Is There Evidence that Barrier Membranes Prevent Bone Resorption in Autologous Bone Grafts During the Healing Period? A Systematic Review

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Introduction: *Autologous bone is considered the "reference standard" for bone-grafting procedures. A barrier membrane covering an autologous bone graft (guided bone regeneration [GBR]) is expected to prevent graft resorption. Good clinical results have been reported for GBR, although potential complications and relatively high costs have been implicated as disadvantages. However, most studies on the subject have been uncontrolled.* ***Purpose:*** *The aim of this systematic review was to evaluate the available evidence that barrier membranes prevent bone resorption in autologous onlay bone grafts. The primary outcome measure was bone resorption.* ***Results:*** *The search yielded 182 articles. Two observers independently appraised 32 relevant studies methodologically, yielding 14 controlled studies. The articles included human and animal experiments with heterogenous objectives and outcome variables. Although most authors concluded that they had found evidence for the protective effect of barrier membrane on bone resorption in bone grafts, this systematic review reveals that the available evidence is too weak to support this. Most included studies were animal experiments; thus, extrapolation to the human situation is difficult. Most studies also had a small number of test sites, and sample size justification was generally not reported. Furthermore, ambiguity and lack of significance were found in many studies, along with additional limitations such as implantation site, nonsuitable designs, and varying outcome measures.* ***Conclusion:*** *Based on a systematic review of the literature, further evidence is needed to determine whether barrier membranes prevent bone resorption in autologous onlay bone grafts.* Int J Oral Maxillofac Implants 2007;22:390–398

Key words: *artificial membranes, bone grafts, bone transplantation, resorption*

The reconstruction of large skeletal deficiencies presents a major surgical challenge. In the facial skeleton, such defects may result from trauma, infection, congenital defects, or tumor resection. In the reconstructive process, there is usually a need for bone or a bone substitute.[1] A specific, frequently occurring clinical situation that may cause significant problems for reconstruction is the atrophic (partially) edentulous jaw. Since the introduction of endosseous implants, partially or totally edentulous patients with severely resorbed jaws can be successfully treated with prosthetic restorations.[2–4] A prerequisite for the placement of dental implants is the presence of sufficient bone to provide for stability and esthetics. Only with sufficient bone can osseointegration be expected.

A considerable number of augmentation methods have been used in attempts to solve the problem of bone deficiency. Widely accepted techniques include guided bone regeneration (GBR),[5] transplantation of autologous bone grafts,[6–8] augmentation with bone substitutes,[9] or a combination of these.[10]

The mechanism of GBR is similar to that of guided tissue regeneration (GTR). A barrier membrane prevents fibroblast mass action to allow osteogenesis within the blood clot that is formed beneath the barrier membrane covering the defect.[11] Furthermore,

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the barrier membrane excludes inhibiting factors and preserves growth factors.[12,13] The major difference between the GBR and GTR techniques is the open connection of the wound with the oral cavity by means of the gingival sulcus in GTR. This allows oral microorganisms to penetrate the wound, which is an important factor in complications. A GBR membrane covering a bony defect or bone graft is ideally primarily closed.

GBR is suitable only for local bony defects. In the case of a large defect, a bone graft can be applied with (ie, underneath) or without a barrier membrane. The bone functions as a scaffold and carrier for living cells. The barrier membrane is expected to prevent bone resorption, since it keeps the osteoinductive substances in place[13,14] and secludes the grafted area from inhibiting factors and connective tissue cells.[15] Furthermore, the barrier membrane serves as a space maintainer, allowing bone regeneration in any remaining space and thus minimizing overall loss of bone volume.[8] Membrane coverage may primarily reduce resorption by enhancing incorporation.[16]

Autologous bone serves as the reference standard for bone-grafting materials.[8,17] However, alternatives such as demineralized bone and porous bovine bone mineral have been extensively investigated with good outcomes.[9,18,19]

Good clinical results regarding barrier membrane coverage have been reported, and many clinicians currently cover bone grafts with a barrier membrane.[1] However, the advantages of barrier membrane application can be doubted, primarily because of the risk of complications caused by nonresorbable membranes perforating the oral mucosa.[20] Membrane exposure during healing has a major negative effect on GBR around dental implants.[21] Thus, a closed situation is essential when an expanded polytetrafluoroethylene (e-PTFE) membrane is used. Moreover, these barrier membranes account for a significant part of the costs in alveolar ridge augmentation prior to implant surgery.[22]

The aim of this systematic review was to appraise the available evidence that barrier membranes prevent the resorption of autologous bone grafts.

