Alveolar ridge augmentation and preservation

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Alveolar ridge augmentation and preservation

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Inhoud

CHAPTER 1

Introduction and outline of the thesis

Owing to its clinical success, the use of dental implants as a foundation for the prosthetic replacement of missing teeth has become widespread in the last decades.[1] Initially, dental implants were mainly used to rehabilitate edentulous patients with fixed or removable implant-supported overdenture. Due to infection, trauma, or physiologic resorption, the dimensions of the alveolar ridge can change after tooth loss (Figure 1).[2, 3] Due to resorption, the alveolar ridge eventually is unable to provide sufficient retention for a regular overdenture. Oral implants offer a solution to this problem. Implant-supported overdentures have become the standard solution for edentulous patients.[4]

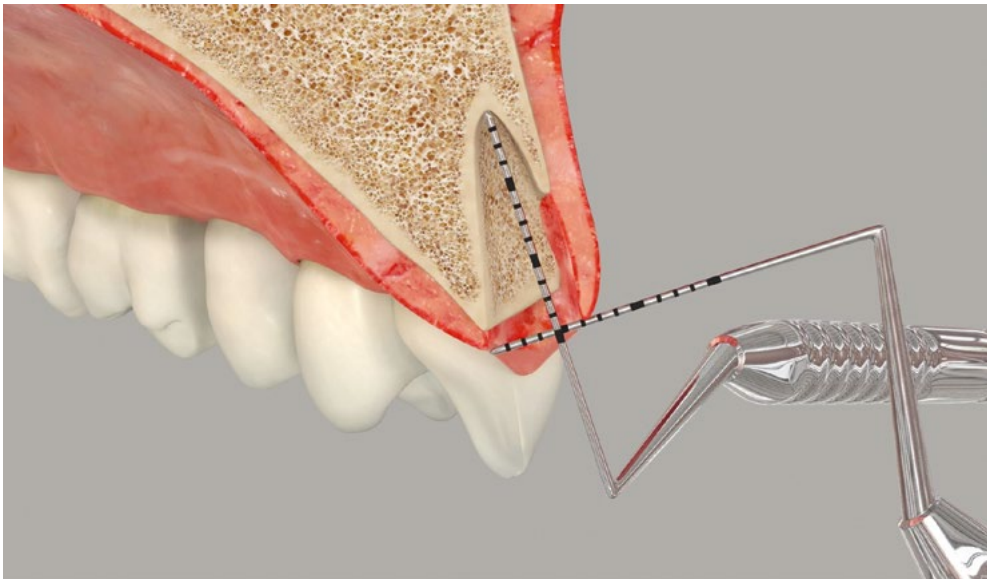


Figure 1 Vertical and horizontal changes of the alveolar ridge after tooth extraction.
Illustration by courtesy of Geistlich Pharma AG, Wolhusen

Due to the high survival rates of oral implants and the decline in edentulism, there has been a shift in attention towards single tooth replacement with dental implants.[5, 6] Currently, implant treatment for single tooth replacement is a predictable treatment option for a failing or missing tooth (Figure 2).[7-9]

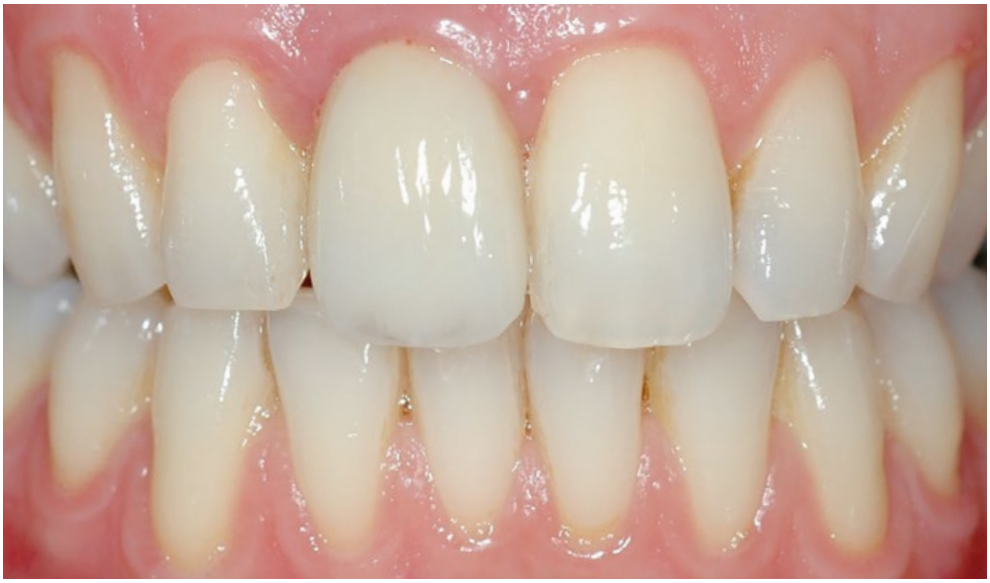


Figure 2 Single tooth replacement with a dental implant in the esthetic zone (right central incisor).

To achieve optimal esthetical results, dental implants must be placed in the correct prosthetic three-dimensional position, with sufficient buccal bone coverage in order to optimize soft tissue esthetics around the dental crown.[10] A minimal buccal bone thickness of 1-2 mm has been suggested for optimal results (Figure 3).[11-13] Additionally, it is advised to keep a distance of 1.5 mm to adjacent teeth and 3.0 mm between implants to prevent interproximal bone loss.[11, 14] Regarding the coronal-apical position, the implant is preferably placed around 3.0 mm below the gingival margin of the planned restoration to optimize the emerging profile of the implant-supported crown.

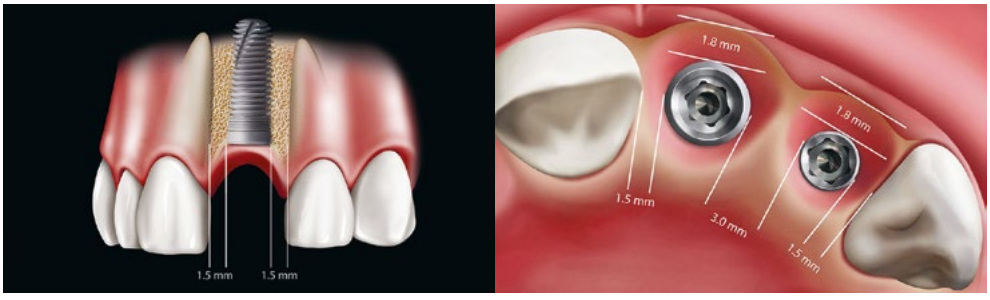


Figure 3 Correct prosthetic 3D position of dental implants.[15]

Different treatment protocols are available for placing dental implants after tooth extraction, such as immediate (0-1 week), early with soft tissue healing (4-8 weeks), early with partial bone healing (12-16 weeks), and late (> 4 months) implant placement.[10, 16] Alveolar ridge preservation (ARP) can be performed prior to early, and late implant placement. The different implant placement protocols can also be combined with bone augmentation procedures before or during implant placement (Figure 4).

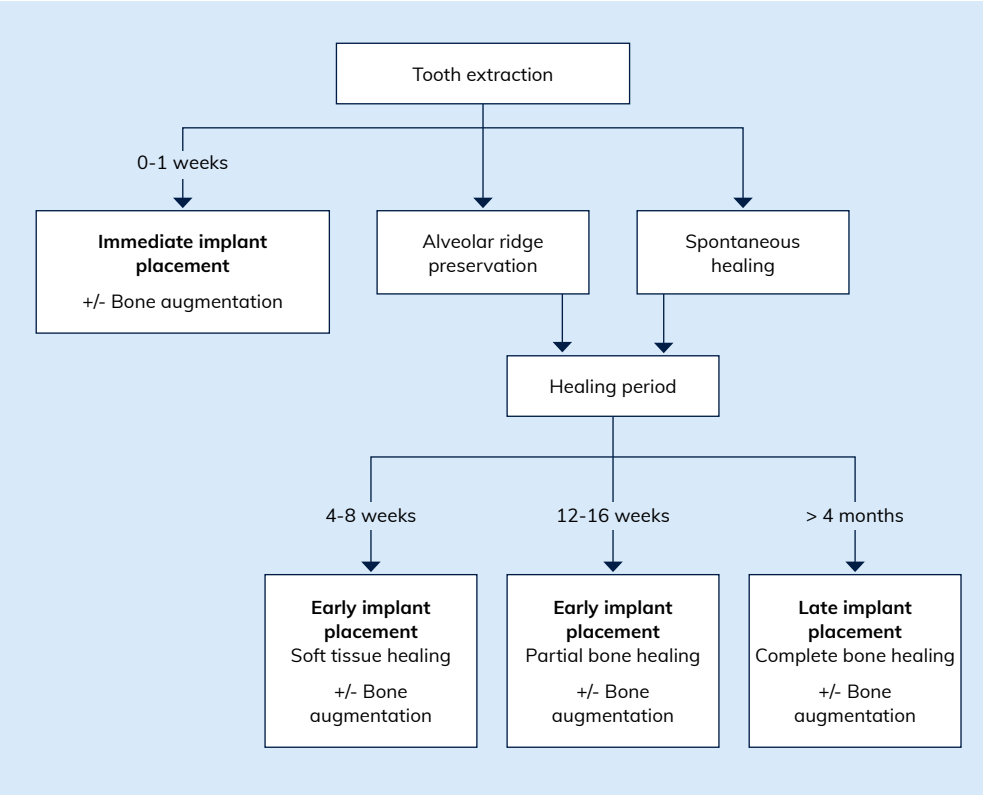


Figure 4 Post-extraction treatment options.

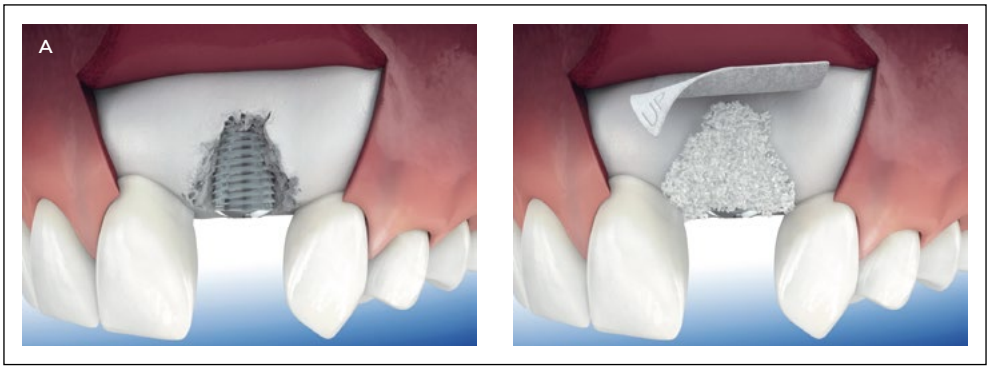
All treatment options have specific indications that vary depending on patient characteristics and the preferences and specific skills of the surgeon (Figure 5).[10, 16] In the literature, both immediate and early implant placement has shown acceptable esthetic outcomes.[7, 8] Immediate implant placement offers the advantage of a shortened protocol, whereas early implant placement might

offer a slightly increased stability of peri-implant hard and soft tissues.[17, 18] Immediate implant placement is mostly chosen for healthy patients with an intact facial bone wall and a thick soft tissue biotype. Additionally, it is also preferred in patients without acute infection and sufficient bone to aid in the primary stability of the implant in a correct prosthetic position. An early placement strategy may be preferred in cases of compromised buccal bone, a thinner soft tissue biotype, acute infections, and sufficient bone to allow for proper implant placement.[10, 16]

Immediate implant placement	**Early implant placement** With soft tissue healing	**Early implant placement** With partial bone healing	**Late implant placement**
• Healthy patients • Intact facial bone wall • Thick soft tissue biotype • Without acute infection • Sufficient bone to allow implant in a correct position	• Healthy patients • Compromised facial bone • Thin soft tissue biotype • Acute infection • Sufficient bone to allow implant in a correct position	• Medical compromised • Larger periapical bone defects • Acute infection • Correct prosthetic implant position not possible	• Medical compromised • Extended bone lesions apical and palatal • Acute infection • Too young for implant placement • Correct prosthetic implant position not possible

Figure 5 The indications for immediate, early and late implant placement.

One of the biggest challenges is the creation or preservation of sufficient bone to optimize implant success. The abovementioned changes in the alveolar ridge after tooth extraction influences the soft-tissue contours. Thus, the clinical and esthetic outcomes, especially in the esthetic zone.[19, 20] Moreover, the alveolar ridge might become too narrow to accommodate the complete bony surrounding of the placed dental implant which in turn may lead to peri-implant bony dehiscence when the oral implant is put in place. Although small buccal dehiscence does not lead to problems in terms of primary stability and osseointegration, it might negatively influence soft tissue esthetics, depending on the smile line and soft tissue type.[21-23] Bone augmentation of the alveolar ridge can be performed to correct these osseous deficiencies, and alveolar ridge preservation might be performed to prevent changes in the alveolar ridge (Figure 6).



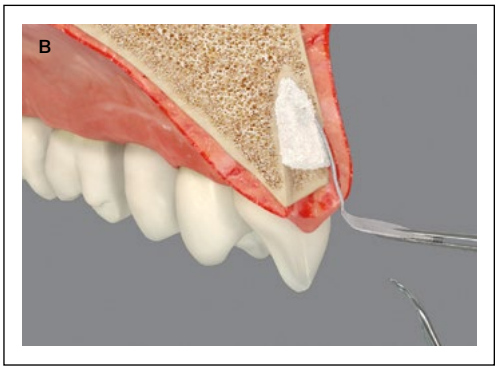


Figure 6 Dental implant requiring alveolar ridge augmentation to correct the osseous defect (a) and alveolar ridge preservation to prevent resorption of the alveolar ridge (b). Illustrations by courtesy of Geistlich Pharma AG, Wolhusen

Alveolar ridge augmentation and the use of barrier membranes

If primary stability and ideal positioning of the implant can be achieved, bone augmentation procedures can successfully be performed simultaneously with implant placement.[24] When there is insufficient bone for optimal positioning, alveolar ridge augmentation is performed prior to the implant placement.[9] To create sufficient height in the posterior maxilla, sinus floor augmentation procedures are performed using autogenous bone grafts, bone substitutes, or a mixture of both.[25] In immediate implant placement protocols, the gap between the implant and the buccal bone wall is often filled with bone augmentation material.[8, 26] In all augmentation procedures, membranes can additionally be used to direct the growth of new bone. This principle is called guided bone regeneration (GBR). Membranes are categorized as non-resorbable or resorbable.

Non-resorbable membranes are mostly made of polytetrafluoroethylene, while resorbable membranes are human-derived, animal-derived, or synthetic polymers.[27] Since the first clinical studies in 1990, the use of membranes has become a widely applied procedure in oral implantology.[28, 29] The combined use of augmentation materials and guided bone regeneration has possible synergistic advantages. The graft supports the membrane and prevents it from collapsing. It also offers a framework for the ingrowth of capillaries and perivascular tissue, and it provides a carrier for factors that enhance bone formation. Furthermore, the membrane is considered to provide an environment that promotes the recruitment and proliferation of osteoprogenitor cells, differentiation of osteoblasts, and osteogenic activity. Thereby allowing the regeneration of bone in open areas and possibly minimizing the loss of graft volume.[30, 31] Although there is sufficient evidence for the successful use of bone augmentation methods in oral implantology, there is no consensus regarding the additional clinical benefit of barrier membranes.

Alveolar ridge preservation for early implant placement

Despite the different bone augmentation techniques used to reconstruct bony deficiencies, bone loss should ideally be prevented. Bone resorption after tooth removal might be minimized by filling the empty alveolus with an augmentation material, usually covered by a soft tissue graft, membrane, or matrix. This procedure is called alveolar ridge preservation (ARP).[32] For late implant placement, 4-6 months after extraction, the application of a biomaterial at the extraction site, results in less vertical and horizontal changes of the alveolar ridge 4-6 months after extraction.[33-35] Adding ridge preservation to an early implant placement protocol might offer the advantage of preventing the need for additional augmentation procedures and optimizing soft tissue esthetics by preserving existing soft and hard tissue volume for future implant placement.[32, 36, 37] In an attempt to create or preserve even more soft tissue volume, a free soft tissue graft or soft tissue substitute might be applied on top of the augmented bone. It has the advantage of sealing the augmented socket from the oral cavity and the possibility of adding soft tissue thickness. Although the application of a free soft tissue punch graft is a relatively straightforward procedure, patient morbidity is increased due to the need for a second surgical site.[38] The use of a substitute

material for soft tissue grafting could prevent this donor site morbidity associated with soft tissue grafts when performing ridge preservation.[33, 39] Unfortunately, there is still a lack of sound clinical evidence regarding the combination of ARP in conjunction with early implant placement.

Aim

The overall aim of this thesis was to evaluate barrier membranes for alveolar ridge augmentation and alveolar ridge preservation in early implant placement. The following research questions were formulated:

1. Does the addition of barrier membranes lead to better clinical outcomes for bone augmentation with simultaneous (one-stage) and delayed (two-stage) implant placement, sinus augmentation surgery, alveolar ridge preservation, and immediate implant placement?
2. Does ridge preservation in early implant placement lead to increased preservation of bone and soft tissue, and thereby less additional bone augmentation procedures at implant placement and improved clinical and esthetic results of dental implants?

Outline of the thesis

In the first part of this thesis, we address the effectiveness of barrier membranes in alveolar ridge augmentation. In the second part, we report on the effects of alveolar ridge preservation in early implant placement. To determine the effects of barrier membranes on different bone augmentation procedures, a systematic review according to the Cochrane Handbook protocol and PRISMA guidelines is reported in *Chapter* 2. Only randomized controlled trials were selected and outcomes investigated were implant failure, complications, horizontal bone gain and resorption, graft resorption, defect height reduction, marginal bone loss around implants, esthetic results, and patient satisfaction.

To further investigate the clinical relevance of membranes in bone augmentation during implant placement, a randomized controlled trial (RCT) is described in *Chapter 3*. In this RCT, the effect of a resorbable hydrogel membrane on one-stage ridge augmentation procedures in small (≤ 4 mm) buccal bony defects in anterior maxillary single-tooth replacement was evaluated. The augmentation

procedure with autogenous bone chips and a synthetic bone substitute was performed with the application of this membrane and compared to the same procedure without a membrane. The outcomes measured included implant survival and success, complications, clinical and radiographic parameters, esthetic results, and patient satisfaction. Follow-up was performed for at least one year after loading.

In *Chapter 4*, patients with a guided bone regeneration procedure are compared to patients without a buccal bone defect at implant placement. The purpose of this prospective trial was to compare implants placed with bone augmentation for a small buccal defect with implants placed completely in the native bone. In this study, esthetic and patient-reported outcomes were evaluated.

Both soft and hard tissue profilometric changes, as well as patient satisfaction following alveolar ridge preservation at single sites in the anterior maxilla, are investigated in *Chapter 5*. The use of a bone substitute material of xenogeneic origin covered with either a xenogeneic collagen matrix or a free gingival graft (punch technique) is compared to spontaneous healing in this randomized controlled trial.

In *Chapter 6*, patient satisfaction, esthetics, clinical outcomes, and soft tissue changes of early placed implants following alveolar ridge preservation in the anterior maxilla with a xenograft covered with a collagen matrix or a free mucosal graft versus spontaneous healing were evaluated 12 months after loading.

A general discussion and future perspectives of this thesis are provided in *Chapter 7*. All of the main findings are discussed, and options for future research are described.

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CHAPTER 2

The clinical value of membranes in bone augmentation procedures in oral implantology: A systematic review of randomised controlled trials

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Eur J Oral Implantol 2016;9(4):335-365

ABSTRACT

Purpose To determine the clinical value of membranes in bone augmentation procedures such as ridge augmentation with simultaneous (one-stage) and delayed (two-stage) implant placement, sinus augmentation surgery, ridge preservation and immediate implant placement.

Materials and Methods In April 2016, Embase, Medline (Ovid-SP), Cochrane Central, Web of Science and PubMed (as supplied by the publisher) were searched. There were no restrictions regarding language or publication date. Randomised controlled trials that reported membranes in bone augmentation procedures with a minimum follow-up period of 6 months after implant loading or that described geometrical changes of the bone graft at re-entry were included. Membrane placement had to be the only variable in the procedure. Outcomes were implant failure, complications, horizontal bone gain and resorption, graft resorption, defect height reduction, marginal bone loss around implants, aesthetic results and patient satisfaction. The results were pooled using fixed-effect models with mean differences (MDs) for continuous outcomes and odds ratios (ORs) for dichotomous outcomes.

Results After screening the titles and abstracts of 1843 papers, 32 potentially eligible articles were selected. Seventeen articles involving 10 trials were included in this review. These studies presented outcome data for 355 patients. Seven trials were considered to be at a high risk of bias, two at a low risk of bias and one at an unclear risk of bias. Insufficient evidence was found to determine whether there were differences in implant failure rates, marginal bone level changes, aesthetic results or patient satisfaction. For one-stage ridge augmentation (two trials; n = 52), there was evidence of more horizontal bone gain (MD: 0.84 mm, 95% CI: 0.46 to 1.21, $p < 0.001$; two trials), defect height reduction (MD: 18.36%, 95% CI: 10.23 to 26.50, $p < 0.001$; two trials), and prevention of graft resorption ($p = 0.004$; one trial) in favour of the membrane-covered group, although substantial heterogeneity was found for horizontal bone gain (Chi^2; $p = 0.05$, $I^2 = 74\%$). There was insufficient evidence to determine whether any differences exist in two-stage ridge augmentation (three trials; n = 81), sinus augmentation

(one trial; n = 104) and ridge preservation (one trial; n = 20). For immediate implant placement (three trials; n = 98), there was evidence of an increased defect height reduction in favour of the membrane-covered groups (MD: 6.25%, 95% CI: 1.67 to 10.82, p = 0.007; two trials), although with substantial heterogeneity (Chi^2; p = 0.03, I^2 = 79%). More complications were observed when a membrane was used (OR: 2.52, 95% CI: 1.07 to 5.93, p = 0.03; three trials).

Conclusions There is insufficient evidence regarding the effects of membranes on bone augmentations procedures to support definitive conclusions. Only 10 studies were included; they had limited sample sizes and short follow-up periods, and the majority were at high risk of bias. However, no difference in implant failure was found, and the possible clinical value is still unknown, as long-term clinical parameters such as marginal bone loss, aesthetic results, and patient satisfaction have been insufficiently studied.

INTRODUCTION

One of the biggest challenges in oral implantology is to create or preserve sufficient bone to successfully place endosseous implants. The dimensions of the alveolar ridge change after tooth extraction, which can negatively influence the possibility of placing implants.[1, 2] Bone augmentation procedures are performed to correct these osseous deficiencies. If primary stability and ideal positioning of the implant can be achieved, bone augmentation procedures can successfully be performed simultaneously with implant placement.[3, 4] In other cases, ridge augmentation must be performed prior to implant placement. After ossification of the grafted material, implants can be placed safely.[5-7] To create sufficient height in the posterior maxilla, sinus augmentation procedures are performed using autogenous bone grafts, bone substitutes, or a mixture of both.[8-10] Bone augmentation procedures are also performed to prevent osseous deficiencies. After the extraction of a tooth, the alveolus is filled with a bone augmentation material; a procedure called ridge preservation.[11-13] For immediate implant placement procedures, several authors described filling the gap between the implant and the buccal bone wall with a bone augmentation material.[14-16]

In all the above-mentioned procedures, additional membranes can be used to direct the growth of new bone, a principle called guided bone regeneration (GBR). Membranes can be categorised as non-resorbable and resorbable varieties. Non-resorbable membranes are made of polytetrafluoroethylene (PTFE), while resorbable membranes are human-derived, animal-derived or synthetic polymers.[17] Since Nyman et al. (1990)[18] and Dahlin et al. (1991)[19, 20] first described GBR in their clinical studies, the use of membranes has become a widely applied concept in oral implantology.

The combined use of bone augmentation materials and GBR has possible synergistic advantages. The bone graft supports the membrane and prevents it from collapsing. It also offers a framework for the ingrowth of capillaries and perivascular tissue, and it provides a carrier for factors that enhance bone formation. On the other hand, the membrane provides an environment that promotes the recruitment and proliferation of osteoprogenitor cells, differentiation to osteoblasts and osteogenic activity, thereby allowing the regeneration of bone in open areas and possibly minimising the loss of graft volume.[21-23]

Although recent research has provided sufficient evidence for the successful use of bone augmentation methods in implant dentistry, there is still no consensus about the beneficial effects of the use of membranes in augmentation procedures. The aim of the present review is to systematically analyse the scientific literature regarding the clinical value of membranes in ridge augmentation procedures with simultaneous (one-stage) and delayed (two-stage) implant placement, sinus augmentation surgery, ridge preservation and immediate implant placement.

MATERIALS AND METHODS

The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) guidelines were followed to ensure the transparency and comprehensiveness of this systematic review.[24] A search protocol was specified in advance and registered at PROSPERO (International prospective register of systematic reviews) nr. CRD42015024342.

Objective

To determine the additional effects of membranes in 1) one-stage ridge augmentation, 2) two-stage ridge augmentation, 3) sinus augmentation surgery, 4) ridge preservation and 5) bone augmentation in immediate implant placement on the following outcome measures: implant failure, complications, horizontal bone gain and resorption, graft resorption, defect height reduction, marginal bone loss around implants, aesthetic results and patient satisfaction.

Criteria for considering studies for this review

Types of studies (S)

Randomised controlled trials (RCTs) of parallel-group design and split-mouth design that assessed membranes in bone augmentation procedures for the placement of endosseous screw-type implants with a minimum follow-up period of 6 months after loading of the implants or a geometrical evaluation of the bone graft procedure at re-entry. In cases where multiple papers described the same research population, the paper with the longest follow-up period was selected; the other papers were used to provide additional data.

Types of participants (P)

Patients in need of a bone augmentation procedure for oral implantology.

Types of interventions and comparisons (I & C)

Bone augmentation procedures for the placement of oral implants (one- and two-stage ridge augmentation, sinus augmentation surgery, ridge preservation and immediate implant placement) with an additional membrane compared to the same bone augmentation procedure without a membrane. Membrane placement had to be the only procedural variable for trials to be considered for this review. Studies that reported on augmentation procedures for peri-implantitis treatment or that used autogenous membranes were excluded.

Types of outcome measures (O)

- Implant failure (implants removed or lost due to mobility, progressive marginal bone loss, infection or mechanical problems).

- Complications (any complication, such as dehiscence and infection).
- Horizontal bone gain/resorption (difference between horizontal measurements performed before graft application and at second re-entry in millimetres (mm)).
- Bone graft resorption (difference between horizontal measurements performed after graft application and at second re-entry in mm).
- Defect height reduction (difference between vertical measurements performed at implant placement before graft application and at second re-entry as a percentage).
- Radiographic horizontal bone gain/resorption (difference between measurements performed on computed tomography scans in mm).
- Radiographic marginal peri-implant bone changes (difference between measurements performed on periapical radiographs in mm).
- Hard and soft tissue aesthetics (evaluated by professionals).
- Patient satisfaction.

PICO question

Are the clinical outcomes (O) for patients in need of a bone augmentation procedure for oral implantology (P) more favourable when using an additional membrane (I) than when a membrane is not used (C)?

Search methods for the identification of studies

The search strategy was developed for EMBASE and appropriately modified for MEDLINE (Ovid-SP), the Cochrane Central Register of Controlled Trials, the Web of Science and PubMed (as supplied by the publisher). The electronic databases were searched through April 2016. The search strategy used a combination of controlled vocabulary and free text terms and was run with the recommended EMBASE and MEDLINE filters to identify randomised controlled trials.[25] The full search protocol for the different databases is displayed in Table 1. No language or data restrictions were applied when searching the electronic databases. Additionally, all references to earlier systematic reviews and selected full-text articles were manually screened for potentially useful additional articles.

EMBASE (Embase and Medline):	('Artificial membrane'/exp OR macrogol/de OR 'Surgical Mesh'/de OR ('surgical mesh' OR membrane* OR liposome* OR bilayer* OR monolayer* OR polytetrafluoroethylene* OR politef OR polytef OR PTFE OR 'Gore-Tex' OR polyethylene* OR 'poly ethylene' OR PEG OR macrogol* OR Carbowax OR MembraGel OR 'Bio-Gide' OR Collaguide OR 'Mem-Lok' OR AlloDerm OR BioMend OR CopiOs OR Creos OR Cytoplast OR BEGO OR Puros OR Neomen OR RTM OR ATRISORB OR mucograft*):ab,ti) AND ('Oral Surgery'/de OR 'Bone transplantation'/exp OR 'Distraction osteogenesis'/de OR 'Bone regeneration'/de OR ((oral NEAR/3 (surgical OR surgery)) OR ((sinus OR socket OR alveolar OR ridge) NEAR/4 (augmentat* OR preservat* OR lift*)) OR ((bone OR osteo* OR osseo*) NEAR/4 (transplant* OR graft* OR autograft* OR regenerat* OR genesis OR integrat*)) OR osseointegrat* OR osteogenes* OR (ridge NEAR/3 (split* OR expansion*)) OR ((onlay OR veneer*) NEAR/3 graft*) OR 'Bio Oss' OR BioOss OR Osteoplant OR Tutobone):ab,ti) AND ('Controlled clinical trial'/exp OR 'Crossover procedure'/de OR 'Double-blind procedure'/de OR 'Single-blind procedure'/de OR (random* OR factorial* OR crossover* OR (cross NEXT/1 over*) OR placebo* OR ((doubl* OR singl*) NEXT/1 blind*) OR assign* OR allocat* OR volunteer* OR trial OR groups OR RCT* OR CCT*):ab,ti) NOT ([animals]/lim NOT [humans]/lim)
MEDLINE (OvidSP):	(exp 'Membranes, Artificial'/ OR exp 'Polyethylene Glycols'/ OR 'Surgical Mesh'/ OR (membrane* OR liposome* OR bilayer* OR monolayer* OR polytetrafluoroethylene* OR politef OR polytef OR PTFE OR Gore-Tex OR polyethylene* OR poly ethylene OR PEG OR macrogol* OR Carbowax OR MembraGel OR Bio-Gide OR Collaguide OR Mem-Lok OR AlloDerm OR BioMend OR CopiOs OR Creos OR Cytoplast OR BEGO OR Puros OR Neomen OR RTM OR ATRISORB OR mucograft).ab,ti.) AND ('Alveolar Ridge Augmentation'/ OR exp 'Bone transplantation'/ OR 'Osteogenesis, Distraction'/ OR exp 'Bone regeneration'/ OR (((sinus OR socket OR alveolar OR ridge) ADJ4 (augmentat* OR preservat* OR lift*)) OR ((bone OR osseo* OR osteo*) ADJ4 (transplant* OR graft* OR autograft* OR regenerat* OR genesis OR integrat*)) OR osseointegrat* OR osteogenesis OR (ridge ADJ3 (split* OR expansion*)) OR ((onlay OR veneer*) ADJ3 graft*) OR (Bio ADJ Oss) OR BioOss OR Osteoplant OR Tutobone).ab,ti.) AND ((Randomized Controlled Trial OR Controlled Clinical Trial).pt. OR (randomized OR randomly OR placebo OR trial OR groups OR RCT* OR CCT*).ab,ti.) NOT (animals NOT humans).sh.
Cochrane Central:	((membrane* OR liposome* OR bilayer* OR monolayer* OR polytetrafluoroethylene* OR politef OR polytef OR PTFE OR 'Gore Tex' OR polyethylene* OR 'poly ethylene' OR PEG OR macrogol* OR Carbowax OR MembraGel OR 'Bio Gide' OR Collaguide OR 'Mem Lok' OR AlloDerm OR BioMend OR CopiOs OR Creos OR Cytoplast OR BEGO OR Puros OR Neomen OR RTM OR ATRISORB OR mucograft):ab,ti) AND ((((sinus OR socket OR alveolar OR ridge) NEAR/4 (augmentat* OR preservat* OR lift*)) OR ((bone OR osteo* OR osseo*) NEAR/4 (transplant* OR graft* OR autograft* OR regenerat* OR genesis OR integrat*)) OR osseointegrat* OR osteogenesis OR (ridge NEAR/3 (split* OR expansion*)) OR ((onlay OR veneer*) NEAR/3 graft*) OR (Bio NEXT/1 Oss) OR BioOss OR Osteoplant OR Tutobone):ab,ti)

▶

Web of Science	TS=(((membrane* OR liposome* OR bilayer* OR monolayer* OR polytetrafluoroethylene* OR politef OR polytef OR PTFE OR 'Gore Tex' OR polyethylene* OR 'poly ethylene' OR PEG OR macrogol* OR Carbowax OR MembraGel OR 'Bio Gide' OR Collaguide OR 'Mem Lok' OR AlloDerm OR BioMend OR CopiOs OR Creos OR Cytoplast OR BEGO OR Puros OR Neomen OR RTM OR ATRISORB OR mucograft)) AND ((((sinus OR socket OR alveolar OR ridge) NEAR/4 (augmentat* OR preservat* OR lift*)) OR ((bone OR osteo* OR osseo*) NEAR/4 (transplant* OR graft* OR autograft* OR regenerat* OR genesis OR integrat*)) OR osseointegrat* OR osteogenesis OR (ridge NEAR/3 (split* OR expansion*)) OR ((onlay OR veneer*) NEAR/3 graft*) OR (Bio NEXT/1 Oss) OR BioOss OR Osteoplant OR Tutobone)) AND (random* OR factorial* OR crossover* OR (cross NEXT/1 over*) OR placebo* OR ((doubl* OR singl*) NEXT/1 blind*) OR assign* OR allocat* OR volunteer* OR trial OR groups OR RCT* OR CCT*) NOT ((animal* OR dog* OR canine OR pig* OR goat* OR horse* OR sheep OR rabbit* OR rat OR rats OR monkey* OR minipig*) NOT human*)) AND DT=Article
PubMed - as supplied by publisher	(membrane*[tiab] OR liposome*[tiab] OR bilayer*[tiab] OR monolayer*[tiab] OR polytetrafluoroethylene*[tiab] OR politef[tiab] OR polytef[tiab] OR PTFE[tiab] OR Gore Tex*[tiab] OR polyethylene*[tiab] OR poly ethylene*[tiab] OR PEG[tiab] OR macrogol*[tiab] OR Carbowax[tiab] OR MembraGel[tiab] OR Bio Gide*[tiab] OR Mem Lok*[tiab] OR AlloDerm[tiab] OR BioMend[tiab] OR CopiOs[tiab] OR Creos[tiab] OR Cytoplast[tiab] OR BEGO[tiab] OR Puros[tiab] OR RTM[tiab] OR ATRISORB[tiab] OR mucograft[tiab]) AND ((((sinus[tiab] OR socket[tiab] OR alveolar[tiab] OR ridge[tiab]) AND (augmentat*[tiab] OR preservat*[tiab] OR lift*[tiab])) OR ((bone[tiab] OR osteo[tiab] OR osteogen*[tiab] OR osseo*[tiab]) AND (transplant*[tiab] OR graft*[tiab] OR autograft*[tiab] OR regenerat*[tiab] OR genesis[tiab] OR integrat*[tiab])) OR osseointegrat*[tiab] OR osteogenesis[tiab] OR (ridge[tiab] AND (split*[tiab] OR expansion*[tiab])) OR ((onlay[tiab] OR veneer*[tiab]) AND graft*[tiab]) OR Bio Oss*[tiab] OR BioOss[tiab] OR Osteoplant[tiab] OR Tutobone[tiab])) AND (random*[tiab] OR factorial*[tiab] OR crossover*[tiab] OR cross over*[tiab] OR placebo*[tiab] OR double blind*[tiab] OR single blind*[tiab] OR assign*[tiab] OR allocat*[tiab] OR volunteer*[tiab] OR trial[tiab] OR groups[tiab]) NOT ((animal*[tiab] OR dog*[tiab] OR canine[tiab] OR pig[tiab] OR pigs[tiab] OR goat*[tiab] OR horse*[tiab] OR sheep[tiab] OR rabbit*[tiab] OR rat[tiab] OR rats[tiab] OR monkey*[tiab] OR minipig*[tiab]) NOT human*[tiab]) AND publisher[sb]

Table 1 Search strategy.

Data collection and analysis

Selection of studies

The titles and abstracts of relevant studies identified through the electronic searches were screened by two authors (BJ and MR). Full-text articles were obtained of the studies that fulfilled the inclusion criteria. These full-text articles, together with the full-text articles found through the manual search, were independently assessed by these authors to determine if they met the inclusion criteria. Disagreements were resolved by discussion. If, following a discussion, it was still unclear whether an article should be included, a third author (JP) was consulted. After selection, the data extraction and risk of bias assessment were performed.

Data extraction and management

The data extraction was performed by one researcher (BJ) according the Cochrane data extraction form[26] and supervised by the other authors (MR, EW, JP). All authors of the potentially eligible articles were contacted for clarification or to obtain missing data.

Data recorded

- Methods: Trial design, location, number of centres, recruitment period and funding source.
- Participants: Inclusion and exclusion criteria, demographics, number of participants.
- Intervention: Details regarding the type of intervention, groups and materials used.
- Outcomes: Outcome measurements and follow-up.

Risk of bias assessment

The risk of bias assessment was performed according the Cochrane Handbook for Systematic Reviews of Interventions, Chapter 8: Assessing risk of bias.[27] Two authors (BJ and MR) independently performed the risk of bias assessment. Any disagreement was resolved by discussion or through consultation with a third author (JP). A judgement was expressed as 'low risk', 'high risk' or 'un-

clear risk' of bias for different categories of bias (selection bias, detection bias, attrition bias, reporting bias and other bias). To ensure that good judgements were made, authors were contacted if data in the original article were missing. After performing this assessment, the overall risk of bias of the included articles was assessed. Studies were categorised as 'low risk of bias' (low risk of bias in all key domains), 'unclear risk of bias' (unclear risk of bias in one or more key domains) or 'high risk of bias' (high risk of bias in one or more key domains).

Measures of treatment effect

For dichotomous outcomes, the estimated effects of the intervention were expressed as odds ratios (ORs) with a 95% confidence interval (CI). For continues outcomes, mean differences (MDs) and standard deviation (SD) were used to summarise the data with a 95% CI.

Unit of analysis issues

The unit of analysis was the patient, not the graft or the implant. If a split-mouth study was performed, the specific quadrants were the unit of analysis. If data were available only for the implant as the unit of analysis, the analysis was performed at implant level. For ease of analysis and interpretation, these data were entered as though they represented patients.

Dealing with missing data

All the authors were contacted to obtain any missing data from the trials. The Cochrane formulae for combining groups (section 7.7.3 of the Cochrane Handbook) were used to combine the means and standard deviations of different conditions and groups, such as mesial and distal radiographic marginal peri-implant bone levels, data for multiple membrane groups and measurements of different distances from the crest. Changes in the alveolar ridge dimension were calculated using formulae for subtracting means and calculating standard deviations.

Assessment of heterogeneity

The significance of all variations in the estimates of the treatment effects from the different trials was assessed using Cochran's test for heterogeneity. Heterogeneity was considered significant if the p-value was < 0.1. I^2 statistics were

used to quantify heterogeneity. I^2 describes the percentage of total variation across studies that is due to heterogeneity rather than to chance, with I^2 over 50% representing moderate to high heterogeneity.

Data synthesis

The meta-analysis was undertaken using RevMan (Review Manager 5.3.5, Copenhagen, Denmark). The ORs were combined for the dichotomous outcomes and the MDs were combined for the continuous outcomes using fixed-effect models. A random effect model was used if there were more than three studies in one meta-analysis. Peto ORs, from fixed effect models, were used when there were zero events in the control or treatment arms or both. A generic inverse variance method of RevMan was used to combine the data from the split-mouth trials with the data from the parallel-group trials, as described by Elbourne et al. (2002)[28]

Subgroup analysis and investigation of heterogeneity

Clinical heterogeneity was assessed by examining the types of participants and interventions for all outcomes in each study. Due to an insufficient number of studies in the meta-analysis subgroup, an analysis was not performed for this group.

Presentation of main results

The results for all outcomes are presented in a summary table. Only the results for more than one trial are shown in the forest plots. The quality of the evidence was assessed with reference to the overall risk of bias of the included studies.

RESULTS

Description of studies

Results of the search

After screening the titles and abstracts of 1843 unique papers, 32 potentially eligible articles were selected (Figure 1). Of the 32 potentially eligible articles,[29-60] 15 had to be excluded. These trials were excluded for the following reasons: membranes were not the only treatment variable (six),[39, 43, 46, 52, 54, 60] outcome measures

relevant to this review were not present (four),[40, 42, 51, 53] the authors confirmed that the studies were not actually randomised controlled trials (two),[44, 55] only membranes were used (one),[49] autogenous pericranium membranes were used (one),[41] and an inappropriate study design was used (one),[56] The study characteristics and the reasons for excluding the full-text evaluated studies are noted in Table 2.

