Guided Bone Regeneration with Collagen Membranes and Particulate Graft Materials: A Systematic Review and Meta-Analysis

Bastian Wessing, Dr Med Dent[1]/Stefan Lettner[2]/
Werner Zechner, Univ Prof Dr med Dr med dent[3]

Purpose: *The aim of this meta-analysis was to evaluate different methods for guided bone regeneration using collagen membranes and particulate grafting materials in implant dentistry.* ***Materials and Methods:*** *An electronic database search and hand search were performed for all relevant articles dealing with guided bone regeneration in implant dentistry published between 1980 and 2014. Only randomized clinical trials and prospective controlled studies were included. The primary outcomes of interest were survival rates, membrane exposure rates, bone gain/defect reduction, and vertical bone loss at follow-up. A meta-analysis was performed to determine the effects of presence of membrane cross-linking, timing of implant placement, membrane fixation, and decortication.* ***Results:*** *Twenty studies met the inclusion criteria. Implant survival rates were similar between simultaneous and subsequent implant placement. The membrane exposure rate of cross-linked membranes was approximately 30% higher than that of non–cross-linked membranes. The use of anorganic bovine bone mineral led to sufficient newly regenerated bone and high implant survival rates. Membrane fixation was weakly associated with increased vertical bone gain, and decortication led to higher horizontal bone gain (defect depth).* ***Conclusion:*** *Guided bone regeneration with particulate graft materials and resorbable collagen membranes is an effective technique for lateral alveolar ridge augmentation. Because implant survival rates for simultaneous and subsequent implant placement were similar, simultaneous implant placement is recommended when possible. Additional techniques like membrane fixation and decortication may represent beneficial implications for the practice.* Int J Oral Maxillofac Implants 2017 (14 pages). doi: 10.11607/jomi.5461

Keywords: *alveolar ridge augmentation, barrier membranes, collagen membranes, decortication, guided bone regeneration, membrane fixation*

Implant dentistry as a field has developed numerous advancements in materials and concepts that are designed to avoid alveolar ridge augmentation. However, there is still a pressing need for bone augmentation in situations where other techniques will not produce esthetic or functional results, such as cases of reduced horizontal or vertical bone volume.[1,2] Numerous alveolar ridge augmentation techniques have been developed, including autologous bone blocks from intra- and extraoral donor sites, ridge splitting and expansion, distraction osteogenesis, sandwich osteoplasty, and guided bone regeneration (GBR).[3]

GBR is an extensively described alveolar ridge augmentation technique that has been shown to produce excellent, reproducible results and high long-term success rates based on high-evidence-level publications.[4–9] GBR uses a resorbable or nonresorbable membrane to create and maintain a space over the bony defect and under the periosteum. Ideally, osteoprogenitor cells should colonize the space over the defect; however, these cells grow relatively slowly. The membranes used in GBR prevent the ingrowth of rapidly proliferating epithelial and connective tissue cells into the defect. GBR was first described by Nyman and Karring in 1979 as a means of guided tissue regeneration based on tissue engineering principles, and numerous studies on the technique were published

[1]Co-Head, Dental Practice Clinic, Luisenhospital, Aachen, Germany.
[2]Biostatistician, Karl Donath Laboratory for Hard Tissue and Biomaterials, Department for Oral Surgery, School of Dentistry, Medical University of Vienna; Austrian Cluster for Tissue Regeneration.
[3]Co-Head, Department for Oral Surgery, University Dental Clinic, Vienna, Austria.

Correspondence to: Dr Bastian Wessing, Dental Practice Clinic, Luisenhospital Boxgraben 99, 52064 Aachen, Germany. Fax: 0049 241 4007278. Email: bastian.wessing@googlemail.com

thereafter.[4,10–14] These early publications primarily used polytetrafluoroethylene (PTFE) membranes as a barrier. Several studies reported that this material had a high membrane exposure rate of 30% to 40%,[15–17] whereas other studies achieved very good results with no membrane exposure reported during the healing phase.[18–20] Due to its rigid mechanical properties, nonresorbable PTFE membranes can create and maintain the necessary space for GBR procedures, especially when the membrane is titanium reinforced. Using these membranes, the investigators achieved horizontal bone gain up to 9 mm and vertical bone gain up to 12 mm.[4,5,19,20] In most studies reporting the use of these membranes, they were fixed to the underlying cortical bone with titanium pins or osteosynthesis screws to keep them in the desired position.[16,21]

Despite their effectiveness, nonresorbable membranes must be eventually removed, which requires surgically reopening the soft tissue.[18,22] To avoid membrane removal surgeries, investigators developed resorbable materials, such as collagen membranes, in the early 1990s. Resorbable membranes have been studied extensively for guided tissue regeneration and GBR.[23–27] Nonchemically cross-linked bioresorbable membranes have good tissue and cell compatibility and lower dehiscence rates compared with PTFE membranes. To date, the biologic aspects of collagen membranes have been investigated thoroughly.[28–30]

One challenging aspect of performing particulate grafts with resorbable membranes is identifying a method to fix the immobilized graft membrane at the desired position. This challenge is a key factor for successful GBR, because poor mechanical immobilization of the particulate graft under the fixed membrane results in increased dehiscence rates and reduced bone regeneration.[16] Several studies reported the use of resorbable or nonresorbable cortical bone pin systems or even sutures to fixate collagen membranes.[31–33] When nonresorbable pins are used, patients may need to undergo an additional surgery to remove the pins. Furthermore, the use of any pins, resorbable or nonresorbable, increases the risk of perforating important anatomical structures, such as the alveolar nerve, maxillary sinus, or roots of adjacent teeth.

To date, there are several systematic reviews or meta-analyses addressing GBR procedures using PTFE membranes. To the authors' knowledge, there is no such publication for resorbable collagen membranes, especially in combination with particulate graft materials, even though these materials are often used in daily practice. Additionally, there are no clear guidelines on the use of collagen membranes with respect to their indications and limitations. The aim of this meta-analysis was to identify relevant clinical studies on GBR using resorbable collagen membranes and particulate graft material for implant dentistry applications that have been reported within the last three decades. This analysis focuses on the quantity of regenerated bone, membrane exposure rate, and the implant survival rate in human studies. The secondary objective was to evaluate whether additional techniques, ie, membrane fixation and additional decortication, produce beneficial clinical outcomes.

MATERIALS AND METHODS

Literature Search

Two independent reviewers (B.W., W.Z.) performed an electronic literature search of the MEDLINE database for papers published between January 1980 and December 2014. The literature search was performed and reported according to the preferred reporting items for systematic reviews and meta-analysis (PRISMA) guidelines[34] (Fig 1). The last date that the literature was searched was December 20, 2014. The literature search was limited to articles published in English. The following search terms, filters, and their combinations were used for this search:

(((((English[Language]) AND ("1980/01/01"[Date - Publication] : "2014/12/30"[Date - Publication])) AND (((((dentistry[MeSH Terms]) AND dental implant[MeSH Terms]) OR dental implants[MeSH Terms]) OR dental implantation[MeSH Terms]) OR dental implantation, endosseous[MeSH Terms])) AND ((((alveolar ridge augmentation[MeSH Terms]) OR alveolar ridge augmentations[MeSH Terms]) OR (guided bone regeneration)) OR GBR)) AND ((((collagen membrane)) OR (resorbable membrane)) OR (absorbable membrane)))

An additional search was performed on EMBASE and the Cochrane Library. Furthermore, a hand-search of the following journals was performed: *The International Journal of Oral & Maxillofacial Implants*, *The International Journal of Periodontics & Restorative Dentistry, Clinical Implant Dentistry and Related Research, Journal of Periodontology,* and *Journal of Clinical Periodontology*. Relevant publications were collected in Citavi 4.0 software, and duplicates were discarded electronically.