MATERIALS AND METHODS

Study Selection

To identify studies related to artificial barrier membranes and resorption of onlay bone grafts, a sensitive search of the literature was conducted in the databases of MEDLINE (1966 to October 2005), OLDMEDLINE (1950 to 1965), EMBASE (1989 to October 2005), and Biological Abstracts (1990 to October 2005). The search was supplemented with a systematic search in the Cochrane Central Register of Controlled Trials (CENTRAL) (1800 to October 2005). The search strategy included the use of MeSH terms from the applied thesaurus and free-text words in the aforementioned databases and is presented in Table 1. The search was completed by checking the references of relevant review articles and eligible studies for additional publications. No language restrictions were used throughout the study selection procedure.

Table 1 Search Strategy

1. Bone resorption (MeSH)
2. Bone transplantation (MeSH)
3. Membrane, artificial (MeSH)
4. 1 AND 2 AND 3
5. Bone resorption AND bone transplantation AND artificial membrane (free text)

Articles were deemed relevant to the topic under investigation (ie, autologous bone and barrier membrane use) on the basis of their titles and abstracts. When agreement was reached, a full-text document of each relevant article was obtained to determine whether the study was eligible for methodologic appraisal. The predetermined inclusion criteria were *(1)* application of autologous bone, *(2)* use of a barrier membrane covering the bone graft, *(3)* primary closure of the surgical wound, and *(4)* use of a control group in which no barrier membrane was applied. Studies handling barrier membranes in periodontal therapy (ie, GTR) were excluded. Two researchers independently assessed eligible studies included for methodologic appraisal. Items that were evaluated were the research question, study design (including randomization method where applicable), control group, and outcome measure. When necessary, agreement on these items was reached in a consensus meeting.

RESULTS

The MEDLINE and OLDMEDLINE databases yielded 173 publications using MeSH-terms and 175 publications when using free text only. The search linking MEDLINE, EMBASE, and Biological Abstracts yielded 32 hits, 28 of which had already been found with the previous search. The CENTRAL search yielded 17 articles, of which 3 had not already been found. The searches yielded 182 publications. Screening of titles and abstracts for relevance revealed 32 publications. After applying the inclusion criteria for methodologic appraisal, 12 articles remained. Systematic reference checking yielded 2 additional articles matching the inclusion criteria (Fig 1).[15,23]

