0.001
2.2.4. Cross-linked resorbable membrane	4		4.195	3.183	5.207	<0.001	89.0	<0.001
2.2.5. Resorbable membrane + particulate autologous	2		2.587	1.764	3.410	<0.001	42.9	0.186
2.2.6. Resorbable membrane + particulate allograft	2		2.336	-0.076	4.749	<0.001	88.4	0.003
2.2.7. Resorbable membrane + particulate xenograft	1	3.950		3.463	4.437	<0.001	-	-
2.2.8. Resorbable membrane + particulate autologous + particulate allograft	2		3.901	3.347	4.455	<0.001	33.7	0.220
2.2.9. Resorbable membrane + particulate autologous + particulate xenograft	1	2.890		2.151	3.629	<0.001	-	-
2.2.10 Resorbable membrane + particulate autologous + particulate xenograft + rhPDGF	1	8.600		6.801	10.399	<0.001	-	-
2.3. Titanium mesh (without membrane)	1	5.200		4.710	5.690	<0.001	-	-
2.3.1. Titanium mesh + particulate xenograft	1	5.200		4.710	5.690	<0.001	-	-
3. Blocks	12		3.464	2.706	4.222	<0.001	97.2	<0.001
3.1. Autologous bone block	7		4.118	3.109	5.126	<0.001	95.9	<0.001

3.1.1. Autologous onlay block	4		3.530	2.209	4.851	<0.001	96.0	<0.001
3.1.2. Autologous interpositional block	1		4.200	3.630	4.770	<0.001	-	-
3.1.3. Shell technique	2		5.495	4.642	6.348	<0.001	71.2	0.060
3.2. Allograft bone block	4	2.030		1.880	2.179	<0.001	0.0	0.556
3.3. Xenograft block	1	3.700		3.192	4.208	<0.001	-	-
4. Particulate synthetic graft	1	2.050		1.436	2.664	<0.001	-	-

IV, inverse-variance weighted (fixed effect) model; DL, DerSimonian and Laird (random effect) model; CI, confidence interval; RCT, randomized clinical trial; CCT, controlled clinical trial

Table 3. Meta-analysis for differences in vertical bone augmentation for comparative studies: Test vs Control (mm)

Control	Test		Weighted Mean Difference				Heterogeneity	
		n	IV/DL	95% CI		P value	I^2	P value
Onlay Block	Guided Bone Regeneration	3[a,b,c]	1.336	0.762	1.911	<0.001	29.2	0.243
Autologous Onlay Block	Autologous Onlay Block + Ti-mesh	1[d]	1.200	0.039	2.361	0.042	-	-
Non resorbable membrane	Resorbable membrane + space maintainer	2[e,f]	-0.156	-0.720	0.408	0.587	0.0	0.738
Guided Bone Regeneration + particulate autologous	Guided Bone Regeneration + particulate allograft	3[g,h,i]	-0.440	-1.961	1.081	0.571	0.0	0.394
PTFE-e membrane + particulate autologous + particulate allograft	PTFE-d membrane + particulate autologous + particulate allograft	1[j]	0.58	-0.800	1.960	0.410	-	-

IV, inverse-variance weighted (fixed effect) model; DL, DerSimonian and Laird (random effect) model; CI, confidence interval

[a] Abrahamsson et al. (2012); [b] Leong et al. (2015); [c] Rocchietta et al. (2016); [d] Roccuzzo et al. (2007); [e] Merli et al. (2007); [f] Cucchi et al. (2017); [g] Fontana et al. (2008); [h] Beitlitum et al. (2010); [I] Simion et al. (1998); [j] Ronda et al. (2014).

Table 4. Surgical intra- and post-operative complications.