Two independent reviewers assessed the abstracts of the selected publications to eliminate irrelevant publications. Publications were retained if they matched the inclusion criteria. If no abstract was available, the original article was used. Following abstract screening, the reviewers analyzed the full text to select the final articles. The reviewers also cross-checked the references of the selected articles to identify any undetected, relevant studies. Following their independent, full-text screenings, the reviewers compared their selections and discussed each publication individually prior to final article inclusion. Any discrepancies between the

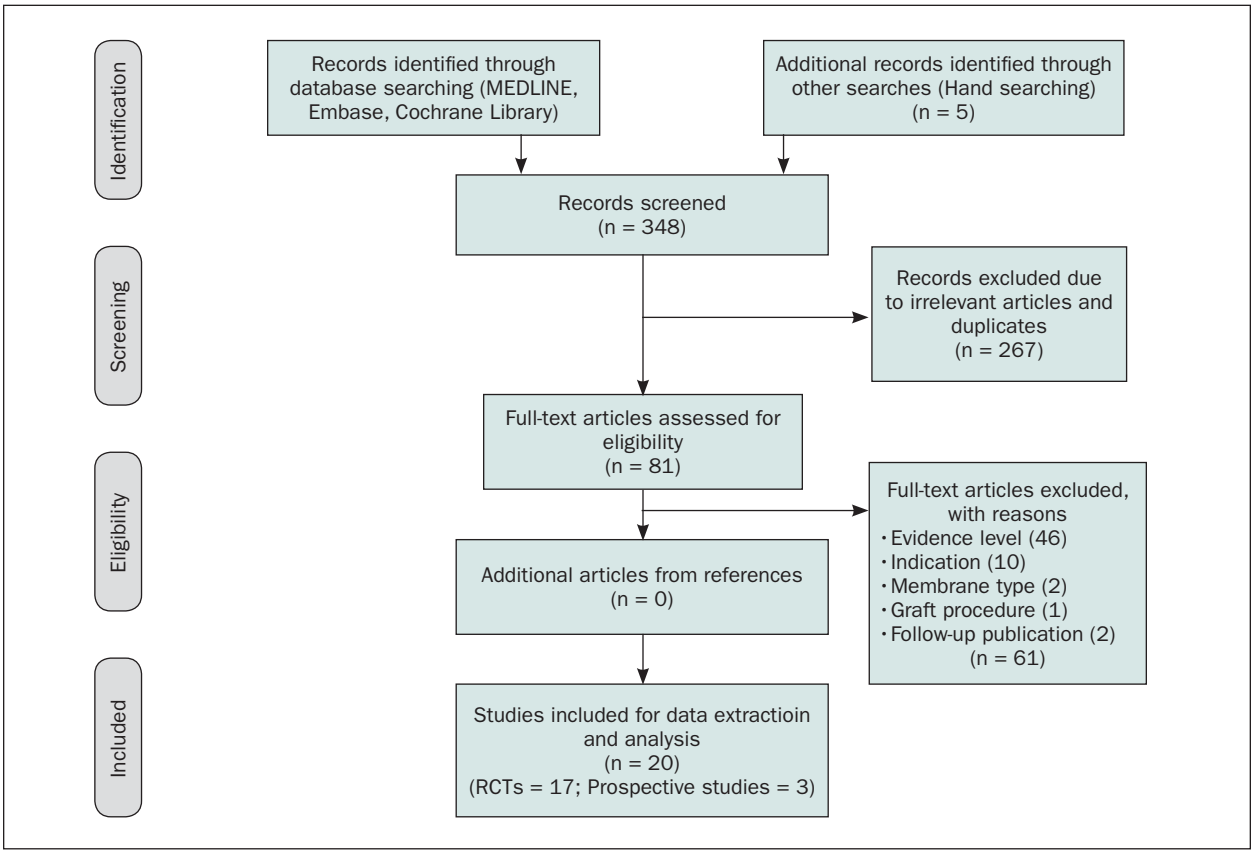

Fig 1 Preferred reporting items for systematic reviews and meta-analysis (PRISMA) flowchart of the search strategy for this systematic review.

two reviewers regarding the inclusion of an article were resolved through a consensus discussion.

Study Selection

Publications were selected based on the Cochrane Collaboration's Patients, Intervention, Comparison, Outcomes (PICO) principle, described below.

Patients. The review included clinical studies of patients treated with dental implants that had simultaneous or previously performed GBR with collagen barrier membranes and particulate graft materials for horizontal and/or vertical bone augmentation. There were no restrictions concerning gender, age, diabetes, or smoking status. Patients with active periodontitis were excluded.

Intervention. The intervention was simultaneous or previously performed bone augmentation using GBR for dental implant therapy. GBR procedures needed to have been performed with particulate materials, such as autologous bone chips, and/or osteoconductive materials, such as allografts, xenografts, or alloplastic bone substitute materials. The GBR procedure needed to be part of a closed healing protocol. Studies had to use resorbable collagen membranes for inclusion.

Comparison. The following comparisons were made: *(1)* GBR procedures in which an immobilized collagen membrane was fixed to the underlying bone using a cortical pin system, sutures, or the cover screw of the implant were compared with GBR procedures in which the collagen membrane was applied to the grafted area, rehydrated with blood or sterile saline, and no further fixation methods were used; *(2)* GBR procedures with partial decortication in the augmented area were compared with GBR procedures without decortication.

Outcomes. The outcome measures included *(1)* implant survival rate, *(2)* membrane exposure rate, *(3)* bone gain with the quantity of regenerated bone measured as millimeters horizontal or vertical, and *(4)* bone loss observed during follow-up.

Study Design

Only randomized controlled trials (RCTs) with evidence level II-2 or higher (cohort or case-control analytic studies) based on the United States preventive services task force classification[35] were included.

Exclusion Criteria

Exclusion criteria were defined as follows: *(1)* animal or in vitro studies; *(2)* evidence level less than II-2; *(3)* studies in extraction sites or studies that used growth factors; *(4)* GBR to correct other indications, such as extraction sites, periodontal defects, or root resection

Table 1 Risk of Bias Assessment for Randomized Clinical Trials Using Cochrane Collaboration's RoB Tool

Study	Random sequence generation	Allocation concealment	Blinding of participants and researchers	Blinding of outcome assessment	Incomplete outcome data	Selective outcome reporting	Other sources of bias
Amorfini et al[42] (2014)	Low	Low	Low	Low	Low	Low	Low
Annen et al[43] (2011)	Low	Low	Low	Low	Low	Low	Low
Van Assche et al[44] (2013)	Unclear	Low	Unclear	Unclear	Low	Low	Low
Becker et al[45] (2009)	Low	Low	Low	Low	Low	Low	Low
Carpio et al[16] (2000)	Unclear	Unclear	Unclear	Unclear	Low	High	Low
Friedmann et al[8] (2002)	Unclear	Unclear	Unclear	Unclear	Low	Low	Low
Friedmann et al[47] (2011)	Low	Low	Unclear	Low	Low	Low	Low
Jung et al[19] (2009)	Low	Unclear	Unclear	Unclear	Low	Low	Low
Meijndert et al[50] (2005)	Low	Low	Unclear	Unclear	Low	Low	Low
Meijndert et al[49] (2008)	Low	Low	Unclear	Low	Low	Low	Low
Merli et al[9] (2014)	Low	Low	Low	Low	Low	Low	Low
Mordenfeld et al[51] (2014)	Low	Low	Low	Unclear	Low	Low	Low
Park and Wang[54] (2007)	Unclear	Unclear	Unclear	Unclear	Low	Low	Low
Park et al[53] (2008)	Low	Unclear	Low	Low	Low	Low	Low
Sisti et al[55] (2012)	Low	Low	Unclear	Unclear	Low	Low	Low
Zitzmann et al[6] (1997)	Low	Unclear	Unclear	Unclear	Low	Low	Low
Zitzmann et al[56] (2001)	Low	Unclear	Unclear	Unclear	Low	Low	Low

defects; *(5)* studies with nonparticulate graft material morphology, such as bone blocks; *(6)* studies that used membranes other than resorbable collagen membranes; or *(7)* shorter follow-up publications of the same study (only one publication with the longest follow-up was used).

Data Extraction

The following information was extracted from selected publications: journal, name of author(s), publication year, study design, intervention type, membrane, graft material or membrane supporting material, time of implant placement (simultaneous or subsequent), membrane fixation method, decortication, mean healing time, membrane exposure rate, horizontal bone gain, vertical bone gain, bone loss, number of patients, number of implants, follow-up period, patients lost to follow-up, and implant survival rate.

If any relevant information was missing from the published results, corresponding authors were contacted via email. Data were entered into a piloted data extraction form (Microsoft Office Excel 2007) by one reviewer (first author) and proofread by a second reviewer (third author).

Quality Assessment and Risk of Bias

The possible risk of bias for the RCTs was determined using the Cochrane Collaboration's risk of bias (RoB) tool (Table 1).[36] The risk of bias for the prospective studies was assessed using the Cochrane risk of bias tool for nonrandomized studies of interventions (ACROBAT-NRSI),[37] which is based on the RoB tool (Table 2).