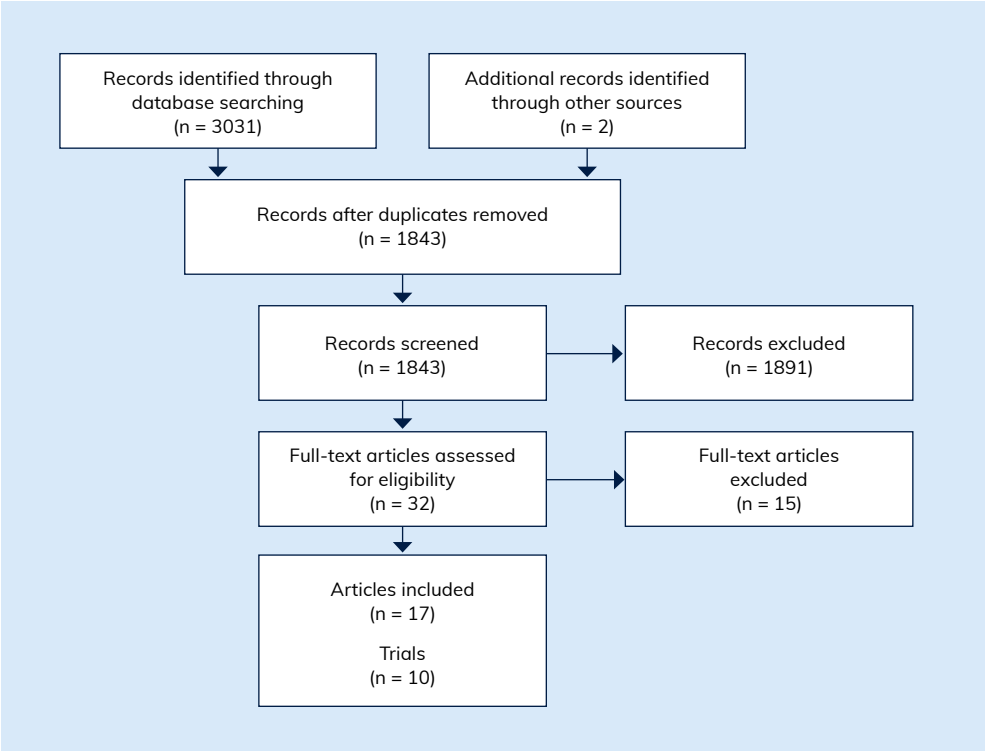

Figure 1 Flow diagram.

Included studies

A total of 17 articles involving 10 trials were identified for inclusion in this review: Antoun et al. (2001)[29] Brkovic et al. (2012)[30] Chen et al. (2005)[31] Chen et al. (2007)[32] Fu et al. (2014)[33] Fu et al. (2014)[45] Heberer et al. (2009)[34] Meijndert et al. (2005)[47] Meijndert et al. (2008)[48] Meijndert et al. (2016)[35] Park and Wang (2007)[50] Park et al. (2008)[36] Torres et al. (2013)[37] Urban and Wenzel (2010)[57] Urban et al. (2012)[58] Urban et al. (2012)[38] Visser et al. (2011)[59]. For more details about these 10 trials, see the tables of study characteristics (Tables 3-12).

Study	Reason for exclusion
Alayan et al. (2015)[39]	This study compared sinus augmentation using anorganic bovine bone mineral with an additional membrane to sinus augmentation using anorganic bovine bone mineral and autogenous bone without an additional membrane. The additional membrane was not the only procedural variable.
Barone et al. (2013)[40]	This study was a histological analysis of maxillary sinus augmentation with and without the additional use of collagen membranes over the osteotomy window. No clinical outcome measures relevant to this systematic review were presented.
Chiapasco et al. (2013)[41]	This study evaluated the use of autogenous pericranium membranes on autogenous onlay bone grafts. The focus of the current review is non-autogenous membranes.
Choi et al. (2009)[42]	This was a pilot study of the effect of membranes on human maxillary sinus grafts. No clinical outcome measures relevant to this systematic review were presented.
Cordaro et al. (2011)[43]	This study described the effect of additional bovine bone mineral and membranes on autogenous two-stage bone grafts. The membrane was not the only procedural variable.
Froum et al. (1998)[44]	This large trial compared different surgical techniques and materials for lateral sinus augmentation. One of the authors informed us that the study was not a randomized controlled trial (Dr Wallace).
Jung et al. (2013)[46]	This randomized trial described ridge preservation with the use of a bone substitute covered with a membrane (matrix) or soft tissue graft. As the soft tissue graft was not performed for the membrane group, the membrane was not the only procedural variable.
Palmer et al. (1994)[49]	This study compared the healing of peri-implant dehiscence defects with and without e-PTFE membranes. Only the abstract could be retrieved. The author responded that no augmentation material was used, only membranes.
Perelman-Karmon et al. (2012)[51]	This trial compared ridge preservation using bovine bone mineral with and without resorbable membrane coverage. No clinical outcome measures relevant to this systematic review were presented.
Raghoebar et al. (2009)[52]	This randomized trial evaluated ridge preservation with the use of autogenous bone and a substitute covered with a membrane (matrix) or soft tissue graft. As the soft tissue graft was not performed for the membrane group, the membrane was not the only procedural variable.
Schlegel et al. (1998)[53]	This trial compared one-stage and two-stage autogenous bone augmentations with and without a membrane. No clinical outcome measures relevant to this systematic review were presented.
Schneider et al. (2014)[54]	This randomized trial evaluated ridge preservation with the use of a bone substitute covered with a membrane (matrix) or soft tissue graft. As the soft tissue graft was not performed for the membrane group, the membrane was not the only procedural variable.
Tarnow et al. (2000)[55]	This split-mouth study compared lateral sinus augmentation with and without a membrane. One of the authors informed us that the study was not a randomized controlled trial (Dr Wallace).
Tawil and Mawla (2001)[56]	This clinical report compared sinus floor augmentation using bovine bone mineral with and without a membrane over the lateral window. This study has an inappropriate study design; it was neither parallel-group nor split-mouth.[10]
Zuffetti et al. (2013)[60]	This study compared ridge preservation with and without buccal augmentation and membrane placement. The additional membrane was not the only procedural variable.

Table 2 Excluded articles (alphabetical order).

Articles	**Antoun et al. (2001)**[29]
Methods	**Trial design:** Randomized, parallel-arm trial. **Location:** Paris, France. **Number of centres:** One (Department of Oral Surgery and Oral Implantology, School of Dentistry, University of Paris). **Recruitment period:** 2009 to 2011. **Funding source:** NobelBiocare AB, Gothenburg, Sweden.
Participants	**Inclusion criteria:** A maxillary or mandibular edentulous ridge that required width augmentation prior to implant placement; the edentulous area must allow placement of at least one standard implant and should not exceed a four-tooth span; in Caddition, an intraoral bone donor site should be available. **Exclusion criteria:** All known contraindications to intraoral surgery. **Age at baseline:** Mean age = 34 (between 18 and 52 years old). **Gender:** M6/F6. **Number randomized:** 12 patients. **Number evaluated:** 12 grafts.
Interventions	**Comparison:** Onlay graft alone or associated with a membrane. Group +M (n = 5) Onlay bone graft with a membrane. Group –M (n = 7) Onlay bone graft without a membrane. **Timing of implant placement:** After 6 months. **Healing protocol:** Submerged. **Implant:** 3.75 mm diameter, 13 or 15 mm-long Brånemark System, NobelBiocare AB, Gothenburg, Sweden (machine-turned surface screw-type implants) **Bone:** Onlay bone block graft, symphysis area (autograft). **Membrane:** Goretex membrane, G-TAM membrane, WL Gore & Associates, Flagstaff, AZ, USA (non-resorbable e-PTFE expanded polytetrauoroethylene). **Duration of follow-up:** Evaluation 6 months after bone graft (re-entry).
Outcomes	**Outcomes:** Complications, horizontal bone gain, horizontal bone resorption, horizontal bone gain on CT. **Data used:** Complications, horizontal bone gain and graft resorption (six months after augmentation).
Notes	A sample size calculation was not performed.

Table 3 Study characteristics: Antoun et al. (2001)[29]

Risk of bias

Bias	Authors judgement	Support for judgement
Random sequence generation (selection bias)	Low	Reported in the article: 'Depending on the result of the treatment randomization the graft was protected, or not protected, with a membrane.' Reply of author: 'the sequence was chosen from tables of random rotation.'
Allocation concealment (selection bias)	Low	Reply of author: 'allocation was concealed by a statistician who was part of the department of surgery (Dr Sitbon) and the randomization was revealed just at the beginning of surgery.'
Blinding of outcome assessment (detection bias)	High	Reply of author: 'allocation concealment was not possible as the non-resorbable membranes had to be removed at the second phase surgery.'
Incomplete outcome data (attrition bias)	Low	All the patients completed the study. One patient did not have a baseline CT-scan and was therefore excluded from the outcome measurements. There were no losses to follow up, no treatment withdrawals, no trial group changes and no major adverse events. Only one patient experienced membrane exposure, which did not preclude successful implant placement.
Selective reporting (reporting bias)	Low	All possible study outcomes seem to have been reported. The author declared that all measured parameters were noted in this article.
Other bias	Low	No other bias was detected.

Articles	**Brkovic et al. (2012)**[30]
Methods	**Trial design:** Randomized, parallel-arm trial. **Location:** Belgrade, Serbia. **Number of centres:** Not stated. **Recruitment period:** Not stated. **Funding source:** Septodont, Saint-Maur-des-Fosses, France.
Participants	**Inclusion criteria:** Age between 20 and 55 years old; ASA I; good oral hygiene; indications for tooth extraction such as fracture of the tooth, non-vital tooth without the possibility of endodontic treatment and restoration, chronic periodontitis, endodontic treatment failure, and periodontal disease; extraction sockets with four intact walls; and an occlusion suitable for the planned prosthodontic treatment. **Exclusion criteria:** Presence of any chronic systemic disease, allergy, medication given within 48 h pre-operatively, presence of purulent periodontal lesions as well as severe periodontal bone loss with a remaining alveolar height of less than 6 mm, history of chronic pain, pregnant or nursing mother, inability to comply with the study protocol, smokers or former smokers who had quit smoking less than two months previously. **Age at baseline:** Not stated. **Gender:** M8/F12. **Number randomized:** 20 patients. **Number evaluated:** 20.
Interventions	**Comparison:** Ridge preservation with and without a barrier membrane. Group +M (n = 9) Ridge preservation with a membrane. Group –M (n=11) Ridge preservation without a membrane. **Timing of implant placement:** After 9 months. **Healing protocol:** Submerged (re-entry after 6 months). **Implant:** NobelReplace, NobelBiocare AB, Gothenburg, Sweden (rough, TiUnite surface screw-type implants). **Bone:** RTR Cone, Septodont, Saint-Maur-des-Fosses, France (Beta-tricalcium phosphate/collagen cone). **Membrane:** BioGide, Geistlich Biomaterials, Wolhusen, Switzerland (bioresorbable collagen membrane). **Duration of follow-up:** Nine months after graft placement (re-entry).
Outcomes	**Outcomes:** Horizontal bone resorption, vertical bone resorption, duration of epithelization, length of the attached gingiva, histologic and histomorphometric analysis. **Data used:** Complications and horizontal bone resorption (nine months after ridge preservation).
Notes	A sample size calculation was not performed.

Table 4 Study characteristics: Brkovic et al. (2012)[30]

Risk of bias

Bias	Authors judgement	Support for judgement
Random sequence generation (selection bias)	Unclear	Reported in the article: 'The 20 patients were randomly assigned to one of two groups for post-extraction socket preservation.' Comment: Unclear how the sequence was generated No reply from the authors.
Allocation concealment (selection bias)	Unclear	Comment: Unclear how the allocation was concealed. No reply from the authors.
Blinding of outcome assessment (detection bias)	Unclear	Comment: Unclear if the researcher performing the measurements was blinded for the treatment allocation. No reply from the authors.
Incomplete outcome data (attrition bias)	Low	All patients completed the study, and there were no losses to follow up, no treatment withdrawals, no trial group changes and no major adverse events.
Selective reporting (reporting bias)	Low	The location of the study protocol was not reported in the article; most relevant outcome measurements appear to have been be reported; there was no reply from the authors.
Other bias	Low	No other bias was detected.

Articles	**Chen et al. (2005)**[31]
Methods	**Trial design:** Randomized, parallel-arm trial. **Location:** Melbourne, Australia. **Number of centres:** One (private periodontal practice). **Recruitment period:** Not stated. **Funding source:** WL Gore & Associates, Flagstaff, AZ, USA.
Participants	**Inclusion criteria:** Over the age of 18 years and in need of immediate implant placement in one maxillary anterior or maxillary premolar tooth site. **Exclusion criteria:** Acute infection, suppuration or sinus formation associated with the tooth; smoking; and psychological or systemic contraindications to treatment. **Age at baseline:** Mean age = 41.8. **Gender:** M29/F33. **Number randomized:** 62 patients. **Number evaluated:** 62.
Interventions	**Comparison:** Different bone augmentation techniques at immediately (sub-merged) placed implants. Group +M (n = 13) Bone augmentation with a resorbable membrane. Group –M (n = 14) Bone augmentation without a membrane. Group C (n = 12) E-PTFE membrane only (data for this group are not used in this systematic review). Group D (n = 11) Resorbable membrane only (data for this group are not used in this systematic review). Group E (n = 12) No augmentation (data for this group are not used in this systematic review). **Timing of implant placement:** Simultaneous with extraction and augmentation. **Healing protocol:** Submerged (re-entry after 6 months). Implant: Brånemark System, NobelBiocare AB, Gothenburg, Sweden (machine-turned surface screw-type implants). **Bone:** Local autogenous bone graft. **Membrane:** Resolut, WL Gore & Associates, Flagstaff, AZ, USA (bioresorbable membrane). Goretex membrane, G-TAM membrane, WL Gore & Associates, Flagstaff, AZ, USA (non-resorbable e-PTFE expanded polytetrauoroethylene). **Duration of follow-up:** Two years after implant loading.
Outcomes	**Outcomes:** Implant failure, defect height reduction, horizontal defect width reduction, horizontal defect depth reduction, horizontal bone resorption (in %). **Data used:** Implant failure (two year after loading); complications, horizontal bone resorption and defect height reduction (six-month after immediate placement).
Notes	A sample size calculation was not performed.

Table 5 Study characteristics: Chen et al. (2005)[31]

Risk of bias

Bias	Authors judgement	Support for judgement
Random sequence generation (selection bias)	Low	Reported in the article: 'Following implant placement, the resultant peri-implant defect was treated randomly in one of five ways.' Reply of author: 'Patients were allocated to their groups by draw of lots (15 lots provided for each experimental group).'
Allocation concealment (selection bias)	Low	Reply of author: 'Randomization took place at the time of surgery, after the extractions were performed and once the implants were placed. The box with the lots was completely obscured.'
Blinding of outcome assessment (detection bias)	High	Reply of author: 'one operator performed all treatments and measurements, therefore he was not blinded.'
Incomplete outcome data (attrition bias)	Low	There were no losses to follow up, no treatment withdrawals, and no trial group changes. Adverse healing was noted at six sites. Two of these sites (one in the augmentation +M group and one in the augmentation –M group) developed abscesses soon after placement. This resulted in the loss of one implant at one site (–M group). The implant at the other site was successfully retained following treatment of the infection with systemic antibiotics (amoxycillin, 1.5 g daily for 5 days). One implant in the –M group subsequently developed a peri-implant infection 6 weeks after surgical re-entry and was later removed.
Selective reporting (reporting bias)	Low	Comment: 'Horizontal bone (labial plate) resorption' was noted only by percentages per group in contrast to other studies and therefore could not be compared with other studies. Reply of author: 'Group 3 membrane + bone: mean 1.545 mm SD 0.688 and Group bone only: mean 0.850 mm SD 0.973' All other possible outcome measurements seem to have been reported.
Other bias	Low	No other bias was detected.

Articles	**Chen et al. (2007)**[32]
Methods	**Trial design:** Randomized, parallel-arm trial. **Location:** Melbourne, Australia. **Number of centres:** One (private periodontal practice). **Recruitment period:** 1999-2000. **Funding source:** Not stated.
Participants	**Inclusion criteria:** Required extraction and replacement of one or several non-adjacent teeth in the maxillary anterior and premolar regions with implant reconstructions. **Exclusion criteria:** Acute infection associated with the tooth of interest and/or clinical attachment loss of 5 mm or more on the buccal aspect of the tooth to be extracted, poor plaque control, untreated chronic periodontitis and systemic and psychological contraindications to treatment; smokers were not excluded. **Age at baseline:** Mean age = 45.2. **Gender:** Not stated. **Number randomized:** 30 patients. **Number evaluated:** 19 at 3 years.
Interventions	**Comparison:** Different bone augmentation techniques for immediately (non-submerged) placed implants. Group +M (n = 10) Bone substitute with a membrane. Group –M (n = 10) Bone substitute without a membrane. Group C (n = 10) No graft (data for this group are not used in this systematic review). **Timing of implant placement:** Simultaneous with extraction and augmentation. **Healing protocol:** Non-submerged. Implant: ITI Implant System, Institute Straumann AG, Waldenberg, Switzerland (solid sand-blasted, large-grit, acid-etched, rough surface screw-type implants). **Bone:** Bio-Oss, Geistlich Pharmaceutical AG, Wolhusen Switzerland (deproteinized bovine bone mineral). **Membrane:** BioGide, Geistlich Biomaterials, Wolhusen, Switzerland (bioresorbable collagen membrane). **Duration of follow-up:** Three years after implant loading.
Outcomes	**Outcomes:** Implant failure, complications, horizontal bone resorption, defect height reduction, plaque index, bleeding index, standardized radiographs, horizontal defect depth reduction, distance from implant shoulder to crest, operator assessed aesthetic outcome, patient satisfaction. **Data used:** Implant failure (three year after loading); complications, horizontal bone resorption, defect height reduction (six months after immediate placement); operator assessed aesthetics and patient satisfaction (immediate after loading).

Table 6 Study characteristics: Chen et al. (2007)[32]

Notes	A sample size calculation was not performed. The authors noted that further research with larger sample sizes would be required to identify the factors influencing the degree of defect fill.

Risk of bias

Bias	Authors judgement	Support for judgement
Random sequence generation (selection bias)	High	Reported in the article: 'In four cases, dehiscence defects of the buccal plate were discovered following extraction of the teeth. For ethical reasons, these cases were randomly allocated to the BG (bone graft) or BG+M (bone graft + membrane) groups only.' Comment: Only two groups were properly randomized (bone augmentation with and without a membrane). The control group was used only if no dehiscence was found and was therefore at high risk of selection bias. This systematic review will use only the data for the other two groups.
Allocation concealment (selection bias)	Low	Reply of author: 'randomisation was done as follows: 10 lots for each group were placed in an opaque container. Patients were screened and after providing consent, teeth have been extracted and implants have been placed allocated to their groups by draw of lots by one of the surgical assistants.'
Blinding of outcome assessment (detection bias)	High	Reply of author: 'one operator performed all treatments and measurements, therefore he was not blinded.'
Incomplete outcome data (attrition bias)	Low	All patients completed the study and there were no losses to follow up and no treatment withdrawals. One patient (bone graft + membrane group) was complicated by abscess formation 4 months following implant placement. This complication was resolved with disinfection during an additional surgery and reconstructed with bone and a membrane.
Selective reporting (reporting bias)	High	Operator-assessed aesthetic outcome, patient satisfaction, marginal bone level and various other clinical parameters were not provided separately for the treatment groups.
Other bias	Low	No other bias was detected.

Articles	**Fu et al. (2014)[33] , Fu et al. (2014)[45]**
Methods	**Trial design:** Randomized, parallel-arm trial. **Location:** Michigan, USA. **Number of centres:** One (University of Michigan, School of Dentistry). **Recruitment period:** 2009 to 2011. **Funding source:** Zimmer Dental Inc., Carlsbad, CA, USA.
Participants	**Inclusion criteria:** At least 18 years old and no more than 80 years old, systemically healthy, good dental health, missing a single tooth in the maxillary anterior and premolar region, crestal residual ridge width of 4 mm and/or associated with an obvious buccal deficiency, residual ridge with an adequate band of keratinized tissue (≥ 2 mm), residual ridge with sufficient vertical bone height to safely place a ≥ 10 mm-long dental implant. **Exclusion criteria:** Poor oral hygiene, severe parafunctional habits, untreated oral diseases, maxillary sinus involvement, conditions that complicate wound healing (uncontrolled diabetes or smoking), conditions that might lead to a possibly lowered regenerative capacity of the bone, (osteoporosis and Paget's disease), pregnant or expecting to become pregnant, history of drug or alcohol abuse, certain medications (bisphosphonates or steroids currently or within the past three months). **Age at baseline:** Mean age = 48.6 (between 31 and 64 years old). **Gender:** M13/F13. **Number randomized:** 26 patients. **Number evaluated:** 26.
Interventions	**Comparison:** Sandwich bone augmentation (SBA) technique with and without a membrane. Group +M (n = 13) SBA technique with a membrane. Group –M (n = 13) SBA technique without a membrane. **Timing of implant placement:** Simultaneous with augmentation. **Healing protocol:** Submerged (re-entry after 6 months). Implant: 3.7 or 4.1 mm diameter, 11.5 or 13 mm-long Zimmer Tapered Screw-Vent, Zimmer Dental Inc., Carlsbad, CA, USA (unknown coated, rough surface screw-type implants). **Bone:** Puros, Zimmer Dental Inc., Carlsbad, CA, USA (cancellous and cortical particulate allograft). **Membrane:** CopiOs pericardium membrane, Zimmer Dental Inc., Carlsbad, CA, USA (resorbable bovine pericardium membrane). **Duration of follow-up:** Six months after loading.

Table 7 Study characteristics: Fu et al. (2014)[33]

Outcomes	**Outcomes:** Fu et al. (2014)[33]: Implant failure, complications, horizontal bone gain, defect height reduction, horizontal bone gain on CT, marginal bone level changes on intraoral radiograph, gingival thickness, crestal ridge width change, defect width reduction, exposed surface area of implant, percentage bone fill, defect depth reduction; Fu et al. (2014)[45]: Outcomes regarding histology, immunohistochemistry, micro-computed tomography and mRNA. Data used: Implant failure, marginal bone level change (six months after loading); complications, horizontal bone gain defect height reduction in percentage, radiographic horizontal bone gain (six months after augmentation).
Notes	A sample size calculation was performed to obtain 80% power in this study when treating 26 patients.

Risk of bias

Bias	Authors judgement	Support for judgement
Random sequence generation (selection bias)	Low	Reported in the article: 'The process of randomization involved the primary researcher (JHF) picking a number ... Patients who had number '0' were allocated to the control group, while those with number '1' were allocated to the test group.'
Allocation concealment (selection bias)	Low	Reported in the article: 'picking a number from an enclosed brown bag.' Comment: primary researcher (JHF) picked the numbers, not the performing surgeon (HLW).
Blinding of outcome assessment (detection bias)	High	Reply of author: 'The researcher assessing the outcome measurements was not blinded to the groups allocation.'
Incomplete outcome data (attrition bias)	Low	All patients completed the study, and there were no losses to follow up, no treatment withdrawals after inclusion, and no trial group changes. In both groups, three patients had an incision line opening, membrane exposure and partial loss of the bone graft material 2 weeks after surgery.
Selective reporting (reporting bias)	Low	All possible study outcomes seem to have been reported in two successive articles[33, 45]. The author declared that all measured parameters were noted in these articles.
Other bias	Low	None detected.

Articles	**Heberer et al. (2009)**[34]
Methods	**Trial design:** Randomized, split-mouth trial. **Location:** Berlin, Germany. **Number of centres:** One (Department of Oral and Maxillofacial Surgery, Charité-Campus Virchow Clinic). **Recruitment period:** Not stated. **Funding source:** Geistlich Biomaterials, Wolhusen, Switzerland.
Participants	**Inclusion criteria:** All the patients were edentulous and showed a severe resorption of the maxilla with a remaining bone volume of less than 5 mm in height on both quadrants. **Exclusion criteria:** Not stated. **Age at baseline:** Mean age = 56 (between 25 and 72 years old). **Gender:** M5/F9. **Number randomized:** 28 quadrants, 14 patients. **Number evaluated:** 28 quadrants.
Interventions	**Comparison:** Iliac onlay grafts in atrophied edentulous patients covered with periosteum or a bioresorbable membrane. Group +M (n = 14) Iliac onlay graft with a membrane. Group –M (n = 14) Iliac onlay graft without a membrane **Timing of implant placement:** 3 months after graft placement. **Healing protocol:** Non-submerged. **Implant:** Camlog RootLine implants, Camlog Biotechnologies, Wimsheim, Germany (abrasive-blasted, acid-etched, rough surface screw-type implants) & ITI Implant System, Institut Straumann AG, Waldenberg, Switzerland (solid sand-blasted, large-grit, acid-etched, rough surface screw-type implants) Bone: Onlay bone block graft, iliac crest (autograft). **Membrane:** BioGide, Geistlich Biomaterials, Wolhusen, Switzerland (bioresorbable collagen membrane). **Duration of follow-up:** After three months evaluation of bone graft (re-entry).
Outcomes	**Outcomes:** Complications, horizontal bone resorption, histologic evaluation. **Data used:** Complications, horizontal bone resorption (3 months after augmentation).
Notes	A sample size calculation was not performed.

Table 8 Study characteristics: Heberer et al. (2009)[34]

Risk of bias

Bias	Authors judgement	Support for judgement
Random sequence generation (selection bias)	Low	Reported in the article: 'The random coverage was based on a randomization list generated with nQuery Advisor 6.0 (Statistical Solutions, Saugus, MA, USA).'
Allocation concealment (selection bias)	Unclear	Comment: Unclear how the allocation was concealed. No reply from the authors.
Blinding of outcome assessment (detection bias)	High	The same surgeon who performed the initial operation took clinical measurements.
Incomplete outcome data (attrition bias)	Low	All patients completed the study and there were no losses to follow up. One patient was not histologically analyzed (without further explanation). There were no treatment withdrawals and no trial group changes. In one patient, a pronounced bone resorption was observed at a dehiscent site on both the membrane and non-membrane-covered areas.
Selective reporting (reporting bias)	High	Only median, minimum and maximum amounts of resorption were noted. No means and standard deviations were provided. Measurements were performed at 56 sites (mini-screws) totalling 112 measurements. No data were reported regarding the distribution of these measurements over the membrane and non-membrane covered grafts or the distribution between the occlusal and lateral screws. Only the complication dehiscence was described; other complications were not recorded. There was no measurement of bone gain, which would have made it more comparable to other studies.[29]
Other bias	Low	No other bias was detected.

Articles	**Meijndert et al. (2016)[35], Meijndert et al. (2005)[47], Meijndert et al. (2008)[48], Visser et al. (2011)[59]**
Methods	**Trial design:** Randomized, parallel-arm trial. **Location:** Groningen, the Netherlands. **Number of centres:** One (Department of Oral and Maxillofacial Surgery and Maxillo-facial Prosthetics, University Medical Centre Groningen). **Recruitment period:** 1999 and 2003. **Funding source:** Geistlich, Wolhusen, Switzerland.
Participants	**Inclusion criteria:** Need for an implant-supported crown to replace a maxillary lost tooth at the location of an incisor, cuspid or first bicuspid; single tooth diastema as a maximum; presence of a horizontal bone deficiency with an anatomy of local bone responding to a class 4 according to Misch & Judy (1987); sufficient occlusal and mesio-distal dimensions for insertion of one implant with a functional prosthetic restoration. **Exclusion criteria:** Presence of clinical active periodontal disease as expressed by the presence of periodontal pockets ≥ 4 mm, gingival bleeding class 2 of the modified bleeding index (BI), oedema, glazing and redness, presence of an acute inflammatory oral disease, smoking, diabetes, a history of pre-prosthetic or implant surgery at the same site as the planned augmentation and implantation, a history of radiotherapy in the head- and-neck region or current chemotherapy, inability (mental and/or physical) to maintain basic oral hygiene procedures. **Age at baseline:** Mean age = 33.3 (± 13.0). **Gender:** M44/F49. **Number randomized:** 93 patients. **Number evaluated:** 72.
Interventions	**Comparison:** Local ridge augmentation with and without a membrane or a bone substitute with a membrane. Group +M (n = 24) Autogenous bone with a membrane. Group –M (n = 29) Autogenous bone without a membrane. Group C (n = 19) Bone substitute with a membrane (data for this group are not used in this systematic review). **Timing of implant placement:** After 3 months. **Healing protocol:** Submerged (re-entry after 6 months). Implant: Straumann Plus implants, Institut Straumann AG, Waldenberg, Switzerland (solid sand-blasted, large-grit, acid-etched, rough surface screw-type implants). **Bone:** Monocortical bone block grafts + particles, symphysis area (autograft) Membrane: BioGide, Geistlich Biomaterials, Wolhusen, Switzerland (bioresorbable collagen membrane). **Duration of follow-up:** Meijndert et al. (2016)[35]: Ten years after loading. Meijndert et al. (2005)[47]: One year after loading. Meijndert et al. (2008)[48]: One year after loading. Visser et al. (2011)[59]: Five years after loading.
Outcomes	**Outcomes:** Meijndert et al. (2008)[48]: Implant failure, complications, marginal bone level changes on intraoral radiograph, plaque index, bleeding index, gingiva index, pocket probing depth, marginal gingiva level, crown aesthetic index; Meijndert et al. (2016)[35]: additionally presented patient satisfaction; Meijndert et al. (2005)[47]: additionally presented horizontal bone gain, histological and histomorphometric outcomes; Visser et al. (2011)[59]: additionally presented care and aftercare outcomes. **Data used:** Implant failure (ten year after loading) complications, marginal bone gain (3 months after augmentation), marginal bone level change, crown aesthetic index, patient satisfaction (10 years after loading).

Table 9 Study characteristics: Meijndert et al. (2016)[35]

Notes	A sample size calculation was not performed. Drop outs: There were two instances of non-attendance in the group with chin bone, two instances of implant loss and five instances of non-attendance in the group with chin bone and a membrane, and two instances of implant loss and 10 instances of non-attendance in the group with a bone substitute and a membrane. The bone substitute with membrane group is not used in this systematic review.

Risk of bias

Bias	Authors judgement	Support for judgement
Random sequence generation (selection bias)	Low	Reported in an earlier article: 'A computer software program randomly placed the participating patients into one of these groups, using a balancing procedure aimed at an equal distribution of patients over the treatment groups regarding variables that may interfere with the outcome of the study.'[48]
Allocation concealment (selection bias)	Low	Reply of author: 'Allocation was concealed. The computer program placed patients in one of the treatment groups. It was not possible for the surgeon to know the group before surgery. It was not possible to wait until the last step in surgery because one of the treatment groups required a total different grafting procedure.'
Blinding of outcome assessment (detection bias)	Low	Reported in the article: 'Assessment was done on colour slides of evaluation period T12 and T120 and was performed by the same prosthodontist who was trained with the index and blinded for the applied treatment procedure.' Reply of author: 'on colour slides, x-rays and at clinical measurement researchers were unaware of treatment group.'
Incomplete outcome data (attrition bias)	Low	Reported in the article: 'At the 1 month and 12 month follow-up, all patients were present for evaluation. At the 120 months' evaluation 17 patients were lost to follow-up due to moving to another part of the country or changing address without notice ... Drop-out was distributed over the treatment groups as followed: two non-attendance in the group with chin bone, two implant loss and five non-attendance in the group with chinbone and membrane, and two implant loss and 10 non-attendance in the group with a bone substitute and membrane.'
Selective reporting (reporting bias)	Low	Although the authors replied that the original protocol was no longer available, all possible outcome measurements seem to have been reported in four successive articles.[35, 47, 48, 59]
Other bias	Low	No other bias was detected.

Articles	**Park et al. (2008)[36] Park and Wang (2007)[50]**
Methods	**Trial design:** Randomized, parallel-arm trial. **Location:** Michigan, USA. **Number of centres:** One (University of Michigan, School of Dentistry). **Recruitment period:** 2004-2005. **Funding source:** Zimmer Dental Inc., Carlsbad, CA, USA.
Participants	**Inclusion criteria:** All patients required single tooth replacement(s) with a dental implant associated with insufficient horizontal bone width, all sites had been edentulous for longer than 6 months, all subjects completed an initial phase of periodontal therapy, if needed, and demonstrated good oral hygiene. **Exclusion criteria:** Any medical contraindications for implant surgery were excluded from the study; in addition, heavy smokers with more than 10 cigarettes per day were excluded. **Age at baseline:** Between 28 and 71 years old. **Gender:** M10/F13. **Number randomized:** 27 implants, 23 patients. **Number evaluated:** 26 (implants were used as the unit of analysis).
Interventions	**Comparison:** Sandwich bone augmentation technique (SBA) with and without two different membranes. Group +M (ADM) (n = 9) SBA technique with a membrane. Group +M (BME) (n = 9) SBA technique with a membrane. Group –M (n = 8) SBA technique without a membrane. **Timing of implant placement:** Simultaneous with augmentation. **Healing protocol:** Submerged (re-entry after 6 months). Implant: 3.7 or 4.1 mm diameter, 10 or 13 mm-long Zimmer Tapered Screw-Vent, Zimmer Dental Inc., Carlsbad, CA, USA (unknown coated, rough surface screw-type implants). **Bone:** Puros, Zimmer Dental Inc., Carlsbad, CA, USA (cancellous and cortical particulate allograft). **Membrane:** ADM (acellular dermal matrix), AlloDerm, BioHorizon, Birmingham, AL, USA (bioabsorbable human skin allograft) & BME, BioMend Extendt, Zimmer Dental Inc., Carlsbad, CA, USA (Bovine collagen membranes). **Duration of follow-up:** Evaluation of the bone graft and implant failure six months after implant placement (re-entry).

Table 10 Study characteristics: Park et al. (2008)[36]

Outcomes	**Outcomes:** Park et al. (2008)[36]: Horizontal bone gain, horizontal bone resorption, defect height reduction, implant failure, defect width reduction, defect area reduction, percentage bone fill; Park and Wang (2007)[50] additionally presented width of buccal keratinized gingiva. **Data used:** Complications, horizontal bone gain, horizontal graft resorption, defect height reduction (six months after augmentation).
Notes	No sample size calculation was performed. The men and woman combined do not add up to 26. One patient in the –M Group with was excluded due to an unforeseen health issue.

Risk of bias

Bias	Authors judgement	Support for judgement
Random sequence generation (selection bias)	Low	Reported in the article: 'implants … were randomized, by picking a code from a brown bag.'
Allocation concealment (selection bias)	Unclear	Reported in the article: 'picking a code from a brown bag.' Comment: Unclear if the allocation was concealed. No reply from the authors.
Blinding of outcome assessment (detection bias)	Low	Reported in the article: 'The examiner (K.W.L.) was blinded of the groups throughout the study.'
Incomplete outcome data (attrition bias)	Low	All but one patient completed the study. One patient in the –M group was excluded due to an unforeseen health issue, which is unlikely to have caused attrition bias. There were no other losses to follow up, no treatment withdrawals, no trial group changes and no major adverse events.
Selective reporting (reporting bias)	Low	The location of the study protocol was not given. Most of the possible outcome measurements seem to have been reported, although it is odd that implant failure was reported only at re-entry and not after one year of loading. No reply from the authors.
Other bias	High	Analyses were performed at the implant level.

Articles	**Torres et al. (2013)**[37]
Methods	**Trial design:** Randomized, parallel-arm trial and a randomized, split-mouth trial. **Location:** Madrid, Spain. **Number of centres:** One (private dental clinic 'Alcala'). **Recruitment period:** 2003-2010. **Funding source:** No corporate funding.
Participants	**Inclusion criteria:** Edentulous patients with insufficient bone height (< 7 mm) in the posterior maxilla for whom a sinus floor augmentation was planned and who underwent rehabilitation with a fixed implant-supported prosthesis. **Split-mouth study:** Bilateral upper posterior edentulous with insufficient bone height (< 4 mm ridge height) assessed by computed tomography (CT) that required a bilateral, two-stage approach. **Exclusion criteria:** Severe systemic disease (ASA III or IV), previous history of chronic sinusitis, pregnancy, diseases affecting bone (osteomalacia, Paget's disease, vitamin D deficiency, hyperthyroidism, cancer or alcoholism), specific medications (corticosteroids, anti-epileptic drugs, bisphosphonates), and perforation of the Schneiderian membrane. **Age at baseline:** Parallel arm: Mean age = 64.9 (between 39 and 81 years old), Split-mouth: not stated. **Gender:** Parallel-arm: M46/F58, Split-mouth: not stated. **Number randomized:** Parallel-arm: 106 patients, Split-mouth: 10 quadrants. **Number evaluated:** 104 patients, Split mouth: 10 quadrants.
Interventions	**Comparison:** Sinus augmentation with and without a membrane over the lateral window. **Parallel-arm:** Group +M (n = 51) Patients with a membrane. Group –M (n = 53) Patients without a membrane. **Split-mouth:** Group +M (n = 5) Sinus augmentations with a membrane. Group –M (n = 5) Sinus augmentations without a membrane. **Timing of implant placement:** Parallel-arm: When residual bone height was ≥4 mm, implants were placed simultaneously with sinus augmentation, otherwise, delayed placements were conducted 6 months after graft surgery. Split-mouth: all delayed. Healing protocol: Submerged (re-entry after 6 months). **Implant:** 4.0-5.0 mm diameter, 10.0-13.0 mm-long Osseotite, Biomet 3i Inc., Palm Beach, FL, USA (acid-etched, rough surface screw-type implants). **Bone:** Bio-Oss, Geistlich Pharmaceutical AG, Wolhusen Switzerland (deproteinized bovine bone mineral). **Membrane:** Bio-Gide, Geistlich Pharmaceutical AG, Wolhusen Switzerland (bioresorbable collagen membrane). **Duration of follow-up:** Evaluation of implants six months after loading.

Table 11 Study characteristics: Torres et al. (2013)[37]

Outcomes	**Outcomes:** Implant failure, bone volume on CT, height of augmented bone, histological and SEM observations. **Data used:** Implant failure (six months after loading) complications (six months after augmentation).
Notes	A sample size calculation was performed to obtain 80% power in this study. Data for the split-mouth study are not used in this systematic review.

Risk of bias

Bias	Authors judgement	Support for judgement
Random sequence generation (selection bias)	Low	Reported in the article: 'Patients or sites were allocated to intervention groups in a randomized sequence using a computer generated random number (GraphPad Software Inc., La Joya, CA, USA).'
Allocation concealment (selection bias)	Low	Reported in the article: 'All surgeries were performed by the same surgeon, who was blinded to group allocation until the last step of the surgery (closure of antrostomy defect).'
Blinding of outcome assessment (detection bias)	Low	Reported in the article: 'Evaluations were performed by the same prosthodontist who was blinded to group allocation throughout the restorative treatment.'
Incomplete outcome data (attrition bias)	Low	All but two patients completed the study; those two patients from the +M group moved to another town[10]. There were no trial group changes and no major adverse events. Partial loss of bone graft material into the subcutaneous space of the maxillary ridge occurred in four cases (–M), but no mucosal dehiscence was observed.
Selective reporting (reporting bias)	High	Full data for the complications were not provided. Patients with perforations of the sinus epithelium were apparently excluded from the study according to the materials and methods section. It is unclear whether patients with a perforation of the Schneiderian membrane were indeed excluded. To ensure measurement reliability, Albrektsson's success criteria were used. Data regarding pocket probing depth, marginal bone level change and mobility were not presented in the article.
Other bias	High	All perforations occurred in the membrane-covered groups, which might introduce a risk of bias.

Articles	**Urban et al. (2012)[38], Urban and Wenzel (2010)[57], Urban et al. (2012)[58]**
Methods	**Trial design:** Randomized, parallel-arm trial. **Location:** Aarhus, Denmark. **Number of centres:** One (Aarhus Dental School, University of Aarhus, Denmark). **Recruitment period:** 2005 to 2007. **Funding source:** No corporate funding.
Participants	**Inclusion criteria:** At least 18 years of age; ASA class 1 or 2; a molar ripe for extraction due to an advanced caries lesion, periodontally compromised tooth, root fracture, periapical pathology or a combination of these; adequate bone available at the implant site for placing a 10-mm-long implant without violating the mandibular canal or the sinus floor assessed using a panoramic radiograph. **Exclusion criteria:** Systemic diseases affecting bone turnover and pregnant or lactating women. **Age at baseline:** Mean age = 50 (between 23 and 70 years old). **Gender:** M48/F44. **Number randomized:** 92 patients. **Number evaluated:** 76.
Interventions	**Comparison:** Different bone augmentation techniques for immediately (sub-merged) placed implants. Group +M (n = 31) Bone substitute with a membrane. Group –M (n = 31) Bone substitute without a membrane. Group C (n = 31) No graft, membrane only (data for this group are not used in this systematic review). **Timing of implant placement:** Simultaneous with extraction and augmentation Healing protocol: Submerged (first re-entry after 4 months, second re-entry after 8 months). **Implant:** 5.0 mm diameter, 10.0-15.0 mm-long Brånemark System, MK III Groovy, NobelBiocare AB, Gothenburg, Sweden (rough, TiUnite surface screw-type implants). **Bone:** Ramus and zygomatic bone-chips (autogenous bone graft). **Membrane:** Ossix membrane, Biomet 3i, Palm Beach Gardens, FL, USA (resorbable collagen membrane). **Duration of follow-up:** Urban and Wenzel (2010)[57]: Immediate after implant placement. Urban et al. (2012)[58]: Eight months after immediate placement. Urban et al. (2012)[38]: One year after loading.

Table 12 Study characteristics: Urban et al. (2012)[38]

Outcomes	**Outcomes:** Implant failure, complications, radiographic marginal bone level changes, pocket probing depth, bleeding index, amount of defect around the implant, experienced discomfort. **Data used:** Implant failure, marginal bone level (one year after loading), complications (eight months after immediate placement).
Notes	Sample size was calculated to include 26 patients in each randomization group. The primary outcome was change in marginal bone level. In the +M group, only 24 patients reached the 12-month end-point.