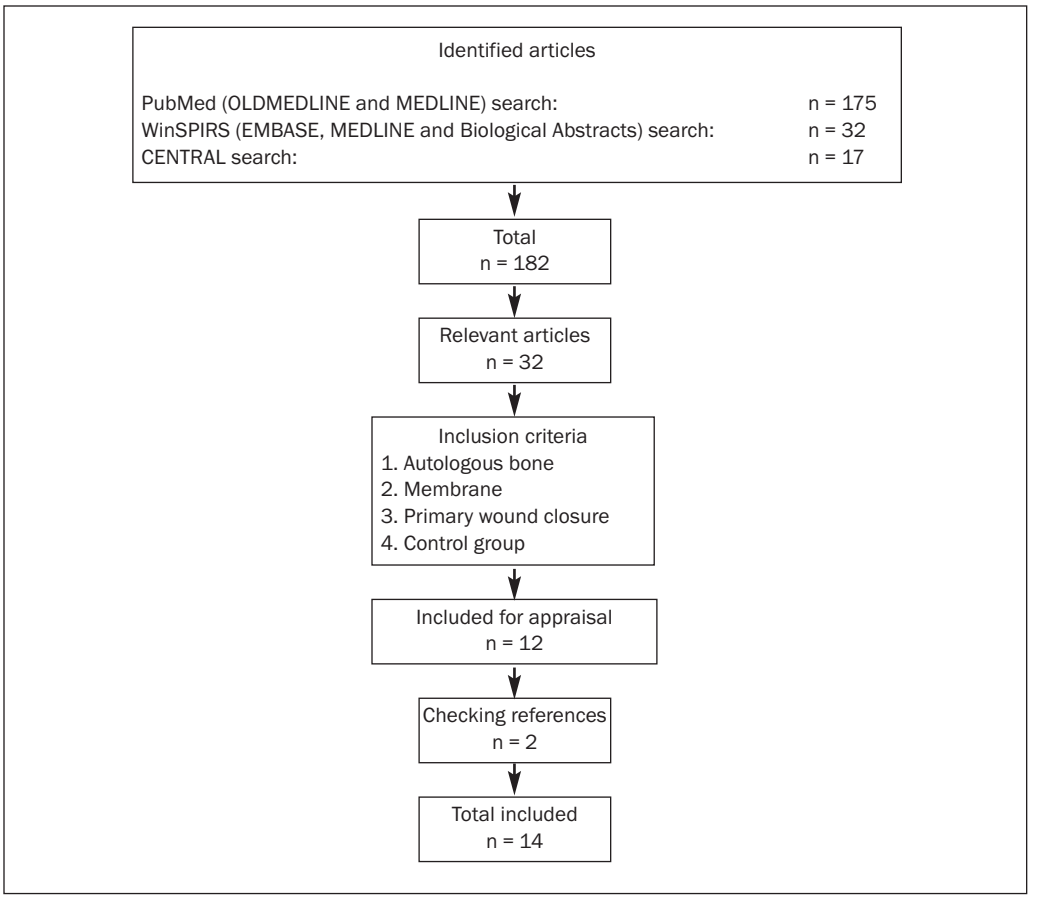

Fig 1 Algorithm of study selection procedure.

The 14 articles included 2 clinical trials and 12 animal experiments. The animal models used included dog, rat, and rabbit models (Table 2).

Outcome variables and measures differed among the publications. Data were presented in absolute, relative, categorical, or descriptive terms. In most studies, statistical analyses were reported; the remaining studies merely displayed their results qualitatively. Outcome variables included histologic parameters (eg, resorption) and clinical factors (eg, implant stability). Most authors used histology or histomorphometrics, but plaster casts and computerized tomographic (CT) scans were also used.

Because of the heterogeneity of the amassed articles, a meta-analysis could not be performed. For this reason the literature is presented as a conventional review (Table 2). All but 2 publications had the same objective (ie, measurement of the effect of barrier membranes on autologous bone grafts).[27,30] Gordh et al[27] concentrated on the influence of recombinant human bone morphogenetic protein-2 (rhBMP-2) on graft volumetric maintenance, and Salata et al[30] were interested in the factors involved in osseointegration in situations where a blood vessel source was unavailable. The latter concluded that membrane-covered grafts demonstrated delayed remodeling. Hindrance of the process of revascularization was probably the cause. Furthermore, the authors stated that resorption was more extensive in membrane-protected sites, although the total amount of bone was higher in these cases. Gordh et al[27] were interested in the effects of rhBMP-2. To this end, 8 different groups were used. Only the 2 control groups, one with and one without a barrier membrane applied, were relevant for the present review. Overall, better results were achieved with the use of a barrier membrane.[27] In their second study,[15] the authors could not demonstrate definite differences concerning graft integration between grafts covered by a barrier membrane and those covered only by the muscle flap. However, minimal signs of graft resorption were found on the membrane side, while almost all control grafts showed signs of peripheral resorption. No significant differences between sides were registered regarding the measured variables. After 20 weeks, a difference in graft incorporation was evident.