Statistical Analysis

Following data extraction, study results were pooled for analysis by a statistician (second author). Several included studies reported a 100% implant survival rate based on the maximum likelihood estimator $\hat{p} = x/n$. Because this estimate implies no variation, it is not useful for this purpose, especially in cases of a small n. Therefore, estimated survival rates were recalculated based on the midpoint estimate for the score interval $\hat{p} = (x + 1.96)/(n + 3.92)$.[38]

To determine the effect on survival rates, generalized mixed-effect models were created using a binomial error estimate. The models included mean healing time, decortication, and fixation method as independent variables and accounted for random study effects.[39,40] To determine effect on bone gain values, multilevel random effects models were created using the same fixed and random effects as those used for

Table 2 Risk of Bias Assessment for Prospective Controlled Studies Using the Cochrane RoB Tool for Nonrandomized Studies of Interventions (ACROBAT-NRSI)

Study	Bias due to confounding	Bias in selection of participants into the study	Bias in measurement of interventions	Bias due to departures from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall bias
Beitlitum et al[46] (2010)	Moderate	Low	Low	Low	No info	Low	Low	Moderate risk
Kim et al[48] (2010)	Moderate	Moderate	Low	Low	No info	Low	Low	Moderate risk
Nemcovsky and Artzi[52] (2002)	Moderate	Low	Low	Low	No info	Low	Low	Moderate risk

the survival rate inference. Ninety-five percent confidence intervals (CI) were calculated using a likelihood profile. All calculations were performed using R version 3.2.2 (R Core Team 2015).[41]

RESULTS

Study Identification and Selection

The electronic search produced 343 publications, and the hand search identified 5 additional publications. The identified publication abstracts were then screened to determine if they roughly met the inclusion criteria prior to a full-text review. In total, 81 publications met the criteria for full-text review. Of these 81 publications, 20 fulfilled all inclusion criteria for this systematic review. The PRISMA flowchart of the search strategy, identification, and selection process is shown in Fig 1.

Risk of Bias

All included RCTs had a low risk of bias except the study by Carpio et al,[16] which had a moderate risk of bias. All three included prospective studies had a moderate risk of bias.

Descriptive Review of Study Characteristics

Of the 20 included publications, 17 reported on RCTs[6,8,9,16,19,42–45,47,49,50,51,53–56] and 3 reported on nonrandomized prospective studies.[46,48,52] Several studies reported on treatment arms that did not meet the inclusion criteria. For example, some studies had treatment arms that did not use membranes or used a non-collagen membrane. Additionally, some treatment arms had control groups that used bone blocks or the treatments were performed in extraction sites. These treatment arms were excluded from the review and meta-analysis. In total, 33 treatment or study arms were investigated. A summary of study characteristics for included treatment arms of the included publications is shown in Table 3.[6,8,9,16,19,42–56] Details of the GBR procedure for each treatment group and the outcomes evaluated in the included publications are shown in Table 4.

All of the included publications were well-designed clinical trials that largely provided the information needed for a systematic review, such as study design, study population, number of implants, number of implant sites undergoing GBR, follow-up period, and implant survival/failure rate. Unfortunately, some publications did not report critical data. In the two publications by Park et al,[53,54] the overall population was reported, but it was unclear how many patients were in each study group. Altogether, 18 publications reported on 460 patients.[6,8,9,16,19,42–52,55,56] In one publication by Friedmann et al,[8] the number of implants in each group was not provided. Publications by Carpio et al[16] and Meijndert et al[50] did not state how many implants were placed in each treatment arm. Overall, 17 publications reported on 733 implants.[6,9,19,42–49,51–56] The follow-up period of the studies was relatively short: 10 publications did not report beyond the second surgical procedure,[8,16,19,43,45,46,48,51–53] 1 publication reported a 6-month follow-up,[47] 4 publications reported a 12-month follow-up after surgical reentry,[42,44,49,50] 2 publications reported a 24-month follow-up,[6,55] 1 publication reported a 59-month follow-up,[56] and 1 publication reported a 72-month follow-up.[9] In one publication, the difference in follow-up between the two study groups could not be determined.[54] The overall mean follow-up time of the included publications was 8.77 months (range, 0–72 months). Only three publications did not report on patients lost to follow-up.[43,53,54]

Fifteen publications reported on simultaneous GBR and implant placement,[6,9,16,19,42–45,47,48,52–56] 4 publications reported GBR and subsequent implant placement following a healing period,[8,49–51] and 1 publication included both simultaneous and subsequent implant placement.[46] Implant survival or failure was reported in 15 publications (Table 3).[6,9,16,19,42–44,46,47,49–53,56]

Table 3 Characteristics of Included Studies

Publication ID/Authors	Year	Study design	No. of patients	No. of implants	Observation period (mo)	Lost to follow-up (n)	Implant survival rate	Implant failure rate
1 Amorfini et al[42]	2014	RCT	8	13	12	0	100%	ND
2 Annen et al[43]	2011	RCT	18	18	0	ND	ND	0%
3 van Assche et al[44]	2013	RCT	14	28	12	0	ND	0%
4 Becker et al[45]	2009	RCT	49	78	0	2	ND	ND
5 Beitlitum et al[46]	2010	(P)CoS	50	106	0	0	ND	n = 0
6 Carpio et al[16]	2000	RCT	23	ND	0	0	ND	21.70%
7 Friedmann et al[8]	2002	RCT	14	No clear assignment	0	0	ND	ND
8 Friedmann et al[47]	2011	RCT	37	73	6	0	100%	ND
9 Jung et al[19]	2009	RCT	18	18	0	0	ND	n = 0
10 Kim et al[48]	2010	(P)CoS	14	21	0	0	ND	ND
11 Meijndert et al[50]	2005	RCT	5	ND	12	0	ND	n = 0
12 Meijndert et al[49]	2008	RCT	29	31	12	0	ND	n = 2
13 Merli et al[9]	2014	RCT	11	11	72	0	ND	n = 0
14 Mordenfeld et al[51]	2014	RCT	13	71	0	0	ND	n = 2
15 Nemcovssky and Artzi[52]	2002	(P)CoS	47	79	0	0	ND	n = 1
16 Park and Wang[54]	2007	RCT	No clear assignment (n= 25 with control group)	20	ND	ND	ND	ND
17 Park et al[53]	2008	RCT	No clear assignment (n= 23 with control group)	18	0	ND	ND	n = 0
18 Sisti et al[55]	2012	RCT	10	10	24	0	ND	ND
19 Zitzmann et al[6]	1997	RCT	25	26	24	0	No clear assignment	n = 0
20 Zitzmann et al[56]	2001	RCT	75	112	59	9	95.40%	No clear assignment

ND = Not detected; (P)CoS = prospective comparative study; RCT = randomized controlled trial.

The estimated implant survival rate calculated from those studies was 99.13% (95% CI, 97.23%–99.96%) (Fig 2). The estimated survival rate for subsequent implant placement was 98.30% (95% CI, 92.49–99.97%), whereas the rate for simultaneous implant placement was 99.75% (95% CI, 99.75%–100%) (Fig 3). There was no significant difference observed between simultaneous and subsequent implant placement with respect to implant survival rate.

Of the 33 included study arms, 21 reported on non–cross-linked collagen membranes and 12 reported on cross-linked collagen membranes. Membrane exposure rate was reported in 25 study arms, and the overall estimated membrane exposure rate was 23.19% (95% CI, 12.70%–39.12%) (Fig 4). The estimated exposure rate was 28.62% (95% CI, 14.14%–49.32%) for cross-linked membranes and 20.74% (95% CI, 11.16%–36.19%) for non–cross-linked membranes (Fig 5).

Bone graft or membrane-supporting materials were well documented in all studies. Fourteen study arms used only anorganic bovine bone mineral (ABBM),[6,8,19,43–45,49,50,52,56] 2 arms used freeze-dried bone allograft (FDBA),[46,53,54] 2 arms used FDBA in combination with autologous bone chips (ABC),[46,53,54] 4 arms used demineralized FDBA (DFDBA),[53] 4 arms used ABBM and ABC with different concentrations,[16,42,51] 3 arms used β-tricalcium phosphate/hydroxyapatite (β-TCP/HA),[44,47] 2 arms used demineralized bone matrix (DBM),[48] 1 arm used ABC and osteosynthesis material (OM),[9] and one arm used only HA.[55] The concentrations of the various supporting material in the composition grafts varied between different studies and between study arms in the same study.