Risk of bias

Bias	Authors judgement	Support for judgement
Random sequence generation (selection bias)	Low	'When the implant had been placed, a dental assistant who drew a lot from a non-see-through bag performed a random assignment.' [57]
Allocation concealment (selection bias)	Low	'When the implant had been placed … a dental assistant … non-see-through bag.' [57]
Blinding of outcome assessment (detection bias)	Low	'The radiographic recordings were blinded to regenerative technique as well as time period.'
Incomplete outcome data (attrition bias)	Low	There was one loss to follow up because the patient died before the 12-month follow-up; there were no treatment withdrawals and no trial group changes. Fifteen implants were determined failures at the time of surgical re-entry (4: bone –M, 3: solely M, 8: bone +M).
Selective reporting (reporting bias)	Low	All possible outcome measurements seem to have been reported in three successive articles,[38, 57, 58] however, the location of the study protocol was not reported in the article and there was no reply from the authors.
Other bias	Low	No other bias was detected.

Characteristics of the trial settings and investigators

Of the 10 included trials, two were performed in Australia,[31, 32] two in the USA,[33, 36] one in France,[29] one in Serbia,[30] one in Germany,[34] one in the Netherlands,[35] one in Spain,[37] and one in Denmark.[38] Eight trials had a parallel-group study design,[29-33, 35, 36, 38] one trial had a split-mouth design,[34] and one trial had both a parallel-group study design and a split-mouth study design (only the data for the parallel-group design study were used in this study).[37] Seven studies received funding from the industry.[29-31, 33-36] The authors of three studies declared no funding was received.[32, 37, 38] Seven studies were performed in a university clinic,[29, 30, 33-36, 38] and three studies were performed in private practices.[31, 32, 37]

Characteristics of participants

The mean age of participants ranged from 33 to 64 years old (minimum age 18; maximum age 81). Two trials did not report the mean age,[30, 36] and one trial did not report the age range.[31] The distribution of men and women was presented in all but one study.[32] Between 12 and 106 patients were selected for each study, with a median of 28 patients.

Inclusion and exclusion criteria of included studies

Main inclusion criteria:

- Missing single tooth in the anterior or premolar maxilla.[33, 35]
- Missing single tooth in the maxilla or mandibula.[36]
- Missing one-to four tooth span in the maxilla or mandible.[29]
- Edentulous in the posterior maxilla.[37]
- Completely edentulous maxilla.[34]
- Single or several non-adjacent teeth in the anterior maxillary and premolar region requiring extraction and replacement.[31, 32]
- Single tooth requiring extraction and replacement.[30]
- Single molar requiring extraction and replacement.[38]
- Augmentation required prior to implant placement and the availability of an intraoral bone donor site.[29, 35]
- Adequate bone available at the implant site for placing 10 mm-long implants.[33, 38]
- All sites were edentulous for longer than 6 months.[36]

- Remaining bone volume of less than 5 mm in height in both quadrants.[34]
- One to seven mm residual bone height.[37]
- Crestal residual ridge width of 4 mm and/or associated with an obvious buccal deficiency.[33]
- Extraction sockets with four intact walls.[30]

Main exclusion criteria:
- Presence of any chronic systemic disease.[30]
- All contraindications to intraoral surgery.[29, 31, 32, 36]
- Severe systemic disease (ASA III or IV).[37]
- Conditions that might interfere with bone metabolism (i.e., osteoporosis, Paget disease, head and neck radiation therapy, and others).[33, 35, 37, 38]
- Certain medications that could interfere with bone metabolism (i.e., corticosteroids, bisphosphonate, and others).[33, 37]
- Diabetes[35] or uncontrolled diabetes.[33]
- Pregnant or nursing mothers.[30, 33, 37, 38]
- Smoking[30, 31, 33, 35] or smoking more than 10 cigarettes per day.[36]
- A history of drug or alcohol abuse.[33]
- Clinically active or untreated periodontitis,[30, 32, 35] periodontal bone loss with a remaining alveolar height of less than 6 mm,[30] or attachment loss of 5 mm or more on the buccal aspect of the tooth.[32]
- Acute inflammatory oral diseases.[31, 32, 35]
- Poor plaque control or inability (mental and/or physical) to maintain basic oral hygiene procedures.[32, 33, 35]
- History of chronic sinusitis[37] or maxillary sinus involvement.[33]
- Severe parafunctional habits.[33]
- A history of preprosthetic surgery or implant surgery at the same site.[35]
- Perforation of the Schneiderian membrane.[37]
- Unknown exclusion criteria.[34]

Sample size

An a priori sample size was calculated in only three studies.[33, 37, 38] One study had not reached the calculated sample size at the time of evaluation.[38] All the other studies did not report sample size calculations.

Baseline comparability between treatment groups

No major baseline differences were described in six studies.[30-33, 35, 37] It was unclear whether major baseline differences existed in three studies.[29, 34, 36] One study had a significantly higher number of smokers in the treatment group compared to the number of smokers in the groups used in this study.[38] One study compared three groups, two of which were treated with different membranes and one of which was not treated with membranes.[36] The former groups were combined into one group for this review, resulting in the placement of 18 implants in the membrane group compared to only eight implants in the non-membrane group.

Characteristics of the interventions

Fu et al. (2014)[33] and Park et al. (2008)[36] evaluated the efficacy of a bioresorbable membrane in one-stage (sandwich) bone augmentation surgery. The use of membranes in two-stage bone augmentation procedures was evaluated in three studies.[29, 34, 35] Antoun et al. (2001)[29] evaluated the use of non-resorbable membranes in combination with onlay bone grafts. Heberer et al. (2009)[34] studied iliac onlay grafts covered with periosteum or a bioresorbable membrane in atrophied edentulous patients. Meijndert et al. (2016)[35] evaluated the effect of bioresorbable membranes on chin grafts. The effect of membranes in sinus augmentation surgery was studied by Torres et al. (2013)[37]. These authors evaluated the use of bioresorbable membranes in combination with a bone substitute in lateral sinus augmentation surgery. Brkovic et al. (2012)[30] evaluated ridge preservation using bone/collagen cones in extraction sockets, either covered by a resorbable membrane or left to heal spontaneously. Three studies evaluated the effect of membranes in bone augmentation procedures with immediate implant placement.[31, 32, 38] Chen et al. (2005)[31] studied the effects of bioresorbable membranes on immediate implant placements in which the gap between the implant and labial plate and the bony dehiscence was filled with autogenous bone. Healing of the implants took place using a submerged technique. Chen et al. (2007)[32] evaluated bioresorbable membranes in combination with a bone substitute; however, in this study, implants healed non-submerged. Urban et al. (2012)[38] used autogenous bone to fill the gap in the molar region and studied the effect of using bioresorbable membranes to cover the graft.

Implant systems

- Eight different implant systems were included in this review:
- Brånemark System (NobelBiocare, Gothenburg, Sweden): machine-turned surface screw-type implants.[29, 31]
- Brånemark System, MK III Groovy (NobelBiocare, Gothenburg, Sweden): rough TiUnite surface screw-type implants.[38]
- Camlog RootLine implants (Camlog Biotechnologies, Wimsheim, Germany): abrasive-blasted, acid-etched, rough surface screw-type implants.[34]
- ITI Implant System (Institut Straumann, Waldenberg, Switzerland): solid, sand-blasted, large-grit, acid-etched, rough surface screw-type implants.[32, 34]
- NobelReplace (NobelBiocare, Gothenburg, Sweden): rough TiUnite surface screw-type implants.[30]
- Osseotite (Biomet 3i, Florida, USA): acid-etched, rough surface screw-type implants.[37]
- Straumann Plus implants (Institut Straumann, Waldenberg, Switzerland): solid, sand-blasted, large-grit, acid-etched, rough surface screw-type implants.[35]
- Zimmer Tapered Screw-Vent (Zimmer Dental, California, USA): unknown coating (two possibilities) rough surface screw-type implants.[33, 36]

Bone used

- Autogenous bone was used in five trials: Onlay bone block graft harvested from the symphysis area,[29] combined or not with bone particles,[35] onlay bone block grafts harvested from the iliac crest,[34] locally harvested bone chips,[31] and bone chips harvested from the ramus and zygomatic areas.[38]
- Allografts were used in two trials:[33, 36] both trials used Puros (Zimmer Dental, California, USA), which contains cancellous and cortical bone particles.
- Xenografts were used in two trials:[32, 37] both used Bio-Oss (Geistlich Pharmaceutical, Wolhusen Switzerland), a deproteinised bovine bone mineral.
- Alloplastic materials were used in one trial:[30] RTR (Cone, Septodont, Saint-Maur-des-Fosses, France), a combined beta-tricalcium phosphate/collagen cone.

Membranes used

- Non-resorbable membranes were used in two studies.[29, 31] Both studies used a Goretex membrane (G-TAM membrane, WL Gore & Associates, Arizona, USA), a non-resorbable e-PTFE (expanded polytetrauoroethylene) membrane.

- Resorbable membranes were used in eight studies. BioGide (Geistlich Biomaterials, Wolhusen, Switzerland), a porcine derived collagen membrane, was used in five studies.[30, 32, 34, 35, 37] The other three studies used CopiOs pericardium membrane (Zimmer Dental, California, USA), a bovine pericardium membrane;[33] AlloDerm (BioHorizon, Alabama, USA), a human skin allograft; BioMend Extendt (Zimmer Dental, California, USA), a bovine derived collagen membrane[36] and the Ossix membrane (Biomet 3i, Florida, USA), a bovine collagen membrane.[38]

Characteristics of outcome measures (including the outcome data provided by the contacted authors)

- Implant failure.[31-33, 35-38]
- Complications.[29-38]
- Horizontal bone gain/resorption.[29-33, 36]
- Graft resorption.[29, 34, 36]
- Defect height reduction.[31-33, 36]
- Radiographic horizontal bone gain/resorption.[29, 33]
- Radiographic marginal bone changes:[33, 35, 38] Two studies compared marginal bone level with bone level before second-phase surgery.[33, 38] The third study compared marginal bone level with bone level 1 month after final crown placement.[35]
- Hard and soft tissue aesthetics:[32, 35] Meijndert et al. (2016)[35] used the Crown Aesthetic Index to evaluate aesthetics. Chen et al. (2007)[32] presented only the number of satisfactory/unsatisfactory post-restoration, operator-assessed aesthetic outcomes.
- Patient satisfaction:[32, 35] Meijndert et al. (2016)[35] used a questionnaire to evaluate aesthetics.[35] Chen et al. (2007)[32] presented only the number of satisfactory/unsatisfactory post-restoration, patient-assessed aesthetic outcomes.

Duration of follow-up

Implant assessment:

- Six months after loading.[33, 37]
- One year after loading.[38]
- Two years after loading.[31]
- Three years after loading.[32]
- Ten years after loading.[35]

Graft assessment:

- Three months after the grafting procedure.[34, 35]
- Six months after the grafting procedure.[29, 31-33, 36]
- Nine months after the grafting procedure.[30]

Calculations performed on data

The Cochrane formulae for combining groups (section 7.7.3 of the Cochrane Handbook) were used to combine the means and standard deviations of different conditions and groups. In three studies, separately scored mesial and distal radiographic marginal bone levels were combined.[33, 35, 38] In one trial, two membrane groups were combined,[36] and in one trial, different measurements of different distances from the crest were merged.[33] Changes of the alveolar ridge dimension were calculated using formulae for subtracting means and standard deviations in two studies.[30, 38]

Risk of bias in included studies

Individual explanations regarding the noted risks of bias are included in the tables of study characteristics (Tables 3-12).

Allocation

Sequence generation

Six studies reported an adequate sequence generation,[33-38] and two authors provided an adequate sequence generation in their replies.[29, 31] A high risk of selection bias was found in the Chen et al. (2007)[32] study because the non-membrane group was used only if no bony dehiscence was present after tooth extraction. One study was judged to have an unclear risk of bias because the randomisation process was insufficiently described and there was no reply from the author.[30]

Allocation concealment

Allocation concealment was adequately performed and reported in three studies.[33, 37, 38] The replies of authors sufficiently explained allocation concealment for four studies; consequently, these studies were considered to be at low risk of bias.[29, 31, 32, 35] In three studies, allocation concealment was not described, and there

was no reply from the authors;[30, 34, 36] therefore, unclear risk of bias was noted. Overall, six of the ten studies were judged to have a low risk of selection bias,[29, 31, 33, 35, 37, 38] one has a high risk of selection bias[32] and three have an unclear risk of selection bias.[30, 34, 36]

Blinding

Blinding of operators and trial participants was not possible in the included trials, which introduces the potential risk of performance bias in all studies. However, blinding of outcome assessment (detection bias) was possible and adequately performed in four studies.[35-38] It was not performed in five studies[29, 31-34] and was unclear in one study.[30]

Incomplete outcome data

All studies were judged to be at low risk of attrition bias, as dropouts were well described and unlikely to be related to treatment. One study found a large number of no-shows in a subgroup; this finding was not analysed in this review and the study was therefore noted as being at low risk of attrition bias.[35]

Selective reporting

Seven studies were judged to be at low risk of reporting bias.[29-31, 33, 35, 36, 38] The other three studies were judged to be at high risk of reporting bias because multiple outcome measurements were not provided per treatment group[32] or were not sufficiently reported[34, 37] or because not all complications were reported.[37]

Other potential sources of bias

Additional sources of bias were identified in two studies.[36, 37] In one study, perforation of the sinus membrane was reported only for the membrane-covered sites.[37] In the other study, the unit of analysis was the implant and not the patient, and some patients received multiple implants.[36] The remaining studies were not at risk of additional bias.

The overall risk of bias is displayed in Figure 2 and summarised in Figure 3. Overall, according to this study's evaluation, two trials are at low risk of bias,[33, 38] seven are at high risk of bias,[29, 31-34, 36, 37] and one study has an unclear risk of bias.[30]

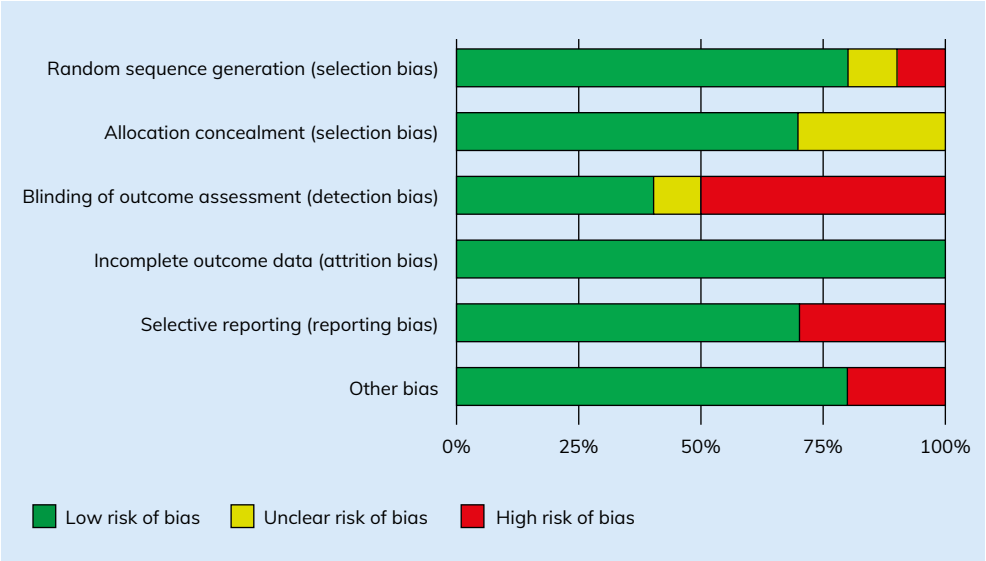

Figure 2 Risk of bias graph.

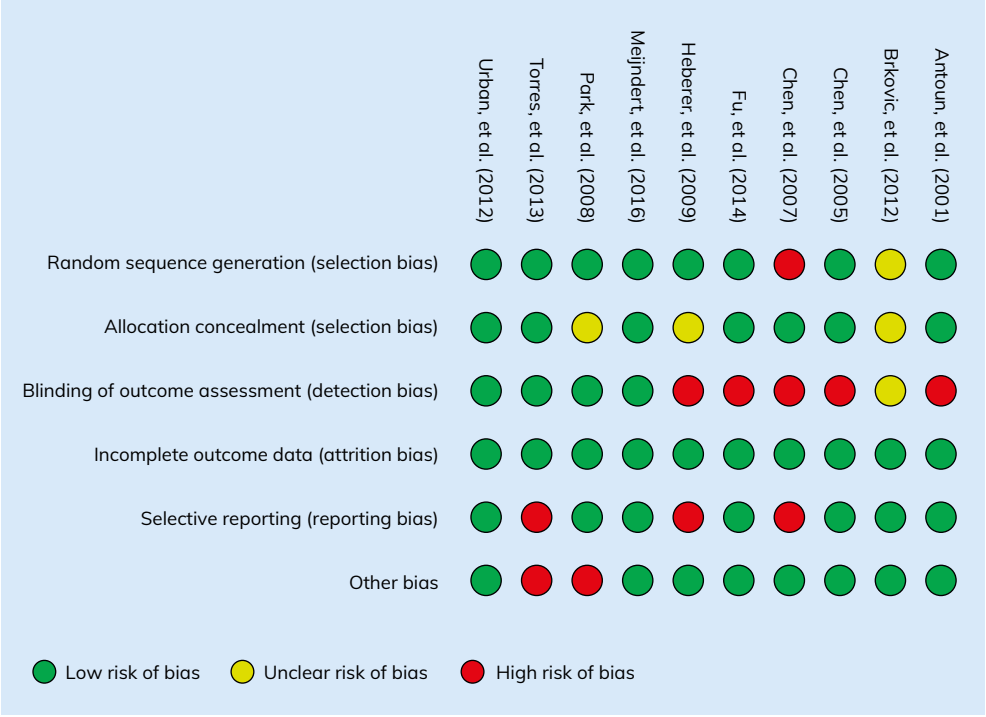

Table 3 Risk of bias summary.

Effects of intervention

Ten studies presented outcome data for 349 patients who had bone augmentation procedures with and without the use of membranes. The results for all outcomes are summarised in Tables 13 to 17. Only the results for more than one trial are shown in the forest plots (Figures 4 to 12).

1. One-stage ridge augmentation (Table 13)

Two trials (n = 47), both at high risk of bias,[33, 36] compared the effects of membranes on the outcomes of one-stage ridge augmentation. The meta-analysis of complications, horizontal bone gain and defect height reduction, at 6 months after augmentation, is shown in Figures 4, 5 and 6. There was no difference in the complication rates of the two treatment groups (OR: 1.38, 95% CI: 0.38 to 5.01, p = 0.62; two trials). Statistically significant differences were found for horizontal bone gain and defect height reduction that favoured the use of membranes. The mean difference for horizontal bone gain was 0.84 mm (95% CI: 0.46 to 1.21, p < 0.00001; two trials), with substantial heterogeneity between the studies (Chi^2 p = 0.05, I^2 = 74%). The difference in defect height reduction was 18.36% (95% CI: 10.23 to 26.50, p < 0.00001; two trials), with no significant heterogeneity (Chi^2 p = 0.24, I^2 = 27%). Fu et al. (2014)[33] additionally studied implant failure (no failures in both groups) and marginal bone level change (MD: 0.40 mm, 95% CI: -0.06 to 1.30, p = 0.26) 6 months after loading and radiographic horizontal bone gain (MD: 0.62 mm, 95% CI: -0.06 to 1.30, p = 0.07) 6 months after augmentation; there were no significant differences. Park et al. (2008)[36] showed significantly more horizontal graft resorption in the group without membranes, with a mean difference of 0.63 mm (95% CI: 1.05 to 0.21, p = 0.004).

2. Two-stage ridge augmentation (Table 14)

Three trials (n = 81) compared the use of membranes in two-stage ridge augmentation.[29, 34, 35] Two studies were at high risk of bias,[29, 34] and one study was at low risk of bias.[35] The meta-analysis of complications and horizontal bone gain, at 3[34, 35] to 6[29] months after augmentation, is shown in Figures 7 and 8. There was no difference in the complication rates of the two treatment groups (OR: 1.95, 95% CI: 0.22 to 17.60, p = 0.55; three trials) and no evidence of heterogeneity (Chi^2; p = 0.48, I^2 = 0%). There was no evidence of a significant difference in

Study	Outcome	Follow-up	Data	Effect estimate (95% CI) p-value
Fu et al. (2014)[33] Parallel group	Implant failure	Six months after loading	0/13 +M 0/13 –M	N/A
	Complications	Six months after augmentation	3/13 +M 3/13 –M	OR 1.00 (0.16, 6.20) p = 1.00
	Horizontal bone gain	Six months after augmentation	N = 13, 1.84 mm (SD 1.34) +M N = 13, 0.30 mm (SD 0.59) –M	MD 1.54 mm (0.74, 2.34) p = 0.0001
	Defect height reduction	Six months after augmentation	N = 13, 81.36 % (SD 6.64) +M N = 13, 60.82 % (SD 14.98) –M	MD 20.54 % (11.63, 29.45) p < 0.00001
	Radiographic horizontal bone gain	Six months after augmentation	N = 13, 1.87 mm (SD 0.97) +M N = 13, 1.25 mm (SD 0.78) –M	MD 0.62 mm (-0.06, 1.30) p = 0.07
	Marginal bone level change	Six months after loading	N = 13, -1.17 mm (SD 0.75) +M N = 13, -1.57 mm (SD 1.03) –M	MD 0.40 mm (-0.29, 1.09) p = 0.26
Park et al. (2008)[36] Parallel group	Complications	Six months after augmentation	7/18 +M 2/8 –M	OR 1.91 mm (0.30, 12.26) p = 0.50
	Horizontal bone gain	Six months after augmentation	N = 18, 1.66 mm (SD 0.59) +M N = 8, 1.02 mm (SD 0.47) –M	MD 0.64 mm (0.22, 1.06) p = 0.003
	Horizontal graft resorption	Six months after augmentation	N = 18, 1.35 mm (SD 0.59) +M N = 8, 1.98 mm (SD 0.47) –M	MD -0.63 mm (-1.05, -0.21) p = 0.004
	Defect height reduction	Six months after augmentation	N = 18, 71.02 mm (SD 24.09) +M N = 8, 63.56 mm (SD 23.88) –M	7.46 mm (-12.48, 27.40) p = 0.46

Table 13 Summary of study outcomes: one-stage ridge augmentation.

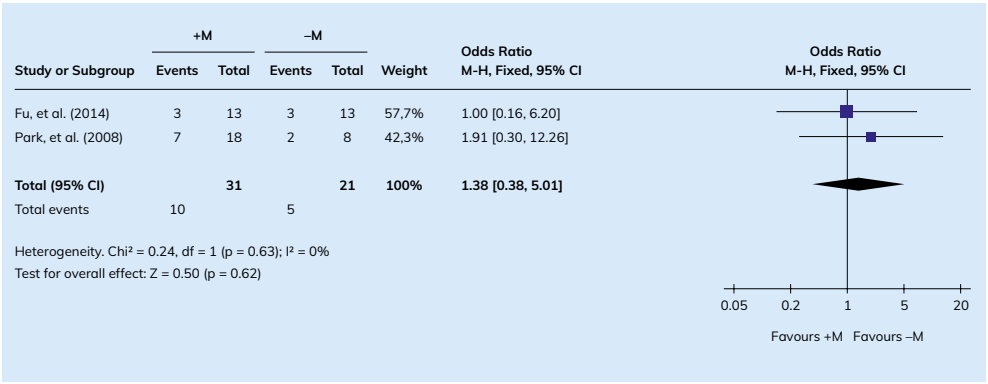

Figure 4 One-stage ridge augmentation: complications at 6 months after augmentation.

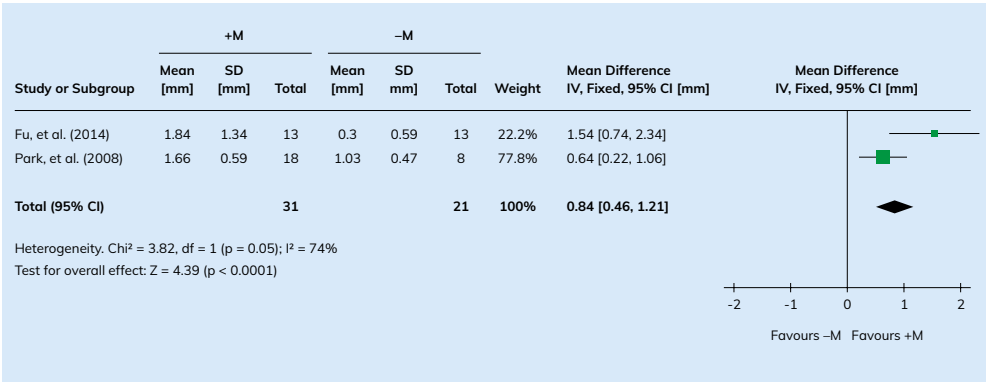

Figure 5 One-stage ridge augmentation: horizontal bone gain at 6 months after augmentation

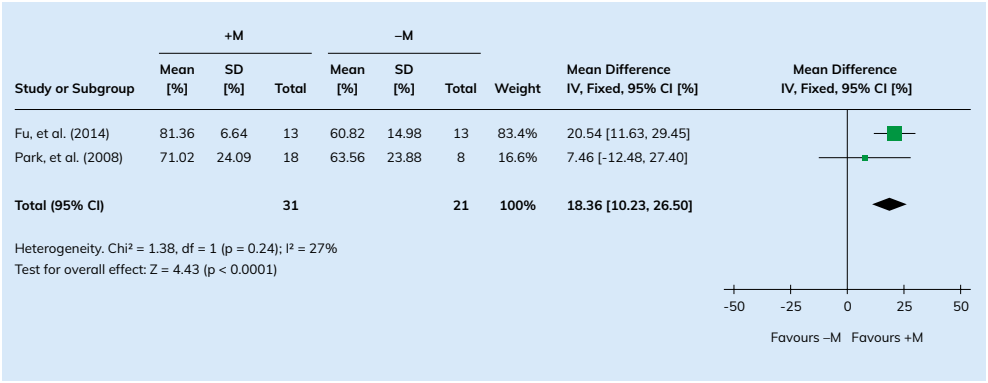

Figure 6 One-stage ridge augmentation: defect height reduction at 6 months after augmentation

Study	Outcome	Follow-up	Data	Effect estimate (95% CI) p-value
Antoun et al. (2001)[29] Parallel group	Complications	Six months after augmentation	1/5 +M 0/7 –M	OR 5.00 (0.17, 150.92) p = 0.35
	Horizontal bone gain	Six months after augmentation	N = 5, 3.7 mm (SD 1.76) +M N = 7, 2.9 mm (SD 1.36) –M	MD 0.8 mm (-1.0, 2.6) p = 0.39
	Graft resorption	Six months after augmentation	N = 5, 0.3 mm (SD 0.36) +M N = 7, 2.3 mm (SD 0.97) –M	MD -2.0 mm (-2.8, -1.2) p < 0.00001
	Radiographic horizontal bone gain	Six months after augmentation	N = 4, 4.2 mm (SD 1.6) +M N = 7, 2.5 mm (SD 1.1) –M	MD 1.7 mm (0, 3.4) p = 0.05
Heberer et al. (2009)[34] Split-mouth	Complications	Three months after augmentation	N = 14, 1 complication on both sides in 1 patient	OR 1.00 (0.06, 17.75) p = 1.00
	Graft resorption	Three months after augmentation	N = 14 Median 1.0 mm (0.3-3.4) +M Median 1.0 mm (0.4-2.1) –M	N/A
Meijndert et al. (2016)[35] Parallel group	Implant failure	Ten year after loading	2/26 +M 0/29 –M	OR 6.01 (0.28, 131.42) p = 0.25
	Complications	Three months after augmentation	0/31 +M 0/31 –M	N/A
	Horizontal bone gain	Three months after augmentation	N = 5, 3.40 mm (SD 1.14) +M N = 5, 3.00 mm (SD 1.00) –M	MD 0.40 mm (-0.93, 1.73) p = 0.56
	Marginal bone level change	Ten year after loading	N = 24, 0.49 mm (SD 1.14) +M N = 29, 0.22 mm (SD 1.07) –M	MD 0.27 mm (-0.33, 0.87) p = 0.38
	Implant Crown Aesthetic Index, mean total penalty score	Ten year after loading	N = 24, 6.5 mm (2-17) +M N = 29, 4.9 mm (1-14) –M	N/A
	Patient satisfaction questionnaire	Ten year after loading	N = 24, 8.6 mm (SD 1.3) +M N = 29, 8.6 mm (SD 1.2) –M	MD 0 mm (-0.68, 0.68) p = 1.00

Table 14 Summary of study outcomes: two-stage ridge augmentation.

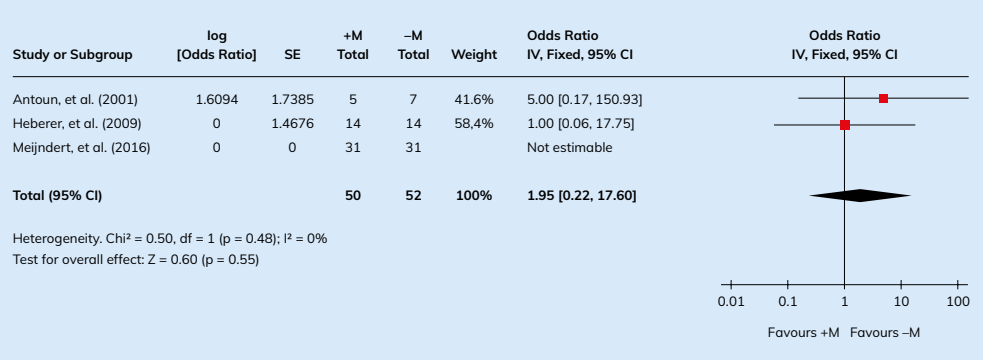

Figure 7 Two-stage ridge augmentation: complications at 3-6 months after augmentation.

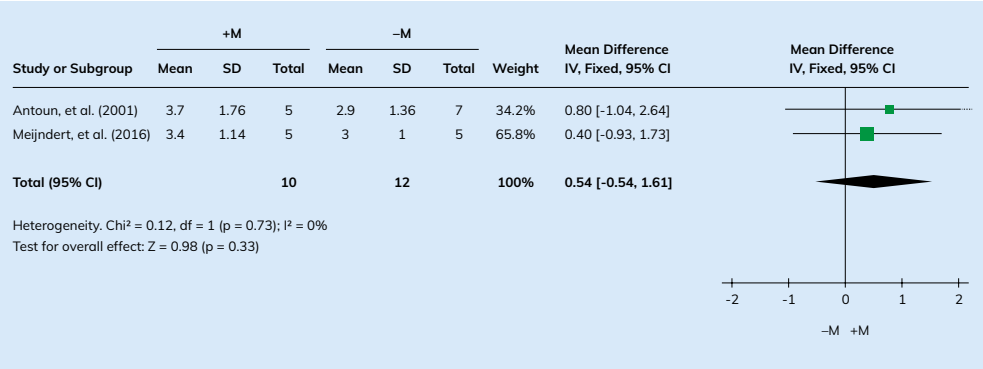

Figure 8 Two-stage ridge augmentation: horizontal bone gain at 3-6 months after augmentation

horizontal bone gain in one of the treatment groups. The mean difference was 0.54 mm (95% CI: -0.54 to 1.61, p = 0.33; two trials), with no evidence of heterogeneity (Chi^2; p = 0.73, I^2 = 0%). Antoun et al. (2001)[29] additionally reported on graft resorption (MD: -2.00 mm, 95% CI: -2.78 to -1.22, p < 0.001) and radiographic horizontal bone gain (MD: 1.70 mm, 95% CI: -0.01 to 3.41, p = 0.05), at 6 months after augmentation. Only graft resorption was significantly higher in the groups without membranes. Heberer et al. (2009)[34] described an equal amount of resorption in both groups (median 1.0 mm, range [0.3 to 3.4] +M; median 1.0 mm, range [0.4 to 2.1] –M) 3 months after augmentation. Meijndert et al. (2016)[35] reported on implant failures (OR: 6.01, 95% CI: 0.28 to 131.42, p = 0.25), marginal bone level changes (MD: 0.27 mm, 95% CI: -0.33 to 0.87, p = 0.38), implant crown

aesthetics (Mean: 6.5, range [2 to 17] +M; mean: 4.9, range: [1 to 14] –M) and patient satisfaction (MD: 0, 95% CI: -0.68 to 0.68, p = 1.00). None of these parameters were significantly different between the treatment groups, after 10 years of loading.

3. Sinus augmentation surgery (Table 15)

Torres et al. (2013)[37] compared the effect of membranes in sinus augmentation surgery (n = 104). The study had a high risk of bias. There was no significant difference between implant failure (OR: 2.63, 95% CI: 0.75 to 9.14, p = 0.13) 6 months after loading. In four patients partial loss of the graft material into the submucosal space occurred in the uncovered group.

Study	Outcome	Follow-up	Data	Effect estimate (95% CI) p-value
Torres et al. (2013)[37] Parallel group	Implant failure	Six months after loading	9/51 +M 4/53 –M	OR 2.63 (0.75, 9.14) p = 0.13

Table 15 Summary of study outcomes: sinus augmentation surgery.

4. Ridge preservation (Table 16)

Brkovic et al. (2012)[30] compared ridge preservation with and without membranes (n = 20); the study had an unclear risk of bias. No complications were observed, and no significant differences in horizontal bone resorption were found (MD: -0.43 mm, 95% CI: -3.09 to 2.23, p = 0.75) at 9 months after ridge preservation.

Study	Outcome	Follow-up	Data	Effect estimate (95% CI) p-value
Brkovic et al. (2012)[30] Parallel group	Complications	Nine months after ridge preservation	0/9 +M 0/11 –M	N/A
	Horizontal bone resorption	Nine months after ridge preservation	N = 9, 0.86 mm (SD 2.71) +M N = 11, 1.29 mm (SD 3.37) –M	MD -0.43 mm (-3.09, 2.23) p = 0.75

Table 16 Summary of study outcomes: ridge preservation.

5. Immediate implant placement (Table 17)

Three trials (n = 98), two at high risk of bias[31, 32] and one at low risk of bias,[38] evaluated the effects of membranes in bone augmentation procedures with immediate implant placement. The meta-analysis of implant failure at 1 to 3 years after loading is shown in Figure 9. There was insufficient evidence to determine whether there is a difference between the use or not, of a membrane on implant failure. The Peto odds ratio for implant failure was 1.69 (95% CI: 0.52 to 5.47, p = 0.38; three trials), with substantial heterogeneity between the treatment groups (Chi^2; p = 0.05, I^2 = 73%).

In terms of the complications at 6 to 8 months after immediate placement, the meta-analysis (Figure 10) found some evidence of a difference in favour of the group without a membrane, where the OR was 2.52 (95% CI: 1.07 to 5.93, p = 0.03; three trials), with no evidence of heterogeneity (Chi^2; p = 0.52, I^2 = 0%). The meta-analysis for horizontal bone resorption and defect height reduction at 6 to 8 months after immediate placement is displayed in Figures 11 and 12. There was insufficient evidence to determine a difference in horizontal bone resorption between the treatment groups, where the MD was 0.48 mm (95% CI: -0.00 to 0.97, p = 0.05; two trials), and there was no heterogeneity among the studies (Chi^2; p = 0.32, I^2 = 1%). The meta-analysis found evidence of more defect height reduction in the membrane-covered group: the MD was 6.25% (95% CI: 1.67 to 10.82, p = 0.007; two trials) with substantial heterogeneity between treatment groups (Chi^2; p = 0.03, I^2 = 79%). Chen et al. (2007)[32] found no significant differences for operator-assessed aesthetics (OR: 2.67, 95% CI 0.36 to 19.71, p = 0.34) and patient satisfaction (OR: 1.00, 95% IC 0.05 to 18.75, p = 1.00) scored after crown placement. Urban et al. (2012)[38] additionally investigated marginal bone level changes at 01 year after loading and found no difference between the treatment groups (MD -0.25 mm, 95% CI -0.86 to 0.36, p = 0.36).

Study	Outcome	Follow-up	Data	Effect estimate (95% CI) p-value
Chen et al. (2005)[31] Parallel group	Implant failure	Two year after implant loading	0/13 +M 2/14 –M	OR 0.19 (0.01, 4.25) p = 0.29
	Complications	Six months after immediate placement	2/13 +M 2/14 –M	OR 1.09 (0.14, 8.75) p = 0.94
	Horizontal bone resorption	Six months after immediate placement	N = 13, 1.55 mm (SD 0.69) +M N = 13, 0.85 mm (SD 0.97) –M	MD 0.70 mm (0.05, 1.35) p = 0.03
	Defect height reduction	Six months after immediate placement	N = 13, 83.1 % (SD 6.6) +M N = 13, 75.3 % (SD 5.8) –M	MD 7.80 % (3.02, 12.58) p = 0.001
Chen et al. (2007)[32] Parallel group	Implant failure	Three years after implant loading	0/5 +M 0/6 –M	N/A
	Complications	Six months after immediate placement	2/10 +M 0/10 –M	OR 6.18 (0.26, 146.78) p = 0.26
	Horizontal bone resorption	Six months after immediate placement	N = 10, 0.6 mm (SD 0.7) +M N = 10, 0.4 mm (SD 0.5) –M	MD 0.2 mm (-0.5, 0.9) p = 0.59
	Defect height reduction	Six months after immediate placement	N = 10, 70.5 % (SD 17.4) +M N = 10, 81.2 % (SD 5.0) –M	MD -10.7 % (-26.5, 5.1) p = 0.18
	Poor operator-assessed aesthetic outcome	Immediate after loading	4/10 +M 2/10 –M	OR 2.67 (0.36, 19.71) p = 0.34
	Poor patient satisfaction	Immediate after loading	1/10 +M 1/10 –M	OR 1.00 (0.05, 18.57) p = 1.00
Urban et al. (2012)[38] Parallel group	Implant failure	One year after loading	8/31 +M 4/30 –M	OR 3.13 (0.74, 13.20) p = 0.12
	Complication	Eight months after immediate placement	19/31 +M 10/30 –M	OR 3.17 (1.11, 9.03) p = 0.03
	Marginal bone level change	One year after loading	N = 23, 0.35 mm (SD 1.12) +M N = 26, 0.6 mm (SD 1.06) –M	MD -0.25 mm (-0.86, 0.36) p = 0.42

Table 17 Summary of study outcomes: immediate implant placement.

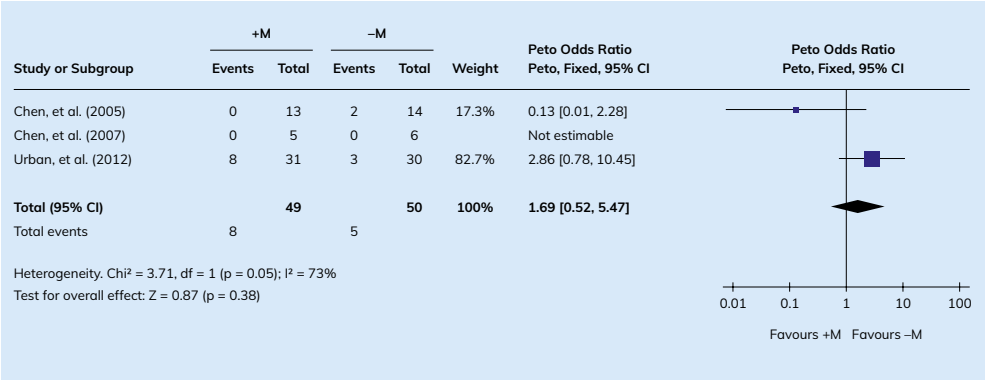

Figure 9 Immediate implant placement: implant failures at 1-3 years after loading.

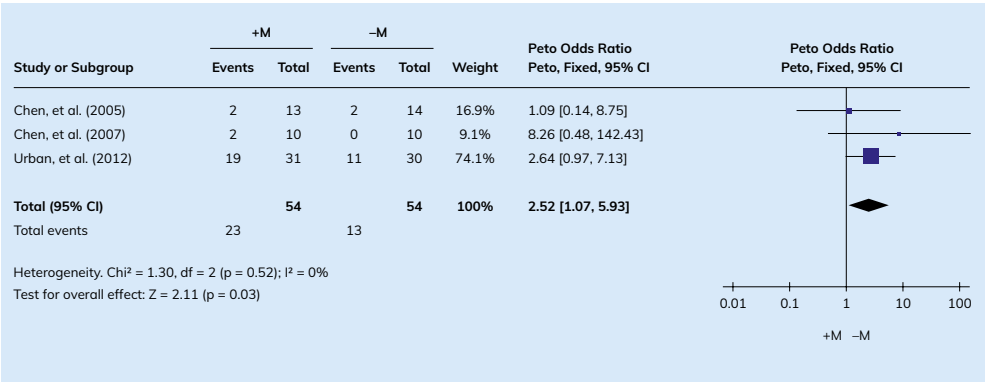

Figure 10 Immediate implant placement: complications 6-8 months after immediate placement.

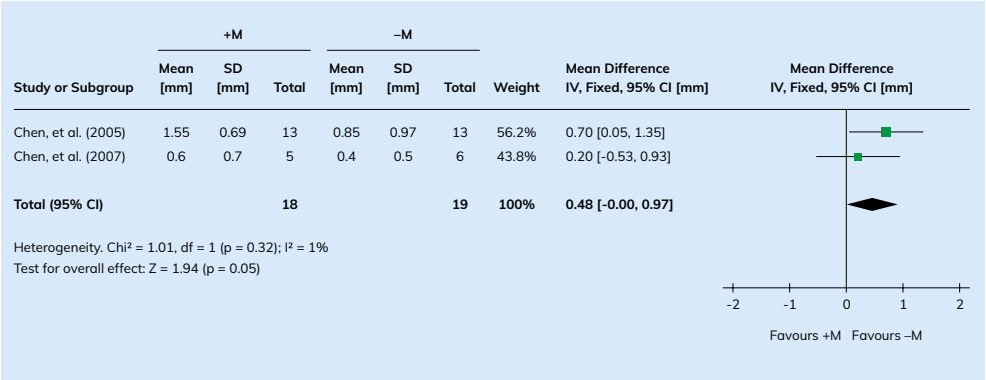

Figure 11 Immediate implant placement: horizontal bone resorption at 6-8 months after immediate placement.