Reference	Procedure	% Complications	Specifications of complications
Artzi et al. 2003	T: Titanium mesh	T: 20	2 cases with exposure of the titanium mesh. Implants could be places without any problem.
Canullo & Sisti 2010	T: GBR	T: 5	1 patient presented a late exposure at 8 weeks and the membrane was immediately removed. The complication didn't jeopardize the implant or the VBA.
Cardaropoli et al. 2013	T: GBR	T: 0	No complication occurred
Chiapasco et al. 2004	T: Distraction	T: 22	1 case with mandibular fracture. 5 cases with mandibular or palatal inclination of the segment. 1 case with incomplete distraction and 1 case with the need of secondary bone grafting
Corrente et al. 1997	T: Particulate graft only	T: 0	No cases with exposure of the graft material.
De Stavola &Tunkel 2013	T: Onlay	T: 0	No exposure of the graft and no complications with the donor site.
Llambés et al. 2007	T: GBR	T: 27.3	2 cases with oral perforation by the implant at 3 months and 1 case with exposure and implant failure.
Mangano et al. 2014	T: Onlay	T: 10	One graft was exposed 2 months after the procedure and the most coronal portion of the graft had to be removed.
Peleg et al. 2010	T: Onlay	T: 0	No cases with exposure of the graft material.
Roccuzzo et al. 2004	T: Onlay + Ti-mesh	T: 38.9	Temporary paraesthesia observed in 5 cases (27.8%). Exposure of the Ti-mesh in 4 patients (22.2%).

Todisco 2010	T: GBR	T: 8	2 patients presented membrane exposure.
Urban et al. 2014	T: GBR	T: 0	No cases with exposure or infection of the membrane.
Yu et al. 2016	T: Onlay	T: 33.3	6 patients required additional grafting (28.6%). 1 patient presented a membrane exposure (4.76%).
Jensen et al.2002	T: Inter-positional graft	T: 46.7-60	Relapse of the segment occurred in 14 segments (46.7%), with 1 presenting a complete regression (the remaining < 1mm). Secondary bone grafting was required in 18 patients (60%).
Anitua et al. 2013	T: Particulate graft only	T: 0	No cases with impaired function of the alveolar nerve.
Canullo & Malagnino 2008	T: GBR	T: 10	1 patient presented a late exposure at 5 months that was cleaned during one month. The VBG was assured and implants could be placed.
Funato et al. 2013	T: GBR with Ti-mesh	T: 15.8	1 early wound dehiscence that needed Ti-mesh removal. 1 late Ti-mesh exposure. 1 case without mature bone for implant placement (GBR was needed again)
Fontana et al. 2015	T: GBR	T: 17.2	3 cases with early membrane exposure (2 had to be immediately removed and 1 was postponed 4 weeks). 2 cases with infection without membrane exposure (membranes were immediately removed).
Froum et al. 2008	T: Distraction	T: 73.3	18 patients required additional bone augmentation. 22 patients failed to achieve buccal augmentation or presented a palatal movement of the transport segment. 4 patients had flap dehiscence. 2 patients had distractor instability. 2 patients had infection. 8 patients had resorption of the transport segment.
Simion et al. 2001	T: GBR	T: 17.3	7 patients presented membrane exposure (13.5%). 2 patients presented local infection (3.8%).
Urban et al.	T: GBR	T: 2.8	1 patient presented a local infection.

2009			
Beitlitum et al. 2010	T: GBR C: GBR	T: 25 C: 33.3	T: 2 cases with membrane exposure. C: 5 cases with membrane exposure. * 12.5% of patients receiving a mandibular procedure had transitory paraesthesia.
Rocchietta et al. 2016	T: Onlay + membrane C: GBR	T: 8.3 C: 8.3	1 patient presented an abscess that affected sites test and control sites. The membrane had to be removed together with the grafts.
Roccuzzo et al. 2007	T: Onlay + Ti-mesh C: Onlay	T: 33.3 C: 58.33	T: 4 patients presented mesh exposure. C: 1 Graft mobilization at implant placement (8,3%). 3 incomplete integration of the graft (25%). 1 temporary parethesia (8,3%). 2 significant graft resorption (16,7%).
Simion et al. 1998	T: GBR C: GBR	T: 20 C: 20	T: 2 patients presented membrane exposure. C: 1 patient presented membrane exposure and 1 patient presented local infection/abscess.
Abrahamsson et al. 2012	T: GBR C: Onlay	T: 40 C: 0	T: 2 cases with perforation of the soft tissue expander and 2 patients with exposure of the titanium mesh. C: No single complication.
Merli et al. 2007	GBR (Particulate)	T: 36.4 C: 45.4	T: 2 major complications: local infections with failure of the augmentation procedure. 2 minor complications (flap dehiscence without suppuration and early infection) which didn't jeopardize the augmentation procedure. C: 1 major complication: Dehiscence + infection with failure of the procedure. 4 Minor complications: 3 Fistulas at different time points (2 weeks, 2 months with re-entry and at abutment connection) and 1 lymph node swelling.
Ronda et al. 2014	T: GBR	T: 0	No single complication.