The number of patients treated in the different grafting groups as well as the follow-up time differed widely between the studies and study arms, rendering

a statistical evaluation of the different protocols unfeasible for most groups. The only group for which a further evaluation was possible was the one treated with pure ABBM. All of the sites in that group were augmented with the same product (Bio-Oss, Geistlich). With a mean follow-up time of 13 months (range 0–59.1 months), the mean implant survival rate in this group was 98.34 (95% CI, 96.06%–99.71%), independent of whether the GBR was simultaneous or prior to implant placement, and the estimated vertical bone gain with pure ABBM was 3.05 mm (95% CI, 2.33–3.77 mm).

The healing time of the augmented bone was reported for all study arms except two.[53] Mean healing time including both simultaneous and subsequent implant placement was 5.88 months (95% CI, 3–8.1 months).

The indication for ridge augmentation was classified as horizontal for 27 study arms and vertical for 3 study arms. One study arm could not be classified. Six publications (9 study arms) did not report vertical or horizontal bone gain or loss.[6,8,48,50,54,55] The results in the remaining publications varied widely in presentation (eg, gain/loss, horizontal/vertical, depth/width, mesial/distal, coronal/apical, and volume/length/percentage) and rarely presented dispersion parameters. This variation made it difficult, and in some cases unfeasible, to compare studies with respect to bone gain or loss parameters.

Among those studies reporting bone gain, the overall mean horizontal bone gain (depth perpendicular to the implant axis) was 2.27 ± 1.68 mm and the mean vertical bone gain was 3.05 ± 1.02 mm (Tables 5 and 6). Only 1 publication (2 study arms) reported horizontal bone gain (width) in the mesiodistal direction on the implant surface.[45] In that study, the horizontal bone gain width was 2.65 ± 2.27 mm for the tested cross-linked membrane and 2.65 ± 2.36 mm for the tested non–cross-linked membrane. Bone loss results were only reported in 5 publications (6 study arms).[9,42,44,49,56] The overall mean vertical bone loss was 0.68 mm (range, 0.11–1.34 mm), with a mean observation period of 33.42 months (range, 12–72 months).

With regard to membrane fixation, 6 arms did not report whether membranes were fixed and 1 was too ambiguous to assign with certainty.[16,42,47,54,55] Twenty arms reported that membranes were not fixed,[8,9,43–46,51–53] and 6 reported fixation with either cortical pins[6,16,19,56] or sutures.[49,50] Because none of the study arms reported on both horizontal bone gain and membrane fixation, two comparable groups could not be created. Therefore, the meta-analysis was performed only on collagen membrane fixation and vertical bone gain, which included 7 study arms without and 1 study arm with fixation. Mean vertical bone gain without membrane fixation was 2.94 ± 1.05 mm and 4.25 mm with fixation (Table 5).

In 11 study arms, no statements were made regarding decortication.[16,42,47,48,52,54,55] Among the remaining study arms, 20 reported that decortication was performed[6,8,9,44–46,49–51,53,56] and 2 specifically stated that decortication was not performed.[43] Mean vertical bone gain was 3.25 ± 2.05 mm without decortication and 3.05 ± 0.88 mm with decortication (Table 5). Mean horizontal bone gain was 0.85 ± 0.35 mm without decortication and 2.98 ± 1.63 mm with decortication (Table 6).

DISCUSSION

Main Findings

The number of publications addressing GBR for ridge augmentation using resorbable collagen membranes has increased substantially over the last two decades. The aim of this systematic review was to summarize the available literature regarding GBR for ridge augmentation using particulate graft material and resorbable collagen membranes to devise evidence-based recommendations and answer the following question: Does collagen membrane fixation or decortication affect the amount of newly regenerated bone when performing GBR?

The systematic literature search yielded numerous publications reporting on clinical studies with widely varying study designs, outcome documentation, and publication methods. The identified publications included a large number of case reports, case series, and retrospective analyses. Due to the risk of uncontrolled bias, only RCTs or prospective controlled studies were included in the review. Immediate implant placement and the use of growth factors were also excluded because they introduced additional biologic factors into the analysis. These exclusion criteria eliminated all but 17 RCTs and 3 prospective controlled studies, which were then screened for quality assessment and data extraction. Among those studies, 16 RCTs had a low risk of bias, and 1 RCT and 3 prospective controlled studies had a moderate risk. Thus, all the identified studies were included in data extraction. Because only RCTs and prospective controlled trials were included, there were one or more study arms in each publication that could be designated as a control group. For data extraction, only study arms that used resorbable collagen membranes and particulate graft materials were included.

Overall, 460 patients receiving 733 implants were included in this review and analysis. The overall mean healing time was 5.88 months. This time is consistent with the 3- to 6-month healing time associated with bone augmentation of alveolar ridges.[57,58] The overall mean follow-up time was 9.72 months (range, 0–72 months) after surgical reentry. Only two studies reported follow-up periods of at least 5 years.[9,56] All but

Table 4 Details of the Guided Bone Regeneration Procedures in the Included Treatment Arms

Publication ID/ Authors	Year	Implant placement	Defect classification	Membrane type	Supporting material	Decortications	Membrane fixation
1 Amorfini et al[42]	2014	Simultaneous	Horizontal	Non–cross-linked	ABC + ABBM + SS	ND	ND
2 Annen et al[43]	2011	Simultaneous	Horizontal	a) Non–cross-linked	ABBM	No	No
2 Annen et al[43]	2011	Simultaneous	Horizontal	b) Cross-linked	ABBM	No	No
3 Van Assche et al[44]	2013	Simultaneous	Horizontal	Non–cross-linked	a) ABBM	Yes	No
3 Van Assche et al[44]	2013	Simultaneous	Horizontal	Non–cross-linked	b) β-TCP/HA	Yes	No
4 Becker et al[45]	2009	Simultaneous	Horizontal	a) Non–cross-linked	ABBM	Yes	No
4 Becker et al[45]	2009	Simultaneous	Horizontal	b) Cross-linked	ABBM	Yes	No
5 Beitlitum et al[46]	2010	Simultaneous and subsequent	a) Horizontal	Cross-linked	a) FDBA	Yes	No
5 Beitlitum et al[46]	2010	Simultaneous and subsequent	b) Vertical	Cross-linked	a) FDBA	Yes	No
5 Beitlitum et al[46]	2010	Simultaneous and subsequent	a) Horizontal	Cross-linked	b) FDBA + ABC	Yes	No
5 Beitlitum et al[46]	2010	Simultaneous and subsequent	b) Vertical	Cross-linked	b) FDBA + ABC	Yes	No
6 Carpio et al[16]	2000	Simultaneous	ND	Non–cross-linked	ABC + ABBM	ND	No clear assignment
7 Friedmann et al[8]	2002	Subsequent	Horizontal	Cross-linked	ABBM + VB	Yes	No
8 Friedmann et al[47]	2011	Simultaneous	Horizontal	Non–cross-linked	β-TCP/HA	ND	ND
8 Friedmann et al[47]	2011	Simultaneous	Horizontal	Cross-linked	β-TCP/HA	ND	ND
9 Jung et al[19]	2009	Simultaneous	Horizontal	Non–cross-linked	ABBM	Yes	Yes
10 Kim et al[48]	2010	Simultaneous	Horizontal	Cross-linked	DBM	ND	Yes
10 Kim et al[48]	2010	Simultaneous	Horizontal	Cross-linked	DBM	ND	Yes
11 Meijndert et al[50]	2005	Subsequent	Horizontal	Non–cross-linked	ABBM + VB	Yes	Yes
12 Meijndert et al[49]	2008	Subsequent	Horizontal	Non–cross-linked	ABBM + VB	Yes	Yes
13 Merli et al[9]	2014	Simultaneous	Vertical	Non–cross-linked	ABC + OM	Yes	No
14 Mordenfeld et al[51]	2014	Subsequent	Horizontal	Non–cross-linked	a) ABC (10%) + ABBM (90%) + FG	Yes	No
14 Mordenfeld et al[51]	2014	Subsequent	Horizontal	Non–cross-linked	b) ABC (40%) + ABBM (60%) + FG	Yes	No
15 Nemcovsky and Artzi[52]	2002	Simultaneous	Horizontal	Non–cross-linked	ABBM	ND	No
15 Nemcovsky and Artzi[52]	2002	Simultaneous	Horizontal	Non–cross-linked	ABBM	ND	No
16 Park and Wang[54]	2007	Simultaneous	Horizontal	a) Non–cross-linked	FDBA	ND	ND
16 Park and Wang[54]	2007	Simultaneous	Horizontal	b) Cross-linked	FDBA	ND	ND
17 Park et al[53]	2008	Simultaneous	Horizontal	a) Non–cross-linked	FDBA	Yes	No
17 Park et al[53]	2008	Simultaneous	Horizontal	b) Cross-linked	FDBA	Yes	No
18 Sisti et al[55]	2012	Simultaneous	Horizontal	Non–cross-linked	HA	ND	ND
19 Zitzmann et al[6]	(1997)	Simultaneous	Horizontal	Non–cross-linked	ABBM	Yes	Yes
19 Zitzmann et al[6]	(1997)	Simultaneous	Horizontal	Non–cross-linked	ABBM	Yes	Yes
20 Zitzmann et al[56]	2001	Simultaneous	Horizontal	Non–cross-linked	ABBM	Yes	Yes