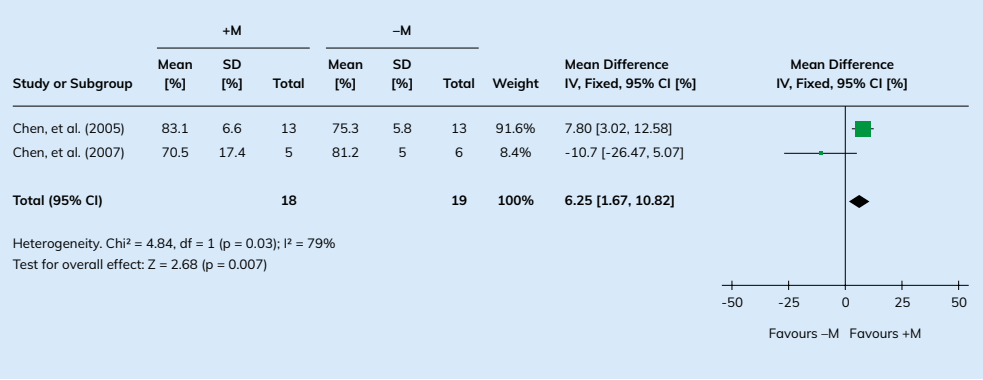

Figure 12 Immediate implant placement: defect height reduction (%) at 6-8 months after immediate placement.

DISCUSSION

Summary of evidence

The objective of this systematic review was to evaluate the effects of using membranes in different bone augmentation procedures. Investigated outcome parameters included implant failure, complications and changes in the dimensions of the ridge/graft and clinical parameters such as radiographic marginal bone changes, aesthetics and patient satisfaction. In total, 10 trials were included in the review and were divided into five groups based on the type of augmentation procedure.

1. One-stage ridge augmentation (two trials; n = 52): There was insufficient evidence to determine a difference in implant failure or complication rate (OR: 1.38, 95% CI: 0.38 to 5.01, p = 0.62; two trials). However, there was some evidence of more horizontal bone gain (MD: 0.84 mm, 95% CI: 0.46 to 1.21, p < 0.00001; two trials), defect height reduction (MD: 18.36%, 95% CI: 10.23 to 26.50, p < 0.00001; two trials), and prevention of graft resorption (p = 0.004; one trial n = 26) in favour of the membrane group, although substantial heterogeneity was found between the studies (Chi^2 p = 0.05, I^2 = 74%) for horizontal bone gain.

2. Two-stage ridge augmentation (three trials; n = 81): There was insufficient evidence to determine a difference in implant failure, complication rate (OR: 1.95, 95% CI: 0.22 to 17.60, p = 0.55; three trials), horizontal bone gain (MD: 0.54 mm, 95% CI: -0.54 to 1.61, p = 0.33; two trials), aesthetics or patient satisfaction between the treatment groups. One study (n = 12) suggested that membranes prevent graft resorption (p < 0.001), while another (n = 14) found no difference.
3. Sinus augmentation (one trial, n = 104): There is insufficient evidence to determine whether there is a difference in implant failure.
4. Ridge preservation (one trial, n = 20): There is insufficient evidence to determine whether there is a difference in complication rate or horizontal bone resorption.
5. Bone augmentation at immediate implant placement (three trials, n = 98). There is insufficient evidence to determine whether there is a difference in implant failure (Peto OR: 1.69, 95% CI: 0.52 to 5.47, p = 0.38; three trials); however, there was some evidence that more complications occurred when using a membrane (OR: 2.75, 95% CI: 1.04 to 7.32, p = 0.04; three trials). There was insufficient evidence to determine whether there is a difference in horizontal bone resorption between treatment groups, but there was some evidence of an increase in defect height reduction in favour of the membrane group (MD: 6.25%, 95% CI: 1.67 to 10.82, p = 0.007; two trials), although with substantial heterogeneity between treatment groups (Chi^2; p = 0.03, I^2 = 79%).

Overall completeness and applicability of evidence

This review included ten randomised controlled trials on the effects of using membranes in bone augmentation procedures. Due to this small number and the limited amount of patients, there is still insufficient evidence to support definitive conclusions.

Most of the included trials reported on only implant failure, complications and measurements regarding the ridge or graft. Only three studies compared more clinical parameters such as peri-implant marginal bone levels[33, 35, 38] and only two studies reported aesthetic outcomes and patient satisfaction.[32, 35] Although there is lack of consensus regarding a set of universally accepted success cri-

teria, trials of dental implants should make an effort to describe parameters of clinical success. The original criteria for implant success suggested by Albrektsson et al. (1986)[61] can be used in addition to an aesthetic score such as the PES/WES[62] and patient satisfaction.

Despite the positive effect of membranes on bone gain and resorption in different studies of one- and two-stage ridge augmentation procedures,[29, 33, 36] the advantages of this additional bone in terms of implant failure and the clinical parameters mentioned above is still unclear. The study by Meijndert et al. (2016)[35] is the only study with a long-term follow-up of ten years that evaluates clinical and radiographic parameters, implant aesthetics, and implant success. None of these parameters was significantly different, suggesting that membranes might not be necessary for long-term success.

Although Chen et al. (2005)[31] found significantly more defect height reduction in immediate implant placement in favour of membranes ($p < 0.001$), he also found significantly more horizontal bone resorption ($p = 0.03$) in this group. According to the author, this specific membrane caused a mild inflammatory response that was observed at second-phase surgery, which might be the cause of the horizontal bone resorption.
Generalisations regarding the results found by this systematic review should be made with extreme caution. All the studies involved carefully selected and relatively healthy patients. The studies were performed in universities or specialist clinical settings by top experts in the field of implantology, which might explain the low failure rates and clinical successes of both treatment groups.

Quality of the evidence

Risk of bias was high to unclear in most of the studies. Sample sizes were relatively small and only three studies reported a sample size calculation.[33, 37, 38]

Potential biases in the review process

There were no events for several of the outcomes; therefore, Peto odds ratios were calculated for these outcomes for the purposes of meta-analysis. This method may lead to conservative estimates. One split-mouth study was analysed

as a parallel-arm study by using a generic inverse variance in RevMan to prevent potential bias.[34] The data of one study with a parallel-arm design and the implant as the unit of analysis were used as a patient-based analysis for ease of analysis and interpretation.[36] Because a limited amount of studies selected, fixed-effect models were used for the meta-analyses; this might result in unjustified significant results, as the confidence intervals are smaller. All analyses were therefore also performed as random effect analyses, but no significant consequences to the results were found.

Seven studies received funding from manufactures,[29-31, 33-36] which might have introduced bias to the selected studies.

Agreements and disagreements with other studies or reviews

Several systematic reviews have been published evaluating different augmentation procedures. These reviews evaluated membranes primarily as a secondary parameter. The reviews included studies with inferior designs and direct comparisons should be interpreted with great care. A systematic review of lateral ridge augmentation by Sanz-Sanchez et al. (2015)[63] concluded that the use of barrier membranes was associated with superior outcomes. Merli et al. (2016)[64] focused on one-stage ridge augmentation and reported that there was insufficient evidence to find that it is a superior treatment. Gielkens and Stegenga (2011)[65] described the use of membranes in a two-stage ridge augmentation procedure and concluded that there was insufficient evidence to suggest that barrier membranes prevent bone resorption. There have been multiple reviews performed regarding sinus augmentation procedures, including Wallace and Froum (2003)[66] and Pjetursson et al. (2008)[67] These authors favoured placing a membrane over the lateral window. However, these reviews also included non-randomised controlled trials.

A more recent Cochrane review by Esposito et al. (2014)[10] stated that no conclusion can be drawn regarding a superior treatment. Systematic reviews regarding ridge preservation and immediate implant placement have not drawn any conclusions regarding membrane use and therefore cannot be compared to the current review.

CONCLUSIONS

Implications for practice

There is insufficient evidence regarding the effects of membranes on bone augmentation procedures to support definitive conclusions. Only 10 studies were included, which had limited sample sizes and short follow-up periods, and the majority were at a high risk of bias. However, no difference in implant failure was found, and the possible clinical value is still unknown, as long-term clinical parameters such as peri-implant marginal bone loss, aesthetic results and patient satisfaction have been insufficiently studied.

Implications for research

Additional well-designed, large, multi-centre randomised controlled trials are needed to support the conclusions of the current literature. Such trials should be correctly designed and conducted according to the Consolidated Standards of Reporting Trials (CONSORT) guidelines.[68] It is suggested that those trials focus on long-term clinical success parameters, aesthetic results and patient satisfaction to evaluate the possible benefits of the additional bone acquired by using membranes.

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CHAPTER 3

The effect of resorbable membranes on one-stage ridge augmentation in anterior single-tooth replacement: A randomized, controlled clinical trial

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ABSTRACT

Aim To evaluate the effect of resorbable membranes on one-stage ridge augmentation procedures in small (2-4 mm) buccal bony dehiscences in anterior maxillary single-tooth replacement.

Materials and Methods Patients with a buccal bony dehiscence after implant placement in the esthetic zone were randomly allocated to one-stage ridge augmentation with (M+) or without a membrane (M–). Second-phase surgery was performed after 8 weeks, and follow-up was performed 1, 6, and ≥ 12 months after loading. Outcomes included implant survival and success, complications, clinical and radiographic parameters, esthetic results and patient satisfaction.

Results Fifty-two patients were randomized to one-stage ridge augmentation with (n = 25) or without use of a membrane (n = 27). No significant differences in implant survival and success have been observed. The risk of having a small mucosal dehiscence was more than six times higher in the M+ group than in the M– group (RR 6.24, 95% CI 0.81-48.21). At the last follow-up, the bleeding index (BI) was marginally higher in the M+ group (14/9/2/0) compared to the M– group (24/2/0/0) (U = 205, Z = -2.97, p = 0.003, r = 0.42). The median change in marginal bone level was statistically lower in the M+ group (0.06 mm) than the M– group (0.60 mm) at last follow-up (U = 120, Z = -2.73, p = 0.006, r = 0.42). Total pink esthetic index (PES) and white esthetic score (WES) and combined PES/WES were not significantly different between treatment groups at more than 12 months after loading. Only the subcategory root convexity/soft tissue color scored significantly lower in the M+ group (1.5) compared to the M– group (2.0) at the last follow-up (U = 172, Z = -2.34, p = 0.019, r = 0.34). No differences were found in patient satisfaction.

Conclusion The use of a resorbable membrane in small buccal bony dehiscences in anterior maxillary single tooth replacement resulted in less marginal bone loss, but showed more mucosal dehiscenses, higher bleeding scores and lower scores on root convexity and soft tissue colour after at least one year of

loading. No effect was seen on implant survival and success, overall aesthetic results and patient satisfaction.
The research protocol was registered at the Dutch Trial Register (NTR) with ID NTR6137.

INTRODUCTION

In the past, the main challenge in oral implantology was to make sure dental implants would osseointegrate and function as a replacement for missing teeth. However, there has been a shift in attention to create predictable, clinical healthy, and esthetically pleasing results. To do so, dental implants should ideally be placed in the correct three-dimensional position, with full bony coverage of the surface of the implant at least 2 mm thick to optimize soft tissue esthetics.[1-3] However, due to infection, trauma or physiologic resorption, the alveolar process can be too narrow to facilitate a complete bony surrounding of the placed dental implant,[4, 5] which may lead to a peri-implant bony dehiscence when placing an implant. Although a small buccal bony dehiscence might not lead to problems in terms of primary stability and osseointegration, it might negatively influence soft tissue esthetics, depending on the smile line and soft tissue bio-type.[2, 6, 7]

To correct a bony dehiscence, ridge augmentation procedures are performed with the use of autogenous bone and bone substitutes. Membranes can be applied to direct the growth of new bone, a principle called guided bone regeneration (GBR). Since Nyman et al. (1990)[8] and Dahlin et al. (1991)[9] described GBR in their first clinical studies, the use of membranes has become a widely applied concept in oral implantology.

The combined use of bone augmentation materials and GBR has possible synergistic advantages. The bone graft supports the membrane and prevents it from collapsing. It also offers a framework for the ingrowth of capillaries and perivascular tissue, and it provides a carrier for factors that enhance bone formation. The membrane itself provides an environment that promotes the recruitment

and proliferation of osteoprogenitor cells, differentiation to osteoblasts and osteogenic activity, thereby allowing the regeneration of bone in open areas and possibly minimizing the loss of graft volume.[10-12]

In several systematic reviews, the success of implants placed in one-stage ridge augmentation procedures (ridge augmentation simultaneous with implant placement) has been reported.[13, 14] However, there is no consensus about the beneficial use of a membrane in these procedures, especially in small buccal dehiscences.[15] Therefore, the aim of this randomized controlled trial was to determine the effect of resorbable membranes on one-stage ridge augmentation in small buccal bony dehiscences in anterior maxillary single-tooth replacement.

MATERIALS AND METHODS

Study design

This study was conducted in accordance with the declaration of Helsinki, good clinical practice and the CONSORT statement (Consolidated Standards of Reporting Trials).[16] The study was designed as a parallel group, randomized, controlled clinical trial (RCT). All procedures and materials were submitted and approved by the local medical ethical committees and registered in the public register of the Dutch Central Committee on Research Involving Human Subjects (CCMO) with study number NL 34657.078.11. The research protocol was also registered at the Dutch Trial Register (NTR) with ID NTR6137.

Eligible patients had to be over 18 years of age and in need of an implant-supported dental crown to replace a single maxillary tooth at the location of an incisor, canine or first/second premolar. Implants were placed in healed ridges, at least 3 months after extraction. The presence of a small bone deficiency at the buccal aspect of the implant of 2 to 4 mm was required for the RCT. This was evaluated after raising the mucoperiosteal flap and placement of the implant (see surgical protocol). The occlusal and mesiodistal dimensions had to be sufficient for the insertion of one implant with a functional prosthetic restoration. Exclusion criteria were as follows: A large bony defect necessitating a two-stage ridge augmentation, the presence of clinically active periodontal disease, the

presence of acute inflammatory oral disease, smoking, uncontrolled diabetes, a history of radiotherapy in the head and neck region or current chemotherapy and disability (mental and/ or physical) to maintain basic oral hygiene procedures.

The study occurred at the University Medical Center Erasmus MC, Rotterdam and the St. Anna Hospital, Geldrop, the Netherlands. All surgical procedures were performed by one surgeon (EW). In close cooperation with the referring prosthodontist, a treatment plan was established that included a surgical component (implant placement and simultaneous bone augmentation) and a prosthetic component in the dental office (dental crown design and placement). Patients with a small buccal bony dehiscence at implant placement were randomly assigned to group M+ (ridge augmentation with membrane) or M– (ridge augmentation without membrane):

M+ A mixture of locally harvested autogenous bone chips and a bone substitute covered with a resorbable membrane.

M– A mixture of locally harvested autogenous bone chips and a bone substitute without a covering membrane.

Surgical protocol

All surgical procedures were performed under local anesthesia. After raising the mucoperiosteal flap at the top of the alveolar process, the exact position of the dental implant was defined as determined by preoperative measurements, dental setup, and surgical guide. Bone level (Straumann® Bone Level, Basel, Switzerland) 4.1- and 3.3-mm implants were placed 3 mm apical to the expected cervical border of the crown. After implant placement, the bony deficiency at the buccal side was evaluated. Patients with a small bony defect (2-4 mm) were included in the study. The augmentation technique implied coverage of the titanium surface of the dental implant with a mixture of autogenous bone chips and synthetic bone substitute (Straumann® BoneCeramic™, Basel, Switzerland). Depending on randomization, subsequent coverage with a resorbable hydrogel membrane (Straumann® MembraGel, Basel, Switzerland) was performed in Group M+. This synthetic polyethylene glycol (PEG) hydrogel membrane biodegrades slower than a standard collagen membrane,[17] with no remnant after 3 months.[18] The membrane was applied as a thin layer over the augmented

site. Following the augmentation procedure, the mucoperiosteal flap was mobilized to facilitate primary closure. The postoperative protocol included rinse with a 0.12% chlorhexidine solution twice daily, 500 mg of amoxicillin three times daily for 5 days, and a NSAID (according to individual requirements). The secondary-phase surgery was performed 8 weeks after implant placement and consisted of a small stab incision without puncture and the placement of a healing abutment.

Prosthetic protocol

The implants were loaded after a healing time of approximately 8-9 weeks. Referring prosthodontists were requested to use individualized zirconium abutments.

Outcome measurements

Implant survival, adverse events and complications

Swelling, mucosal dehiscence and adverse events were evaluated 2 and 6 weeks after implant placement. The non-osseointegration of an implant was scored as an early failure.

Implant success

A combination of different success criteria as suggested by the systematic reviews by Donos et al. (2008)[19] and Ong et al. (2008)[20] was used to score implant success. These success criteria were based on the original criteria of Albrektsson et al. (1986)[21] and adapted by Buser et al. (1990)[22]. In addition, Karoussis et al. (2004)[23] added pocket probing depth criteria based on two studies regarding peri-implantitis.[24, 25] This resulted in the following criteria for success: the absence of mobility, the absence of persistent subjective complaints (pain, foreign body sensation and/or dysesthesia), the absence of recurrent peri-implant infection with suppuration, the absence of a continuous radiolucency around the implant, no pocket probing depth (PPD) of ≥ 5 mm with bleeding on probing (BOP), PPD of > 5 mm, no vertical bone loss of > 1.5 mm in the first year and no vertical bone loss of > 0.2 mm annually in the following years. Cases were individually scored as ‘successes’ when all the above-mentioned criteria were met.

Clinical assessment

Different clinical parameters were assessed 1, 6 and at least 12 months after placement of the crown. The Mombelli Plaque Index (PI) was used to qualify the amount of plaque retained.[26] The Mühlemann bleeding index (BI) modified by Mombelli was used to evaluate bleeding.[27] The gingival index (GI) was used to evaluate the condition of the gingiva.[28] The distance between the marginal border of the gingiva and the tip of the pocket probe was scored as the pocket probing depth (PPD). The width of the attached mucosa (WAM) buccal to the implant-supported crown was measured using the 'attached mucosa index'.[29] These clinical parameters were scored by one independent and blinded clinician in each center. These clinicians were instructed about the study and the clinical parameters they had to evaluate. These parameters are also used in the standard follow-up of our implantology patients and are therefore not calibrated between the clinicians.

Radiographic assessment

Marginal bone levels were measured on standardized digital periapical radiographs. Individualized putty molds were used to ensure reproducibility of the x-ray equipment. OsiriX (OsiriX v.7.0.1., Pixmeo SARL, Bernex, Switzerland) software was used to measure the distance from implant shoulder to the marginal bone crest. The implant length was used as reference to calibrate these digital measurements. Measurements were performed twice by one blinded researcher, with an interval of 3 months between measurements (BJ). Radiographs were taken before and directly after implantation and 1, 6, and 12 months after placement of the crown.

Esthetic assessment

The modified peri-implant soft tissue index or pink esthetic index (PES) was used to evaluate soft tissue esthetics (Fürhauser, Florescu, Benesch, Mailath & Watzek, 2005). It reflected the following five items: mesial papilla, distal papilla, curvature of the facial mucosa, level of the facial mucosa, and root convexity/ soft tissue color and texture at the facial aspect of the implant site. The white esthetic score (WES) was used to evaluate the esthetics of the crown;[6] this WES is based on the five following items: general tooth form; outline and volume

of the clinical crown; color, which includes the assessment of the dimension's hue and value; surface texture; and translucency and characterization. These esthetic parameters were determined by two blinded researchers (BJ and JP) using digital photographs (Canon 500D, 100 mm F2.8 macro, Canon Inc., Tokyo, Japan) at 1, 6, and 12 months after placement of the final crown.

Patient satisfaction evaluation

Patient satisfaction was evaluated by a questionnaire using Visual Analog Scales (VAS 0-10) that focused on the overall satisfaction with the dentition, the impact of the surgery, pain, swelling, and satisfaction with the crown and the soft tissue. Patient questionnaires were used preoperatively and 1, 6, and 12 months after placement of the crown.

Statistics

The primary endpoint used for sample size calculation was the change in the marginal bone level at least 12 months after loading. Sample size calculation was based on the difference between the two independent groups (Independent Samples T-test). A difference of means of 0.5 mm between the M+ group and the M– group plus an additional measuring error of 0.12 mm was considered a relevant difference (Meijndert et al., 2004). The standard deviation was expected to be 0.63 mm.[30] This led to 23 patients/group for a power of 90% and an alpha of 0.05. Sample size calculation was calculated using G*Power (Version 3.1.9.2, Heinrich Heine Universität, Düsseldorf, Germany). To compensate for expected dropouts, patients were included until the smallest group had 25 patients. Dichotomous outcomes were checked for significant differences, by calculating the relative risks (RR's) with their respective 95% confidence intervals (95%CI's). For the ordinal and continuous outcomes, means were calculated for normal distributed data and medians for non-normal distributed data. Means were presented together with standard deviations (SD's) and medians with the first and third interquartile ranges. To observe possible differences between treatment arms in continuous (non-normal distributed) and ordinal parameters, the nonparametric Mann-Whitney U test was used. Effect sizes were calculated using the formula $r = Z/\sqrt{N}$.[31] The Intraclass Correlation Coefficient was determined for the PES/WES totals and marginal

bone levels. All analyses were performed using SPSS (Version 21.0.0 for Mac, SPSS Inc., IBM Corporation, Chicago, USA). A p-value of < 0.05 was considered a significant difference. The patient was the unit of analysis.

Randomization

For allocation of the participants, a computer-generated simple unrestricted randomization was used. Allocation was concealed in opaque, sealed envelopes made by Dr. Ir. W.C.J. Hop from the department of Biostatistics, Erasmus Medical Center Rotterdam. The allocation sequence was concealed from the surgeon (EW) until the very last step in the surgical procedure (membrane placement). Patients were not blinded, as this was not possible. The surgeon (EW) was blinded until the last step in the procedure (membrane application). Reporting of clinical measurements was blinded, as reporting clinicians were unaware of the treatment group. Investigators (BJ&JP) were not aware of the allocation during radiographic and esthetic assessment.

RESULTS

Patients

Patients were recruited between April 2011 and February 2014, and the last follow-up visit was performed in November 2016. The median follow-up was 16 months after loading with a minimum follow-up of 12 months and the longest follow-up 56 months. The flow diagram of patients assessed, allocated, and analyzed is displayed in Figure 1. In total, 86 patients were assessed for eligibility. No buccal bony dehiscence after implant placement was seen in 31 patients (implants completely surrounded by pristine bone). These patients were included in another clinical trial. Two patients declined to participate, and one patient had part of the tooth still in situ and was therefore excluded. Fifty-two patients had a small buccal bony dehiscence after implant placement and were randomly allocated to group M+ (n = 25) or group M– (n = 27). All patients received their assigned treatment. Examples of one-stage ridge augmentation with a membrane and without a membrane are displayed in Figure 2. No patients were excluded from analysis. Baseline characteristics of the included patients are displayed in Table 1.

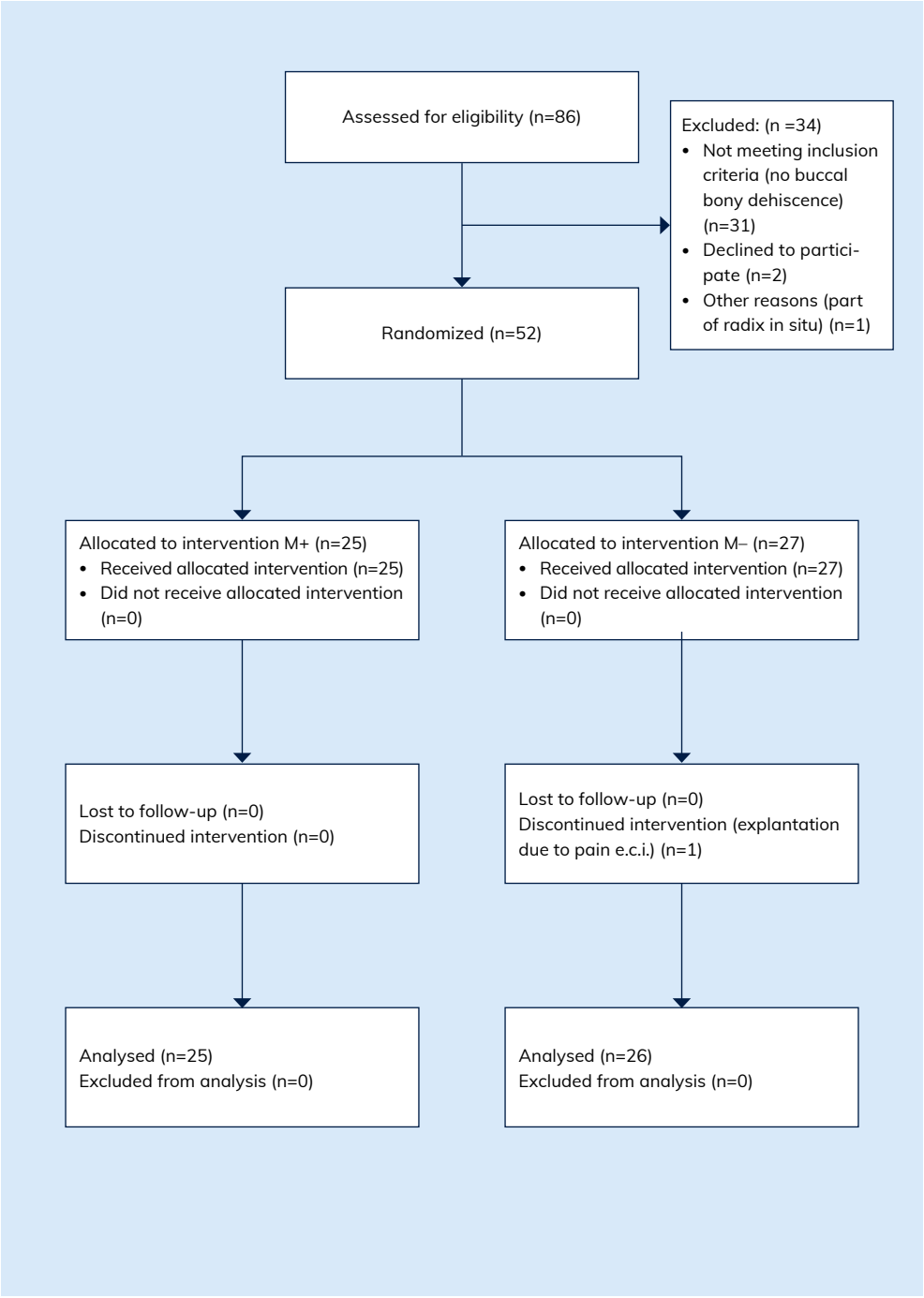

Figure 1 CONSORT Flow Diagram.

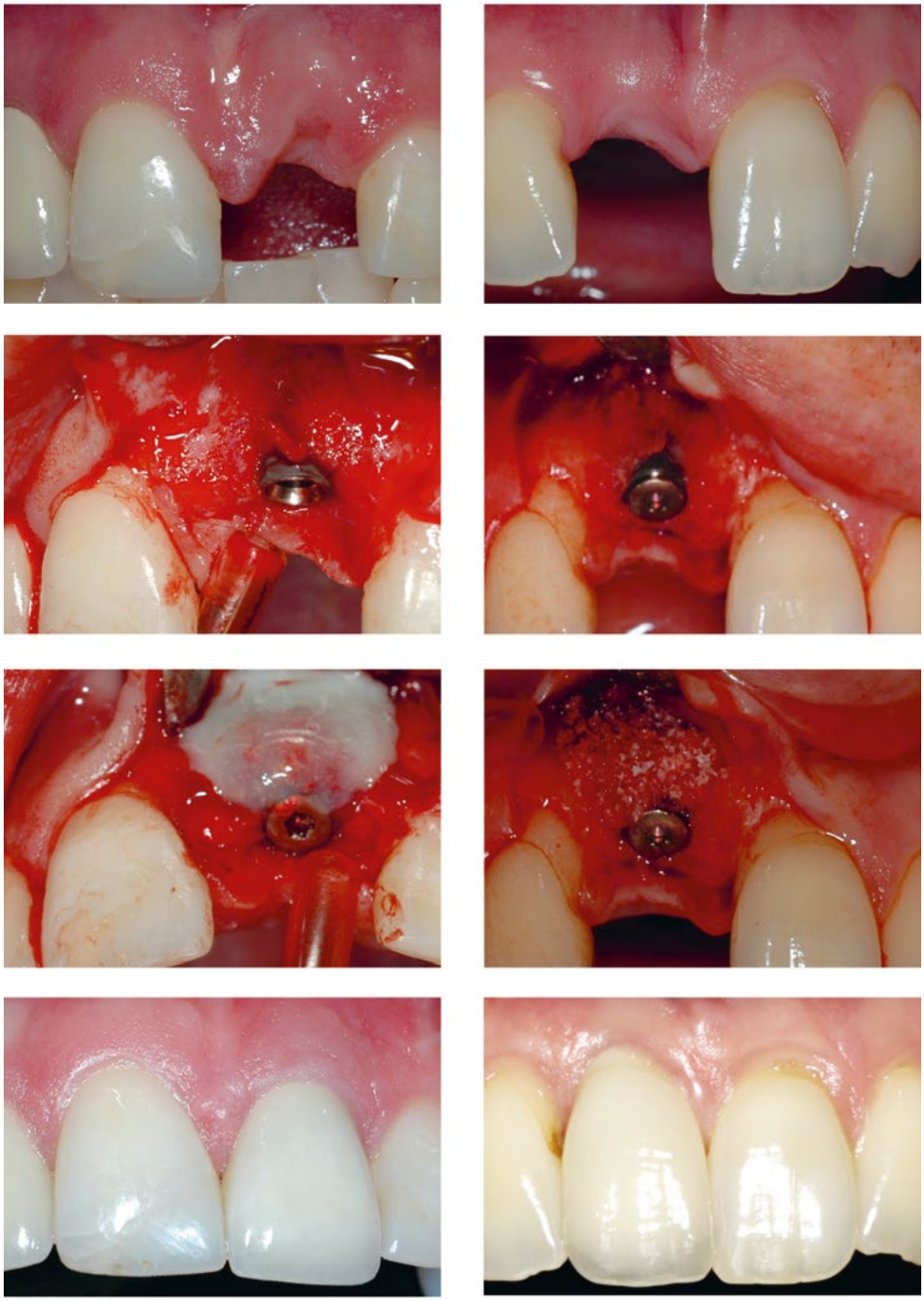

Figure 2 Examples of one-stage ridge augmentation with a membrane (left) and without a membrane (right).

	M+	M–
Number of patients	25	27
Mean age (SD)	45.04 (10.88)	49.04 (14.15)
Gender (male/female)	15/10	15/12
Center (EMC/STA)	3/22	5/22
Median months after extraction (Q1-Q3)	5.00 (5.00-6.50)	5.00 (4.00-8.80)
Cause of tooth loss (infection/fracture/resorption/ agenesis/unknown)	17/2/0/1/5	19/2/1/1/4
Implant location (I/C/P)	21/0/3	22/3/2
Implant length (8/10/12 mm)	1/8/16	1/9/17
Implant diameter (3.3/4.1 mm)	14/11	13/14

Table 1 Baseline characteristics for one-stage ridge augmentation with a membrane (M+) and without a membrane (M–), SD, Standard Deviation; Q1-Q3, first and third interquartile range; EMC, Erasmus Medical Center; STA, St. Anna Hospital; I, Incisive; C, Canine; P, Premolar.

Implant survival, adverse events and complications

Two weeks after implant placement, no abnormal swelling, mucosal dehiscence, infections, or other adverse events had taken place. 6 weeks after implant placement, six of 25 patients (24.0%) in group M+ and one of 26 patients (3.85%) in group M– showed a small mucosal dehiscence (< 2 mm). The risk of having a small mucosal dehiscence was more than six times higher in the M+ group than in the M– group (RR 6.24, 95% CI 0.81-48.2). These patients were instructed to rinse with chlorhexidine 0.12 ml/L twice daily. One of these patients (group M+) showed a partial loss of the graft at second-phase surgery. No other complications were seen during follow-up. One implant was removed because of unexplained pain (group M–). This implant was properly integrated and showed no signs of inflammation. This resulted in an implant survival of 25 of 25 (100%) in group M+ and 26 of 27 (96.3%) in group M– after a minimum of 12 months of loading (RR 1.03, 95% CI 0.96-1.12).

Implant success

At the last follow-up, none of the implants showed any sign of mobility. None of the patients had any severe subjective complaints (the maximal pain score was 1.9 on a scale from 0 to 10). Although no patients experienced recurrent

peri-implant infection with suppuration, five patients (four of 25 in group M+ and one of 26 in group M–) showed mild inflammation characterized by a slight redness of the mucosa (Gingiva Index 1) and one showed moderate inflammation; redness, edema, and glazing (Gingiva Index 2) in group M– at the last follow-up visit. None of the patients showed a continuous radiolucency around the implant. Two patients in group M– exceeded the maximal crestal bone loss of > 1.5 mm in the first year and > 0.2 mm annually in the following years. One patient in group M+ had a PPD of > 5 mm. One additional patient in group M– had a PPD of 5 mm combined with a (point) BOP. Overall, this resulted in a success in 24 of 25 patients in de M+ group (96.0%), and 23 of the 27 patients in the M– group (85.2%), with a relative risk of 1.13 (95% CI 0.94-1.34).

Clinical assessment

Plaque, bleeding, and gingival scores were low and stayed low during the follow-up period (Table 2). A Mann-Whitney U test was run to determine if there were differences between the two groups. At the last follow-up, the bleeding index (BI) was marginally higher in the M+ group (BI: 14/9/2/0) compared to the M– group (BI: 24/2/0/0) ($U = 205$, $Z = -2.97$, $p = 0.003$, $r = 0.42$). Figure 2 shows a bar chart of the distribution. Pocket probing depth was measured at four sites (mesial, buccal, distal, and palatal) and displayed in Table 3. The median PPD's were all lower than 3 mm and stable over time. No significant differences were found.

	M+	M-	p-value	Effect size
1 month after loading	n = 25	n = 21		
Plaque index	22/1/2/0	18/1/2/0	0.821	0.033
Beeding index	14/9/2/0	18/3/0/0	0.026	0.328
Gingiva index	20/4/1/0	19/2/0/0	0.313	0.149
6 months after loading	n = 24	n = 18		
Plaque index	21/3/0/0	14/3/1/0	0.377	0.136
Beeding index	15/8/1/0	14/4/0/0	0.269	0.171
Gingiva index	20/4/0/0	17/1/0/0	0.277	0.168
≥ 12 months after loading	n = 25	n = 26		
Plaque index	22/1/2/0	23/1/1/1	0.987	0.002
Beeding index	14/9/2/0	24/2/0/0	0.003	0.417
Gingiva index	21/4/0/0	24/1/1/0	0.339	0.118

Table 2 Clinical assessment: plaque index, bleeding index, gingival index (values 0/1/2/3) for one-stage ridge augmentation with a membrane (M+) and without a membrane (M–).

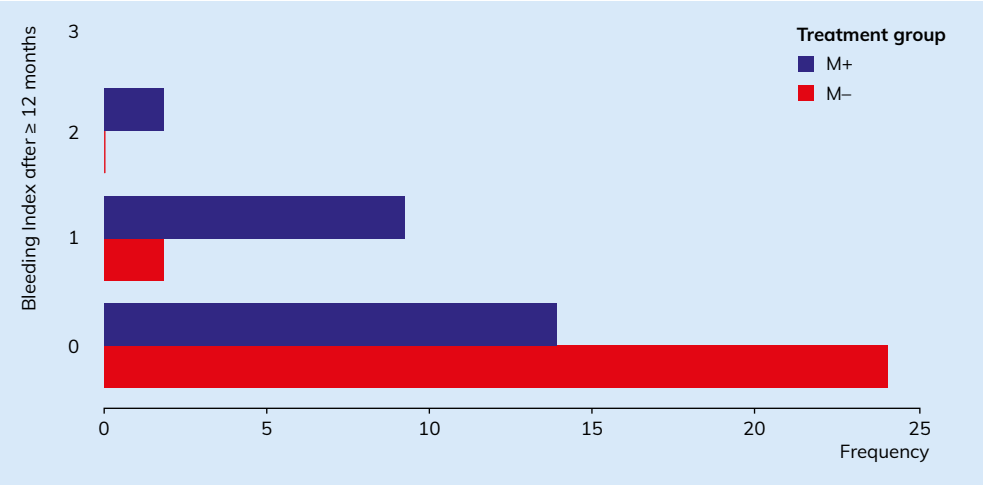

Figure 2 Bar chart of the bleeding index (values 0/1/2/3) at least 12 months after loading for one-stage ridge augmentation with a membrane (M+) and without a membrane (M–).

	M+	M-	p-value	Effect size
1 month after loading	n = 24	n = 21		
Mesial	2.5 (2.0-2.5)	2.5 (1.5-2.8)		
Buccal	2.0 (1.0-2.0)	2.0 (1.0-2.0)		
Distal	2.0 (1.6-2.9)	2.0 (1.8-2.3)		
Palatal	2.0 (1.0-2.0)	2.0 (1.5-2.0)		
Average	2.0 (1.7-2.4)	2.0 (1.6-2.4)	1.000	0.000
6 months after loading	n = 24	n = 18		
Mesial	2.0 (2.0-2.9)	2.0 (1.5-2.6)		
Buccal	2.0 (2.0-3.0)	2.0 (1.0-2.3)		
Distal	2.3 (2.0-2.9)	2.0 (1.5-3.0)		
Palatal	2.0 (2.0-2.8)	2.0 (1.0-3.0)		
Average	2.1 (1.9-2.5)	2.0 (1.5-2.5)	0.245	0.179
≥ 12 months after loading	n = 24	n = 25		
Mesial	2.5 (2.0-3.0)	2.5 (2.0-3.0)		
Buccal	2.0 (2.0-3.0)	2.0 (2.0-3.0)		
Distal	2.5 (2.0-3.0)	2.0 (2.0-3.0)		
Palatal	2.0 (2.0-2.8)	2.0 (2.0-3.0)		
Average	2.3 (2.0-2.7)	2.0 (1.9-3.0)	0.707	0.054

Table 3 Clinical assessment: median pocket probing depth in mm (first and third interquartile range) for one-stage ridge augmentation with a membrane (M+) and without a membrane (M–).

Radiographic assessment

Changes in marginal bone levels at 1, 6, and ≥ 12 months after implant loading are displayed in Table 4. The median change in marginal bone level was statistically lower in the M+ group (0.06 mm) than in the M– group (0.60 mm) at last follow-up (U = 120, Z = -2.73, p = 0.006, r = 0.42). A histogram of the change in marginal bone level at least 12 months after loading is shown in Figure 3.

	M+	M-	p-value	Effect size
1 month after loading	n = 18	n = 17		
Mesial	0.00 (0.00-0.18)	0.17 (0.00-0.64)		
Distal	0.00 (0.00-0.27)	0.00 (0.00-0.44)		
Average	0.04 (0.00-0.20)	0.10 (0.00-0.37)	0.227	0.207
6 months after loading	n = 17	n = 17		
Mesial	0.02 (0.00-0.40)	0.50 (0.19-0.72)		
Distal	0.00 (0.00-0.28)	0.40 (0.12-0.74)		
Average	0.14 (0.00-0.28)	0.53 (0.19-0.74)	0.002	0.532
>12 months after loading	n = 20	n = 23		
Mesial	0.00 (0.00-0.44)	0.46 (0.00-1.12)		
Distal	0.00 (0.00-0.20)	0.59 (0.00-0.90)		
Average	0.06 (0.00-0.35)	0.60 (0.00-0.94)	0.006	0.416

Table 4 Radiographic assessment: median change in marginal bone level in mm (first and third interquartile range) for one-stage ridge augmentation with a membrane (M+) and without a membrane (M–).

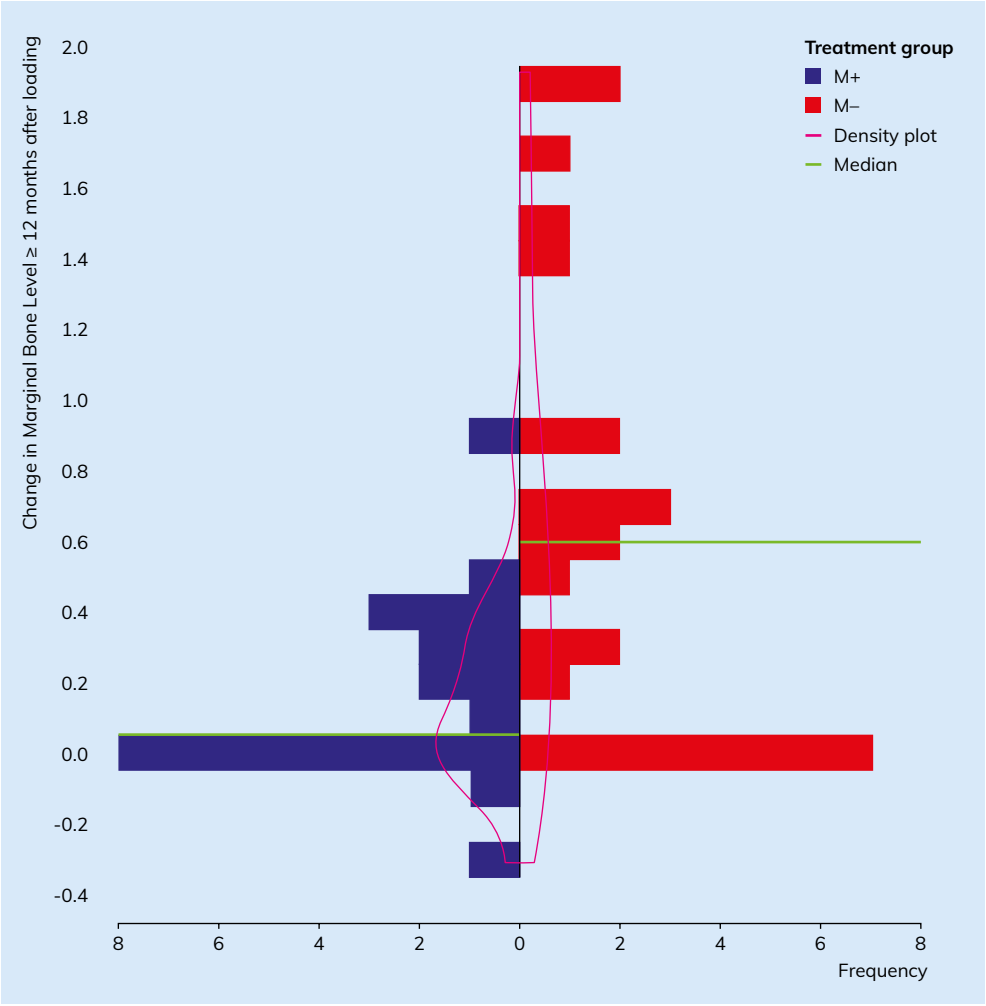

Figure 3 Histogram of the change in marginal bone level (mm) at least 12 months after loading for one-stage ridge augmentation with a membrane (M+) and without a membrane (M–).