Table 2 Characteristics of Included Studies

Study	Graft	Barrier membrane	Explantation site	Implantation site	Surgical access	Max. no. of test sites per group	No. and species	Follow-up	NB	Limitations
Alberius et al[16]	Autologous bone, disc-shaped	e-PTFE	Mandibular angle	Calvarial roof	Extraoral	16	28 rats	12 wk	Inlay design also tested	• Extraoral implantation site • Limited external validity • No data-assessment description
Antoun et al[8]	Autologous bone	e-PTFE	Mandibular symphysis area	Maxilla and mandible	Intraoral approach	5	12 humans	6 mo	Patients randomly allocated to membrane or graft-alone group	• No split-mouth design design • Follow-up not long enough
Chiapasco et al[22]	Autologous bone chips, corticocancellous bone blocks	e-PTFE	Bone chips harvested intraorally, bone blocks from the chin, retromolar area, iliac crest, and calvaria	Maxilla and mandible	Intraoral approach	15	30 humans	6 to 8 mo	2 groups: • Bone blocks without barrier membrane (small and large defects) • Bone chips, membrane (limited defects)	• No statistical comparison because of bias resulting from treatment choice by clinician and differences in donor site and defect extension
Donos et al[7]	Autologous corticocancellous bone	e-PTFE	Ischium	Maxilla and mandible	Intraoral (maxilla), Extraoral approach (mandible)	6	51 rats	60, 120, 180 d	3 test groups: • Maxilla augmentation • Mandible augmentation with gold-coated implants • Mandible augmentation with titanium implants	• Suitability of design doubtful; major part of grafts was lost
Donos et al[24]	Autologous cortical bone	e-PTFE	Mandible	Maxilla	Intraoral	5	20 rats	15, 30, 60, 90 d		• Suitability of design doubtful; major part of grafts was lost
Donos et al[25]	Autologous cortical bone	e-PTFE	Mandibular angle	Mandible, inferior border	Extraoral approach	6	30 rats	15, 30, 60, 120, 180 d		
Donos et al[26]	Autologous membranous, enchondral bone	e-PTFE	Calvaria (membranous), ischium (enchondral)	Mandible, inferior border	Extraoral approach	8	25 rats	5 mo, 11 mo	4 test groups: membranous and enchondral bone transplanted to mandible (split mouth) with or without membrane. Animals sacrificed at 5 and 11 mo. Membrane removed after 5 mo; 3 rats died during the experiments.	• Long follow-up considering faster metabolism
Gordh et al[15]	Heterologous bone	e-PTFE	Femur and tibia	Cranium under temporalis	Extraoral	7	21 rats	12, 20 wk	2 experiments: *(1)* membrane-covered and bare bone grafts; *(2)* both sides received barrier membranes. After 12 wk, membranes removed from 1 side	• Extraoral implantation site • Limited external validity

Table 2 continued Characteristics of Included Studies

Study	Graft	Barrier membrane	Explantation site	Implantation site	Surgical access	Max. no. of test sites per group	No. and species	Follow-up	NB	Limitations
Gordh et al[27]	Heterologous bone	e-PTFE	Femur and tibia	Cranium under *m.temporalis*	Extraoral	6	48 rats	4, 20 wk	Aim of study was to measure the effect of rhBMP-2	• Extraoral implantation site • Limited external validity • Different objective
Jensen et al[28]	Autologous bone	e-PTFE	Iliac crest	Mandible	Extraoral approach	4	4 dogs	6 mo	Also augmentation with DFDB, irradiated DFDB, and controls injected with blood tested.	• Small number of test sites
Lundgren et al[23]	Autologous bone	Poly lactide-glycolide	Skull	Skull	Extraoral	8	8 rabbits	12 wk	Round graft accompanied by particulate bone placed in circular defect	• Extraoral implantation site • Limited external validity • Inlay design • Particulate bone decisive factor
Rasmusson et al[29]	Autologous bone, disc-shaped	e-PTFE	Calvarium	Proximal tibial metaphyses	Extraoral	6	9 rabbits	8, 24 wk	Barrier membrane removal after 8 weeks in all subjects, some followed for additional 16 weeks	• Extraoral implantation site • Limited external validity
Salata et al[30]	Autologous cortical bone	e-PTFE	Radius	Mandibular inferior border	Extraoral approach	8	14 rabbits	6, 24 wk	Design in which implants were placed in 1 animal at different times on contra-lateral sides; implants examined at 6 and 24 weeks after placement.	• Different objective
Von Arx et al[31]	Autologous bone	e-PTFE	Molar area	Mandible	Intraoral approach	3	3 dogs	6 mo	Defects introduced 2 months before implantation	• Inlay design

e-PTFE = expanded polytetrafluoroethylene; NB = *nota bene*.