Yes = positive; No = negative; ND = not detected/reported value; ABBM = anorganic bovine bone material; ABC = autologous bone chips; β-TCP = beta tricalciumphosphate; CM = collagen membrane; DBM demineralized bone matrix; FDBA = freeze-dried bone allograft; FG = fibrin glue; HA = hydroxyapatite; OP = osteosynthesis materials; SS = saline solution; VB = venous blood.

three publications reported on patient loss to follow-up. The overall estimated implant survival rate in this analysis was 99.13% (95% CI, 97.23%–99.96%), which was much higher than that reported in another systematic review by Aghaloo and Moy evaluating GBR with any membrane type.[3] However, Aghaloo and Moy excluded studies with a follow-up period shorter than 12 months, which could substantially influence the overall survival rate. When looking at the distribution of implant failures, 20 study arms reported no implant loss, 5 arms reported 1 lost implant, 3 arms reported 2 lost implants, and 1 study reported 5 lost implants. All study arms reporting at least one loss were part of larger studies with more patients. This could indicate potential publication bias produced by smaller studies with respect to implant loss. The high

Healing time of regenerated bone (mo)	Membrane exposure rate	Horizontal bone gain	Vertical bone gain	Bone loss
6	Yes	No	No	Yes
6	Yes	Yes	Yes	No
6	Yes	Yes	Yes	No
6.4	Yes	Yes	Yes	Yes
6.4	Yes	Yes	Yes	Yes
4	Yes	Yes	Yes	No
4	Yes	Yes	Yes	No
5–7	Yes	Yes	No	No
5–7	Yes	No	Yes	No
5–7	Yes	Yes	No	No
5–7	Yes	No	Yes	No
6	Yes	Yes	Yes	No
7	Yes	No	No	No
6	Yes	Yes	No	No
6	Yes	Yes	No	No
6	Yes	No	Yes	No
a) 4	No	No	No	No
b) 6	No	No	No	No
6	No	No	No	No
6	No	No	No	Yes
4/6	Yes	No	Yes	Yes
8/1	Yes	Yes	No	No
8/1	Yes	Yes	No	No
6–8	Yes	No	Yes	No
6–8	Yes	No	Yes	No
ND	No	No	No	No
ND	No	No	No	No
6	Yes	Yes	Yes	No
6	Yes	Yes	Yes	No
3–4	No	No	No	No
4 mandible 6 maxilla				
4 mandible 6 maxilla	Yes	No	No	No
4 mandible 6 maxilla	No	No	No	Yes

number of publications with short follow-up periods can be explained by the primary outcome of these investigations, which was the amount of bone gain at surgical reentry.

In the current review, the implant survival rates for simultaneous and subsequently placed implants were 99.75% and 98.3%, respectively. While there was a 1.45% difference in implant survival depending on implant placement timing, it was not statistically significant. Furthermore, it seems unlikely that the difference would be clinically relevant. With this equivalence in mind, simultaneous GBR and implant placement has several advantages, such as reduced numbers of surgeries, which lowers the risk of morbidity, reduces healing time, and increases patient comfort. The simultaneous approach is often the preferred method for correcting alveolar ridge defects during implant placement.

Analysis of studies that had used particulate ABBM for GBR with collagen membranes showed high implant survival rates of 98.34% and an estimated vertical defect reduction of 3.05 mm with a mean follow-up time of 13 months. Unfortunately, due to the limited number of study arms and variability of study arms, no other comparisons were statistically feasible.

Numerous studies have noted a difference in membrane exposure rates between non–cross-linked and cross-linked collagen membranes, although reports differ widely for both groups.[22,43,45] In this review, the membrane exposure rate was 28.62% for cross-linked membranes and 20.74% for non–cross-linked membranes. Again, this difference is not statistically significant. The current evidence slightly favors the use of non–cross-linked membranes due to the lower exposure rates. Because there were no publications reporting the difference in bone gain in patients with and without membrane exposure, the direct outcome of membrane exposure could not be determined in this review. Another systematic review by Sanz-Sánchez et al[59] comparing several techniques and materials for lateral ridge augmentation showed that bone gain with respect to defect reduction was significantly higher in nonexposed sites. This observation also agrees with a meta-analysis by Machtei evaluating the effect of membrane exposure on the amount of newly regenerated bone.[60]

The overall mean horizontal bone gain (ie, the depth perpendicular to the implant axis) was 2.27 ± 1.68 mm. The mean vertical bone gain was 3.05 ± 1.02 mm. The one study reporting the horizontal bone gain (width) in the mesiodistal direction had a mean value of 2.64 mm.[45] In a systematic review evaluating the effectiveness of lateral bone augmentation on alveolar crest dimensions, the mean bone gain for all studies was 3.90 mm (95% CI, 3.52–4.28 mm)[59]; the authors of that review included a broader range of experimental methods including the use of bone blocks and growth factors. When looking at the values for equivalent methods, the results of the present study are similar to those reported in their analysis.

Only four studies reported on radiographically confirmed vertical bone loss during follow-up. In these studies the overall mean vertical bone loss was

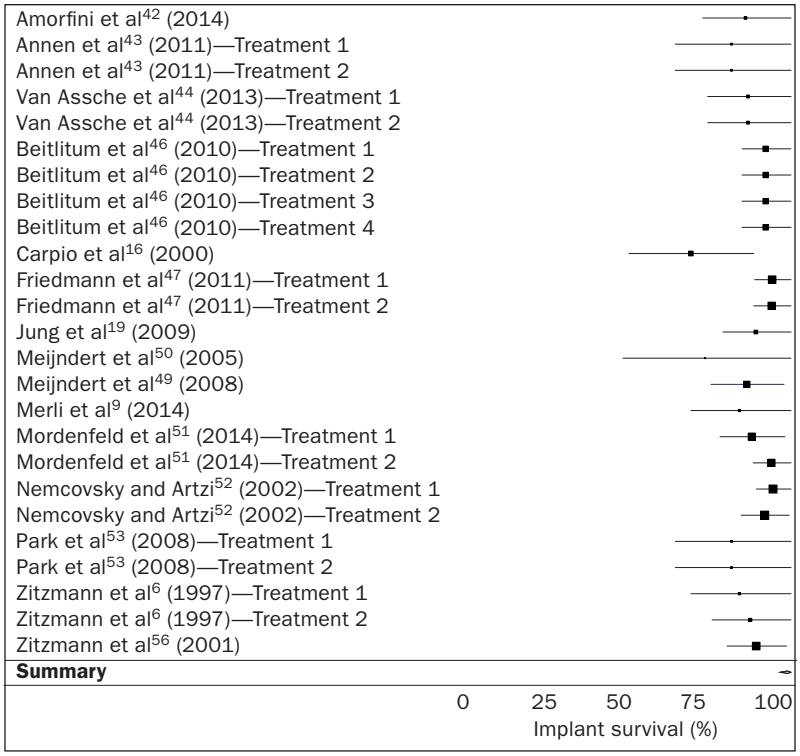

Fig 2 Forest plot of implant survival rates for all included studies. Estimated survival rate of 99.13% (CI, 97.23%–99.96%).