Esthetic assessment

The PES and WES of the different categories are displayed in Table 5. Total PES and WES and combined PES/WES were not significantly different between the treatment groups at more than 12 months after loading. Only the subcategory root convexity/soft tissue color scored significantly lower in the M+ group (1.5) compared to the M– group (2.0) at the last follow-up ($U = 172$, $Z = -2.34$, $p = 0.019$, $r = 0.34$). Figure 4 shows a bar chart of the distribution.

	M+	M-	p-value	Effect size
1 month after loading	n = 24	n = 21		
PES	6.3 (5.5-7.9)	7.0 (5.5-7.8)	0.740	0.049
WES	9.0 (8.1-9.5)	9.0 (8.1-9.5)	0.746	0.048
PES/WES	15.5 (14.0-17.0)	16.5 (13.8-17.0)	0.664	0.065
6 months after loading	n = 22	n = 15		
PES	8.0 (6.5-8.6)	7.5 (7.0-9.0)	0.705	0.008
WES	9.0 (8.5-9.5)	9.0 (8.5-10.0)	0.963	0.062
PES/WES	17.3 (15.0-18.0)	17.5 (15.5-18.0)	0.579	0.091
> 12 months after loading	n = 22	n = 25		
PES	7.8 (7.0-9.0)	8.0 (6.5-9.5)	0.897	0.019
WES	9.5 (8.5-9.6)	9.5 (8.0-9.5)	0.449	0.112
PES/WES	17.0 (16.0-18.5)	16.5 (15.0-19.0)	0.834	0.031

Table 5 Esthetic assessment: median (first and third interquartile range) of the pink and white esthetic items: total pink esthetic index (PES) and white esthetic score (WES) on a scale from 0 to 10 and total PES/WES on a scale from 0 to 20, for one-stage ridge augmentation with a membrane (M+) and without a membrane (M–).

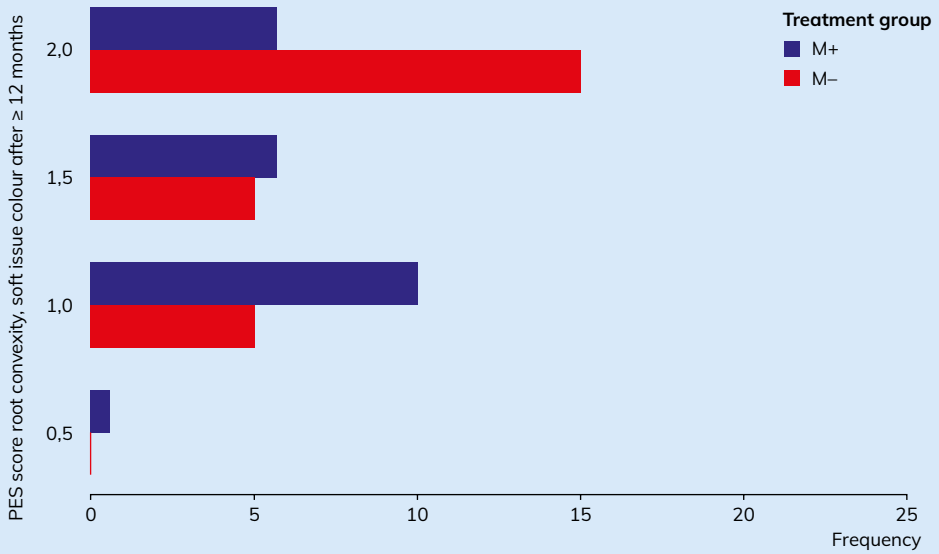

Figure 4 Bar chart of pink esthetic index (PES) subcategory root convexity/ soft tissue color (values 0 to 2) at least 12 months after loading for one-stage ridge augmentation with a membrane (M+) and without a membrane (M–).

Patient satisfaction evaluation

The patient satisfaction questionnaire scores are shown in Table 6. Patients were highly satisfied with their crown in the M+ group (9.1) and the M– group (9.6). Also, the soft tissues scored high values in M+ group (8.5) and the M– group (9.2). In the membrane-covered group, an acceptable result (scores with ≥ 6) for the crown was reached in 100% (25 of 25), and in the group without a membrane, an acceptable result was found in 96.2% (25 of 26) of the cases. For soft tissue esthetics, an acceptable result was reported in 96% (24 of 25) of the M+ group and 96.2% (25 of 26) of the M– group. Overall, patient satisfaction did not differ significantly between both treatment arms.

	M+	M-	p-value	Effect size
Before implant placement	n = 25	n = 27		
Satisfaction with dentition	5.4 (2.4-7.2)	6.5 (3.6-7.2)	0.595	0.074
Expected impact of surgery	2.3 (1.2-4.1)	4.1 (1.8-6.0)	0.124	0.213
Pain	0.3 (0.1-1.3)	0.4 (0.0-1.7)	0.890	0.019
Swelling	0.3 (0.1-0.8)	0.3 (0.0-1.3)	0.875	0.022
Expected satisfaction with crown	9.0 (8.4-9.5)	8.9 (8.1-9.3)	0.527	0.088
Expected satisfaction with soft tissue	8.3 (7.1-9.1)	8.2 (6.2-9.1)	0.621	0.069
1 month after loading	n = 24	n = 21		
Satisfaction with dentition	8.5 (8.0-9.2)	8.5 (7.7-9.4)	0.785	0.041
Impact of surgery	1.9 (0.6-5.7)	1.4 (1.0-2.8)	0.466	0.109
Pain	0.4 (0.1-0.8)	0.3 (0.1-1.6)	0.529	0.094
Swelling	0.3 (0.0-0.8)	0.2 (0.0-0.8)	0.826	0.033
Satisfaction with crown	9.1 (8.7-9.8)	9.7 (8.5-10.0)	0.639	0.070
Satisfaction with soft tissue	8.1 (6.8-9.3)	8.5 (6.9-9.0)	0.785	0.041
6 months after loading	n = 24	n = 17		
Satisfaction with dentition	8.8 (8.5-9.5)	9.0 (8.1-9.7)	0.937	0.012
Impact of surgery	2.0 (0.5-4.7)	1.6 (0.5-4.7)	0.825	0.035
Pain	0.2 (0.0-0.9)	0.2 (0.1-0.6)	0.501	0.105
Swelling	0.2 (0.0-0.6)	0.2 (0.0-0.6)	0.787	0.042
Satisfaction with crown	9.6 (8.7-9.9)	9,2 (8.0-9.8)	0.206	0.200
Satisfaction with soft tissue	7.9 (7.3-9.4)	9.0 (7.6-9.6)	0.450	0.118
> 12 months after loading	n = 25	n = 26		
Satisfaction with dentition	8.3 (7.5-9.4)	8.4 (7.8-9.7)	0.657	0.062
Impact of surgery	2.1 (0.8-4.9)	2.4 (0.4-3.1)	0.534	0.087
Pain	0.2 (0.0-0.9)	0.2 (0.0-0.4)	0.516	0.091
Swelling	0.1 (0.0-0.9)	0.2 (0.0-0.3)	0.554	0.083
Satisfaction with crown	9.1 (8.6-9.9)	9.6 (8.5-9.9)	0.726	0.049
Satisfaction with soft tissue	8.5 (7.9-9.5)	9.2 (6.6-9.9)	0.545	0.085

Table 6 Patient satisfaction evaluation: median (first and third interquartile range) of the VAS scores on a scale from 0 to 10, for one-stage ridge augmentation with a membrane (M+) and without a membrane (M–).

Inter- and intra-observer correlation

Measurements of the PES/WES were performed independently by two blinded researchers (BJ and JP) on digital photographs. The interobserver intraclass correlation coefficient for the PES/WES totals was 0.738, with a 95% CI of 0.628-0.815. Measurements of radiographs were performed blinded and twice by one researcher (BJ). The intraobserver intraclass correlation coefficient for the marginal bone level was 0.905, with a 95% CI of 0.882-0.923.

DISCUSSION

This randomized, controlled clinical trial evaluated single-tooth replacement in one-stage ridge augmentation procedures with or without a resorbable membrane regarding implant survival and success, complications, clinical and radiographic parameters, aesthetic results and patient satisfaction after more than one year of loading. Currently, there are only two randomized controlled trials comparing one-stage ridge augmentations with and without membranes.[32, 33] These studies concluded that the addition of a barrier membrane prevented horizontal buccal bone resorption and enhanced bone thickness. No effect was seen on implant survival after 1 year of loading. These studies described large (5.81-7.77 mm) defect heights and failed to mention parameters of implant success and soft tissue esthetics.

Implant survival, adverse events and complications

Implant survival was high in both the membrane-covered group and the group without a membrane. This was also shown in other studies comparing one-stage ridge augmentations with or without membranes.[32, 33] Park et al. (2008)[32] found 100% osseointegration in both groups 6 months after implant placement. Fu et al. (2014)[33] also found a 100% survival rate, with a follow-up of 6 months after loading. Other studies evaluating one-stage ridge augmentation found comparable results. A survival rate of 100% after 5 years of loading was also shown by Jung and Ramel in 32 patients where one-stage ridge augmentation was performed with the same hydrogel as the current study.[34, 35] Buser et al. (2011)[36] found a survival rate of 100% after 3 years in a case series of 20 patients

using porcine-derived collagen membrane over autogenous bone chips and deproteinized bovine bone mineral. Benic et al. (2009)[37] investigated one-stage guided bone regeneration with a follow-up of 5 years. Similar results were found with a 100% survival rate (n = 34).

In our study the risk of having a mucosal dehiscence was over six times higher in the membrane covered group. This was in line with a pre-clinical study evaluating the same membrane[38] and although less evident, the study of Park et al. (2008)[32] comparing one-stage bone augmentation procedures with and without membranes.

Implant success

Implant success was high in both groups, with success rates of 96.0% in the membrane-covered group and 85.2% in the group without a membrane after more than 12 months of loading. Other comparable studies only reported on implant survival/failure and not about implant success parameters.[32-34, 38] Buser et al. (2011)[36] did describe success using their own criteria and found 100% success in their cohort of 20 patients.[22] Our current study showed lower success percentages, as stricter criteria were used regarding pocket probing depths and bleeding index. Ramel et al. (2012)[35] described an implant survival of 100% and noted no clinical abnormalities using the same membrane as the current study in one-stage ridge augmentations. However, the maximal change in bone level of 2.31 mm in their study suggested that there were implants with a bone loss exceeding the threshold of 1.5 mm in the first year after loading. At 3 years after loading, two implants showed a bone loss of > 2 mm, resulting in a comparable calculated implant success of at most 85%.

Clinical assessment

Plaque, bleeding, and gingival index were low and stayed low during the observation period. The medians of the PPDs were all below 3 mm and were stable over time. This is similar to the other studies reporting on these clinical parameters.[34, 36, 37] More bleeding sites were seen in the membrane-covered group ($U = 205$, $Z = -2.97$, $p = 0.003$, $r = 0.42$).

Radiographic assessment

Median change in marginal bone level was statistically lower in the M+ group (0.06 mm) than in the M– group (0.60 mm) at last follow-up (U = 120, Z = -2.73, p = 0.006, r = 0.42). Despite the non-normal distribution, means and standard deviations of the changes in marginal bone level were also calculated to make the data comparable to other studies. A mean of 0.16 mm (SD 0.26) was found in the M+ group and a mean of 0.65 mm (SD 0.64) in de M– group was found at last follow-up. These findings were in line with comparable studies. At six months after loading, Fu et al. (2014)[33] found a combined mean radiographic vertical bone loss of 1.17 mm (SD 0.75) with and 1.57 mm (SD 1.03) without a membrane.[15] Ramel et al. (2012)[35] found a change in marginal bone level at 1 year after loading of 0.43 mm (SD 0.56) when using current studied membrane. Buser et al. (2011)[36] found 0.18 mm (SD 0.20) in comparable procedures in the esthetic zone after 1 year. A recent systematic review evaluating marginal bone levels around the same type of implants showed a comparable loss of marginal bone of 0.49 mm after an average of 1-2 years of loading.[39]

Esthetic assessment

Total PES and WES scores were not significantly different between treatment groups. Again to make the data comparable to others studies means and standard deviations were calculated. The mean PES scores (7.77 SD 1.44 M+ and 7.72 SD 1.89 M–) and mean WES scores (9.11 SD 0.95 M+ and 8.92 SD 0.97 M–) were comparable to those of other studies. Buser et al. (2011)[36] showed a mean PES of 8.1 and a mean WES of 8.65 at 1 year after loading. Belser et al. (2009)[6] found comparable results in the original article describing PES/WES (7.8 SD 0.88 / 6.9 SD 1.47). Santing et al. (2013)[40] studied the results of the same type of implants used in this study after two-stage bone augmentation and reported comparable PES and WES scores (6.9 SD 1.8 / 7.5 SD 1.7 for the WES). Root convexity and soft tissue color scored significantly worse in the M+ group (U = 172, Z = -2.340, p = 0.019, r = 0.34). As significant more dehiscences were noted in the M+ group, this might have negatively influenced this esthetic parameter. The hydrogel membrane used in this study may lead to more graft particle resorption of the used synthetic bone substitute, as previously reported in a nonclinical study.[18] This also might have contributed to the unfavourable scores of root convexity and soft tissue colour.

Patient satisfaction evaluation

Patients were highly satisfied with their dentition, crown and soft tissues after implant placement in both groups. There was no significant difference in the perceived impact of surgery, pain or swelling. In a study by Santing et al. (2013)[40], general patient satisfaction on a VAS scale was 8.9 SD 1.1, which was in line with our results. In their study, 95% of the patients were satisfied (4 and 5 on a 5-point scale) with the colour of the crown, 96.7% were satisfied with the form, 90.0% with the colour of the mucosa and 86.7% with the form of the mucosa.

Meijndert et al. (2016)[41] showed a mean overall patient satisfaction score of 8.5 and 82.4% of the patients showed acceptable results with the crown and 42.9% with the mucosa. In our study with a membrane, an acceptable result for the crown was noted by 100% (25/25) of the patients and in 96.2% (25/26) of the cases in the group without a membrane. For soft tissue aesthetics, 96% (24/25) noted an acceptable result in the group with and 96.2% (25/26) in the patients the group without a membrane. Pjetursson et al. (2005)[42] also investigated patient satisfaction in a cohort study after 10 years. Satisfaction with esthetics was comparably high: 97% were highly satisfied with a VAS of 93% (SD 13.97).

Limitations of this study

As primary outcome data were originally based on t tests, the sample size was underestimated. For the adjusted sample size based on the minimal asymptotic relative efficiency (ARE) of the Mann-Whitney U test relative to the t test, the sample size required to achieve a power of 90% was not achieved. However, a sample size needed to reach a power of 80% was accomplished at the final follow-up. Additionally, it must be noted that this study was only powered for the primary outcome.

Although this study used a hydrogel PEG membrane, which is not commonly used, Ramel et al. (2012)[37] concluded in their randomized controlled trial that the hydrogel membrane was just as successful as the standard collagen membrane for the treatment of bony dehiscences around dental implants after

follow-up periods of 1-3 years. Further follow-up of the same study by Jung et al. (2015)[34] showed that the hydrogel membrane performed just as successfully as the standard collagen membrane concerning implant survival rate, dimensions of the buccal bone and peri-implant mucosa after 5 years follow-up.

Strengths

This study has a low risk of bias according the Cochrane Risk of Bias assessment tool for RCT's.[43] To prevent selection bias, random sequence generation for allocation of the participants was performed by a computer-generated simple unrestricted randomization. Allocation was concealed in opaque, sealed envelopes. The allocation sequence was concealed from the surgeon (EW) until the very last step in the surgical procedure (membrane application). Clinical investigator (BJ&JP) were not aware of the allocation during assessment to prevent detection bias. As there were low losses in follow-up, there is a low risk of attrition bias. Risk of reporting bias was low because all outcomes originally described in the registered protocol are reported.

CONCLUSION

The use of a resorbable membrane in small buccal bony dehiscences in anterior maxillary single-tooth replacement resulted in less marginal bone loss, but showed more mucosal dehiscenses, higher bleeding scores and lower scores on root convexity and soft tissue color after at least 1 year of loading. No effect was seen on implant survival and success, overall esthetic results, and patient satisfaction.

Conflict of interest and funding

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CHAPTER 4

Esthetics and patient-reported outcomes of implants placed with guided bone regeneration and complete native bone: A prospective controlled clinical trial

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ABSTRACT

Purpose When encountering a buccal bone defect during implant placement, guided bone regeneration (GBR) is a well-accepted method for bone reconstruction. However, it is still unclear if the esthetic and patient-reported outcomes are comparable to implants placed in native bone. The purpose of this prospective trial was to compare implants placed with a GBR procedure for a small (≤ 4 mm) buccal defect with implants placed completely in native bone (control).

Materials and Methods Patients were allocated to the GBR group or control group during implant placement in the esthetic zone. Implants were placed after at least 12 weeks of healing of the extraction sockets. A buccal bone defect of ≤ 4 mm resulted in allocation to the GBR group. Follow-up was performed until 12 months after loading. Outcome measurements were as follows: esthetic scores, patient-reported outcome measurements, implant survival and complications, clinical indices, and radiographic measurements.

Results In total, 45 patients were included, of which 23 underwent a GBR procedure after implant placement, and in 22 patients no GBR was necessary. No significant differences in esthetic outcomes were seen between the two groups. At the final follow-up, a mean pink esthetic score (PES) of 7.8 (SD: 1.5) was seen for the GBR group and 8.4 (SD: 1.4) for the control group. Regarding the white esthetic score (WES), a mean of 9.1 (SD: 1.0) was found for both groups. Patients of both groups were equally satisfied with their mucosa and crown. A mean visual analog score (VAS) for the soft tissues of 8.6 (SD: 1.0) in the GBR group and 8.8 (SD: 0.9) for the control group was noted. A mean VAS of 9.2 (SD: 0.8) was noted for the crown in the GBR group and 8.6 (SD: 2.0) in the control group. Implant survival was 100%, and there were no significant differences in complications, plaque/bleeding/gingiva indices, width of attached mucosa, and marginal bone loss.

Conclusion Implants placed in the esthetic zone with GBR or complete native bone coverage showed successful esthetic outcomes and satisfied patients with predictable clinical and radiographic parameters after more than 1 year

of loading. Within the limits of this study, GBR for a small buccal bone defect seems to be a reliable technique with good esthetics and patient-reported outcomes.

INTRODUCTION

Ideally, implants are placed in the optimal prosthetic location, with full native bone coverage and a thick, healthy gingiva to optimize soft tissue esthetics. However, the alveolar ridge might become too narrow for complete bone surrounding of the dental implant due to ridge alterations after trauma, infection, or physiologic resorption.[1, 2] Small bone defects do not necessarily lead to implant loss, but might negatively influence soft tissue esthetics, and patient reported outcomes.[3-5]

To get esthetically pleasing results, different treatment options are available to prevent these ridge alterations, such as immediate and early implant placement and ridge preservation.[6] Immediate implant placement,[7, 8] as well as early placement,[9, 10] leads to acceptable esthetic outcome.[11, 12] Ridge preservation might offer the advantage of optimizing soft tissue esthetics.[13] In patients with a buccal bone deficiency at implant placement, different bone augmentation procedures can be performed to correct these defects, ie, by using autogenous bone or bone substitutes. Furthermore, membranes are used to direct new bone formation, also known as guided bone regeneration (GBR). GBR has become a widely accepted treatment modality in oral implantology.[14, 15]

There are several trials comparing implants placed with GBR versus implants placed completely in native bone.[16-21] Unfortunately, none of these trials prospectively investigated the esthetic results and patient reported outcome measurements.

The objective of this prospective controlled clinical trial was to compare implants placed with a GBR procedure for a small buccal bone defect (≤ 4 mm) with those placed completely covered by alveolar bone in terms of esthetic results and patient-reported outcomes as the primary outcomes. Furthermore, this study assessed implant survival, complications, and clinical and radiographic results.

MATERIALS AND METHODS

Design

The study protocol was approved and registered by the medical ethical committees, the central committee on human subjects and the Dutch trial register (MEC 2011.039; NL34657.078.11; NL5956). A comparison between the GBR group of current study with an augmentation procedure without membrane has been previously published.[22] This research was conducted according the principles of the Declaration of Helsinki. The transparent reporting of evaluations with nonrandomized designs (TREND) guidelines were used for reporting.[23]
In this prospective controlled clinical trial, implants placed with a GBR procedure for a small buccal bone defect (GBR group) were compared to implants placed completely covered by native alveolar bone (control group). Patients were allocated to the GBR or control group after placement of a single implant in the esthetic zone (incisor/canine/first premolar). Bonelevel 3.3- and 4.1-mm-diameter implants were placed depending on the mesial-distal and bucco-palatal volume/space available (Straumann). Patients were considered for inclusion in this study when they fulfilled the following criteria.

The inclusion criteria were as follows:

- Over 18 years of age
- One missing tooth on the location of an incisor, cuspid or first premolar
- GBR group: buccal bone defect of ≤ 4 mm
- Control group: implant surface completely in native bone

The exclusion criteria were as follows:

- Expected bone defect of > 4 mm
- Augmentation procedure for bone defect without membrane
- Active periodontitis or acute oral infections
- Uncontrolled diabetes
- Smoking
- Current chemotherapy
- Head and neck radiotherapy
- The inability to maintain basic oral hygiene

Surgical procedure

Implants were placed after at least 12 weeks of healing of the extraction socket. Surgeries were performed at the University Medical Center Erasmus MC, Rotterdam and the St. Anna Hospital, Geldrop, the Netherlands. All surgical procedures were performed by one surgeon (E.W.). The GBR procedure was performed after implant placement by covering the surface of the implant with an equal amount of locally harvested autogenous bone chips and BoneCeramic, a synthetic bone substitute (Straumann). The next step was the application of MembraGel, a resorbable hydrogel membrane (Straumann). This surgical procedure is shown in Figure 1. Stage-two surgery (by a small slit incision) and abutment connection were performed 8 weeks after implant placement.

Outcome measurements

Esthetic scores

Peri-implant soft tissue esthetics were evaluated by the modified pink esthetic index (PES) and implant crown esthetics were scored with the modified white esthetic score (WES).[24, 25] The PES/WES scores were separately evaluated by two researchers on digital photographs made using a standardized protocol. The researchers were unaware of treatment allocation during the evaluation.

Patient-reported outcomes

Patient-reported outcomes were measurements with questionnaires using a visual analog scale

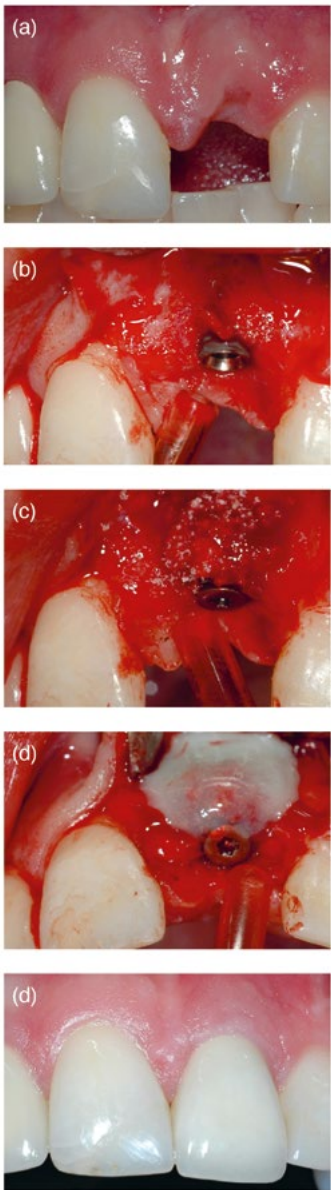

Figure 1 Implant placement with GBR (a) initial situation, (b) bone defect at the buccal site of the implant, (c) bone augmentation, (d) membrane application, (e) clinical situation 1 year after loading.

(VAS scale: 0 to 10). The questions focused on satisfaction with the implant crown, peri-implant soft tissues, and total dentition. Patient-reported outcomes were assessed preoperatively, 1 and 6 months after loading, and at the final follow-up.

Implant survival and complications

Mucosal dehiscence, swelling, and other early complications were scored at 2, 6, and 8 weeks after surgery. Survival was scored until at least 12 months of loading/abutment connection.[26]

Clinical indices

The clinical indices were evaluated after 1, 6, and at least 12 months of loading. The modified Plaque Index (PI), Bleeding Index (BI), Gingival Index (GI), Width of Attached Mucosa (WAM), and Pocket Probing Depth (PPD) were evaluated.[27-30] These parameters were scored and noted by independent clinicians (B.J., J.P.) unaware of treatment allocation.

Radiographic measurements

Digital periapical radiographs were used to measure changes in the marginal bone levels (MBLs). To standardize this process, individual putty molds were used for the x-ray equipment. Radiographs were taken after implant placement and 1, 6, and at least 12 months of loading. OsiriX (OsiriX v.7.0.1., Pixmeo SARL) was used to measure the distance between the crestal bone level and implant shoulder. The implant length was used as a reference for the calculations. All measurements were performed twice and were blinded to treatment allocation. The average of both measurements was used for statistical analysis.

Statistical analysis

Relative risks (RRs) with their 95% confidence intervals (95% CI) were calculated for dichotomous outcomes. Means with standard deviations (SDs) were calculated for normally distributed data and medians with their first (Q1) and third quartiles (Q3) of the interquartile range for non-normally distributed data (ordinal and continuous outcomes). For the non-normally distributed data,

means and SDs of the final follow-up visits were also calculated for comparison to other studies. A Mann-Whitney U test was used to observe differences between continuous, non-normally distributed, and ordinal parameters and presented with their effect sizes (r).[31] Differences between categorical outcomes were evaluated by the Fisher-Freeman-Halton test. A Friedman test was used to observe differences between time points of all ordinal data. For the total scores of the PES/WES and change in MBL, an intraclass correlation coefficient (ICC) was calculated by using a two-way mixed model of the consistency type. Statistical analysis was performed with SPSS (Version 20.0.0 for Mac, SPSS Inc, IBM Corporation).

RESULTS

Baseline characteristics

Patients were recruited between April 2011 and February 2014. The median follow-up was 13 months, with a minimum of 12 and maximum of 56 months. Implants were placed after at least 3 months with a median of 5 months. Two outliers were found. One patient in the GBR group was missing the lateral incisor for more than 13 years, and one patient in the control group missed the first premolar for 10 years. Seventy-five patients were assessed for eligibility (Figure 2). Two patients declined to take part in the present study. One patient received immediate implant placement and was therefore excluded. In 50 patients, a bone defect was seen after implant placement. Twenty-seven of these patients were randomized to an augmentation procedure without a membrane and were not analyzed in this article.[22] Eventually, in 23 patients, a GBR procedure was performed. From the 75 patients, 22 did not have a bone defect at the moment of implant placement and received an implant in complete native bone. No patients were lost to follow-up.

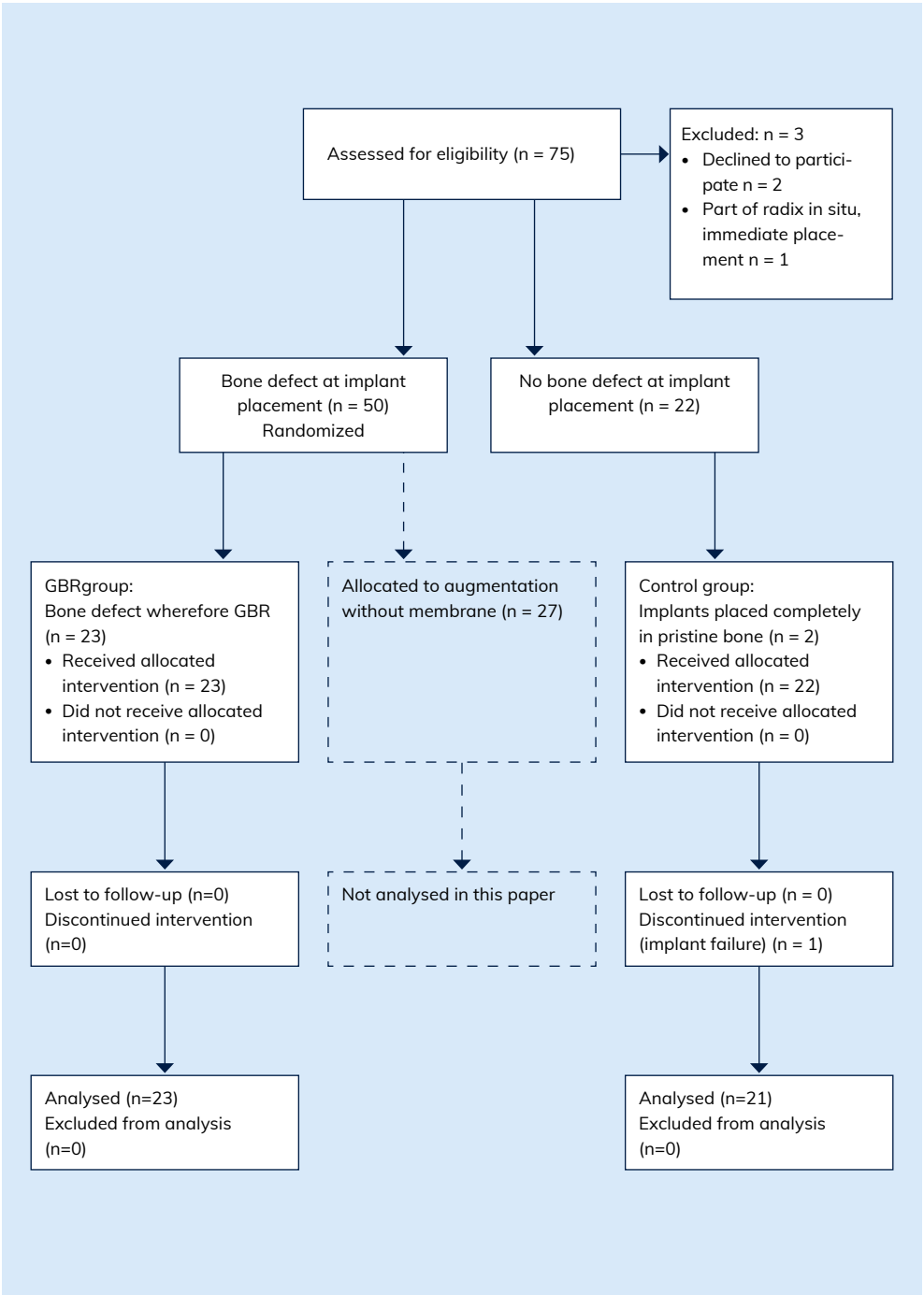

Figure 2 Flow diagram.

At baseline (Table 1), the distribution of implants placed in the incisor, canine, and premolar region was not equal in both groups ($\chi 2(3) = 14.798$, $p < 0.001$). In the GBR group, 22 implants were placed in the incisor region and 1 in the first premolar area. In the control group, 11 implants were placed in the incisor region, 3 in the canine area, and 8 in the first premolar region. Significantly more men (14/20) needed an augmentation than women (9/25) ($\chi 2(1) = 5.140$, $p = 0.036$).

	GBR	Control
Number of patients	23	22
Age	44.26 (10.58)	47.05 (15.52)
Gender (female/male)	9/14	16/6
Center (Erasmus MC/St. Anna)	3/20	4/18
Months after extraction	5 (5-7)	5 (4-6)
Cause of tooth loss (infection/fracture/ /agenesis/unknown)	15/2/1/5	18/3/1/0
Location of implant (first incisor/second incisor/canine/first premolar)	15/7/0/1	4/7/3/8
Length of implant (8/10/12 mm)	0/7/16	1/7/14
Diameter of implant (3.3/4.1 mm)	14/9	12/10

Mean and standard deviation noted for age and median, first and third quartile for months after extraction.

Table 1 Baseline characteristics.

Esthetic scores

Table 2 shows the median PES, WES and combined scores for GBR and control. There were no significant differences between the two groups at any of the time points. At final follow-up a mean PES of 7.8 (SD: 1.5) was seen for the GBR group and a mean of 8.4 (SD: 1.4) for the control. Regarding the WES, a mean of 9.1 (SD: 1.0) was found for both groups. One patient in both groups scored lower than 6 points for the soft tissue esthetics. A significant improvement of the PES scores was found during the follow-up ($\chi 2(2) = 40.587$, $p < 0.001$).

	GBR	Control
1 month after loading	n = 22	n = 22
Mesial papilla	1.0 (1.0-1.6)	1.0 (0.8-1.0)
Distal papilla	1.0 (1.0-1.5)	1.0 (0.5-1.5)
Curvature labial mucosa	1.5 (1.0-2.0)	2.0 (1.5-2.0)
Level labial mucosa	1.5 (1.0-2.0)	2.0 (1.5-2.0)
Root convexity soft tissue color and texture	1.3 (1.0-1.5)	1.8 (1.5-2.0)
Total modified PES	6.0 (5.4-8)	7.0 (6.4-7.6)
	p = 0.249 r = 0.037	
Tooth form	2.0 (1.5-2.0)	2.0 (1.5-2.0)
Tooth volume/outline	2.0 (1.5-2.0)	2.0 (1.5-2.0)
Color	1.8 (1.5-2.0)	2.0 (1.5-2.0)
Surface texture	2.0 (1.9-2.0)	2.0 (2.0-2.0)
Translucency	2.0 (1.5-2.0)	2.0 (1.5-2.0)
Total modified WES	9.0 (8.00-9.5)	9.00 (8.4-9.6)
	p = 0.424, r = 0.064	
Combined PES/WES	15.5 (13.9-16.6)	15.8 (14.4-17.1)
6 months after loading	n = 20	n = 19
Mesial papilla	1.5 (1.0-2.0)	1.5 (1.0-2.0)
Distal papilla	1.5 (1.1-2.0)	1.0 (1.0-1.5)
Curvature labial mucosa	2.0 (1.5-2.0)	2.0 (2.0-2.0)
Level labial mucosa	1.5 (1.0-2.0)	2.0 (1.5-2.0)
Root convexity soft tissue color and texture	1.5 (1.0-1.5)	2.0 (1.5-2.0)
Total modified Pink Esthetic Score	8.00 (6.5-8.9)	8.0 (7.0-8.5)
	p = 0.403, r = 0.065	
Tooth form	2.0 (1.5-2.0)	2.0 (2.0-2.0)
Tooth volume/outline	2.0 (1.5-2.0)	2.0 (1.5-2.0)
Color	1.8 (1.5-2.0)	2.0 (1.5-2.0)
Surface texture	2.0 (2.0-2.0)	2.0 (2.0-2.0)
Translucency	1.8 (1.5-2.0)	2.0 (1.5-2.0)
Total modified WES	9.0 (8.5-9.5)	9.0 (8.5-10.0)
	p = 0.473, r = 0.076	
Combined PES/WES	17.0 (15.0-18.0)	17.0 (16.0-18.0)
After 12 months of loading	n = 20	n = 19
Mesial papilla	1.8 (1.0-2.0)	1.5 (1.0-2.0)
Distal papilla	2.0 (1.5-2.0)	1.5 (1.0-1.5)
Curvature labial mucosa	2.0 (1.1-2.0)	2.0 (2.0-2.0)
Level labial mucosa	1.5 (1.0-2.0)	2.0 (2.0-2.0)
Root convexity soft tissue color and texture	1.3 (1.0-1.9)	2.0 (1.5-2.0)
Total modified PES	7.5 (7.0-9.0)	9.0 (8.0-9.5)
	p = 0.170, r = 0.027	
Tooth form	2.0 (1.5-2.0)	2.0 (2.0-2.0)
Tooth volume/outline	2.0 (1.5-2.0)	2.0 (1.5-2.0)
Color	2.0 (1.5-2.0)	2.0 (1.5-2.0)
Surface texture	2.0 (2.0-2.0)	2.0 (1.6-2.0)
Translucency	2.0 (1.6-2.0)	2.0 (1.5-2.0)
Total modified WES	9.5 (8.5-9.5)	9.5 (8.1-10)
	p = 0.781, r = 0.123	
Combined PES/WES	17.0 (15.0-18.0)	18.0 (15.5-19.0)
	p = 0.265, r = 0.042	

Median, first and third quartile of the 5 parameters (scores from 0-2) of the modified Pink and White Esthetic Scores (PES and WES), the total PES and WES (scores from 0-10) and the combined PES/WES (scores from 0-20). A Mann-Whitney U-test was used to calculate significance levels (p-values) which are presented with their effect sizes (r).

Table 2 Esthetic assessment.

Patient-reported outcomes

In both groups, patients were very satisfied with their implant crown and peri-implant soft tissues (Table 3). No significant differences were found. A mean visual analog score (VAS) for the soft tissues of 8.6 (SD: 1.0) in the GBR group and 8.8 (SD: 0.9) for the control group was found. A mean VAS of 9.2 (SD: 0.8) was found for the crown in the GBR group and 8.6 (SD: 2.0) in the control group. Only one patient in the control group scored lower than 6 for soft tissue esthetics. Patients rated their dentition significantly higher due to the treatment over the follow-up period ($\chi 2(3) = 41.336$, $p < 0.001$).

Visual Analogue Scale	GBR	Control	p-value	Effect Size (r)
Before surgery	n = 23	n = 22		
Expected satisfaction with implant crown	9.2 (8.4-9.5)	8.5 (7.8-9.2)	0.152	0.214
Expected satisfaction with peri-implant soft tissues	8.5 (7.1-9.1)	8.1 (6.7-8.6)	0.323	0.147
General satisfaction with dentition	6.0 (3.7-7.2)	6.7 (4.5-8.2)	0.358	0.137
1 month after loading	n = 22	n = 22		
Satisfaction with implant crown	9.1 (8.8-9.8)	9.2 (8.1-10.0)	0.991	0.002
Satisfaction with peri-implant soft tissues	8.1 (6.7-9.2)	8.4 (5.4-10.0)	0.646	0.069
General satisfaction with dentition	8.5 (8.0-9.3)	8.5 (7.5-9.8)	0.760	0.046
6 months after loading	n = 22	n = 21		
Satisfaction with implant crown	9.6 (8.9-9.9)	9.7 (8.1-10.0)	0.899	0.019
Satisfaction with peri-implant soft tissues	7.9 (7.4-9.2)	9.2 (7.5-9.9)	0.330	0.149
General satisfaction with dentition	8.7 (8.4-9.3)	9.1 (7.4-9.8)	0.679	0.063
After 12 months of loading	n = 23	n = 20		
Satisfaction with implant crown	9.3 (8.6-9.9)	9.4 (8.1-9.9)	0.374	0.137
Satisfaction with peri-implant soft tissues	8.7 (8.0-9.7)	8.9 (8.1-9.9)	0.478	0.110
General satisfaction with dentition	8.4 (7.5-9.4)	8.5 (8.0-9.5)	0.826	0.034

Median, first and third quartile of the patient reported outcomes measured on a visual analogue scale from 0 to 10. A Mann-Whitney U-test was used to calculate significance levels (p-values) which are presented with their effect sizes (r).

Table 3 Patient reported outcome measurements.

Survival and complications

After 6 weeks, a mucosal dehiscence of less than 2 mm was seen in 6 out of 23 patients in the GBR group and 3 out of 22 patients in the control group (RR: 0.86, 95% CI: 0.64-1.15). These patients were advised to keep rinsing with a chlorhexidine 0.12% solution. One partial loss of the graft was seen, and one patient in the control group showed a small fistula at 6 weeks after implant placement that resolved spontaneously. All implants were integrated and functioning until the last follow-up visit, without subjective complaints, infection with suppuration, mobility, or a continuous radiolucency around the implant.

Clinical indices

During the complete follow-up, the plaque, bleeding, and gingival indices, width of the attached mucosa, as well as the PPDs did not differ between treatment groups (Table 4). However, the PPD did increase statistically significantly over time from a median of 2.0 (1 month) to 2.1 (6 months) and 2.3 (12 months) ($\chi 2(2) = 40.587$, $p < 0.001$).