The number of experimental sites (ranging from 3 to 16), as well as the receptor site, type of bone, surgical access, and follow-up differed between the studies (Table 2). Most authors placed bone grafts on intact bone or in freshly created spaces. Von Arx et al,[31] however, introduced defects 2 months prior to the transplantation of bone into these defects. The results of that study demonstrated that barrier membrane coverage was preferable. Augmented sites with membrane protection showed positive healing results with a preserved ridge profile. Nonprotected grafts underwent bucco-crestal resorption. Chiapasco et al[22] and Rasmusson et al[29] found no evidence that barrier membranes provided protection from bone graft resorption. Chiapasco et al[22] found both methods reliable for the reconstruction of narrow edentulous ridges. However, due to increased costs and the risk of wound infection in case of membrane exposure, these authors prefer reconstruction without the use of barrier membranes in case of narrow ridges. The results of the other study[29] showed an increase in volume of the bone grafts on the tested side as long as the barrier membrane was in place. After removal of the barrier membrane, the resorption rate was higher on the test side compared to the control side, resulting in similar bone heights at the end of the experiment. Therefore, the authors concluded that barrier membranes do not have any preventive effect on bone resorption.

The studies performed by Jensen et al[28] and Antoun et al[8] revealed the opposite. They found significantly less bone resorption in the grafts covered with a barrier membrane. Jensen et al[28] stated that a barrier membrane improved both graft volume incorporated and bone-implant interface contact in fox hounds. The other study was performed on humans.[8] A positive effect of barrier membranes on bone resorption at 6 months following surgery was observed, and a longer follow-up was recommended.

All authors except Alberius et al[16] and Gordh et al[15,27] used fixation screws or placed implants during the first surgery. Fixation screws can be applied in the GBR technique to secure the barrier membrane and/or graft. Alberius et al[16] stated that barrier membranes promote bone deposition in freshly created defects. The onlay grafts generally resorbed, but the grafts covered by a barrier membrane seemed more active, developed an increased cancellous component, and showed less pronounced volumetric loss.

Donos et al[7,24–26] experimented with different implants, implantation sites, and different types of bone. In 2 of these studies, the rat maxilla was augmented in a split-mouth design.[7,24] In both studies histologic analysis demonstrated that in situations where the barrier membrane was not exposed to the oral environment during healing, the grafts were in continuity or integrated with the bone at the recipient site. In the majority of cases, however, the barrier membrane became exposed or the graft and implant were lost. In these cases the grafts presented extensive resorption and there was lack of bone continuity. These findings correspond to those on the non–membrane-treated sites. The authors endorsed the importance of closure of the operated area.

In the other experiments, mandibular augmentation procedures were tested.[7,25,26] At the sites treated with barrier membranes, the grafts were integrated with the underlying or newly formed bone, and the dimensions of the alveolar ridge were increased. The grafts in the control groups presented significant gradual resorption and varying degrees of integration in the recipient bone.[7,25,26] The enchondral grafts showed more resorption than the membranous ones. No significant differences were found between groups treated with different types of microimplants, except that the titanium implants demonstrated improved bone-implant contact. Removal of the membrane after a follow-up period of 5 months resulted in a decrease in dimensions at 11 months, with sizes similar to the baseline measurements (ie, the measurement at implantation). At 5 months the dimensions were increased.[26] The authors concluded that bone grafting in combination with barrier membrane application eliminates the risk of graft resorption and ensures integration. Furthermore, GBR improved the predictability of bone augmentation and provided long-term volume stability.[7,25,26]

As shown in Table 2, all barrier membranes were composed of nonresorbable e-PTFE, except the resorbable lactide-glycolide barrier membranes used by Lundgren et al.[23] Statistically significant differences were found for height and volume of the augmented bone in favor of the covered transplants.

DISCUSSION

In mandibular and maxillary augmentation procedures bioresorbable and nonresorbable bone-regenerating membranes are extensively applied for covering bone grafts and bone substitutes as part of pre-implant surgery. The rationale for this approach is that it may prevent resorption of onlay bone grafts and hold together granular bone substitutes or ground bone.