	C: GBR	C: 0	
Cucchi et al. 2017	T: GBR C: GBR	T: 21 C: 15	T: 3 major complications: abscess without exposition, early exposure with infection, and late exposure with infection. 1 minor complication: late exposure without infection. C: 2 major complications: 1 abscess without exposition and 1 early membrane with infection. 1 minor complication: late membrane exposure without infection.
Leong et al. 2015	T: Onlay + membrane C: GBR	T: 77.8 C: 30	T: 7 out of 9 blocks presented soft tissue dehiscence and incision line openings. 1 block was lost. C: 3 out of 10 surgical sites experiences wound dehiscence and incision line opening.
Fontana et al. 2008	T: GBR C: GBR	T: 20 C: 20	T: 1 case presented paraesthesia that solved spontaneously before two months. C: 1 case with infection without membrane exposure that had to be removed. Implants could be placed.

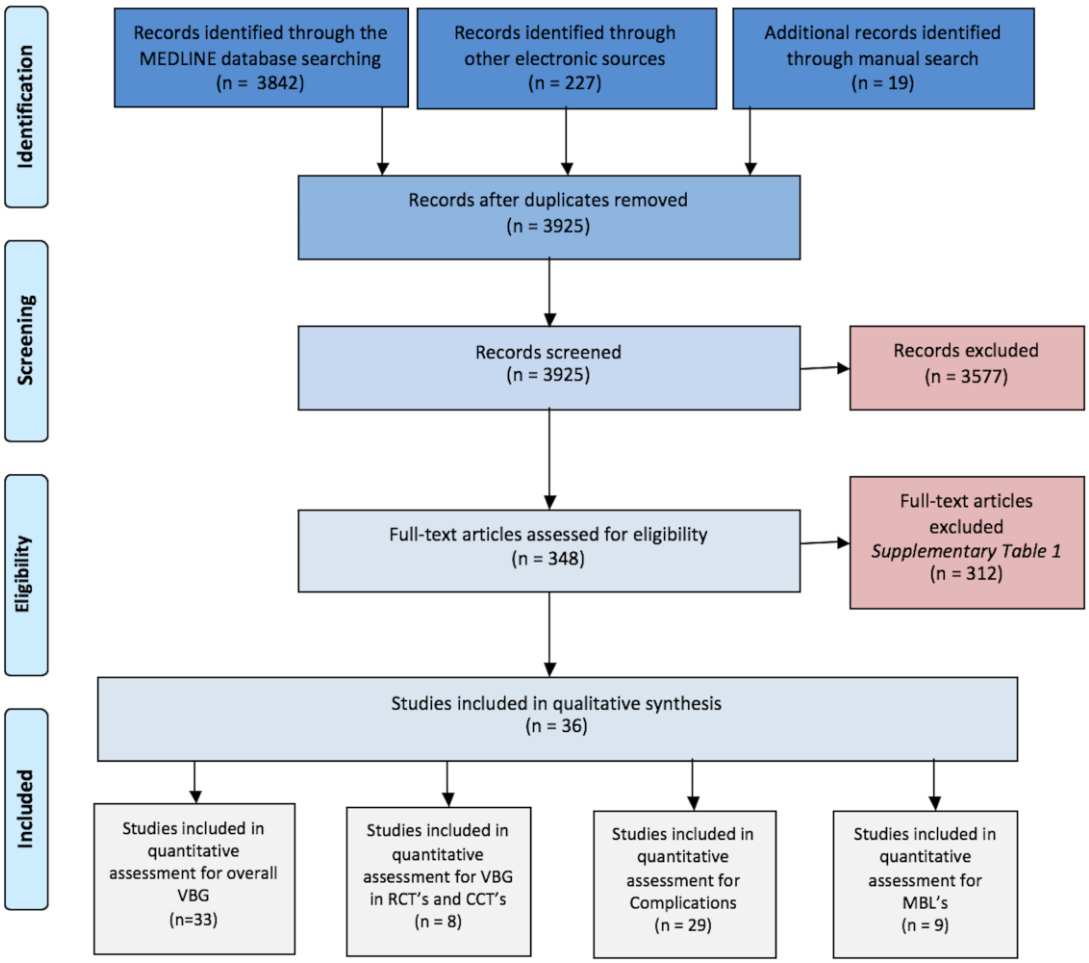
T: Test; C: Control; GBR: guided bone regeneration; VBA: vertical bone augmentation; Ti: titanium.