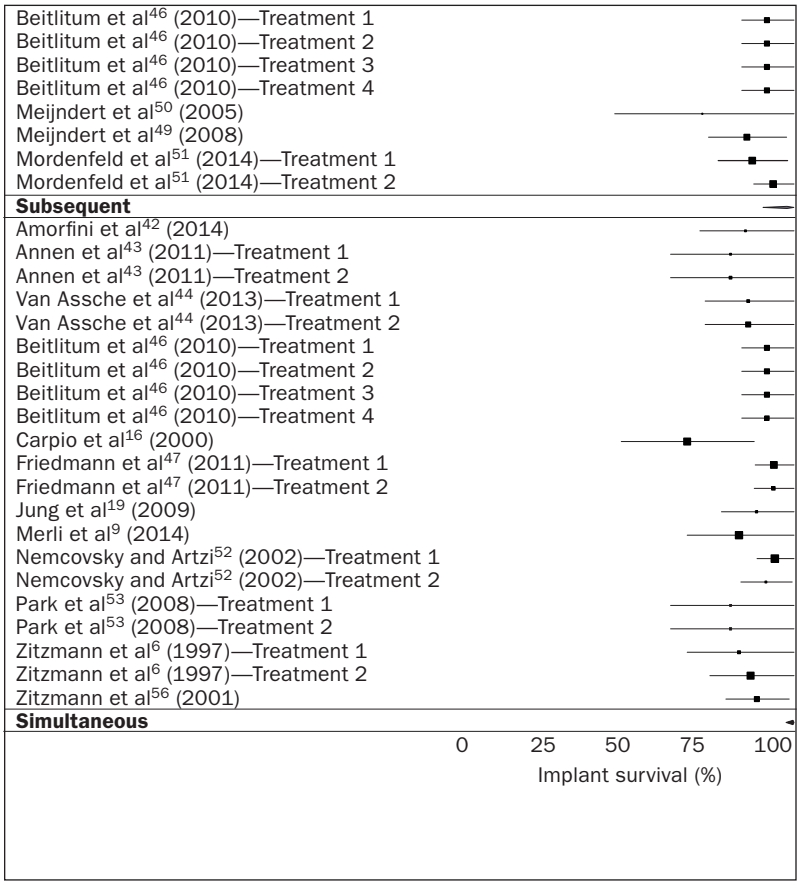

Fig 3 Forest plot of implant survival rates based on the time of implant placement. Estimated survival rate for subsequent implant placement 98.30% (CI, 92.49%–99.97%). Estimated survival rate for simultaneous implant placement 99.75% (CI, 99.75%–100%).

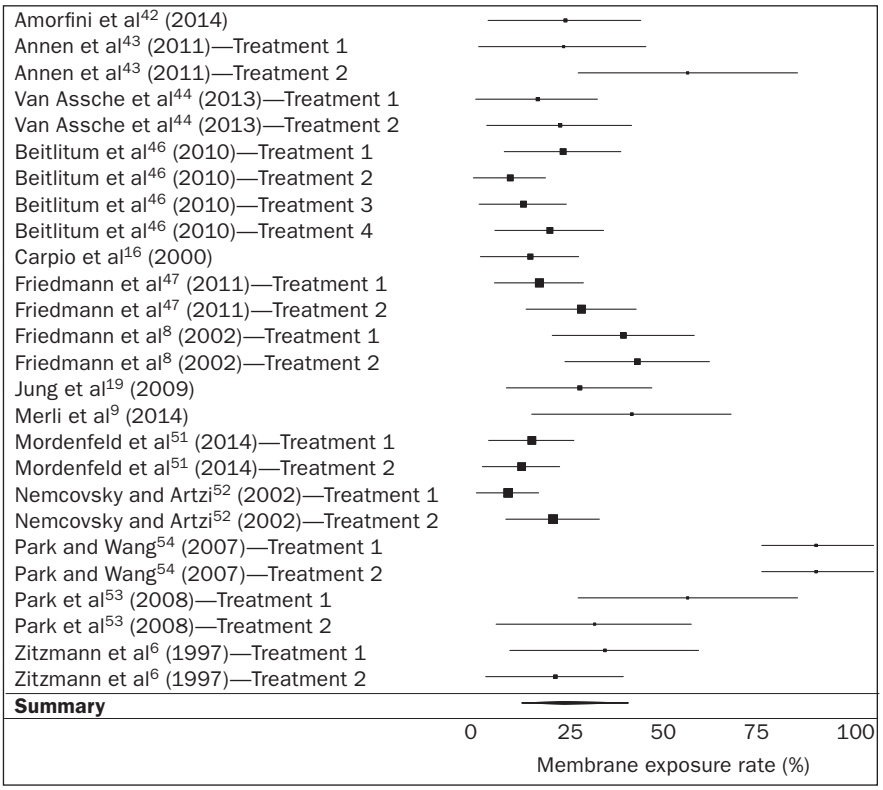

Fig 4 Forest plot of membrane exposure rates. Overall estimated membrane exposure rate 23.19% (CI, 12.70%–39.12%).

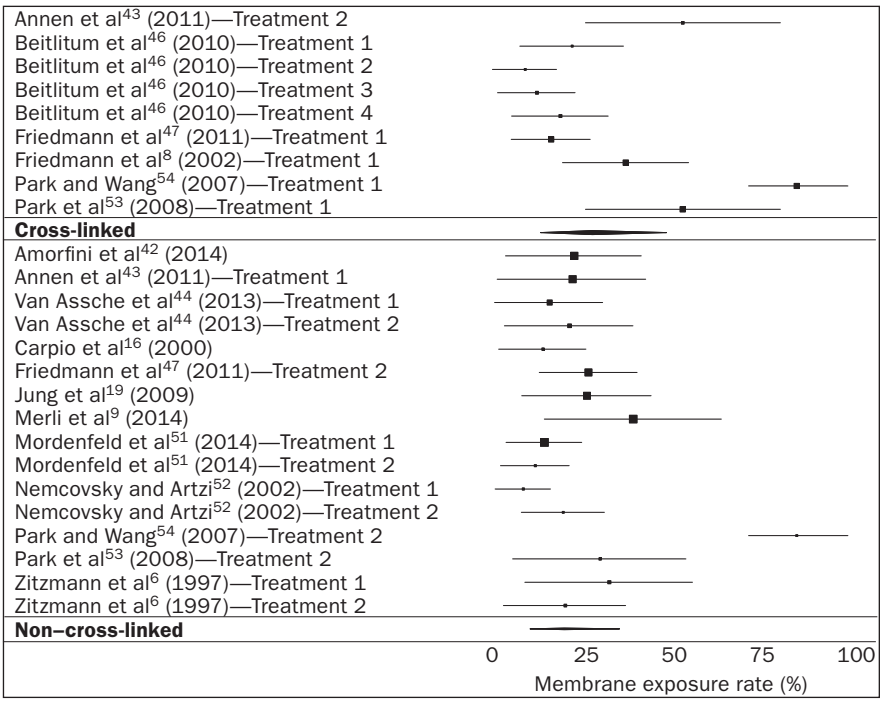

Fig 5 Forest plot of membrane exposure rate comparing cross-linked and non–cross-linked membranes. Estimated membrane exposure rate of cross-linked membranes 28.62% (CI, 14.14%–49.32%). Estimated survival rate for non–cross-linked membranes 20.74% (CI, 11.16%–36.19%).

Table 5 Vertical Bone Gain (mm) Based on Decortication and Membrane Fixation

		Mean	SD	Median	IQR	n	Missing
Membrane	Fixed	4.25		4.25	0.00	6	5
	Not fixed	2.94	1.05	3.00	1.44	21	14
Decortication	No	3.25	2.05	3.25	1.45	2	0
	Yes	3.05	0.88	3.24	1.12	21	15
	Total	3.05	1.02	3.00	1.34	34	25

SD = standard deviation; IQR = interquartile range; n = number of study arms.

Table 6 Horizontal Bone Gain (Depth in mm) Based on Decortication and Membrane Fixation

		Mean	SD	Median	IQR	n	Missing
Membrane	Fixed					6	6
	Not fixed	2.27	1.68	1.66	1.92	21	15
Decortication	No	0.85	0.35	0.85	0.25	2	0
	Yes	2.98	1.63	2.67	2.25	21	17
	Total	2.27	1.68	1.656	1.92	34	28

SD = standard deviation; IQR = interquartile range; n = number of study arms.

0.968 ± 0.258 mm with a mean observation period of 33.42 months (range, 12–72 months). The different treatment modalities could not be compared due to differences in reporting and study design. The highest vertical bone loss value, 1.34 mm, was measured at the 5-year follow-up of a long-term study.[56] According to the success criteria devised by Albrektsson et al,[61] all of the implants included in this analysis were successful based on their bone resorption values.