In a previous review, Nevins et al[32] concluded that large bone grafts used for ridge reconstruction purposes might benefit from barrier membranes because they reduce the inevitable resorption of bone grafts. However, their review included uncon-

trolled studies. More recently, clinical studies with sufficient numbers of patients have been performed; these studies have shown good results with barrier membranes in combination with autologous bone grafts. Nevertheless, most of these studies are uncontrolled[33] or used merely a barrier membrane or bone substitute combined with a barrier membrane as a control.[34] Because of this lack of adequate control groups, numerous articles were excluded from the present review, and this led to a minimal amount of useful data. Controlled trials comparing a resorbable collagenous membrane/ bone graft test group and an autologous graft control group were not found. Most studies on the use of a resorbable collagenous membrane have focused on bone substitutes.[35]

In this review, the prevention of bone resorption was chosen as the primary outcome variable, since the current method of choice is a staged approach (ie, bone augmentation preceding implant placement).[36] However, successful grafting is usually measured as a function of implant retention, despite significant resorption of the graft.[28]

It is difficult to draw a clinically relevant conclusion from the reviewed studies because of the small number of human studies and test sites, ambiguity, and lack of significant results. Because of major differences in outcome variables, measures, and study designs and lack of data-assessment description,[16] it was not possible to perform a meta-analysis. Therefore, the clustered effect size remains unknown. Consequently, the best available evidence supporting the use of barrier membranes to prevent bone resorption in autologous onlay bone grafts is weak. To actually answer the research question, randomized controlled trials should be performed and problems related to measuring bone volume must be solved.

In 12 articles, the authors stated that barrier membrane-application was beneficial in the prevention of bone resorption; in 2 publications, it was not recommended that membranes be used to cover autologous onlay bone grafts.[22,29] Only 6 studies demonstrated statistically significant results.[7,8,23,25,26,28] However, the total number of test sites per group was rather small, ie, 4 to 8 (Table 2). In contemporary science a minimum of 10 test sites has been proven necessary to gather reliable evidence in in-vivo experiments.[37] All reviewed studies use a marginal number of test sites. None of the included studies reported sample size requirements. The required sample sizes are much larger than those that have been generally used.[38] Three study designs (Table 2) performed measurements at only 1 time point in the follow-up, and no long-term follow-up was reported.

A general issue in animal experiments is interpretation of the data. According to Roberts et al[39] bone formation and remodeling is about 2 and 3 times faster in rabbits as compared to dogs and humans, respectively. It is hazardous to extrapolate the results to the human situation. Ideally, a human model is chosen, but it can be difficult to attain sufficient statistical power. Unfortunately, the included studies performed in humans have some additional drawbacks (Table 2).[8,22]

Donos et al[7,24–26] used split-mouth designs. Overall, their experiments were well-designed (Table 2). Reproducibility was tested, and short- and long-term follow-up periods were applied. Their conclusions were based on objective measures. However, most of the designs of the included studies had some limitations that precluded a valid conclusion (Table 2).

Despite the paucity of data, it seems accepted that barrier membranes prevent bone resorption. Therefore, most research appears to be focused on the logical consequence of this (ie, development of better membranes[6] or bone substitutes).[34] Furthermore the studies yielded in this review show conclusions based on the assumption of a positive effect size. However, this review shows that the available evidence is weak. Some preventive effect may be expected.[25] Research should instead focus on the question "Do barrier membranes prevent bone resorption in autologous onlay bone grafts?"

Thus, there is not sufficient evidence that barrier membranes prevent bone resorption in onlay bone grafts. This does not imply that this procedure is contraindicated in bone grafting, provided that (nonresorbable) barrier membrane exposure is prevented during the healing period. Furthermore, most bone substitutes consist of small particles. These may be applied in combination with autologous bone chips or blocks, a situation that is often seen in clinical practice. When used with particulate bone products, barrier membrane application is necessary to secure these granules and not to prevent bone resorption. In the authors' opinion, supported by the conclusions in the reviewed articles, the application of barrier membranes may have a positive effect; however, this conclusion remains to be firmly established. Future research with sufficient numbers of animals and test sites acquired by power analysis, and, most importantly, randomized controlled trials should be executed to demonstrate clinical evidence in support of the use of barrier membranes.

CONCLUSION

The conclusion, drawn on the basis of the best available evidence, is that barrier membranes show some preventive effect on graft resorption. However, the evidence whereupon this conclusion is based is weak. Well-designed animal experiments and clinical randomized controlled trials are necessary to provide a definitive answer to the research question.

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