Table 5. Meta-analysis for prevalence of complications (%) by intervention.

Group:Subgroup	n	Weighted Mean Incidence					Heterogeneity	
		IV	DL	95% CI		P value	I^2	P value
All	29		16.9	12.5	21.2	<0.001	80.0	<0.001
Study design								
RCT (all)	6		23.2	12.2	34.3	<0.001	73.6	<0.001
RCT (split)	1	20.0		0.0	44.8	<0.001	-	-
RCT (parallel)	5		24.0	11.7	36.2	<0.001	78.2	<0.001
CCT	4		23.3	12.0	34.5	<0.001	83.4	<0.001
Case Series	18		13.6	7.8	19.4	<0.001	80.9	<0.001
Time of implant placement								
Staged	15		22.3	13.4	31.3	<0.001	84.4	<0.001
Simultaneous	11		11.8	6.7	17.0	<0.001	49.8	0.010
Intervention								
1. Distraction osteogenesis	3		47.3	0.0	98.0	<0.001	95.9	0.047
2. Guided Bone Regeneration	20		12.1	8.2	15.9	<0.001	42.7	0.010
2.1. Non resorbable membrane	13	6.9		4.1	9.7	<0.001	22.6	0.186
2.1.1. Non resorbable membrane (PTFE-e)	11	8.0		4.7	11.3	<0.001	23.6	0.192

2.1.2. Non resorbable membrane (PTFE-d)	3	4.1		0.0	9.4	<0.001	6.2	0.344
2.2. Resorbable membrane	8		22.7	11.5	33.9	<0.001	63.9	0.005
2.2.1. Resorbable membrane + space maintainer (Ti-mesh/plate)	4	23.3		12.7	33.8	<0.001	0.0	0.417
2.2.2. Resorbable membrane without space maintainer	4		21.0	4.2	37.9	<0.001	68.6	0.013
2.2.3. Native collagen resorbable membrane	4		24.4	1.3	47.4	0.019	77.1	0.004
2.2.4. Cross-linked resorbable membrane	4	22.4		12.9	32.0	<0.001	0.0	0.807
2.3. Titanium mesh	1	20.0		0.0	44.8	<0.001	-	-
3. Blocks	9		23.9	11.3	36.6	<0.001	83.1	<0.001
3.1. Autologous bone block	6		22.9	9.1	36.8	0.006	75.8	<0.001
3.1.1. Autologous onlay block	4		26.1	7.2	45.0	0.007	78.5	<0.001
3.1.2. Shell technique	2		17.8	0.0	45.9	<0.001	82.5	0.017
3.2. Allograft bone block	2		39.2	0.0	100	<0.001	96.3	<0.001
3.3. Xenograft block	1	10.0		0.0	28.6	<0.001	-	-
4. Particulate synthetic graft	1	2.2		0.0	8.1	<0.001	-	-

IV, inverse-variance weighted (fixed effect) model; DL, DerSimonian and Laird (random effect) model; CI, confidence interval; RCT, randomized clinical trial; CCT, controlled clinical trial



VBG: vertical bone gain; RCT's: randomized controlled trials; CCT's: controlled clinical trials; MBL's: marginal bone levels.