	GBR	Control	p-value	Effect Size (r)
1 month after loading	n = 23	n = 22		
Plaque	20/1/2/0	19/2/1/0	1.000	0
Bleeding	13/8/2/0	11/9/2/0	0.693	0.059
Gingiva	18/4/1/0	20/0/4/0	0.313	0.150
WAM	0/4/3/16	0/2/0/20	0.097	0.248
PPD	2.0 (1.8-2.4)	2.1 (1.5-2.4)	0.927	0.014
6 months after loading	n = 22	n = 21		
Plaque	19/3/0/0	16/4/1/0	0.369	0.137
Bleeding	14/7/1/0	12/9/0/0	0.765	0.046
Gingiva	18/4/0/0	18/3/0/0	0.732	0.052
WAM	0/4/5/13	0/2/2/17	0.137	0.227
PPD	2.1 (2.0-2.5)	2.1 (2.0-2.6)	0.787	0.041
After 12 months of loading	n = 23	n = 21		
Plaque	20/1/2/0	19/2/0/0	0.654	0.068
Bleeding	13/9/1/0	16/5/0/0	0.155	0.215
Gingiva	19/4/0/0	20/1/0/0	0.192	0.196
WAM	0/3/7/11	0/2/8/11	0.889	0.022
PPD	2.3 (2.0-2.6)	2.5 (2.0-2.9)	0.293	0.160

Plaque-, bleeding- and gingiva-index, width of the attached mucosa with possible values of 0/1/2/3 and the median, first and third quartile of the pocket probing depth in mm. A Mann-Whitney U-test was used to calculate significance levels (p-values) which are presented with their effect sizes (r).

Table 4 Clinical indices and pocket probing depth.

Radiographic measurements

The change in the MBL was not statistically significantly different between the two groups for all follow-up time points (Table 5). After completion of the study, the GBR group showed a mean change in MBL of 0.1 mm (SD: 0.2) versus a mean of 0.5 mm (SD: 0.8) in the control group. The MBLs did not increase significantly over time ($\chi 2(2) = 4.594$, $p = 0.101$).

	GBR	Control	p-value	Effect Size (r)
1 month after loading	n = 17	n = 16		
Mesial	0.0 (0.0-0.2)	0.2 (0.0-0.5)	0.097	0.013
Distal	0.0 (0.0-0.3)	0.0 (0.0-0.3)	0.873	0.148
Average	0.1 (0.0-0.2)	0.2 (0.0-0.5)	0.186	0.030
6 months after loading	n = 16	n = 20		
Mesial	0.0 (0.0-0.4)	0.4 (0.0-0.6)	0.149	0.023
Distal	0.0 (0.0-0.3)	0.1 (0.0-0.5)	0.164	0.022
Average	0.1 (0.0-0.3)	0.2 (0.00.7)	0.102	0.016
After 12 months of loading	n =19	n =18		
Mesial	0.0 (0.0-0.4)	0.2 (0.0-0.9)	0.169	0.023
Distal	0.0 (0.0-0.2)	0.0 (0.0-0.5)	0.731	0.118
Average	0.0 (0.0-0.3)	0.1 (0.0-0.6)	0.257	0.039

Median, first and third quartile of the change in marginal bone level in mm. A Mann-Whitney U-test was used to calculate significance levels (p-values) which are presented with their effect sizes (r).

Table 5 Radiographic assessment.

Inter- and intraobserver correlation

The interobserver ICC determined for the total PES/ WES scores was 0.767 (95% CI: 0.666 to 0.837), and the intraobserver ICC for the change in MBL was 0.972 (95% CI: 0.965-0.978).

DISCUSSION

Implant placement combined with a GBR procedure and implant placement completely in native bone showed similar esthetic results and equally satisfied patients. Comparable results were seen regarding implant survival, complications, and clinical and radiographic parameters after at least 1 year of loading.

Baseline characteristics

In the GBR group, most implants were placed in the incisor region, while in the control group they were mainly placed in the premolar region. It is known that sockets in the premolar area have a thicker buccal bone wall with less resorption when compared to extraction sockets in the incisor region.[1, 32] As a result, a GBR-procedure was less frequently needed in the premolar region.

Esthetic scores

In the present study, at the final follow-up, a mean PES of 7.8 (SD: 1.5) was seen for the GBR group and a mean of 8.4 (SD: 1.4) for the control group. Regarding the WES, a mean of 9.1 (SD: 1.0) was found for both groups. This is the first study comparing GBR with a control group on esthetic outcomes, so no comparison with the literature was possible. The PES and WES scores of the present study were therefore compared to other studies on single tooth replacement in the esthetic zone with different placement protocols.[6] Two studies regarding immediate implant placement with immediate provisional restoration found a mean PES of 7.5 (SD: 1.6) and a mean WES of 8.1 (SD: 0.9) in alveolar sockets without bone defects and a mean PES of 7.5 (SD: 1.6) and a mean WES of 8.1 (SD: 0.9) with a buccal bone defect.[7, 8] Follow-up was 1 year of loading. Two studies regarding early implant placement with only soft tissue healing (4 to 8 weeks) found a mean PES of 8.1 and a mean of WES 8.7 with bone-level implants after 1 year of loading and a mean PES of 7.8 and a mean WES of 6.9 after 2-4 years of loading for tissue level implants.[9, 24] One study used early placement with partial bone healing (12 weeks) and found a mean PES of 6.9 (SD: 1.8) and WES of 7.5 (SD: 1.7) after one year. Half of their patients received a bone graft before implant placement, which might explain the lower scores.[33] A study regarding late implant placement (> 3 months) found much lower PES/WES scores with a mean PES of 6.3 (SD: 1.7) and mean WES of 7.3 (SD: 1.5) found at 1-year follow up.[34] In the present study, the PES and WES scores were comparable to the literature regarding immediate and early implant placement for both groups. Although follow-up was only 1 year, other long-term studies the soft tissue esthetic scores show that the soft tissue esthetics seem to be stable over time after the first year of loading.[5, 35]

Patient-reported outcomes

The patients of both groups were pleased with their implant crown, peri-implant soft tissues, and their dentition in general after treatment, which is comparable to previous literature where patients were also satisfied with single-tooth replacement in the esthetic zone.[33-36] These other studies showed general patient satisfaction of 8.5 (SD: 1.0) to 9.0 (SD: 1.0) for single-tooth replacement in the esthetic zone. The patients in the present study also rated their dentition significantly higher due to the treatment.

Survival and complications

In both groups implant survival was high. Comparable studies previously reported survival rates in the GBR group varying between 84.6% and 100%, with a follow-up ranging from 2 to 15 years.[16-21] In the control groups survival rates of 91.7% to 100% were found. In a trial using the same hydrogel for the GBR-procedure as present study, a survival rate of 100% was found in 32 patients with 5 year follow-up.[37, 38] In agreement with the current literature, implants placed in combination with GBR seemed to show similar survival to implants placed in completely native bone.

Clinical indices

The low plaque, gingiva and bleeding indices and PPDs are similar to the other studies reporting these clinical parameters.[16, 17, 19-21] Patients can be informed that buccal bone defect requiring GBR does not lead to a less healthy situation. The statistically significant increase of the PPD over time from a median of 2.0 to 2.3 mm is in line with the increased esthetic scores for the mesial and distal papillae and is not of pathologic origin.

Radiographic measurements

Comparable studies previously reported a change in MBL varying from 0.7 mm (SD: 0.8) to 2.4 mm (SD: 0.16) for GBR and 0.5 mm (SD: 0.4) to 2.36 mm (SD: 0.17) for control.[16, 17, 19-21] A change in MBL of 0.43 mm (SD: 0.56) was found one year after loading when the same hydrogel membrane as present study was used.[38] Bone-level implants in general showed a comparable change in MBL of 0.49 mm after 1 to 2 years of loading.[39] In line with the literature, it can be concluded that the change in MBL seems to be stable for implants placed in combination with GBR and in complete native bone.

Strengths and limitations

Strengths of the study are the prospective design and proper patient selection. The only variable that differed for allocation was the presence of a buccal bone defect after implant placement. This design ensures highly comparable groups. Another strength of the study was the blinded evaluation of both clinicians and investigators. This was the first study prospectively comparing these two groups on esthetic and patient-reported outcome measurements. Sample size calculation for this study population was based on the change in MBL.[40] No sample size calculation for the esthetic- and patient-reported outcomes was performed.

It should be noted that not all baseline characteristics were equal between the two groups. As expected in the control group, there were significantly more patients with an implant in the first premolar area. In the (first) premolar area the buccal bone is generally somewhat more thick then in the incisor and cuspid area.[41] Due to this difference in facial bone thickness more resorption occurs in these sites, leading to a higher need for GBR.[2] This finding potentially could have led to more favorable results in the control group, but no significant differences were found.

Furthermore, we investigated an uncommon hydrogel PEG membrane, potentially reducing the generalizability of the results. Different animal studies showed at re-entry, that this hydrogel might be an effective barrier against soft-tissue ingrowth.[42-44] A human study evaluating clinical and CBCT data concluded that this hydrogel membrane is comparable to the more-used collagen membranes for treating bone defects around oral implants till 5 years of loading.[37, 38] The research protocol was written in 2011 when a CBCT-scan was not part of the regular clinical follow-up and the medical ethical committee did not approve CBCT for study purposes. Although follow-up is only 1 year after loading, the esthetic and patient reported outcomes seem to be stable over time after the first year of loading.[5, 35]

CONCLUSIONS

Implants placed in the esthetic zone with a GBR procedure or complete native bone coverage showed successful esthetic outcomes and satisfied patients with predictable clinical and radiographic parameters after more than 1 year of loading. Within the limits of this study, GBR for small buccal bone defects seems to be a reliable technique with satisfying esthetics and patient-reported outcomes.

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CHAPTER 5

Soft tissue contour and radiographic evaluation of ridge preservation in early implant placement: A randomized controlled clinical trial

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ABSTRACT

Objectives To compare two ridge preservation techniques and spontaneous healing in terms of hard and soft tissue changes 2 months after tooth extraction.

Materials and Methods The study was designed as a randomized controlled trial and included 75 patients. After single tooth extraction in the maxillary incisor/premolar area, patients were randomly allocated to one of the following groups: (a) ridge preservation with a xenogeneic bone substitute covered with a collagen matrix (CM-group), (b) ridge preservation with a xenogeneic bone substitute covered with a free palatal graft (PG-group) or (c) spontaneous healing (control). Eight weeks after tooth extraction, implants were placed and clinical, profilometric and radiographic evaluations were performed. In addition, the need for further guided bone regeneration (GBR) at implant placement was assessed. The differences between the treatment groups were compared with the One-way ANOVA or Kruskal-Wallis test with the corresponding post hoc analysis. The proportions of the categorical parameters were compared with the Fisher's exact test.

Results Seventy-five patients underwent early implant placement 8 weeks after tooth extraction and were evaluated. CM-group (-0.9 SD 0.6 mm) and PG-group (-1.0 SD 0.8 mm) showed less horizontal bone resorption compared to the control group (-3.2 SD 2.1 mm) ($p < 0.001$). Moreover, the necessity of GBR at implant placement was significantly less in CM-group (32%) and PG-group (24%) when compared to control group (72%) ($p = 0.001$). Patients in CM-group experienced less pain than PG-group, one week after tooth extraction ($p = 0.042$). No significant differences were found regarding graft evaluation, post-operative complications, and soft tissue contour.

Conclusion Ridge preservation using a xenogeneic bone substitute covered with a collagen matrix or a palatal graft, results in less bone resorption and fewer GBR procedures at early implant placement compared to spontaneous healing.

INTRODUCTION

Replacement of a single tooth in the esthetic zone by means of implant therapy is a demanding procedure. Following tooth extraction, the alveolar ridge undergoes horizontal and vertical bone loss.[1-3] This can negatively influence the ridge contour and thus the esthetic outcome.[4] In order to achieve optimal esthetic results, both the bone and soft tissue contour should be preserved as good as possible. Ridge preservation is used to reduce the resorption of the ridge.[5] The main goal of alveolar ridge preservation (ARP) procedures is to preserve both hard and soft tissue volume for future implant placement.[5, 6] Landsberg described a modified ridge preservation technique called 'socket seal surgery', where flap elevation is avoided and bone and soft tissue grafting is combined prior to implant placement.

In addition to the application of a bone substitute material, an epithelialized palatal graft is used to seal the extraction site from the oral cavity immediately after tooth extraction.[7] The application of a biomaterial at the extraction site, which is then covered with a collagen matrix or a free soft tissue graft, results in less vertical and horizontal changes of the alveolar ridge 4-6 months after extraction and can lead to good esthetic results at future implant sites.[8-10] Combining ARP with early implant placement might offer the advantage of optimizing the soft tissues but without the drawback of a prolonged healing period[11].

Although applying a free soft tissue punch graft is a relatively straightforward procedure, patient morbidity is increased due the second surgical site.[12] The use of a substitute material for soft tissue grafting would prevent donor morbidity associated with soft tissue grafts when performing ARP.[8, 13] This is one of the first studies to evaluate two ARP techniques with spontaneous healing for early implant placement. The aim of current study was to evaluate the clinical results, profilometric and radiographic changes, as well as patient satisfaction following alveolar ridge preservation (ARP) in single sites in the anterior maxilla comparing the use of a bone substitute material of xenogeneic origin covered with either a xenogeneic collagen matrix or a free gingival graft (punch technique) versus spontaneous healing.

MATERIALS AND METHODS

Study design

The study protocol was approved by the medical ethical committee, the central committee on human subjects (MEC-2015-016; NL49965.078.14) and registered in the Dutch trial register (NL6497). This research was conducted according the principles of the Declaration of Helsinki. The CONSORT statement was used for reporting.[14] The study was designed as a randomized controlled clinical trial with patients being randomly allocated to one of two ARP techniques or a negative control group:

CM-group Demineralized bovine bone mineral with added 10% collagen (Geistlich Bio-Oss® Collagen, Geistlich Pharma: DBBM-C), and covered with a collagen matrix (Geistlich Mucograft® Seal, Geistlich Pharma: CM).

PG-group Emineralized bovine bone mineral with added 10% collagen (DBBM-C) covered with an autogenous soft tissue 'punch' graft harvested from the palate (PG).

Control Spontaneous healing

Randomization and treatment allocation

The patients were randomized in either the CM-group, PG-group or control by digital software allocation according to the block method.[15] The allocation sequence was concealed from the surgeon (JP) in opaque, sealed envelopes, until the very last step in the surgical procedure (just after surgical removal of the tooth). Patients were not blinded as this was not possible. Reporting of clinical measurements was blinded, as the reporting clinician (JP) was unaware of the treatment group. The investigators were not aware of the allocation during the analysis of the data.

Study population

All operations were performed at the Erasmus University Medical Center, Rotterdam and the Catherina Hospital, Eindhoven, the Netherlands. All patients were referred for implant placement by their general practitioner. In close cooperation with the referring dentist, a treatment plan was set up that includ-

ed a surgical phase (extraction, ARP and implant placement) and a prosthetic phase in the dental office of the referring dentist (dental crown placement). All surgeries were performed by one surgeon (JP). Patients were considered for inclusion in this study when they fulfilled the following criteria:

Inclusion criteria
- Over 18 years of age
- Single tooth replacement
- Maxillary tooth at the location of an incisor, cuspid or first/second premolar
- Patients able and willing to understand and follow the study procedures

Exclusion criteria
- Ongoing periodontal disease and bone loss
- Smoking
- Uncontrolled diabetes
- History of radiotherapy in the head-and-neck region
- Current chemotherapy
- Disability to maintain basic oral hygiene procedures

Surgical procedure

Tooth extraction was performed carefully in order to preserve the buccal bone plate and the surrounding soft tissues. A flapless procedure was performed using periotome, elevators, and forceps. If needed, a drill was used to remove the tooth in multiple pieces. After extraction, any existing granulation tissue was removed and the socket was rinsed with sterile saline.

CM-group

The soft tissue borders of the alveolus were de-epithelialized using a rotating diamond burr. The DBBM-C was placed within the socket up to the level of the lingual/palatal bone plate. The CM was placed on top of the DBBM-C and sutured to the gingival margins of the socket with 4 to 6 interrupted sutures (No. 4-0 Ethilon, Ethicon).

PG-group

The soft tissue borders of the alveolus were de-epithelialized using a rotating diamond burr. The DBBM-C was placed within the socket up to the level of the lingual/palatal bone plate. A suitable site for graft harvesting at the patient's palate was chosen, keeping a distance of 4 to 5 mm to the gingival margin. A free gingival graft with a target thickness of 4- to 5-mm thickness was harvested with a biopsy punch and gently removed with a sharp tissue elevator. Bleeding was stopped by compression with a sterile gauze. The soft tissue defect (mucosa or periosteum) was then covered with a tissue glue (Histoacryl, B. Braun Medical B.V.). The harvested graft was placed on top of the DBBM-C and sutured to the marginal gingiva of the socket with 4 to 6 interrupted sutures (No. 4-0 Ethilon, Ethicon). If the harvested graft was higher than the buccal or palatal soft tissues of the recipient sites, the graft was adapted according to these dimensions.

Control

After cleaning and rinsing the socket with sterile saline solution, a cross-mattress suture (No. 4-0 Ethilon, Ethicon) was used to keep the blood clot in place allowing spontaneous healing of the site.

All patients in the three treatment groups were instructed to rinse twice a day with a 0.12% Chlorhexidine solution and received pain medication (Ibuprofen) and antibiotics (Amoxicillin) for 5 days. Sutures were removed after 1 week.

Implant placement

Eight weeks after tooth extraction implants were placed. The implants placed had a diameter of 4.1 or 3.3 mm, and a length of 8 to 12 mm (Bone Level Tapered implants, Institute Straumann AG). After raising a mucoperiosteal flap from the top of the alveolar process, implants were placed according to the manufacturers guidelines. In case of thin a thin buccal plate (< 1 mm) or a dehiscence at the buccal aspect, a guided bone regeneration (GBR) was performed. This implied coverage of the titanium surface of the dental implant with locally harvested autogenous bone, covered with DBBM (Geistlich Bio-Oss®, Geistlich Pharma AG) and subsequent coverage with a resorbable membrane (Geistlich Bio-Gide®, Geistlich Pharma AG). The autogenous bone chips were harvested via the existing flap or a relatively small extension of the flap.

Outcome measurements

Figure 1 shows an overview of the treatment and follow-up sequence of the three treatment groups. Figure 2 illustrates the surgical procedure in the three different groups and follow-up after 1 and 8 weeks. The null hypothesis is that there is no difference between the three treatment groups for the following outcome measurements.

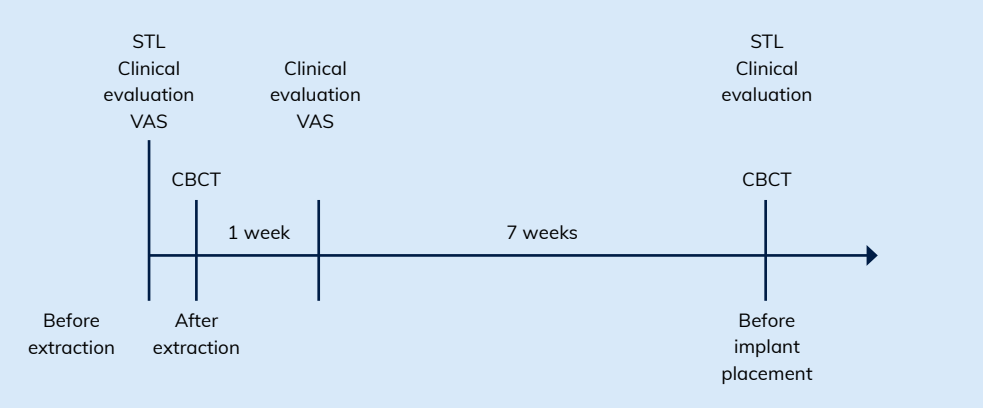

Figure 1 Overview of the treatment and follow-up sequence.

Clinical evaluation of the soft tissue healing after ridge preservation

The status of the grafted area was visually assessed at 1 and 8 weeks following grafting 9. The soft tissue was classified as:

- Integrated: supplied with blood, indicated by a reddish tissue color
- Fibrinoid: covered with fibrin and responding by bleeding after removal of the fibrinoid surface
- Incomplete (partially integrated): incomplete wound closure, area of epithelial invagination, and access to the graft material with a periodontal probe
- Necrotic (not integrated): no signs of blood supply

Clinical evaluation of the soft tissue healing was carried out by one person (JP). All adverse events such as signs of infection, post-operative bleeding, and allergic reactions were evaluated during all follow-up visits.

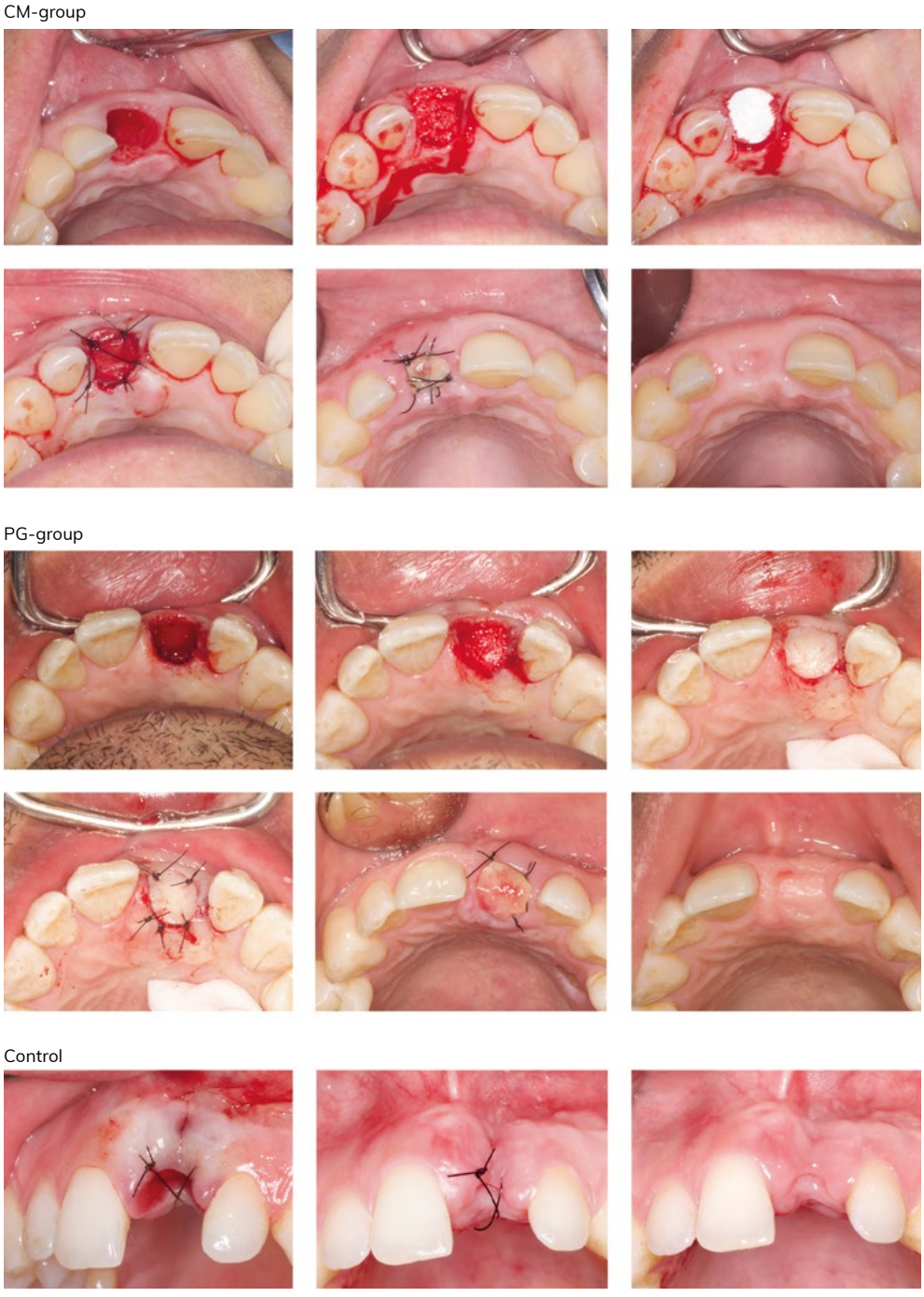

Figure 2 The surgical procedure in the three different groups and follow-up after 1 and 8 weeks.

Horizontal soft tissue contour changes

Alginate (Cavex CA37, Cavex Holland) impressions of the patients were taken at baseline (before extraction) and 8 weeks thereafter at the time of implant placement. Alginate was mixed using an automatic alginate mixer (Cavex Alginate Mixer, Cavex Holland). Pouring and casting was performed the next day by the dental laboratory. For the evaluation of the soft tissue contour changes, the poured plaster models were scanned with a surface scanner (7Series Model & Impression Scanner, Dental Wings). The obtained standard tessellation language (stl)-files were imported into a software for profilometric analysis (Swissmeda/SMOP). Digital cast models representing the time point before extraction and before implant placement (8 weeks after extraction) were superimposed by selecting three common points in both models for an automatic superimposition, followed by manual superimposition of both models in all three dimensions. The relevant area for the measurements of contour changes was defined according to previous studies on ridge contour alterations.[16-18] The area was defined horizontally by the mesial and distal papillary midline and vertically by the mucogingival line, and was measured 1 mm apical to the pre-extraction gingival margin. The area of interest was a rectangle measuring 4 mm in width and 2 mm in height. The mean change in the soft tissue contour per area was obtained by calculating in millimeters the mean value of all distances in labial direction contained in that area of interest.

Horizontal and vertical radiographic changes

To perform the radiographic measurements, cone-beam computer tomograph (CBCT) scans at baseline (before extraction) and at 8 weeks post-extraction (before implant placement) were processed using the same software for profilometric analysis. The smallest field possible for the CBCT device and maximal axial slice thickness of 1 mm was used. The horizontal and vertical measurements were calculated using the center of the long axis of the alveolus as a reference (Figure 3). The most apical point of the extraction socket was defined in the baseline image and two reference lines were subsequently drawn. The vertical reference line was drawn in the center following the long axis of the extraction socket crossing the apical reference point. The horizontal reference line was drawn perpendicular to the vertical line crossing the apical reference point.

The following measurements with respect to these reference points and lines were performed in the center of the extraction socket at baseline and at 8 weeks post-extraction:

- The horizontal ridge width measured at -1, -3 and -5 mm depth from the level of the palatal crest parallel to the horizontal reference line.
- The vertical ridge height measured from the apex of the alveolus to the buccal and palatal crest parallel to the vertical reference line.

Soft tissue dimensions at implant placement

Both the CBCT and the STL data obtained at 8 weeks post-extraction were imported into the above-described analysis software. Both were superimposed by selecting three common points to both surfaces for the automatic superimposition, followed by the manual superimposition in the three dimensions. The vertical reference line was drawn in the center following the long axis of the healed extraction socket crossing the apex (Figure 4). The horizontal reference line was drawn perpendicular to the vertical line at -1 mm depth from the palatal bone crest. The following measurements were then performed in the center of the extraction socket at 8 weeks post-extraction:

- The horizontal thickness of the tissue was calculated in millimeters on the buccal and palatal side.
- The vertical thickness of the tissue was calculated in millimeters at the center vertical reference line of the alveolus.

Necessity of additional augmentation

A thin buccal wall (< 1 mm) or dehiscence of the buccal wall after implant placement was reconstructed with the above-mentioned GBR technique. Necessity of this additional augmentation was recorded and evaluated.

Patient-reported outcomes

At follow-up, the influence of the treatment on patient satisfaction was investigated by a patient's questionnaire (before treatment and 1 week after tooth extraction by a visual analog scale (VAS) ranging from 1-10. Pain, swelling, and impact of the surgery were evaluated.

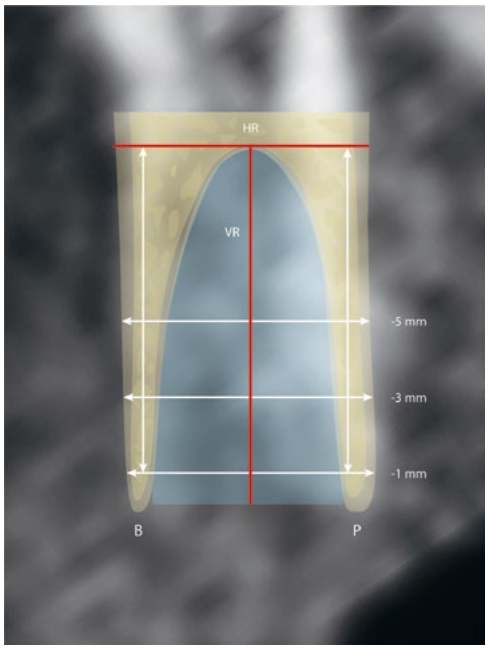

Figure 3 Horizontal and vertical radiographic changes. HR, horizontal reference line; VR, vertical reference line; B, buccal side; P, palatal side.

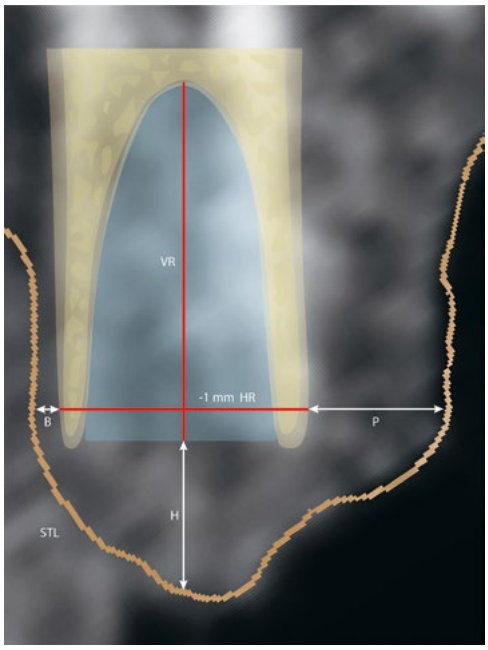

Figure 4 Soft tissue dimensions. HR, horizontal reference line; VR, vertical reference line; B, buccal mucosal thickness; P, palatal mucosal thickness; H, mucosal height; STL, superimposed soft tissues.

Statistical analysis

For nominal and dichotomous outcome data, significant differences between groups were calculated using the Fisher-Freeman-Halton exact test with post hoc pairwise Fisher's exact tests. A p-value < 0.05 was considered a significant difference. A Bonferroni correction for multiple comparisons was used. For the continuous outcomes, means were presented together with standard deviations (SD's) and medians with the first and third interquartile ranges. Means and SD's were additionally calculated for the non-normal distributed data to compare the data to other studies. To observe possible differences between the 3 treatment arms, the one-way ANOVA was used and presented. If a significant difference was observed between the groups from the one-way ANOVA, a Tukey's honestly significant difference post hoc analysis was performed to check which specific groups differed. If there were outliers the test was re-run

without the outliers to check is results were different. If other assumptions for the ANOVA were not met (assessed by the Shapiro-Wilk test of normality and Levene's test of homogeneity of variances), the non-parametric Kruskal-Wallis test was used and were significantly different, post hoc analysis was performed using Dunn's procedure. A Bonferroni correction for multiple comparisons was used for both procedures and adjusted p-values were presented. As thin wall phenotypes (incisor and cuspid area) often show a progressive bone resorption in contrary to thicker bone wall biotypes (premolar area), a subgroup analysis was performed with the patients receiving an implant in the incisors/cuspid area and premolar area separately.[4]

All analyses were performed using IBM SPSS Statistics for Mac, version 26.0: IBM Corp. Sample size calculation of this randomized controlled trial is based on the change in marginal soft tissue between the three groups one year after 1 year of loading. For similar patients, the SD of these changes was 0.58 mm.[19] A difference of 0.5 mm is considered a relevant difference leading to 21 patients/group for a power of 80% and alpha = 0.05. To allow for some drop-out cases, 25 patients per group were randomized.

RESULTS

Baseline characteristics

Patients were recruited between June 2015 and June 2017. The CONSORT flow diagram of patients assessed, allocated, and analyzed is displayed in Figure 5. During inclusion 75 patients were assessed for eligibility and randomized to one of the 3 groups (25 patients in each group). One patient in the control group was wrongly treated according the palatal graft-group (PG-group) protocol. As suggested by the CONSORT guidelines this patient was analyzed according randomization. No patients were lost over the 8-week follow-up. In total, 36 patients were included for treatment in the incisor/cuspid area and 39 patients for the premolar area. Baseline characteristics are shown in Table 1.

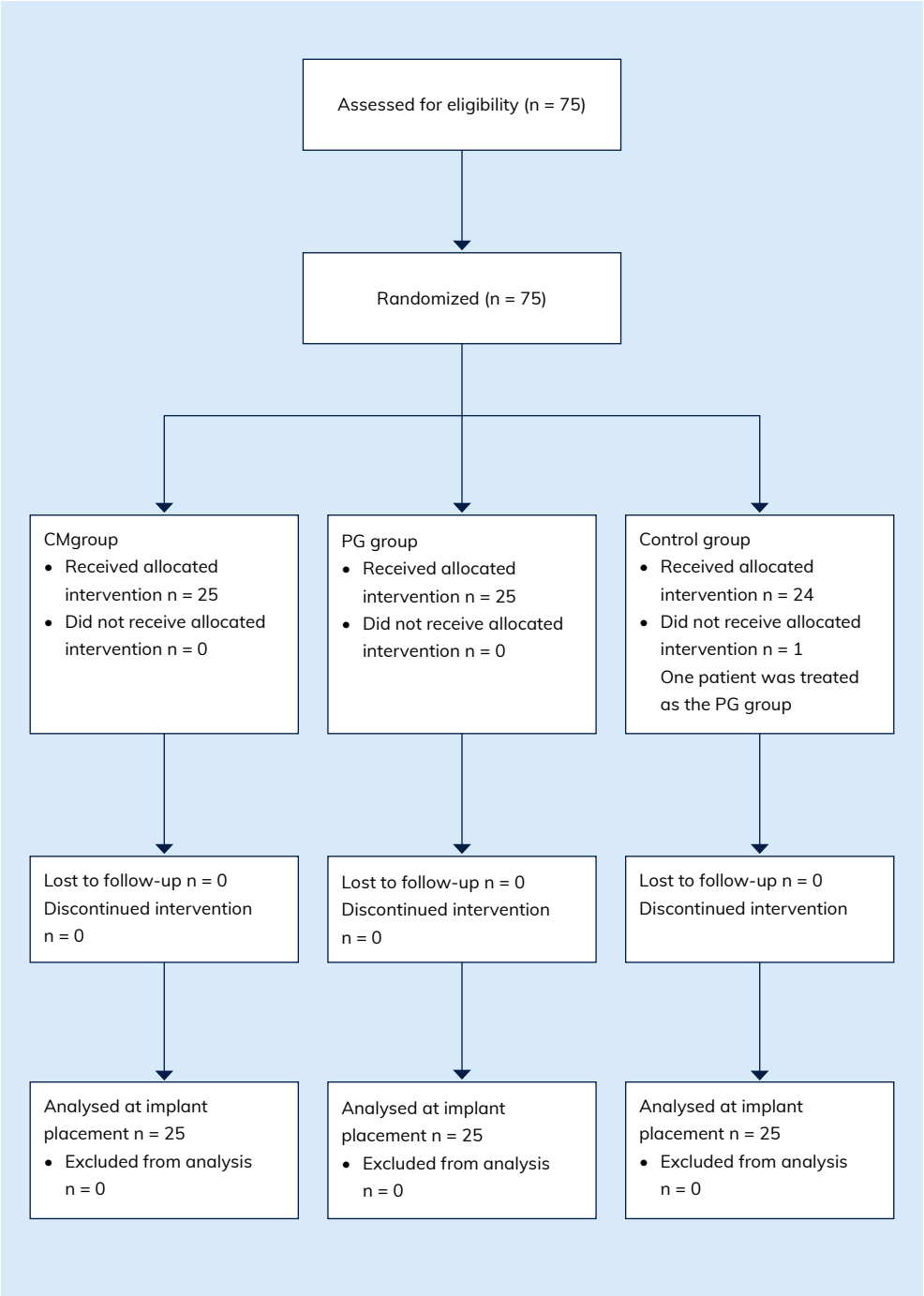

Figure 5 Flow diagram.

Group	CM	PG	Control
Number of patients	25	25	25
Age (mean and SD)	49 (16)	50 (13)	44 (12)
Gender (female/male)	13/12	11/14	18/7
Center (EMC/CZE)	17/8	16/9	17/8
Cause of tooth loss (fracture/infection/resorption)	17/6/2	17/8/0	17/6/2
Location of implant (I1, I2, C, P1, P2)	8/2/4/4/7	7/6/0/6/8	7/4/0/6/8
Plaque index (0/1/2/3)	23/0/1/0*	23/0/2/0	22/2/1/0
Bleeding index (0/1/2/3)	16/7/1/0*	15/7/2/1	17/4/4/0
Gingiva index (0/1/2/3)	22/1/1/0*	18/3/4/0	21/1/3/0
Pocket probing depth (mean and SD)	2.5 (0.7)	2.6 (1.1)	2.4 (0.7)

CM: Collagen Matrix; PG: palatal graft; mean and standard deviation noted for age; EMC: Erasmus Medical Center; CZE: Catherina Hospital Eindhoven *One radix was completely covered by gingiva.

Table 1 Baseline characteristics.

Graft evaluation and complications

One week after ridge preservation all sites were clinically evaluated. In the group receiving a collagen matrix (CM-group), 10 grafts (40%) were judged as integrated, 12 as fibrinoid (48%), 2 as partially integrated (8%), and 1 as not integrated (4%). InAQ11 the group receiving an autologous graft (PG-group), 13 grafts (52%) were judged as integrated, 8 as fibrinoid (32%), 1 as partially integrated (4%), and 3 as not integrated (12%). The distribution was not statistically different between both groups ($p = .496$). After eight weeks all sites in the CM-group had fully healed, whereas in group PG 2 grafts (8%) still showed incomplete healing. One patient in group PG had an allergic skin reaction to chlorhexidine, which cleared spontaneously. Another patient in PG-group needed bipolar electrocoagulation of the donor area because of prolonged bleeding. Apart from this, no complications occurred.

Horizontal soft tissue contour changes

The mean change of soft tissue contour measured -1.5 SD 0.6 mm in CM-group, -1.3 SD 0.8 mm in PG-group, and -1.7 SD 0.9 mm in the control group. There were no statistically significant differences between the different groups, $F(2, 72) = 1.875$, $p = 0.161$.

Horizontal radiographic changes

The median horizontal radiographic changes at 1, 3, and 5 mm below the crest are presented in Table 2. One mm below the crest the mean change in the CM-group measured -0.9 SD 0.6 mm, in the PG-group -1.0 SD 0.8 mm, and -3.2 SD 2.1 mm in the control group. This difference was statistically different between the groups, $H(2) = 25.899$, $p < 0.001$. Post hoc analysis revealed that both the difference between the CM and the control group (MD 2.3 mm, 95% CI 1.3-3.2, $p < 0.001$) as well as the difference between the PG- and control-group (MD 2.2 mm, 95% CI 1.2-3.1, $p < 0.001$) were statistically significant.

	CM n = 24	PG n = 25	Control n = 24	p-value
1 mm below crest	-1.0 (-.3; -1.4)	-.8 (-.6; -1.3)	-2.5 (-1.6; -4.7)	< 0.001*
3 mm below crest	-.6 (-.3; -1.2)	-.6 (-.1; -.9)	-1.8 (-.8; -3.1)	< 0.001**
5 mm below crest	-.6 (-.1; -1.0)	-.2 (-.1; -.4)	-.9 (-.3; -1.3)	0.002***

Median, first and third quartile of the bone and soft tissue dimensions in mm at implant placement; CM: Collagen matrix; PG: Palatal graft. A Kruskal-Wallis test was used to calculate significance levels (p-values). Pairwise comparisons were performed using Dunn's procedure with a Bonferroni correction for multiple comparisons: *CM-Control p < 0.001, PG-Control p < 0.001 ** CM-Control p = 0.001, PG-Control p < 0.001 *** PG-Control = 0.001

Table 2 Horizontal radiographic changes.

Vertical radiographic changes

The median vertical changes at the buccal and palatal crest are presented in Table 3. At the buccal aspect, the mean change in the CM-group measured -0.8 SD 0.8 mm, in the PG-group -0.5 SD 0.8 mm and -2.3 SD 1.8 mm in the control group. The difference in change was statistically different between the different groups, $H(2) = 25.322$, $p < 0.001$. Post hoc analysis revealed that the difference between the CM and control (MD 1.5 mm, 95% CI 0.7-2.4, $p < 0.001$) as well as the difference between the PG and control (MD 1.8 mm, 95% CI 0.9-2.7, $p < 0.001$) were statistically significant.

	CM n = 24	PG n = 25	Control n = 24	p-value
Buccal	-0.8 (-0.1; -1.1)	-.5 (-0.1; -0.9)	-1.9 (-1.4; -3.0)	< 0.001*
Palatal	-0.4 (-0.2; -0.8)	-.2 (-0.1; -0.7)	-1.3 (-0.8; -2.2)	< 0.001**

Median, first and third quartile of the bone and soft tissue dimensions in mm at implant placement; CM: Collagen matrix; PG: Palatal graft. A Kruskal-Wallis test was used to calculate significance levels (p-values). Pairwise comparisons were performed using Dunn's procedure with a Bonferroni correction for multiple comparisons: *CM-Control p < 0.001, PG-Control p < 0.001 ** CM-Control p = 0.001, PG-Control p < 0.001

Table 3 Vertical radiographic changes.

At the palatal aspect, the mean change in the CM-group was -0.5 SD 0.6 mm, in the PG-group -0.3 SD 0.6 mm and -1.6 SD 1.0 mm in the control group. The difference was statistically different between the different groups, $H(2) = 28.646$, $p < 0.001$. Post hoc analysis revealed that the difference between the CM- and control-group (MD 1.0 mm, 95% CI 0.5-1.6, $p = 0.001$) as well as the difference between the PG- and control-group (MD 1.3 mm, 95% CI 0.8-1.8, $p < 0.001$) were statistically significant.