Role of Membrane Fixation and Decortication

The results of this meta-analysis indicate that the amount of newly regenerated vertical bone is much higher when the collagen membrane is fixed (mean 4.25 mm) than when it is not (mean 2.94 mm), even though this difference did not reach statistical significance. Because the amount of evidence for the compared groups differed substantially, it is difficult to draw conclusions from this result. Of the 6 study arms reporting on fixed membranes, only 1 reported bone gain, whereas 7 of the 21 arms reporting on membranes without fixation reported bone gain. The increased bone gain seen with fixed membranes can be explained by one of the basic principles of GBR, ie, that a space should be maintained under the membrane to prevent its collapse. Fixing the membrane immobilizes the particulate bone graft at the desired position. It also prevents migration of the graft into surrounding tissues during suturing and volume loss.[31]

Decortication may affect the amount of horizontal bone gain. In this review, the mean horizontal bone gain (depth, perpendicular to the alveolar ridge) was 2.98 mm with decortication and 0.85 mm without decortication. Numerous publications have reported that perforation of the alveolar corticalis gives progenitor cells more access to the grafted site and ensures better nutrition and revascularization, especially in cases of dense bone.[6,31,45] A review of animal studies investigating bone decortication for GBR could not determine the impact of this technique because of the small number of trials included and heterogeneous study protocols.[62] In that review, there were only 2 study arms reporting on GBR without decortication compared with 20 arms with decortication. Additionally, one of the GBR without decortication study arms used a cross-linked membrane that has had a high membrane exposure rate (56%).[43] However, cortical perforation seemed to have no effect on vertical bone gain when considering arms within the same study, indicating that perforation of the alveolar corticalis may have a positive effect on more distant areas of the graft, such as perpendicular to the implant axis or the alveolar ridge.

CONCLUSIONS

The literature search identified enough evidence-based data from relevant clinical studies to perform a systematic review and meta-analysis on GBR with particulate graft material and resorbable collagen membranes.

Based on the findings of this systematic review and meta-analysis, GBR with particulate graft material and resorbable collagen membranes is an effective technique for lateral alveolar ridge augmentation prior to or simultaneously with dental implant placement, having similar implant survival rates compared to pristine bone. Therefore, it can be concluded that a simultaneous approach is indicated whenever possible, as it reduces the

number of surgeries, which lowers morbidity, reduces treatment time, and increases patient comfort.

Statements for vertical ridge augmentation with the mentioned materials cannot be given to date based on the available data.

Anorganic bovine bone mineral is an effective grafting material for GBR that provides sufficient newly regenerated bone as well as high implant survival rates.

Early exposure of collagen membranes during GBR is a relatively common complication and has to be expected in approximately one-fifth of the cases. Although the membrane exposure rates for cross-linked membranes were 30% higher than for non–cross-linked membranes, a direct effect on the quantity of bone gain as well as implant outcomes could not be identified in this meta-analysis.

The results of the meta-analysis showed weak evidence that the fixation of collagen membranes with pins or sutures increased the amount of newly regenerated bone. Decortication of the alveolar cortical bone also led to an increased alveolar ridge width, even though these values did not reach statistical significance. These findings may represent beneficial additional techniques for the practice when performing GBR.

ACKNOWLEDGMENTS

The authors declare that they have not received any financial support and have no potential conflict of interest with respect to authorship or publication of this article.

REFERENCES

1. Khzam N, Arora H, Kim P, Fisher A, Mattheos N, Ivanovski S. A systematic review of soft tissue alterations and aesthetic outcomes following immediate implant placement and restoration of single implants in the anterior maxilla. J Periodontol 2015;86:1321–1330.
2. Nisand D, Picard N, Rocchietta I. Short implants compared to implants in vertically augmented bone: A systematic review. Clin Oral Implants Res 2015;26(suppl):170–179.
3. Aghaloo TL, Moy PK. Which hard tissue augmentation techniques are the most successful in furnishing bony support for implant placement? Int J Oral Maxillofac Implants 2007;22(suppl):49–70.
4. Jovanovic SA, Spiekermann H, Richter EJ. Bone regeneration around titanium dental implants in dehisced defect sites: A clinical study. Int J Oral Maxillofac Implants 1992;7:233–245.
5. Simion M, Jovanovic SA, Trisi P, Scarano A, Piattelli A. Vertical ridge augmentation around dental implants using a membrane technique and autogenous bone or allografts in humans. Int J Periodontics Restorative Dent 1998;18:8–23.
6. Zitzmann NU, Naef R, Schärer P. Resorbable versus nonresorbable membranes in combination with Bio-Oss for guided bone regeneration. Int J Oral Maxillofac Implants 1997;12:844–852.
7. Jung RE, Fenner N, Hämmerle CH, Zitzmann NU. Long-term outcome of implants placed with guided bone regeneration (GBR) using resorbable and non-resorbable membranes after 12-14 years. Clin Oral Implants Res 2013;24:1065–1073.
8. Friedmann A, Strietzel FP, Maretzki B, Pitaru S, Bernimoulin JP. Histological assessment of augmented jaw bone utilizing a new collagen barrier membrane compared to a standard barrier membrane to protect a granular bone substitute material. Clin Oral Implants Res 2002;13:587–594.
9. Merli M, Moscatelli M, Mariotti G, Rotundo R, Bernardelli F, Nieri M. Bone level variation after vertical ridge augmentation: Resorbable barriers versus titanium-reinforced barriers. A 6-year double-blind randomized clinical trial. Int J Oral Maxillofac Implants 2014;29:905–913.
10. Nyman S, Karring T. Regeneration of surgically removed buccal alveolar bone in dogs. J Periodontal Res 1979;14:86–92.
11. Gottlow J, Nyman S, Karring T, Lindhe J. New attachment formation as the result of controlled tissue regeneration. J Clin Periodontol 1984;11:494–503.
12. Dahlin C, Linde A, Gottlow J, Nyman S. Healing of bone defects by guided tissue regeneration. Plast Reconstr Surg 1988;81:672–676.
13. Simion M, Baldoni M, Rossi P, Zaffe D. A comparative study of the effectiveness of e-PTFE membranes with and without early exposure during the healing period. Int J Periodontics Restorative Dent 1994;14:166–180.
14. Buser D, Brägger U, Lang NP, Nyman S. Regeneration and enlargement of jaw bone using guided tissue regeneration. Clin Oral Implants Res 1990;1:22–32.
15. Lang NP, Hämmerle CH, Brägger U, Lehmann B, Nyman SR. Guided tissue regeneration in jawbone defects prior to implant placement. Clin Oral Implants Res 1994;5:92–97.
16. Carpio L, Loza J, Lynch S, Genco R. Guided bone regeneration around endosseous implants with anorganic bovine bone mineral. A randomized controlled trial comparing bioabsorbable versus non-resorbable barriers. J Periodontol 2000;71:1743–1749.
17. Becker W, Dahlin C, Becker BE, et al. The use of e-PTFE barrier membranes for bone promotion around titanium implants placed into extraction sockets: A prospective multicenter study. Int J Oral Maxillofac Implants 1994;9:31–40.
18. Hämmerle CH, Brägger U, Schmid B, Lang NP. Successful bone formation at immediate transmucosal implants: A clinical report. Int J Oral Maxillofac Implants 1998;13:522–530.
19. Jung RE, Hälg GA, Thoma DS, Hämmerle CH. A randomized, controlled clinical trial to evaluate a new membrane for guided bone regeneration around dental implants. Clin Oral Implants Res 2009;20:162–168.
20. Urban IA, Jovanovic SA, Lozada JL. Vertical ridge augmentation using guided bone regeneration (GBR) in three clinical scenarios prior to implant placement: A retrospective study of 35 patients 12 to 72 months after loading. Int J Oral Maxillofac Implants 2009;24:502–510.
21. Kirsch A, Ackermann KL, Hurzeler MB, Durr W, Hutmacher D. Development and clinical application of titanium minipins for fixation of nonresorbable barrier membranes. Quintessence Int 1998;29:368–381.
22. Friedmann A, Strietzel FP, Maretzki B, Pitaru S, Bernimoulin JP. Observations on a new collagen barrier membrane in 16 consecutively treated patients. Clinical and histological findings. J Periodontol 2001;72:1616–1623.
23. Chung KM, Salkin LM, Stein MD, Freedman AL. Clinical evaluation of a biodegradable collagen membrane in guided tissue regeneration. J Periodontol 1990;61:732–736.
24. Sevor JJ, Meffert R. Placement of implants into fresh extraction sites using a resorbable collagen membrane: Case reports. Pract Periodontics Aesthet Dent 1992;4:35–41.
25. Colangelo P, Piattelli A, Barrucci S, Trisi P, Formisano G, Caiazza S. Bone regeneration guided by resorbable collagen membranes in rabbits: A pilot study. Implant Dent 1993;2:101–105.
26. Sevor JJ, Meffert RM, Cassingham RJ. Regeneration of dehisced alveolar bone adjacent to endosseous dental implants utilizing a resorbable collagen membrane: Clinical and histologic results. Int J Periodontics Restorative Dent 1993;13:71–83.
27. Cochran DL, Douglas HB. Augmentation of osseous tissue around nonsubmerged endosseous dental implants. Int J Periodontics Restorative Dent 1993;13:506–519.
28. Bunyaratavej P, Wang HL. Collagen membranes: A review. J Periodontol 2001;72:215–229.
29. Rothamel D, Schwarz F, Sculean A, Herten M, Scherbaum W, Becker J. Biocompatibility of various collagen membranes in cultures of human PDL fibroblasts and human osteoblast-like cells. Clin Oral Implants Res 2004;15:443–449.
30. Siar CH, Toh CG, Romanos G, Ng KH. Subcutaneous reactions and degradation characteristics of collagenous and noncollagenous membranes in a macaque model. Clin Oral Implants Res 2011;22:113–120.

31. Hämmerle CH, Jung RE, Yaman D, Lang NP. Ridge augmentation by applying bioresorbable membranes and deproteinized bovine bone mineral: A report of twelve consecutive cases. Clin Oral Implants Res 2008;19:19–25.
32. Urban IA, Nagursky H, Lozada JL. Horizontal ridge augmentation with a resorbable membrane and particulated autogenous bone with or without anorganic bovine bone-derived mineral: A prospective case series in 22 patients. Int J Oral Maxillofac Implants 2011;26:404–414.
33. Urban IA, Nagursky H, Lozada JL, Nagy K. Horizontal ridge augmentation with a collagen membrane and a combination of particulated autogenous bone and anorganic bovine bone-derived mineral: A prospective case series in 25 patients. Int J Periodontics Restorative Dent 2013;33:299–307.
34. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. Int J Surg 2010;8:336–341.
35. U.S. Preventive Services Task Force. Guide to clinical preventive services: Report of the U.S. Preventive Services Task Force. Baltimore: Williams & Wilkins, 1989:24.
36. Higgins JP, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011;343:d5928.
37. Sterne JAC, Higgins JPT, Reeves BC, on behalf of the development group for ACROBAT-NRSI. A Cochrane risk of bias assessment tool for non-randomised studies of interventions (ACROBAT-NRSI), Version 1.0.0. 24 September 2014. http://www.riskofbias.info. Accessed 26 July 2017.
38. Agresti A, Coull BA. Approximate is better than "exact" for interval estimation of binomial proportions. Am Stat 1998;52:119–126.
39. Bates D, Mächler M, Bolker B, Walker S. Fitting linear mixed-effects models using lme4. J Stat Software 2015;67(1).
40. Viechtbauer W. Conducting meta-analyses in R with the metafor package. J Stat Software 2010 2010;36(3).
41. R Core Team. A language and Environment for Statistical Computing. Vienna, Austria: R Foundation for Statistical Computing, 2015.
42. Amorfini L, Migliorati M, Signori A, Silvestrini-Biavati A, Benedicenti S. Block allograft technique versus standard guided bone regeneration: A randomized clinical trial. Clin Implant Dent Relat Res 2014;16:655–667.
43. Annen BM, Ramel CF, Hämmerle CH, Jung RE. Use of a new cross-linked collagen membrane for the treatment of peri-implant dehiscence defects: A randomised controlled double-blinded clinical trial. Eur J Oral Implantol 2011;4:87–100.
44. Van Assche N, Michels S, Naert I, Quirynen M. Randomized controlled trial to compare two bone substitutes in the treatment of bony dehiscences. Clin Implant Dent Relat Res 2013;15:558–568.
45. Becker J, Al-Nawas B, Klein MO, Schliephake H, Terheyden H, Schwarz F. Use of a new cross-linked collagen membrane for the treatment of dehiscence-type defects at titanium implants: A prospective, randomized-controlled double-blinded clinical multicenter study. Clin Oral Implants Res 2009;20:742–749.
46. Beitlitum I, Artzi Z, Nemcovsky CE. Clinical evaluation of particulate allogeneic with and without autogenous bone grafts and resorbable collagen membranes for bone augmentation of atrophic alveolar ridges. Clin Oral Implants Res 2010;21:1242–1250.
47. Friedmann A, Gissel K, Soudan M, Kleber BM, Pitaru S, Dietrich T. Randomized controlled trial on lateral augmentation using two collagen membranes: Morphometric results on mineralized tissue compound. J Clin Periodontol 2011;38:677–685.
48. Kim YK, Kim SG, Lim SC, Lee HJ, Yun PY. A clinical study on bone formation using a demineralized bone matrix and resorbable membrane. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2010;109:e6–e11.
49. Meijndert L, Raghoebar GM, Meijer HJ, Vissink A. Clinical and radiographic characteristics of single-tooth replacements preceded by local ridge augmentation: A prospective randomized clinical trial. Clin Oral Implants Res 2008;19:1295–1303.
50. Meijndert L, Raghoebar GM, Schüpbach P, Meijer HJ, Vissink A. Bone quality at the implant site after reconstruction of a local defect of the maxillary anterior ridge with chin bone or deproteinised cancellous bovine bone. Int J Oral Maxillofac Surg 2005;34:877–884.
51. Mordenfeld A, Johansson CB, Albrektsson T, Hallman M. A randomized and controlled clinical trial of two different compositions of deproteinized bovine bone and autogenous bone used for lateral ridge augmentation. Clin Oral Implants Res 2014;25:310–320.
52. Nemcovsky CE, Artzi Z. Comparative study of buccal dehiscence defects in immediate, delayed, and late maxillary implant placement with collagen membranes: Clinical healing between placement and second-stage surgery. J Periodontol 2002;73:754–761.
53. Park SH, Lee KW, Oh TJ, Misch CE, Shotwell J, Wang HL. Effect of absorbable membranes on sandwich bone augmentation. Clin Oral Implants Res 2008;19:32–41.
54. Park SH, Wang HL. Clinical significance of incision location on guided bone regeneration: Human study. J Periodontol 2007;78:47–51.
55. Sisti A, Canullo L, Mottola MP, Covani U, Barone A, Botticelli D. Clinical evaluation of a ridge augmentation procedure for the severely resorbed alveolar socket: Multicenter randomized controlled trial, preliminary results. Clin Oral Implants Res 2012;23:526–535.
56. Zitzmann NU, Schärer P, Marinello CP. Long-term results of implants treated with guided bone regeneration: A 5-year prospective study. Int J Oral Maxillofac Implants 2001;16:355–366.
57. Kahnberg KE. Treatment of bone-deficient ridges in implant rehabilitation. In: Andersson L, Kahnberg KE, Pogrel MA (eds). Oral and Maxillofacial Surgery. Chichester, West Sussex: John Wiley & Sons, 2012:405–414.
58. McAllister BS, Haghighat K. Bone augmentation techniques. J Periodontol 2007;78:377–396.
59. Sanz-Sánchez I, Ortiz-Vigón A, Sanz-Martín I, Figuero E, Sanz M. Effectiveness of lateral bone augmentation on the alveolar crest dimension: A systematic review and meta-analysis. J Dent Res 2015;94(suppl):s128–s142.
60. Machtei EE. The effect of membrane exposure on the outcome of regenerative procedures in humans: A meta-analysis. J Periodontol 2001;72:512–516.
61. Albrektsson T, Zarb G, Worthington P, Eriksson AR. The long-term efficacy of currently used dental implants: a review and proposed criteria of success. Int J Oral Maxillofac Implants 1986;1:11–25.
62. Greenstein G, Greenstein B, Cavallaro J, Tarnow D. The role of bone decortication in enhancing the results of guided bone regeneration: A literature review. J Periodontol 2009;80:175–189.