Soft tissue dimensions at implant placement

The median buccal/palatal/vertical soft tissue dimensions at implant placement are shown in Table 4. No significant differences were found between the three groups for the buccal, palatal, and vertical mucosal dimensions at implant placement.

	CM n = 24	PG n = 25	Control n = 25	p-value
Buccal mucosa	1.6 (1.3; 1.9)	1.3 (0.9; 1.8)	1.7 (1.2; 3.1)	0.067
Palatal mucosa	2.5 (1.9; 3.2)	3.0 (1.9; 3.5)	3.3 (2.8; 4.0)	0.067
Mucosal height	2.5 (2.1; 3.0)	2.4 (1.9; 2.9)	2.4 (1.8; 3.1)	0.846

Median, first and third quartile of the bone and soft tissue dimensions in mm at implant placement; CM: Collagen matrix; PG: Palatal graft. A Kruskal-Wallis test was used to calculate significance levels (p-values).

Table 4 Soft tissue dimensions at implant placement.

Necessity of additional augmentation

Additional GBR was needed in 32% of the sites in CM-group, in 24% in PG-group and in 72% in the control group ($\chi(2) = 13.277$, $p = .001$). The difference was significant comparing CM to control ($\chi(1) = 8.013$, $p = .010$) and for PG to control ($\chi(1) = 11.538$, $p = .002$). The risk difference was 40% between CM-group and control and 48% between PG-group and control.

Patient-reported outcomes

Median scores for pain were significantly different between groups after extraction $H(2) = 6.283$, $p = 0.043$. The median score for the CM-group was 0 (0-1.8), for PG-group 2.0 (0.3-3.8), and for the control group 1.0 (0-5.5) at one week after extraction. The post hoc analysis only revealed a significant difference in median pain scores after ridge preservation for the CM-group compared with the PG-group ($p = 0.042$). No significant differences were found for neither the impact of the implant surgery nor the experienced swelling (Table 5).

	CM	PG	Control	p-value
Before surgery	n = 24	n = 24	n = 25	
Expected impact of surgery	7.0 (3.0; 8.0)	6.0 (3.0; 8.0)	6.0 (2.5; 7.5)	0.569
Pain	0.5 (0; 4.0)	1.0 (0; 4.0)	0 (0; 5.0)	0.879
Swelling	0 (0; 2.8)	1.5 (0; 5.0)	0 (0; 5.0)	0.424
One week after removal	n = 24	n = 24	n = 25	
Impact of removal	4.0 (1.3; 7.0)	3.5 (2.3; 6.0)	3.0 (1.0; 5.0)	0.555
Pain	0 (0; 1.8)	2.0 (0.3; 3.8)	1.0 (0; 5.5)	0.043*
Swelling	0 (0; 1.0)	1.5 (0; 2.8)	0 (0; 1.0)	0.054

Median, first and third quartile of the patient reported outcomes measured on a visual analogue scale from 0 to 10; CM: Collagen matrix; PG: Palatal graft. A Kruskal Wallis-test was used to calculate significance levels (p-values). Pairwise comparisons were performed using Dunn's procedure with a Bonferroni correction for multiple comparisons: *CM-PG p = 0.042.

Table 5 Patient reported outcome measurements.

Subgroup analysis

Only for soft tissue contour changes, the subgroup analysis revealed a different outcome compared to the analysis of the whole group. Subgroup analysis showed that for the incisor/cuspid area the mean change measured -1.5 SD 0.6 mm in the CM-group, -1.7 SD 0.6 mm in the PG-group, and -2.3 SD 0.9 mm in the control group. This difference was statistically different between the groups, $F(2, 33) = 3.661$, $p = 0.037$. Post hoc analysis revealed that the mean difference between the CM and control group (MD 0.8 mm, 95% CI 0.1-1.5 $p = 0.031$) was statistically significant. Subgroup analysis for the premolar area was not significantly different between the three groups.

DISCUSSION

This randomized controlled clinical study compared two different ridge preservation techniques with spontaneous healing when early implant placement was performed. Ridge preservation using a particulated xenogenic bone substitute covered with either a collagen matrix (CM) or an autologous palatal connective tissue graft (PG) resulted in less horizontal and vertical bone resorption compared to spontaneous healing (control group) 8 weeks after tooth extraction. This was in accordance with earlier studies, where ridge preservation resulted in less vertical and horizontal resorption 4-6 months after tooth removal.[8, 10, 20] Although ridge preservation reduced bone resorption in current study, there was no significant difference in horizontal soft tissue contour changes between both techniques and the control group. In the subgroup analysis, there was a statistically significant difference in the mean change in horizontal soft tissue contour changes between the CM-group and the control group for the incisor/cuspid area. However, this difference was minimal and might not be clinically relevant. This was also reported in earlier studies, where only a limited protective effect was seen at the labial ridge contour when compared to spontaneous healing. The lack in significant difference could also be related to the area of interest selected for the analysis.[13, 21] Alginate was the impression material used, while an intra-oral scan would be more precise. Unfortunately, during the start of the inclusion no intra-oral scan was available for this study.

The present study showed no significant difference between the three groups for the buccal, palatal, and vertical mucosal dimensions at 8 weeks post-extraction. The change in mucosal thickness could not be calculated between the two time-points since the baseline STL was obtained prior to extraction and the CBCT-scan was performed right after the extraction.

Covering the augmented extraction socket with a collagen matrix or an autologous graft might be important to facilitate maximal healing of the bone graft when performing ridge preservation.[10, 21] When compared to other studies, the present results showed less integration of the palatal graft.[9, 20] This difference might be explained by the current study scoring the graft as a total in contrary to applying a digital planimetry and expressing the scores as a percentage of the entire grafted area.[9] Although a higher amount of necrosis was found in the PG-group when compared to the CM-group, the differences were not statistically significant. Harvesting a free connective palatal graft can be a painful procedure, where most of the pain is experienced in the first days postoperatively.[22, 23] In the present study, patients in the CM-group experienced significantly less pain when compared to the patients in group PG. To our knowledge, so far, no other clinical studies comparing a palatal graft with a substitute for ARP and evaluating patient-reported outcomes exist. According to the results from this study, a collagen matrix is associated with less morbidity, less necrosis, and less change in soft tissue volume in the incisal/cuspid area and might therefore be preferred over a palatal graft when performing ridge preservation procedures.

Although ridge preservation resulted in less bone loss compared with spontaneous healing and the amount of additional GBR needed at the time of implant placement was less in the ARP groups, additional GBR was still needed in a large percentage the ARP patients. This is in line with earlier studies describing results ranging from 0%-45% additional augmentations in ridge preservation groups and 0%-100% in groups that were left for spontaneous healing.[6, 11, 24, 25] The augmented DBBM-C is still quite soft at early implant placement and some particles are easily displaced during drilling of the osteotomy resulting in the need of additional augmentation.[26]

As mentioned in earlier studies,[8, 13] a power analysis would lead to approximately 240 patients to achieve a power of 81% to detect a difference measuring 0.5 mm with a SD of 1 mm. This is practically not feasible and the power of the current

study was based on the marginal change in soft tissue after 1 year of loading. Compared to earlier publications the present study was able to include more than double the number of patients for each group. Thus, a subgroup analysis was performed to evaluate the incisor/cuspid and bicuspid area separately. To prevent the associated bias, subgroups analysis was performed for all outcomes. Additionally, it must be noted that the buccal bone thickness and integrity was not calculated and could be of influence. The relevance regarding the clinical and esthetic outcomes of the implants 12 months after loading will be reported in the 1-year follow-up.

The study was performed using CONSORT and the Cochrane Risk of Bias assessment tool to keep bias as low as possible.[27] Selection bias was prevented by using a computer-generated random sequence generation. Allocation was concealed in opaque, sealed envelopes. The allocation sequence was concealed from the surgeon (JP) until the very last possible step in the surgical procedure. Blinding of the outcome assessment (detection bias) was ensured as investigators (BJ, AG, NN & JP) were not aware of the allocation during the assessments. It must be noted that surgeon (JP) might remember the allocated procedure during clinical follow-up. There were no losses to follow-up, resulting in a low risk of attrition bias. Risk of reporting bias was low because all outcomes originally described in the registered protocol are reported.

CONCLUSION

Ridge preservation in the esthetic zone applying a particulated xenogenic bone substitute covered with a collagen matrix or an autogenous palatal punch results in less bone resorption and less need of additional bone augmentation at early implant placement compared to spontaneous healing.

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CHAPTER 6

Early implant placement with or without alveolar ridge preservation in single tooth gaps renders similar esthetic, clinical and patient-reported outcome measures: one-year results of a randomized clinical trial

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ABSTRACT

Objectives To test whether early implant placement with alveolar ridge preservation (ARP) results in different esthetic, clinical and patient-reported outcome measures (PROMs) compared to early implant placement without ARP.

Material and Methods Seventy-five patient requiring single tooth extraction in the anterior maxilla were recruited. Following tooth extraction, the patients were randomly allocated to three groups: 1) ARP using demineralized bovine bone mineral containing 10% collagen (DBBM-C) covered by a collagen matrix (CM) (n = 25), 2) ARP using DBBM-C covered with a palatal graft (PG) (n = 25), 3) spontaneous healing (control) (n = 25). Eight weeks after tooth extraction a CBCT was taken and early implant placement was performed in all patients. Esthetic, clinical and PROMs were evaluated one-year post-loading.

Results A total of 70 patients were available for re-examination at one-year post-loading. The median mid-facial mucosal margin change amounted to -0.02 mm (IQR -0.27 to 0.46) in group CM, -0.13 mm (IQR -0.44 to 0.25) in group PG and -0.14 mm (IQR -0.29 to 0.07) in control group, with no significant differences between the groups. Mean PES scores amounted to 7.0 ± 1.4 in group CM, 7.1 ± 1.5 in group PG and 7.3 ± 1.7 in control group without significant differences between the groups. Plaque, bleeding on probing, and probing depth did not differ between treatment groups. PROMs in general revealed no significant differences between the groups.

Conclusion Early implant placement with ARP using either a collagen matrix or a palatal graft rendered similar esthetic, clinical, and PROMs compared to early implant placement without ARP. When a failing tooth can be replaced with an implant within 2 months after tooth extraction, the added value of ARP might be clinically negligible.

INTRODUCTION

Following tooth extraction, the alveolar ridge undergoes evident horizontal and vertical reduction leading to an alteration of the ridge profile.[1] This alteration of the alveolar ridge has been extensively studied and documented. Systematic reviews have revealed a reduction of the alveolar ridge by approximately 50% in the first 3-6 months, affecting mainly the buccal area.[2, 3] This substantial reduction may impede the replacement of missing teeth with dental implants in a prosthetically ideal position. Moreover, this may also yield unpleasant esthetic outcomes since the soft tissues are also affected.[4] In order to overcome these drawbacks alveolar ridge preservation procedures have been introduced.

Alveolar ridge preservation (ARP) is a common and well-established procedure that aims at maintaining the alveolar ridge following tooth extraction to subsequently allow for the placement of dental implants in a prosthetically driven position[5, 6]. It should be noted that ARP cannot prevent the physiological ridge alterations after tooth extraction but it can limit the extent to which these occur.[5] In addition, ARP can simplify implant placement procedure since it reduces the necessity of simultaneous guided bone regeneration (GBR) at early implant placement (4-8 weeks after tooth extraction).[7, 8] Despite these promising findings, there is still a lack of sound clinical evidence regarding the combination of ARP with early implant placement.

Early implant placement involves the placement of dental implants 4-8 weeks after tooth extraction.[9, 10] This surgical protocol takes place before most of the hard tissue alterations occur, but allows proper soft tissue healing. Early implant placement might offer a slightly increased stability of the peri-implant hard and soft tissues leading to more favorable esthetic outcomes than immediate implant placement.[11, 12] Recent studies have shown that ARP followed by early implant placement reduces the frequency of simultaneous GBR at implant placement thereby simplifying the surgical procedure.[5, 13] Therefore, it is reasonable to suggest that this approach might also optimize the clinical, esthetic and patient-reported outcome measures (PROMs). How-

ever, there is a lack evidence of whether ARP can improve the afore-mentioned outcomes applying an early implant placement protocol.

According to the Consensus Report of the XV European Workshop in Periodontology, clinical studies regarding early implant placement are lacking[11]. This is of utmost importance since it affects the decision-making process and limits the application of this treatment protocol in routine clinical practice.

Therefore, the aim of the present randomized controlled trial was to test whether early implant placement with ARP results in different clinical, esthetics and PROMs than early implant placement without ARP after one-year of loading.

MATERIALS AND METHODS

Study design

The study was designed as a RCT. The study protocol was approved by the medical ethical committee, the central committee on human subjects (MEC-2015-016; NL49965.078.14) and registered in the Dutch trial register (NL6497). This research was conducted according the principles of the Declaration of Helsinki. The CONSORT statement was used for reporting.[14]

Study design with in- and exclusion criteria, together with the results of the soft tissue contour and radiographic evaluation at implant placement, have been previously reported in detail[8]. In brief, after tooth extraction patients were randomly allocated to one of following treatment modalities:

CM-group: Demineralized bovine bone mineral with 10% collagen (DBBM-C, Geistlich Bio-Oss® Collagen, Geistlich Pharma, Switzerland), and covered with a collagen matrix (CM, Geistlich Mucograft® Seal, Geistlich Pharma, Switzerland).

PG-group: DBBM-C covered with an autogenous soft-tissue 'punch' graft (PG) harvested from the palate.

Control: Spontaneous healing.

Study population

Fully dentate patients in the anterior maxilla requiring a single tooth extraction in the anterior zone (incisor, canine or first/second premolar) leading to a single tooth gap were considered for inclusion. Patients were referred for implant placement by their general practitioner. Patients exhibiting ongoing periodontal disease, smoking, uncontrolled diabetes, current chemotherapy or a history of radiotherapy in the head-and-neck region were excluded. Before tooth extraction, clinical parameters including plaque index (PI), modified bleeding index (mBI), gingival index (GI) and probing depth were assessed at 6 sites per tooth (mesiobuccal, buccal, distobuccal, distolingual, lingual and mesiolingual).

Furthermore, CBCT scans were taken at different timepoints. At first a CBCT scan was taken after tooth extraction, and a second one, prior to implant placement[8]. All surgeries were performed by the same surgeon (JP).

Surgical procedure

Tooth extraction was performed using a flapless approach and taking care of preserving the buccal bone plate as well as the surrounding soft tissues. After tooth extraction, the patients were randomly assigned to one of the treatment modalities. For CM, the socket was filled with DBBM-C up to the level of the lingual/palatal bone plate. The soft tissue borders of the alveolus were de-epithelialized using a rotating diamond burr and a CM was placed on top and sutured to the gingival margins of the socket with interrupted sutures (6-0 Ethilon, Ethicon, USA). For PG a free epithelialized gingival graft of 4-5 mm thickness harvested with a biopsy punch was placed on top and sutured to the socket with interrupted sutures (6-0 Ethilon, Ethicon, USA). The donor site was covered with a tissue adhesive (Histoacryl, Braun Medical B.V., Germany). For the control group, a cross-mattress suture was performed allowing spontaneous healing.

All patients were instructed to rinse twice a day with 0.12% chlorhexidine and received pain medication (Ibuprofen) and antibiotics (Amoxicillin) for 5 days.[15] Sutures were removed after 1 week.

Implant placement

Eight weeks after tooth extraction early implant placement was performed in all groups. The implants had a diameter of 3.3-4.1 mm and a length of 8-12 mm (Bone Level Tapered, SLActive, Roxolid, Institute Straumann AG, Switzerland) depending on the bone and space available. After raising a full-thickness flap, implant bed preparation took place according to the manufacturer's guidelines and implants were placed. In case of a thin peri-implant buccal bone thickness (PBT) (< 2 mm)[16-18] or a dehiscence at the buccal aspect, guided bone regeneration (GBR) was performed. This implied the coverage of the buccal aspect with locally harvested autogenous bone chips combined with DBBM granules (Bio-Oss®, Geistlich Pharma, Switzerland) and a resorbable membrane (Bio-Gide®, Geistlich Pharma, Switzerland). Primary tension-free flap closure was performed by means of single interrupted sutures.

Follow-up

After the surgical procedures the patients were referred to the dental office of the referring dentist for prosthetic treatment. Implants were restored with cemented or screw-retained fixed prosthesis according to the preference of the referring dentist. The patients were reexamined 1-4 weeks after crown delivery (Baseline: BL), 6 months (FU-6m) and at one-year (FU-1) follow-up. Figure 1 shows a representative clinical case of each group before implant placement and at FU-1.

Outcome measurements

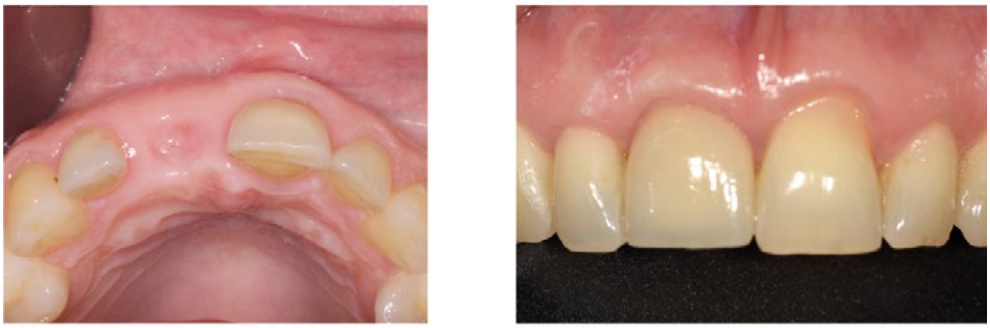
Primary outcome:

- Change of the mid-facial marginal mucosal margin between BL and FU-1.

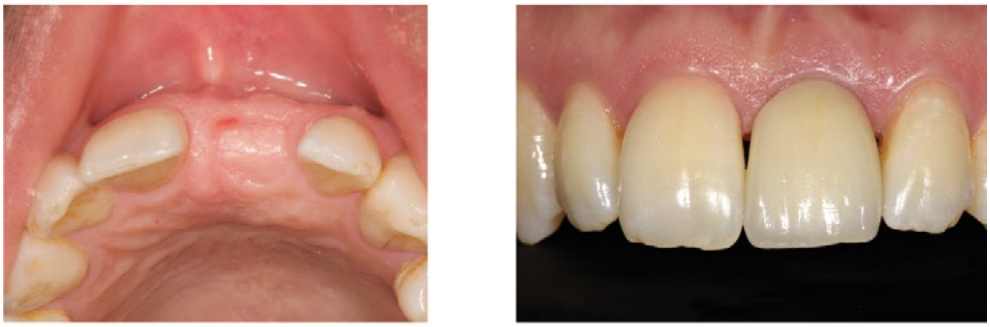
Secondary outcomes:

- Peri-implant esthetic score (PES) and White esthetic score (WES)
- Complications, implant-survival and success
- Plaque index (PI)[19]
- Modified bleeding index (mBI)[20]
- Gingival index[19]
- Probing depth (PD) and bleeding on probing (BOP)
- Patient-reported outcome measures (PROMs)

CM-group



PG-group



Control

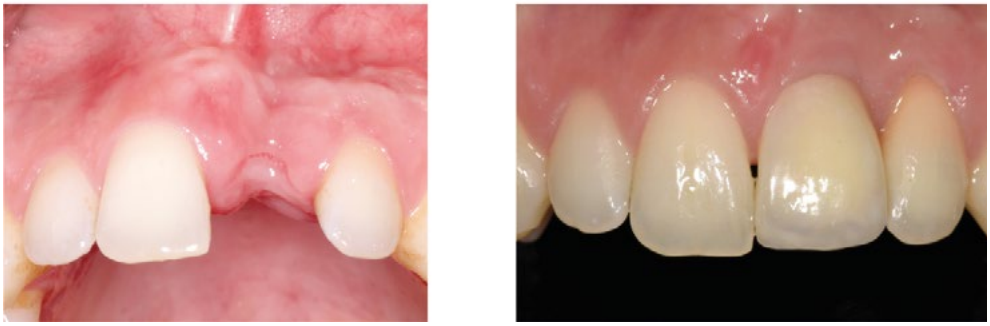


Figure 1 Examples of patients in group CM, PG and control before implant placement and after 1 year of loading (FU-1).

Change of the mid-facial mucosal margin

Alginate impressions were taken at BL, FU-6 and one- FU-1 of follow-up and dental casts were fabricated. Cast models were scanned with a 3D scanner (7Series Model, Canada). The obtained STL files were imported into an image analysis software (Swissmeda-Software) as previously described.[21-23] Digital casts were superimposed automatically by the software and manually adjusted with the implant crown serving as the reference. Measurements were performed by a calibrated, blinded evaluator with access to the STL files only.

A longitudinal slice was selected dividing the crown mesiodistally into two equal parts (Figure 2). A line coinciding with the tooth axis was then drawn in the transversal images of the sections. Changes in mid-facial mucosal margin between BL and FU-1 of follow-up were assessed by calculating clinical crown height changes in mm in an apico-coronal direction from the incisal edge to the mucosal/gingival margin axis. In case of digitized casts with irregularities at the mid-facial mucosal margin, the longitudinal slice was slightly moved to allow a correct measurement. All the measurements were performed twice by the same blinded investigator with one week apart between the measurements.

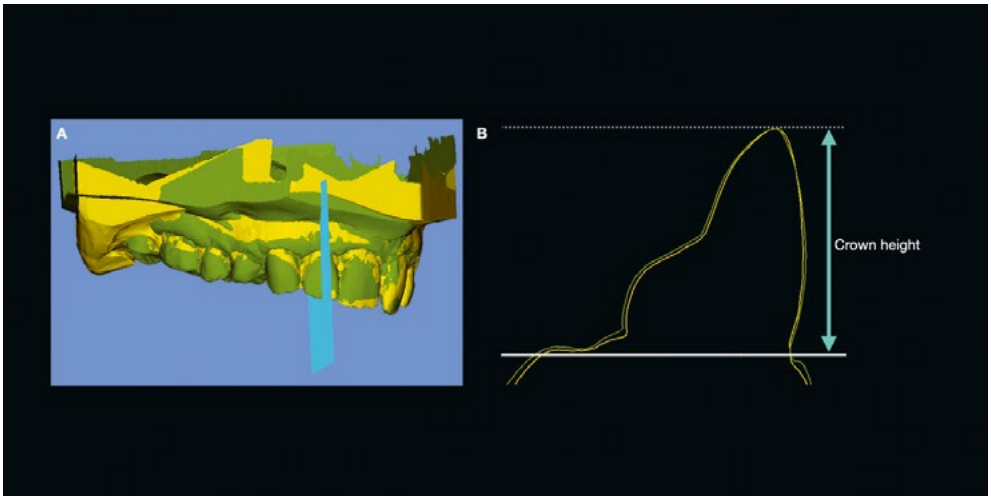


Figure 2 Measurement of the change of midfacial mucosal margin via superimposition of STL models. A) Superimposition of baseline STL model (yellow) and one-year follow-up (green). Blue slice indicates a longitudinal slice dividing the crown mesiodistally into two equal parts. B) The length of the crown height was measured and the change of the length between baseline and one-year follow-up was calculated.

Esthetic outcomes

Esthetic outcomes were evaluated using the modified PES and WES.[24, 25] The PES/WES scores were evaluated independently by two blinded researchers on the basis of digital photographs following a standardized protocol.

Complications, implant-survival and success

Mucosal dehiscence, swelling, infection, bleeding, allergic reactions and other complications were assessed at 2 weeks as well as at BL, FU-6m and FU-1. Implant survival was defined as implant in place and stable assessed by hand testing. Implant success was defined by the lack of all of the following: mobility, persistent subjective complaints, PD ≥ 5 mm and BOP.

Clinical parameters

PI, mBI, GI and PD were recorded at BL, FU-6m and FU-1 by two calibrated clinicians (JP/BJ) who were unaware of the treatment allocation.

Patient-reported outcome measures (PROMs)

PROMs were assessed with questionnaires using a visual analogue scale (VAS-scale 0-10) at BL, FU-6m and FU-1. The questionnaires focused on experienced pain, swelling and stress of surgery. Furthermore, patient satisfaction regarding the implant crown, the peri-implant soft tissues and the total dentition was also evaluated.

Randomization and treatment allocation

According to the block randomization method[26], patients were randomly allocated to one of the 3 treatment groups. The patient allocation sequence was concealed from the surgeon (JP) in opaque, sealed envelopes until the very last step of the surgical procedure. The patients were not blinded.

Statistical analysis

The metric variables with mean, standard deviations, median, quartiles were described. Linear models using generalized estimation equations (GEE) were conducted to assess changes of esthetic, clinical and PROMS over time according the treatment group. Wald's Chi^2 statistic was used to conclude about main

effects and interactions. This methodological approach was used because of the within-subject correlation of repeated measurements through the follow up. Post-hoc tests were carried out correcting by Bonferroni's criteria. The sample size calculation of the present study was based on the change in the marginal gingival margin after 1 year of loading using an early placement protocol.[27] Assuming a 0.5 mm difference in the marginal gingival margin as clinically relevant along with a common SD of 0.58 mm,[27] with a power of 80% and a type I error rate of 5%, 21 participants per group were needed to find significant differences. To compensate for possible drop-out, 25 participants per group were recruited.

RESULTS

Study sample

From the total of patients screened, 75 were included and randomized into one of the treatment groups (25 patients per group). Figure 2 shows the CONSORT flow diagram. One patient in the control group was not treated according to the randomization and was treated according to the PG protocol instead. This patient was analyzed according to the randomization as suggested by the CONSORT guidelines. Five patients (two in CM, one in PG and 2 in control) were lost over the one-year follow-up. One patient in the control group had an early implant failure. Patient characteristics are shown in Table 1.

Change in mid-facial mucosal margin

The median change of the mid-facial mucosal margin between baseline and FU-1 amounted to -0.02 mm (IQR -0.27 to 0.46) in group CM, -0.13 mm (IQR -0.44 to 0.25) in group PG and -0.14 mm (IQR -0.29 to 0.07) in control group, with no significant differences between the groups ($p = 0.136$). The negative numbers indicate a coronal migration of the mid-facial mucosal margin. This migration was statistically significant ($p = 0.046$) but the magnitude of this migration was similar between groups ($p = 0.336$).

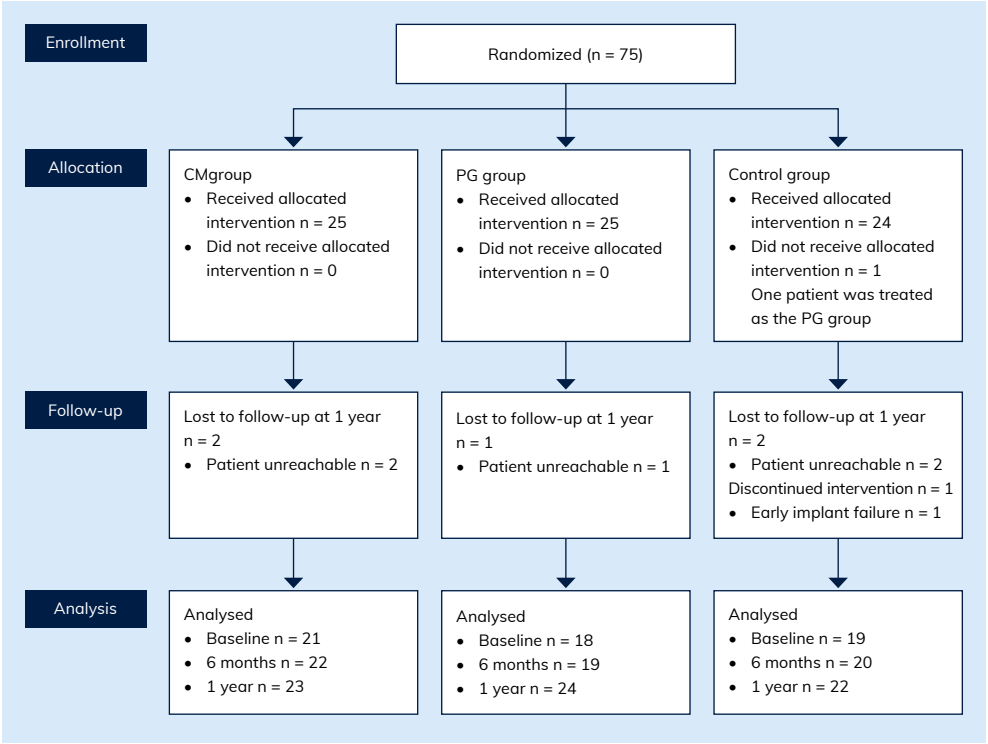


Figure 2 CONSORT Flow Diagram.

Group	CM	PG	Control
Number of patients included	25	25	25
Age (years)	49 ± 16	50±13	44 ±12
Gender (female/male)	13/12	11/14	18/7
Center (EMC/CZE)	17/8	16/9	17/8
Cause of tooth loss (fracture/infection/resorption)	17/6/2	17/8/0	17/6/2
Location of implant (I1, I2, C, P1, P2)	8/2/4/4/7	7/6/0/6/8	7/4/0/6/8
Implant length 8/10/12 mm	0/7/18	0/6/19	1/8/16
Implant diameter 3.3 / 4.1 mm	4/21	9/16	9/16
ARW at -1 mm	8.5 ± 1.2	8.1 ± 1.5	8.9 ± 1.5
ARW at -3 mm	9.5 ± 1.3	8.9 ± 1.5	9.6 ± 1.5
ARW at -5 mm	10.1 ± 1.5	9.4 ± 1.7	9.7 ± 1.5
Buccal bone height	10.1 ± 2.4	9.0 ± 3.9	9.6 ± 3.9
Palatal bone height	10.8 ± 2.1	10.4 ± 2.1	10.6 ± 2.7

Frequencies of the actual values and the means ± SD; CM, Collagen Matrix group; PG, palatal graft group; EMC: Erasmus Medical Center; CZE: Catherina Hospital Eindhoven; ARW, Alveolar Ridge Width and buccal/palatal bone height measured on CBCT after tooth extraction.

Table 1 Patient characteristics.

Esthetic scores

Table 2 shows the mean PES and WES scores for CM, PG and the control group. There were no significant differences between the groups ($p = 0.837$) at any time point ($p = 479$). From baseline to FU-1 the PES scores improved significantly ($p < 0.001$). The magnitude of this improvement was similar through all groups ($p = 0.479$). At FU-1, PES scores amounted to 7.0 ± 1.4 in group CM, 7.1 ± 1.5 in group PG and 7.3 ± 1.7 in control group. Four patients in the CM-group, 6 patients in the PG-group and 5 patients in the control group scored lower than 6 points for the soft tissue esthetics.

	CM	PG	Control	p-value (Treatment effect)	p-value (Interaction effect)	p-value (Time effect)
PES						
BL	6.3 ±1.1 n = 18	6.2 ±1.6 n = 18	6.1 ±1.4 n = 19			
FU-6m	6.8 ±1.3 n = 20	6.8 ±1.3 n = 18	7.0 ±1.4 n = 19			
FU-1	7.0 ±1.4 n = 22	7.1 ±1.5 n = 22	7.3 ±1.7 n = 21			
				0.837	0.479	<0.001
	CM	**PG**	**Control**	**p-value (Treatment effect)**	**p-value (Interaction effect)**	**p-value (Time effect)**
WES						
BL	7.2 ±1.5 n = 18	7.7 ±1.6 n = 18	7.6 ±1.4 n = 19			
FU-6m	7.3 ±1.4 n = 20	7.6 ±1.5 n = 18	7.8 ±1.0 n = 19			
FU-1	7.3 ±1.7 n = 22	7.8 ±1.3 n = 22	8.0 ±0.9 n = 21			
				0.359	0.682	0.219

Mean ± SD of PES and WES using a scale from 0 to 10; Changes over time and differences between the treatment groups were assesed using generalized estimation equations (GEE). Wald's Chi^2 statistic was used to conclude about main effects and interactions. PES index increased significantly over time ($p < 0.001$) and the increment was similar through all 3 treatment groups ($p = 0.479$) No differences in PES or WES index were found at any timepoint ($p > 0.05$).

Table 2 Esthetic outcomes of the treatment groups via the modified pink esthetic index (PES) and the modified white esthetic score (WES) at Baseline (BL), 6-month (FU-6m) and one-year (FU-1) follow-up.

Complications, implant-survival and success

During the healing period, two patients in the CM-group developed a cervical fistula without suppuration after placement of the crown at the referring dental office. These patients reported no subjective complaints nor any other signs of infection. Both sites were treated conservatively by flushing the fistula using a syringe with chlorhexidine 0.12%. As this did not resolve the fistula, the area was surgically explored, however, more abnormalities were seen. The fistulas disappeared spontaneously but at FU-1 a new fistula was seen in one of the patients. As this patient did not report any subjective complaints or showed signs of infection the situation was monitored.

The implant survival rates were similar across the groups amounting to 100% in CM and PG, and to 95.7% in the control group ($p = 0.657$) at FU-1. Only one patient in the control group had an early failure.

Implant success amounted to 95,7% in CM, 87,5% in PG and 91.4% for control at FU-1, without significant differences between the groups ($p = 0.865$). Two patients in PG presented one site with PD = 5 mm with BOP. One patient in the PG and one patient in control group presented one site with PD > 5 mm.

The plaque-, bleeding-, gingiva index and the pocket probing depth

During the FU-1, PI, mBI, GI as well as the PD did not differ between treatment groups at any time point (Table 3). PD changed significantly over time ($p = 0.019$) and the changes were similar through all 3 treatment groups ($p = 0.353$). The mean PD values amounted 2.7 ± 0.6 mm in CM, 3.0 ± 0.7 mm in PG and 2.5 ± 0.8 for control group at FU-1. The median values of mBI and PI amounted to 0 in all groups during the follow-up. Four patients showed mild inflammation (GI = 1) and two showed moderate inflammation (GI = 2) at FU-1.

	CM	PG	Control	p-value (Treatment effect)	p-value (Interaction effect)	p-value (Time effect)
PI						
BL	19/2/0/0	15/1/1/1	18/0/1/0			
FU-6m	18/4/0/0	16/2/0/1	19/0/1/0			
FU-1	21/0/1/0	21/1/1/1	21/0/1/0			
				0.464	0.725	0.995
	CM	**PG**	**Control**	**p-value (Treatment effect)**	**p-value (Interaction effect)**	**p-value (Time effect)**
mBI						
BL	15/4/2/0	13/5/0/0	15/4/0/0			
FU-6m	16/5/1/0	12/7/0/0	14/5/1/0			
FU-1	15/8/0/0	16/6/2/0	18/3/1/0			
				0.756	0.833	0.698
	CM	**PG**	**Control**	**p-value (Treatment effect)**	**p-value (Interaction effect)**	**p-value (Time effect)**
GI						
BL	20/0/1/0	17/1/0/0	17/2/0/0			
FU-6m	21/0/1/0	18/1/0/0	18/2/0/0			
FU-1	21/0/2/0	21/3/0/0	21/1/0/0			
				0.849	0.667	0.464
	CM	**PG**	**Control**	**p-value (Treatment effect)**	**p-value (Interaction effect)**	**p-value (Time effect)**
PD						
BL	2.7 ± 0.9	2.7 ± 0.7	2.4 ± 0.7			
FU-6m	3.1 ± 1.0	3.0 ± 0.6	2.6 ± 0.8			
FU-1	2.7 ± 0.6	3.0 ± 0.7	2.5 ± 0.8			
				0.092	0.353	0.019

Frequencies of the actual values (0/1/2/3) of the PI, BI and GI and mean ± SD of PD. Changes over time and differences between the treatment groups were assesed using generalized estimation equations (GEE). Wald's Chi^2 statistic was used to conclude about main effects and interactions. No differences in PI, mBI and GI were found at any timepoint ($p > 0.05$). PD changed significantly over time ($p = 0.019$) and the changes were similar through all 3 treatment groups ($p = 0.353$). Abbreviation: PI, plaque index; mBI, modified bleeding index; PD, probing depth, CM, Collagen matrix group; PG, palatal graft group.

Table 3 Periodontal clinical parameters at Baseline (BL), 6-month (FU-6m) and one-year (FU-1) follow-up.

Patient-reported outcome measures (PROMs)

In general, PROMS were similar between the groups, with no significant differences at any time point ($p > 0.05$) (Table 4). Patients in group PG reported a higher swelling than CM and control group ($p = 0.038$). Patients were very satisfied with their implant crown and peri-implant soft tissues at all timepoints, with no significant differences between the groups ($p = 0.752$) (Table 4). The visual analogue score (VAS) for the satisfaction with the implant-supported crown amounted to 9.0 ± 1.2 (group CM), 8.8 ± 1.1 (group PG) and 9.1 ± 1.0 (control group) at FU-1. Similarly, VAS scores for the satisfaction with peri-implant soft tissues amounted to 8.0 ± 1.8 (group CM), 8.1 ± 1.7 (group PG) and 8.3 ± 1.5 (control group) at FU-1. Two patients in the CM-group and two patients in the PG-group experienced subjective complaints of the operated jaw (VAS > 2) at FU-1. Only two patients in the CM and one patient in the control group showed a score lower than 6 for peri-implant soft tissues satisfaction.

	CM	PG	Control	p-value (Treatment effect)	p-value (Interaction effect)	p-value (Time effect)
VAS: General satisfaction with dentition						
BL	8.1 ± 1.1	8.1 ± 2.3	8.3 ± 1.3			
FU-6m	7.8 ± 1.3	8.4 ± 1.9	8.4 ± 1.0			
FU-1	7.9 ± 1.4	8.0 ± 2.1	7.9 ± 1.4			
				0.753	0.315	0.348

	CM	PG	Control	p-value (Treatment effect)	p-value (Interaction effect)	p-value (Time effect)
VAS: Impact of surgery						
BL	4.0 ± 2.5	4.8 ± 3.1	4.0 ± 2.2			
FU-6m	4.5 ± 2.7	5.2 ± 2.7	3.9 ± 2.2			
FU-1	3.9 ± 2.8	5.0 ± 2.8	4.7 ± 2.7			
				0.365	0.514	0.601

▶

	CM	PG	Control	p-value (Treatment effect)	p-value (Interaction effect)	p-value (Time effect)
VAS: Pain in the operated jaw						
BL	0.1 ± 0.3	0.9 ± 2.2	0.5 ± 1.5			
FU-6m	0.4 ± 1.7	0.9 ± 2.2	0.3 ± 1.3			
FU-1	0.2 ± 1.4	0.4 ± 1.0	0.2 ± 1.3			
				0.311	0.776	0.579
	CM	**PG**	**Control**	**p-value (Treatment effect)**	**p-value (Interaction effect)**	**p-value (Time effect)**
VAS: Swelling in the surgical area						
BL	0 ± 0	0.7 ± 2.1	0.1 ± 0.3			
FU-6m	0.5 ± 1.8	0.7 ± 2.0	0.0 ± 0.2			
FU-1	0.4 ± 1.4	0.4 ± 1.1	0 ± 0			
				0.038	0.146	0.49
	CM	**PG**	**Control**	**p-value (Treatment effect)**	**p-value (Interaction effect)**	**p-value (Time effect)**
VAS: Satisfaction with the implant-supported crown						
BL	9.1 ± 0.9	8.6 ± 2.4	9.1 ± 1.2			
FU-6m	9.0 ± 0.9	8.9 ± 1.6	9.0 ± 1.4			
FU-1	9.0 ± 1.2	8.8 ± 1.1	9.1 ± 1.0			
				0.752	0.909	0.978
	CM	**PG**	**Control**	**p-value (Treatment effect)**	**p-value (Interaction effect)**	**p-value (Time effect)**
VAS: Satisfaction with the peri-implant soft tissues						
BL	8.1 ± 2.1	8.1 ± 2.4	8.5 ± 1.8			
FU-6m	8.1 ± 2.0	8.4 ± 1.5	8.3 ± 2.1			
FU-1	8.0 ± 1.8	8.1 ± 1.7	8.3 ± 1.5			
				0.785	0.918	0.994

Mean ± SD of PROMS using a visual analogue scale (VAS) from 0 to 10. Changes over time and differences between the treatment groups were assesed using generalized estimation equations (GEE). Wald's Chi^2 statistic was used to conclude about main effects and interactions. Group PG showed significantly more swellling according to the VAS scale. No other significant differences in PROMS were found at any timepoint ($p > 0.05$). Abbreviation: CM, Collagen matrix group; PG, palatal graft group.

Table 4 Patient-reported outcome measures (PROMs) of the treatment groups at Baseline (BL), 6-month (FU-6m) and one-year (FU-1) follow-up.

DISCUSSION

The present RCT comparing early implant placement with and without ARP at one-year follow-up predominantly revealed: i. favorable and similar esthetic outcomes across the three treatment modalities ii. comparable clinical outcomes between the two ARP groups and the control group, iii. similar PROMs between the groups.

Supracrestal tissue height (mid-facial mucosal margin) changes were minimal and similar between the groups. The minimal changes indicate a stability of the buccal supracrestal tissue height when early implant placement is applied, which is consistent with previous clinical data.[24, 28, 29] This stability might also be attributed to the performance of simultaneous GBR at implant placement, which was performed whenever a thin peri-implant buccal bone thickness (< 2 mm) was found. Clinical studies[18] and systematic reviews[30] have recommended a minimum bone thickness of 2 mm to avoid vertical soft tissue changes. Interestingly, there was some supracrestal tissue height gain. One might speculate that a soft tissue graft and the soft tissue thickening induced by spontaneous healing in the control group may had stimulated a gain in the mid-facial mucosal margin.[31-33] Even though these findings were positive, it should be emphasized that mid-facial mucosal margin changes have been assessed using different methods, thus undermining the comparison between studies.[11]

Esthetic outcomes including the peri-implant soft tissue conditions were similar between the two ARP groups and the control group, with no significant differences at any time point. The PES values were relatively within the range of the few available clinical studies on early implant placement after ARP. A recent RCT compared early implant placement versus late implant placement after ARP in periodontally compromised non-molar extraction sites.[29] In that study, the median PES scores in the early implant placement group amounted to 5 at one-year of loading.[29] Those lower PES scores compared to the present findings are most likely explained by the lack of papillary tissues observed in that study resulting in decreased PES scores. In contrast, a recent case series applying early implant placement in 10 patients after ARP revealed a median PES score

of 10 at one-year follow-up.[34] Moreover, outcomes from a prospective study also revealed higher PES scores.[28] In that latter study, where early and immediate implant placement were compared, mean PES scores amounted to 9.3 in the early implant placement group at one-year of loading.[28] The higher PES scores observed in these two studies as compared with the present values could be attributed to methodological differences in the PES evaluation. The present study applied the modified PES evaluation using a scale from 0-10[24] whereas the other two studies[28, 34], applied the original PES evaluation score using a scale from 0-14, thereby increasing the PES scores.[25]

The implant survival rates were similar across the groups amounting to 100% in CM and PG, and to 95.6% in the control group. These survival rates are in line with earlier studies where implants were placed following ARP.[29, 35-39]

Periodontal parameters compatible with peri-implant health were observed across the groups up to one-year after loading. This was indicated by the mean PD values around 3 mm, with no significant differences between the groups. The healthy conditions of the peri-implant tissues were further supported by the median values of mBI and PI which amounted to 0 in all groups. These findings are largely in agreement with previous reports.[29, 35-37, 40]

PROMs revealed high levels of satisfaction in all groups and without significant differences. These positive levels of satisfaction are consistent with a recent clinical report where early implant placement was applied.[28] In that study, the authors reported mean values of about 9 points at the different parameters using a VAS scale. Those values compare well with the present results. It should be noted, however, that clinical data about PROMs in ARP and early implant placement are scarce thus limiting the comparison with previous studies[11]. With respect to the patient's discomfort there were no marked differences between the groups. Nonetheless, patients reported significantly more discomfort in the PG-group. This observation was not unexpected as the PG-group required a donor site for the harvesting of the autogenous soft-tissue graft, which can be a painful procedure, particularly during the first days after surgery.[41, 42] These drawbacks, nevertheless, can be easily overcome by using a collagen matrix[7]

thereby replacing an autogenous soft-tissue graft without clinical disadvantages. The latter is supported by a recent systematic review revealing that no specific ARP procedure is superior.[5]

The present findings indicate that early implant placement is optimal for short-term esthetic outcomes. Interestingly, these positive outcomes were also obtained without ARP, supporting the notion that when a failing tooth can be replaced with an implant within 2 months after tooth extraction, the added value of ARP might be clinically negligible.[43] These observations might be related to the fact that 72% of the patients from the control group required simultaneous GBR at implant placement[13] as opposed to the patients of CM and PG group who required significantly less GBR at implant placement ($p < 0.05$) – 32% of the patients in CM and 24% in PG.[13] Another explanation for the lack of differences between the groups might be the shorter healing period (2 months) after ARP. ARP procedures traditionally involve a healing period of 4-6 months[5] and a shorter healing period may be insufficient for proper graft consolidation[44, 45] thus weakening the added benefit of ARP. Notwithstanding, there has been an emerging clinical and research interest to reduce the healing period following ARP.[7, 13, 29, 34]

The present study has a number of limitations. A healing period of 8 weeks after ARP might be insufficient for proper graft consolidation thereby hampering the possible added benefit of ARP.[44, 45] In terms of PROMs, the generalization of the present findings cannot be broadly generalized, since these types of outcomes have been commonly neglected.[11] Given the mucosal scarring that may occur at 5 years following implant placement with ARP[46], the stability of the supracrestal tissue height and the lack of differences across the groups should be interpreted with caution. Finally, the keratinized mucosa width was not measured, thereby limiting the interpretations of the present findings.

Together with consideration of cost and patient preference, these findings can assist clinicians in the decision-making process in daily practice. Future multicenter RCTs are warranted to confirm and generalize the present observations.

CONCLUSION

Early implant placement with ARP using demineralized bovine bone mineral with 10% collagen covered by either a collagen matrix or a palatal graft rendered similar clinical, esthetics and PROMs compared to early implant placement without ARP after one-year of loading.

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CHAPTER 7

General discussion and future perspectives

Single tooth replacement with dental implants is a safe and reliable treatment option.[1-3] Despite the success of the treatment, it is still important to optimize the procedure to achieve the most predictable and esthetically satisfactory results. One of the biggest challenges in oral implantology is the creation or preservation of sufficient alveolar bone to optimize implant success. The research described in this thesis investigated two procedures often performed during or before dental implant placement: alveolar ridge augmentation and preservation. The first part of this thesis studied the effects of barrier membranes in different augmentation procedures. The second part evaluated ridge preservation for early implant placement in single-tooth replacement.

Alveolar ridge augmentation and the use of barrier membranes

To place implants in the correct prosthetic position, bone augmentation procedures are often necessary to correct the osseous deficiencies of the alveolar ridge, which arise after tooth removal. These procedures can be performed simultaneously with implant placement if primary stability and ideal positioning of the dental implant are achieved (one-stage ridge augmentation).[4] If not, a bone augmentation must be performed prior to implant placement (two-stage ridge augmentation).[3] A minimal bone thickness of 1-2 mm buccal to the implant has been suggested for optimal results.[5, 6] Alveolar Ridge Preservation (ARP) might prevent changes of the alveolar ridge and thereby osseous deficiencies at future implant placement. The empty alveolus is grafted with an augmentation material which can be sealed by a mucosal graft, matrix, or membrane.[7] In case of immediate implant placement after tooth removal, the gap between the implant and buccal bone wall is usually grafted with a bone substitute or autogenous bone.[2, 8] During these procedures Guided Bone Regeneration (GBR) can be performed in which barrier membranes are applied to give direction to the growth of new bone.[9] Our systematic review showed insufficient evidence to support definitive conclusions regarding the effects of membrane for most bone augmentation procedures. However, for one-stage ridge augmentation, there was evidence of more horizontal bone gain and defect height reduction in favor of the membrane-covered group. A more recent systematic review did not find any new RCTs regarding one-stage ridge augmentation and advised the combination of a graft material and barrier membrane for optimal defect re-

duction.[10] Other systematic reviews recently published did not show additional bone gain or prevention of bone resorption when additional membranes were used for two-stage augmentations[11] or benefits for immediate implant placement.[12] Recent RCTs evaluating the use of membranes during ARP showed no advantage of a membrane on the buccal surface. However, it showed more bone resorption when the socket was not sealed from the oral environment with a membrane or mucosal graft.[13, 14] Therefore, it is advisable to use a membrane in one-stage ridge augmentation and as a seal for ARP if no mucosal graft is used.

Survival, success, and complications

In our study, no effect of the hydrogel membrane was observed on implant survival and success for small one-stage augmentation procedures. This was in line with other studies comparing a GBR procedure to those without a membrane.[15, 16] In addition, implants placed in combination with GBR showed similar survival rates compared to implants placed in completely native bone.[4, 17-21] However, our study showed an increased risk of mucosal dehiscence before the second-phase surgery in the membrane-covered group. This high amount of exposure was in line with a pre-clinical study evaluating the same hydrogel membrane.[22] Nevertheless, studies that used regular resorbable membranes also showed a considerable amount of early implant-exposures.[15] Although the mucosal dehiscence in our study was only small, an underlying negative effect on the bone augmentation procedure might be expected.[15, 23] Despite this shortcoming, no negative effects were observed on the implant success rate. Comparable studies reported only on implant survival rates and not on implant success.[15-17, 24] Our study showed lower success percentages when compared to the general literature, as additional criteria were used regarding pocket probing depths and bleeding indices.[25] We believe that there is a need for universally accepted parameters of clinical implant success to make the studies more comparable. The original criteria for implant success suggested by Albrektsson et al. (1986)[26] can be used, combined with periodontal parameters (pocket depth of < 5 mm without bleeding on probing),[27] the esthetic score such as the PES (minimal score of 7)[28] and patient satisfaction grading (general satisfaction of > 7 on a VAS scale).

Radiographic parameters

The change in marginal bone level (MBL) was used as a parameter for the stability of the hard tissues around the implants. The mean change was in favor of the membrane-covered groups and was comparable to implants placed in native bone. The change in MBL was in line with the literature, where a change from 0.7 mm to 2.4 mm for GBR groups and 0.5 mm to 2.4 mm for the control groups were observed for implants placed in native bone.[4, 16, 17, 19-21] The MBL is most stable for implants placed in combination with barrier membranes and for implants placed in complete native bone. An interesting recent study investigated the spontaneous healing of small buccal bone defects after implant placement (without augmentation) and compared these to GBR-reconstructed defects.[29, 30] This was investigated in an RCT regarding single-tooth replacement in the posterior area. The mean change in the buccal vertical bone height was, as expected, in favor of the GBR group, but the defects left for spontaneous healing showed comparable results regarding implant survival and health of the soft tissues. However, a mean difference between the two groups (0.41 mm) after 18 months of loading was noted regarding the change in marginal bone level. Interestingly, this difference disappeared over time after a longer follow-up.

Esthetic scores

The esthetics were evaluated using the modified pink esthetic index (PES) and the modified white esthetic score (WES).[31, 32] The total PES scores did not differ between implants placed in combination with GBR, bone augmentation without a membrane, or implants placed in native bone. Our RCT found that sub-parameter 'root convexity and soft tissue color' scored significantly worse in the GBR group. This can be explained by the high amount of dehiscence in the GBR group, which could have negatively influenced this esthetic parameter. In the current study, we used a hydrogel membrane that is not commonly used for GBR procedures. The hydrogel membrane may have led to more dehiscence and graft particle resorption of the synthetic bone substitute used.[22, 33] Although this membrane was introduced to facilitate easy application, in practice, it was quite difficult to apply a thin smooth layer. The steep learning curve resulted in a high number of complications during the start of product usage. Interestingly, although this hydrogel membrane is no longer

commercially available, it produced very good results in a recent RCT regarding ARP.[34] The hydrogel membrane also produced very good results compared to the standard membrane regarding clinical soft tissue parameters for alveolar ridge augmentation.[35]

Patient-reported outcomes

Implant placement in combination with GBR, bone augmentation without a membrane, and implants placed in native bone resulted in high patient satisfaction. Patients were highly satisfied with their dentition, crown, and soft tissues after implant placement in all three groups. Our patients noted 95-96% acceptable results for soft tissues. There were no significant differences in the perceived impact of surgery, pain, or swelling. Although there is a trend towards more patient-reported outcomes in implant research, it is still not a common practice and it was therefore hard to compare it to the literature.[36] In this thesis, we used a non-validated questionnaire based on a VAS scale. We did not use the OHIP-NL, an in Dutch translated and validated a 49-item questionnaire regarding oral health-related quality of life.[37] We believe this is a great questionnaire for patients with multiple missing teeth and dental impairment. However, it is not specific enough to detect minor differences in single tooth replacement with dental implants. The development of abbreviated OHIP versions such as the OHIP-NL14 for clinical use is a good initiative but currently only validated for temporomandibular dysfunction.[38] An adapted OHIP version validated for single tooth replacement might be useful for studies and clinical practice.

Alveolar ridge preservation for early implant placement

The different timing protocols for implant placement have specific indications, advantages, and disadvantages.[39, 40] Early implant placement is a proven concept with excellent results. Immediate implant placement offers a shortened and simplified procedure, early implant placement offers a slightly increased stability of the peri-implant hard and soft tissues.[41, 42] Combining early implant placement with ARP might reduce the need for GBR procedures and further optimize the soft tissue esthetics.[7, 40, 43] The main goal of the ARP procedure itself is to preserve as much as possible soft and hard tissue volume.[7, 44] In an attempt to do so, an epithelialized palatal graft can be applied over the aug-

mented ridge.[45] Because donor site morbidity of these grafts is quite high,[46-48] the use of a substitute material would avoid donor-side morbidity.[49, 50] In late implant placement, ARP resulted in less vertical and horizontal changes of the alveolar ridge. Thus, it created a good starting point for future implant placement.[49, 51, 52] In contrast to late implant placement, less is known on combining ARP with early implant placement.[43]

Alveolar ridge alterations

Ridge alterations were evaluated using superimposed CBCT scans. Ridge preservation resulted in less horizontal and vertical bone resorption compared to spontaneous healing 8 weeks after tooth extraction. This was in accordance with earlier studies, where ridge preservation resulted in less vertical and horizontal resorption 4-6 months after tooth removal.[49, 51, 53] Although ridge preservation resulted in less bone loss compared with spontaneous healing and the amount of additional GBR-procedures needed at the time of implant placement was less in the ARP group, additional GBR was still needed in a large percentage of ARP patients. This is also in line with earlier studies which described results ranging from 0%-45% additional augmentations in ridge preservation groups and 0%-100% in groups that were left for spontaneous healing.[43, 44, 52, 54] The augmented particulate xenograft is still quite soft at early implant placement and some particles are easily displaced during drilling for osteotomy resulting in the need for additional augmentation.[55] In our study we used blocks of 90% particulate demineralized bovine bone mineral with added 10% collagen to fill the empty alveolus. The bone blocks were chosen because we expected easier handling for filling the alveolar socket compared to regular particulate bone minerals.[56] However, shaping the block to the root anatomy was technically more demanding than the application of particulate bone. Additionally, one could argue that adding autogenous bone to the substitute would accelerate the bone remodeling process and lead to more compact bone at early implant placement.[58] Interestingly, there is very limited literature regarding the additional use of autogenous bone for alveolar ridge preservation.[44] Moreover, there are no studies available with faster resorbing alloplastic/allograft material for ARP combined with early implant placement. A recent systemic review on different materials in ARP included studies with healing times of 4-6 months.[44]

Soft tissue alterations

Soft tissue contour changes were investigated by profilometric measurements of superimposed STL file slices. The soft tissue thickness was measured by superimposing STL files over CBCT scans.[58-60] There was no difference in horizontal soft tissue contour changes between the two techniques and the control group. This was also reported in earlier studies, where only a limited protective effect was seen at the labial ridge contour when compared to spontaneous healing.[50, 61] Our study did not show a significant difference between the three groups for the buccal, palatal, and vertical mucosal dimensions at 8 weeks post-extraction. This is an interesting contradiction in our study. As ridge preservation resulted in less horizontal and vertical bone resorption, and the profilometric measurements were equal. One might expect more soft tissue in the group with spontaneous healing. The lack of a significant difference in profilometric changes might be related to the small area of interest selected for the analysis.[50, 61] Additionally, alginate was used as the impression material, whereas, an intraoral scan would have been more precise.

Esthetic scores

Esthetic outcomes (PES/WES), including the stability of the soft tissues, were similar between the two ARP groups and the control group, with no significant differences at any time point. These PES values are within the range of the few available clinical studies on early implant placement and/or ARP.[52, 62, 63] The higher PES scores observed in two studies[62, 63], as compared with the present values, could be attributed to methodological differences in the PES evaluation. The present study applied a modified PES evaluation using a scale from 0 to 10[31]. Conversely, both aforementioned studies applied the original PES evaluation score using a scale from 0 to 14. Thereby increasing the PES scores.[32] Interestingly, these positive outcomes were also obtained with and without ARP. This intriguing finding might be related to the fact that most of the patients in our control group underwent GBR during implant placement. Moreover, ARP procedures traditionally involve a healing period of 4-6 months. A shorter healing period might be insufficient for proper graft consolidation and thus may reduce the added benefit of ARP.[64, 65]

Midfacial gingiva level

The vertical soft tissue changes were minimal and similar between the groups. These minimal changes indicate the stability of the buccal vertical soft tissues when early implant placement is applied, which is consistent with previous clinical data.[31, 52, 63]

Patient-reported outcomes

Patient-related outcomes revealed high levels of satisfaction in all groups, with no significant differences. These positive levels of satisfaction are consistent with a recent clinical report in which early implant placement was applied. However, it should be noted that patient-reported outcomes in ARP and early implant placement are scarce, thus limiting the comparison with previous studies.[63, 66] Concerning the patient's discomfort, there was a significant difference between the groups after 1-week, the group sealed with a palatal graft reported more discomfort than the other groups. This observation was not unexpected because harvesting soft tissue from the palate is a painful procedure, particularly during the first days after surgery.[47, 48] This can easily be overcome by the use of a collagen matrix[43] to replace an autogenous soft-tissue graft. Moreover, a recent systematic review revealed that no specific ARP procedure is superior.[44] Therefore, the additional costs of using a collagen matrix instead of a palatal graft might be justified because of the lower patient morbidity.

Future perspectives

As techniques and materials in oral implantology are continuously evolving, it would be interesting to investigate different biomaterials. Evaluating a slow resorbing xenograft with or without a membrane might be an interesting choice for alveolar ridge augmentation or contour augmentation during implant placement. Also, the new generation non-resorbable membranes look very promising and show a lower risk of infection.[67] Regarding the investigated parameters, one might discuss the need for additional information on buccal bone thickness. In future protocols, a small-field CBCT scan at intake and follow-up to evaluate the 3rd dimension prior to implant placement should be considered.

A healing period of 8 weeks after ARP with a slow-resorbing biomaterial might be insufficient for proper graft consolidation, leading to displaced bone particles

during implant placement. It would be very interesting to evaluate faster integrating biomaterials for ARP before early implant placement, such as allografts, alloplastic material, or a combination of a slow-volume stable xenograft with the autogenous bone for faster remodeling. As the first explorative randomized trial comparing immediate implant placement with ARP for late implant placement is very interesting.[68, 69] We would like to perform a randomized trial comparing immediate implant placement with early implant placement after ARP. In both groups, we would use a slow-resorbing graft material mixed with autogenous bone. To seal the implanted or grafted alveolus, a collagen matrix will be used.

Although our study showed no clinical advantage of ARP after 12 months, it would be interesting to investigate other outcomes such as surgical difficulty at implant placement. One could argue that ARP is a more straightforward procedure than GBR, and placing an implant in an already augmented ridge might be technically less challenging. We are currently evaluating and analyzing the results of bone volume and profilometry after 12 months of loading and are planning to call back patients after a longer follow-up period.

In general, pre-implantological procedures are relatively expensive and cannot be afforded by all patients. Therefore, a study on the cost-effectiveness of both treatment protocols would be valuable. Preventing additional bone or soft tissue augmentation may reduce treatment time and cost. The ARP study was conducted in close and constructive collaboration with the University of Zurich. This demonstrates the importance of bringing together multidisciplinary expertise from different centers to improve the methodology and data analysis.

GENERAL CONCLUSION

Implant-success, soft/hard tissue dimensions, esthetic results, and patient satisfaction of implants placed after alveolar ridge augmentation and preservation are evaluated in this thesis. There is insufficient evidence regarding the clinical effects of membranes in most bone augmentation procedures. The additional use of a resorbable membrane in small augmentation procedures is beneficial for the radiographic marginal bone level, but not for any other clinical parameter.

A GBR procedure for small buccal bone defects seems to be a reliable technique with satisfactory esthetics and patient-reported outcomes equal to implants placed in native bone. Early implant placement with ARP using either a collagen matrix or a palatal graft resulted in similar clinical, esthetic, and patient-reported outcomes as early implant placement without ARP. Whenever a failing tooth can be replaced by early implant placement, ARP might not be indicated for favorable esthetic outcomes.

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Summary

The general introduction and outline of this thesis are presented in *Chapter 1*. Single tooth replacement with dental implants has become a predictable treatment option for failing or missing teeth. The correct prosthetic three-dimensional position is mandatory to create predictable, clinically healthy, and esthetically pleasing results. There are different timing protocols available for placing dental implants after tooth extraction, such as immediate (0-1 week), early with soft tissue healing (4-8 weeks), early with partial bone healing (12-16 weeks), and late (> 4 months) implant placement. Due to infection, trauma, or physiologic resorption, the alveolar process can be too narrow to facilitate a complete bony surrounding of the dental implant. Different treatment options are available to create or preserve sufficient alveolar bone. Bone augmentation procedures can be performed before or during implant placement to reconstruct the bony deficiencies. Membranes can also be used to direct the growth of new bone, a principle called 'Guided Bone Regeneration' (GBR). Bone resorption after tooth removal might be minimized by filling the empty alveolus with an augmentation material, usually covered by a mucosal graft, membrane, or matrix. This procedure is called 'Alveolar Ridge Preservation' (ARP). In this thesis, we investigated the use of barrier membranes for alveolar ridge augmentation procedures and the effect of ARP on early implant placement.

As there is no consensus on the use of barrier membranes and to provide a complete overview of the studies with the highest level of evidence, a systematic review was performed and noted in *Chapter* 2 to assess these effects in different augmentation procedures. This systematic review evaluated barrier membranes for alveolar ridge augmentation with simultaneous (one-stage) and delayed (two-stage) implant placement, sinus augmentation procedures, ARP, and immediate implant placement. Outcomes were implant failure, complications, horizontal bone gain and resorption, graft resorption, defect height reduction, marginal bone loss around implants, esthetic results, and patient satisfaction. Even though 17 articles reported on 10 randomized trials with a total of 355 included patients, insufficient evidence was found to determine whether

implant failure rates, marginal bone level changes, esthetic results, or patient satisfaction differed. For one-stage augmentations, there was evidence of more horizontal bone gain (MD: 0.84 mm, 95% CI: 0.46-1.21, $p < 0.001$), defect height reduction (MD: 18.36%, 95% CI: 10.23-26.50, $p < 0.001$), and prevention of graft resorption ($p = 0.004$) in favor of the membrane-covered group. For immediate implant placement, there was evidence of an increased defect height reduction in favor of the membrane-covered groups (MD: 6.25%, 95% CI: 1.67-10.82, $p = 0.007$). There is insufficient evidence regarding the effects of membranes on most other bone augmentation procedures to support any definitive conclusions.

As there was evidence of more horizontal bone gain and defect height reduction in one-stage alveolar ridge augmentation in favor of the membrane-covered group, a randomized controlled trial (RCT) was performed. The RCT in *Chapter 3* evaluated the effect of a resorbable hydrogel membrane on one-stage bone augmentation for small alveolar bone defects during implant placement in the esthetic zone. Patients with a buccal bone defect after implant placement were allocated to ridge augmentation with ($n = 25$) or without the barrier membrane ($n = 27$). No significant differences in implant survival and success were observed at the final follow-up (12 months after loading). The risk of having a small mucosal dehiscence was more than six times higher in the membrane-covered group (RR: 6.24, 95% CI 0.81-48.21). The median change in marginal bone level was statistically lower in the membrane-covered group (0.06 mm) than in the non-covered group (0.60 mm) at the final follow-up ($U = 120$, $Z = 2.73$, $p = 0.006$, $r = 0.42$). The total pink esthetic index (PES) and white esthetic score (WES) were not significantly different between the treatment groups. In addition, no differences were observed in patient satisfaction.

In *Chapter 4*, a prospective controlled trial is described in which the esthetic and patient-reported outcomes were compared between implants placed with a small GBR-procedure with implants placed completely in native bone. During implant placement, patients were allocated to the GBR group with a buccal bone defect of 4 mm or less. In total, 45 patients were included, of which 23 underwent a GBR procedure after implant placement, and in 22 patients,

no GBR was necessary. No significant differences in esthetic outcomes were observed between the two groups. At the final follow-up, a mean PES of 7.8 (SD 1.5) was seen for the GBR group versus 8.4 (SD 1.4) for the patients in whom no bone augmentation was necessary. Patients in both groups were equally satisfied with the esthetics of their mucosa and crown. The mean visual analog score (VAS) for the soft tissues of 8.6 (SD 1.0) in the GBR group and 8.8 (SD 0.9) for the patients without bone augmentation. A mean VAS score of 9.2 (SD 0.8) was noted for the crown in the GBR group and 8.6 (SD 2.0) in the group without bone augmentation. Implant survival was 100% in both groups, and there were no significant differences in complications, plaque/bleeding/gingiva-indices, the width of attached mucosa, and marginal bone loss.

As there is only limited evidence regarding the clinical advantages of ARP in early implant placement, an RCT was performed. A study to evaluate the dimensional hard and soft tissue changes after tooth extraction in the esthetic region treated with ARP before early implant placement is described in *Chapter 5*. ARP was performed using a xenogeneic bone substitute covered with either a collagen matrix or a free palatal graft and compared to spontaneous healing. This study evaluated the effects until the moment of early implant placement (8-10 weeks after tooth extraction). Twenty-five patients were allocated to each group. The patients treated with ARP and covered with the collagen matrix (-0.9 SD 0.6 mm) and the palatal graft (-1.0 SD 0.8 mm) showed less horizontal bone resorption compared to spontaneous healing (-3.2 SD 2.1 mm) ($p < 0.001$). Moreover, the necessity of GBR at implant placement was significantly lower in patients treated with ARP covered with the collagen matrix (32%) and the palatal graft (24%) than in those with spontaneous healing (72%) ($p = 0.001$). Patients treated with the collagen matrix experienced less pain than those treated with the palatal graft one week after tooth extraction ($p = 0.042$). No significant differences were found in graft evaluation, postoperative complications, or soft tissue contour.

The study in *Chapter 6* is the one-year follow-up after implant loading in the above-mentioned RCT. The aim was to test whether early implant placement with ARP results in different esthetic, clinical, and patient-reported outcome

measures compared to early implant placement without ARP. Eight weeks after tooth extraction, early implant placement was performed in all the patients. Clinical, esthetic, and patient-reported outcomes were evaluated 1 year after loading the implant. A total of 70 patients were available for re-examination at the 1-year follow-up. Periodontal parameters, PES/WES scores, and patient-reported outcomes revealed no significant differences between the groups one year after loading. The median mid-facial gingival change was -0.02 mm (Q1: -0.27, Q3 0.46) in the collagen matrix covered group, -0.13 (Q1: -0.4, 0.25) in the palatal graft group and -0.14 mm (Q1: -0.29, Q3: 0.07) in control. PES scores were 7.0 (SD 1.4) in the collagen matrix group, 7.1 (SD 1.5) in the palatal graft group, and 7.3 (SD 1.7) in the control group.

In *Chapter 7*, a general discussion and future perspectives are outlined. To conclude, there is insufficient evidence regarding the clinical effects of membranes in most bone augmentation procedures. The additional use of a resorbable membrane in small augmentation procedures is beneficial for the radiographic marginal bone level, but not for the other investigated parameters. A GBR procedure for small buccal bone defects was a reliable technique with satisfactory esthetics and patient-reported outcomes equal to implants placed in native bone. Early implant placement with ARP using either a collagen matrix or a palatal graft resulted in similar clinical, esthetic, and patient-reported outcomes as early implant placement without ARP. Whenever a failing tooth can be replaced by early implant placement, ARP might not be indicated for favorable esthetic outcomes. In future studies, it might be interesting to evaluate faster integrating biomaterials for ARP before early implant placement, such as allografts, alloplastic material, or a combination with a slow-volume stable xenograft and an autogenous bone. In addition, a study comparing immediate implant placement with early implant placement after ARP would be of great interest.

Samenvatting

De algemene inleiding en overzicht van dit proefschrift staat beschreven in *Hoofdstuk 1.* Enkeltandsvervanging door middel van implantaten is een voorspelbare behandeling voor een falend of ontbrekend element. De juiste driedimensionale prothetische positie van een implantaat is vereist om een voorspelbaar, klinisch gezond en esthetisch optimaal resultaat te bereiken. Er zijn verschillende protocollen beschikbaar met betrekking tot het tijdstip voor het plaatsen van implantaten na het trekken van een tand of kies. Zo is er directe implantaatplaatsing (binnen 0-1 week), vroege implantaatplaatsing met genezing van de weke delen (na 4-8 weken), vroege implantaatplaatsing met gedeeltelijke botgenezing (na 12-16 weken) en late implantaatplaatsing (na > 4 maanden). Als gevolg van infectie, trauma of fysiologische resorptie na extractie kan de processus alveolaris te smal zijn om een volledige botbedekking van het implantaat mogelijk te maken. Er zijn verschillende behandelingen om voldoende alveolair bot te creëren of te behouden. Een botopbouw kan worden uitgevoerd vóór of tijdens de plaatsing van het implantaat om deze botdefecten te reconstrueren. Membranen kunnen worden aangebracht om de groei van nieuw bot te sturen, een principe dat 'Guided Bone Regeneration' (GBR) wordt genoemd. Ook kan worden getracht de botresorptie na het verwijderen van een tand te minimaliseren door de lege alveolus te vullen met augmentatie materiaal, meestal bedekt met een mucosa transplantaat, membraan of matrix. Deze procedure wordt 'Alveolar Ridge Preservation' (ARP) genoemd. In dit proefschrift hebben we het gebruik van membranen voor alveolaire botopbouw procedures en het effect van ARP voor vroege implantaatplaatsing onderzocht.

Aangezien er geen consensus bestaat over het gebruik van membranen en om een compleet overzicht te geven van de onderzoeken met het hoogste bewijsniveau, werd in *Hoofdstuk 2* een systematische literatuurstudie beschreven waarin het huidige bewijs met betrekking tot membranen bij verschillende botopbouw procedures is onderzocht. Er werd gekeken naar botopbouw procedures tijdens (één-fase) en na (twee-fase) het plaatsen van een implantaat, tijdens een sinusbodemelevatie, tijdens ARP en bij een botopbouw tijdens directe implantaat-

plaatsing. Ondanks dat er 17 artikelen over 10 gerandomiseerde onderzoeken met in totaal 355 patiënten werden geselecteerd, was er onvoldoende bewijs om te bepalen of er duidelijke verschillen waren in verscheidene uitkomstmaten zoals verlies van implantaat, veranderingen in marginaal botniveau, esthetische resultaten of patiënttevredenheid. Echter, indien membranen gebruikt werden tijdens een botopbouw in dezelfde procedure met het plaatsen van een implantaat, was er gering bewijs voor meer horizontale botwinst (MD: 0.84 mm, 95% CI: 0.46-1.21, $p < 0.001$), vermindering van defecthoogte (MD: 18.36%, 95% CI: 10.23-26.50, $p < 0.001$) en preventie van transplantaatresorptie ($p = 0.004$). Ook was er een verhoogde afname van de defecthoogte in het voordeel van de membraan bedekte groepen als het implantaat direct werd geplaatst na extractie (MD: 6.25%, 95% CI: 1.67-10.82, $p = 0.007$). Aangezien er bewijs lijkt te zijn voor meer horizontaal botwinst en reductie van defecthoogte in gevallen waarbij een botopbouw gecombineerd wordt met een implantaat plaatsing, werd er een gerandomiseerde gecontroleerde studie (RCT) uitgevoerd naar de effecten van resorbeerbare membranen in deze situatie.

De gerandomiseerde klinische studie beschreven in *Hoofdstuk 3* evalueerde het effect van een resorbeerbaar hydrogel membraan tijdens een botopbouw voor kleine defecten tijdens implantaat plaatsing in de esthetische zone. Patiënten met een buccaal botdefect na plaatsing van het implantaat werden verdeeld over twee groepen, botopbouw met ($n = 25$) of zonder membraan ($n = 27$). Er werden geen significante verschillen in overleving en succes van implantaten gezien 12 maanden na plaatsen van de implantaten. Het risico op een kleine mucosale dehiscentie was meer dan zes keer groter bij de patiënten met een membraan bedekte botopbouw (RR 6.24, 95% CI 0.81-48.21). De mediane verandering van het marginale botniveau was significant lager bij patiënten met een membraan (0.06 mm) dan bij de patiënten zonder membraan (0.60 mm) ($U = 120$, $Z = -2.73$, $p = 0.006$ $r = 0.42$). De totale 'Pink Esthetic Score' (PES) en 'White Esthetic Score' (WES) en gecombineerde PES / WES waren niet significant verschillend tussen de behandelingsgroepen. Er werden geen verschillen gevonden in patiënttevredenheid.

In *Hoofdstuk 4* werd een prospectief gecontroleerd onderzoek uitgevoerd om de esthetische en de patiënt gerapporteerde tevredenheid te evalueren van im-

plantaten geplaatst met een kleine botopbouw (GBR-procedure). Deze methode werd vergeleken met patiënten waarbij het implantaat volledig in eigen bot geplaatst kon worden. Patiënten werden toegewezen aan de GBR-groep indien er sprake was van een buccaal botdefect van 4 mm of minder. In totaal werden 45 patiënten geïncludeerd, waarvan er 23 een GBR-procedure ondergingen. Bij 22 patiënten was geen GBR nodig en konden de implantaten volledig in eigen bot worden geplaatst. Er werden geen significante verschillen in esthetische uitkomsten gezien tussen de twee groepen. Bij de laatste follow-up werd een gemiddelde PES-score van 7.8 (SD 1.5) gezien bij de patiënten met een GBR-procedure en 8.4 (SD 1.4) voor de patiënten waar geen botopbouw noodzakelijk was. Patiënten van beide groepen waren even tevreden over hun tandvlees en kroon. Er was geen sprake van verlies van implantaten in beide groepen en er waren geen significante verschillen in het aantal complicaties, plaque-/bloeding-/gingivaindices, breedte van aangehechte mucosa en marginaal botverlies.

Aangezien er slechts beperkt bewijs is met betrekking tot de klinische voordelen van ARP voor vroeg geplaatste implantaten, werd een RCT uitgevoerd voor implantaten in de esthetische zone. Om de driedimensionale veranderingen in het esthetische gebied van harde en zachte weefsels na tandextractie met ARP te evalueren, werd een gerandomiseerde klinische studie beschreven in *Hoofdstuk 5*. ARP werd uitgevoerd met een xenogene botvervanger bedekt met ofwel een collagene matrix (n = 25) of een vrij palatum transplantaat (n = 25). Deze groepen werden vergeleken met spontane genezing (n = 25). In deze eerste studie werd gekeken naar de effecten tot het moment van vroege implantatieplaatsing (8 weken na tandextractie). De ARP-patiënten bedekt met een collageen matrix (-0.9 SD 0.6 mm) en palatum transplantaat (-1.0 SD 0.8 mm) vertoonden minder horizontale botresorptie vergeleken met de groep met spontane genezing (-3.2 SD 2.1 mm) ($p < 0.001$). Bovendien was de noodzaak van additionele GBR bij implantaat plaatsing significant minder bij de ARP-patiënten bedekt met een collagene matrix (32%) en palatum transplantaat (24%) in vergelijking met de controlegroep (72%) ($p = 0.001$). Patiënten met een collagene matrix ervaarden minder pijn dan de patiënten behandeld met een palatum transplantaat één week na extractie ($p = 0.042$). Er werden geen significante verschillen gevonden met betrekking tot het aspect van het transplantaat, postoperatieve complicaties en weke delen contour.

De studie beschreven in *Hoofdstuk 6* is de follow-up één jaar na belasten van de implantaten van bovengenoemde RCT. Het doel was om te onderzoeken of vroege implantaatplaatsing met ARP resulteerde in andere esthetische, klinische en door de patiënt gerapporteerde uitkomstmaten in vergelijking met vroege implantaatplaatsing zonder ARP. Acht weken na extractie werd bij de patiënten een implantaat geplaatst. Klinische, esthetische en patiënt gerapporteerde uitkomsten werden 1 jaar na het belasten geëvalueerd. In totaal waren 70 patiënten beschikbaar voor evaluatie tijdens de follow-up van 1 jaar. Parodontale parameters, PES/WES en patiënt gerapporteerde uitkomsten, onthulden geen significante verschillen tussen de groepen. De mediane midfaciale gingivale verandering bedroeg -0.02 mm (Q1: -0.27, Q3: 0.46) bij de patiënten bedekt met een collagene matrix, -0.13 (Q1: -0.4, Q3: 0.25) bij de patiënten met een palatum transplantaat en -0.14 mm (Q1: -0.29, Q3: 0.07) bij spontane genezing. PES-scores bedroegen 7.0 (SD 1.4) voor de patiënten met een collagene matrix, 7.1 (SD 1.5) bij een palatum transplantaat en 7.3 (SD 1.7) bij spontane genezing.

In *Hoofdstuk 7* werden de algemene discussie en toekomstperspectieven geschetst. Concluderend is er slechts beperkt bewijs met betrekking tot de klinische effecten van membranen bij de meeste botopbouw procedures. Het extra gebruik van een resorbeerbaar membraan bij kleine botopbouw procedures is gunstig voor het marginale botniveau, maar niet voor enige andere onderzochte parameter. Een GBR-procedure voor kleine buccale botdefecten lijkt een betrouwbare techniek te zijn met even goede esthetiek en vergelijkbare patiënt gerapporteerde tevredenheid als implantaten volledig geplaatst in eigen bot. Vroege implantaatplaatsing met ARP met behulp van een collageenmatrix of een palatale graft leverde vergelijkbare klinische, esthetische en door de patiënt gerapporteerde resultaten op in vergelijking met vroege implantaatplaatsing zonder ARP. Wanneer een tand vervangen gaat worden door middel van vroege implantaatplaatsing, is ARP mogelijk niet geïndiceerd voor gunstige esthetische resultaten. In toekomstige studies zou het interessant kunnen zijn om sneller integrerende biomaterialen voor ARP te evalueren voor vroege implantaatplaatsing, zoals allografts, alloplastisch materiaal of de combinatie van een langzaam volume stabiel xenotransplantaat met autoloog bot. Ook zou een studie waarin onmiddellijke implantaatplaatsing wordt vergeleken met vroege implantaatplaatsing na ARP de moeite waard zijn.

Curriculum Vitae

Persoonlijke gegevens

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2011 - 2015	Geneeskunde – Vrije universiteit Amsterdam
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Werkervaring

2021 - heden	KIVO – Erasmus Medisch Centrum, Rotterdam
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2011 - 2016	Tandheelkunde en implantologie – SmileClinic, Rotterdam

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Interesses

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PhD Portfolio

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Erasmus MC Afdeling: MKA-chirurgie
PhD periode: 2015-2021
Promotor: Prof.dr. E.B. Wolvius
Copromotor: Dr. J. Pijpe

PhD training

	Jaar	Werkdruk (ECTS)
Algemene cursussen		
Research Integrity	2015	0.5
BROK (Good Clinical Practice)	2015	1.0
Specifieke cursussen		
• NVOI cursus pre-implantologische chirurgie, UMCG	2016	1.0
• Stage implantologie en pre-implantologische chirurgie, afdeling MKA Erasmus MC	2017	7.0
• Implantologie en pre-implantologische chirurgie tijdens overige stages, afdeling MKA Erasmus MC	2017-2020	7.0
• Kaakchirurg In Opleiding (KIO) cursus Implantologie, Leiden	2019	2.0
Seminars en workshops		
• Wetenschaps bijeenkomsten MKA, Erasmus MC	2015-2020	1.0
• iQual meetings, Amsterdam	2015-2019	1.0
• ITI study club, Rotterdam	2015-2020	1.0
Presentaties		
• NVMKA najaarscongres, Amersfoort	2015	1.0
• Research Meeting MKA Erasmus MC	2015	1.0
• NVMKA najaarscongres, Den Haag	2017	1.0

	Jaar	Werkdruk (ECTS)
Presentaties (vervolg)		
• IQual, Krimpen aan den IJssel	2017	1.0
• NVMKA najaarscongres, Helmond	2018	1.0
• ITI studieclub, Rotterdam	2018	1.0
• ITI studieclub, Eindhoven	2018	1.0
• IQual, Amsterdam	2018	1.0
• Refereeravond MKA, Rotterdam	2018	1.0
• ITI congres Benelux, Rotterdam	2019	1.0
• ICOMS, Rio de Janeiro	2019	1.0
• AAOMS, Boston	2019	1.0
Nationale en internationale conferenties		
• NVMKA najaarscongres, Amersfoort	2015	1.0
• EAO Congres, Madrid	2017	1.0
• NVMKA najaarscongres, Den Haag	2017	1.0
• ITI World Symposium, Bazel	2017	1.0
• NVMKA najaarscongres, Helmond	2018	1.0
• Osteology Barcelona	2019	1.0
• ITI congress Benelux, Rotterdam	2019	1.0
• ICOMS, Rio de Janeiro	2019	1.0
• AAOMS, Boston	2019	1.0

Onderwijs

	Jaar	Werkdruk (ECTS)
Lecturing		
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Supervising practicals and excursions, Tutoring		
• Co-assistenten begeleiden	2017-2021	1.0

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Over de auteur

Brend P. Jonker werd 3-8-1989 geboren in Rotterdam. Na zijn middelbare school verhuisde hij naar Amsterdam voor zijn studies tandheelkunde en geneeskunde. Hij behaalde zijn diploma tandheelkunde in 2011 aan de faculteit tandheelkunde (ACTA) van de Universiteit van Amsterdam en zijn diploma geneeskunde in 2015 aan het VU Medisch Centrum.

Gedurende zijn tweede studie is hij gestart met werken in een tandartspraktijk en verwijscentrum voor orale implantologie in Rotterdam. Hierdoor raakte hij verder geïnteresseerd in de verschillende aspecten van orale implantologie. In 2015 startte hij zijn onderzoek naar botaugmentaties aan de afdeling Mondziekten-, Kaak- en Aangezichtschirurgie van het Erasmus Medisch Centrum, te Rotterdam. Dit vormde de basis voor het huidige promotieonderzoek.

Van 2017 tot en met 2020 was hij AIOS MKA-chirurgie in het EMC en is in 2021 gestart als KIVO aldaar.

Brend brengt zijn vrije tijd graag door met familie en vrienden. Daarnaast houdt hij van sporten en actieve snowboard- en kitesurf-vakanties. Brend is getrouwd met Vera Jonker-Negenborn en heeft een dochter Florien Jonker.