

Horizontal bone augmentation by means of guided bone regeneration

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Oral implants are a means to anchor dental prostheses in situations of partial or complete edentulism. Over the years, implant dentistry has developed into a field supported by a sound preclinical and clinical evidence base. Through the evolved clinical concepts and treatment strategies, patients may now benefit from excellent solutions for improving quality of life. Furthermore, the medium- and long-term results of properly executed dental-implant treatments yield high survival and success rates of dental prostheses. A number of factors critical for the long-term survival of implants and implant-supported reconstructions have been identified over time. One prerequisite is a sufficient amount of bone at the implant recipient site to allow osseointegration of the endosseous implant surface. Following the introduction of oral implants into the dental field, implants were usually placed in areas of sufficient bone to improve the predictability of osseointegration of the implant. More recently, implants have been placed in positions that are optimal for fabrication of the planned reconstruction. One key factor responsible for such adaptation of the clinical procedures is the high predictability and the success of the bone regeneration procedures. Currently, the most appropriate approach for treatment with dental implants is first of all to plan the desired prosthetic reconstruction and then to place the implants in the three-dimensional position optimal for achieving the planned treatment result and the regeneration of bone necessary to osseointegrate the implants.

The best documented and most widely used method to augment bone in localized alveolar defects is guided bone regeneration. Based on a series of experimental studies, a biological principle of healing was discovered by Nyman & Karring in the early 1980s. The work of these investigators was aimed at regener-

ating lost periodontal tissues (116, 158, 160). They found that the cells which first populate a wound area determine the type of tissue that ultimately occupies the original space. From this knowledge, they developed a technique, utilizing barrier membranes, which prevented undesired cells from accessing the wound and, at the same time, allowed cells with the capacity to form the desired tissue to access the wound space. This technique was termed guided tissue regeneration and it led to novel possibilities to regenerate periodontal tissues, including new root cementum, periodontal ligament and alveolar bone (81, 82, 157, 161).

Soon thereafter, guided tissue regeneration was applied for the regeneration of bone tissue (for review see 88, 92, 156). A large series of animal experiments (52, 54, 55, 194) and human clinical studies (15, 27, 128, 129, 159, 229) have documented guided bone regeneration to be a successful method for augmenting bone in situations where there is inadequate bone volume for the placement of endosseous dental implants. Furthermore, when implants are placed and a bone defect results, leaving part of the endosseous surface of the implant exposed, a large body of literature documents guided bone regeneration to be successful for predictable bone formation (16, 51, 53, 108, 127, 129).

In clinical practice the development of guided bone regeneration has substantially influenced the possibility of implant use. Bone augmentation procedures have allowed the placement of implants in jaw bone areas lacking an amount of bone sufficient for standard implant placement. Therefore, the indications for implants have broadened to include jaw regions with bone defects and those with a bone anatomy that is unfavorable for implant anchorage. Such situations occur as a result of congenital, post-traumatic

or postsurgical defects, or may be caused by disease processes.

The aim of this review is to present the scientific and clinical basis of guided bone regeneration and the accepted clinical procedures, and to provide an outlook into possible future options related to bone augmentation.

Membranes

Over the past three decades, a large variety of barrier membranes have been used for guided bone regeneration procedures. The criteria required to select appropriate barrier membranes for guided bone regeneration encompass biocompatibility, integration by the host tissue, cell occlusiveness, space-making ability and adequate clinical manageability (95). Additionally, documentation on the procedures and materials regarding clinical safety and long-term effectiveness needs to be available to recommend their use in humans. The barrier membranes used for guided bone regeneration procedures can be classified as nonresorbable or resorbable (Table 1). In turn, resorbable membranes can be classified as natural or synthetic, depending on their origin.

Nonresorbable membranes

Expanded polytetrafluoroethylene (e-PTFE) membranes were the first generation of clinically well-documented barrier membranes used for guided bone-regeneration procedures (53, 76, 238). e-PTFE is a synthetic polymer with a porous structure, which does not induce immunologic reactions and resists enzymatic degradation by host tissues and microbes. Integration of titanium reinforcement within e-PTFE membranes increases their mechanical stability and allows the membranes to be individually shaped.

These characteristics have been claimed to be advantageous for the successful treatment of challenging defects that lack the support of the membrane by the adjacent bone walls. Successful treatment outcomes following large lateral and vertical augmentations by means of e-PTFE membranes have been clinically documented (29, 37, 199).

An increased rate of soft-tissue complications after premature membrane exposure has been reported as a disadvantage of the use of e-PTFE membranes (38). Once exposed to the oral cavity, the porous surface of e-PTFE membranes is rapidly colonized by oral microbes (205, 210). This often leads to infections of the adjacent tissues and to the subsequent need for early membrane removal, resulting in impaired bone regeneration (80, 85, 149, 193, 198, 238). Another disadvantage of e-PTFE membranes is the need for re-entry surgery and membrane removal, which is associated with patient morbidity and the risk of tissue damage. To overcome such drawbacks and to simplify the surgical protocols, resorbable membranes have been developed.

Resorbable membranes

A variety of resorbable membranes have been evaluated for use in guided bone regeneration procedures (138, 200, 238) (Table 1). Resorbable membranes have the following advantages: no need for membrane-removal surgery and thus elimination of the need to expose the regenerated bone; a wider range of surgical techniques possible at abutment connection; better cost-effectiveness; and decreased patient morbidity. However, the difficulty of maintaining the barrier function for an appropriate length of time is considered a major drawback of resorbable membranes. In addition, depending on the material, the resorption process of the membrane may interfere with wound healing and

Table 1. Membranes used for guided bone regeneration procedures

Nonresorbable	Resorbable	
	Natural	Synthetic
e-PTFE	Native collagen	Polyglactin
d-PTFE	Cross-linked collagen	Polyurethane
Titanium foil	Freeze-dried fascia lata	Polylactic acid
Micro titanium mesh	Freeze-dried dura mater	Polyglycolic acid
		Polylactic acid/polyglycolic acid copolymers
		Polyethylene glycol

e-PTFE, expanded polytetrafluoroethylene; d-PTFE, dense polytetrafluoroethylene.

bone formation. Finally, the lack of stability of the material makes the use of membrane-supporting materials mandatory.

Membranes made of native collagen exhibit good tissue integration, fast vascularization and biodegradation without a foreign-body reaction (163, 180, 181). Native collagen membranes are well documented and have been shown to render good results and low complication rates in both animal (101, 162, 196) and human (93, 111, 149, 238) studies. Currently, native collagen membranes are the standard treatment for the majority of guided bone regeneration indications (88). Another advantage of the use of native collagen membranes for guided bone regeneration is spontaneous healing in the presence of mucosal dehiscence. In contrast to nonresorbable membranes, epithelialization of the exposed collagen achieving secondary wound closure is spontaneous (73, 74, 238). This is a significant clinical advantage because, in the case of soft-tissue complications, the membrane does not require any surgical interventions and can be left in place.

The major drawbacks of native collagen membranes may be caused by their unfavorable mechanical properties, such as poor resistance to collapse (101, 190, 207, 236), and by the fast degradation, resulting in an early loss of barrier function (143, 163, 237). The rapid biodegradation of native collagen by the enzymatic activity of host tissues and microbes has been demonstrated in animal models (181, 193, 195). However, it is important to emphasize that the degradation time of native collagen may vary considerably, depending on its source and its original structure (180).

Several physical, chemical and enzymatic processes for cross-linking collagen fibrils have been developed, in order to prolong the degradation time of the membranes (25, 122, 144, 172, 235). A recent study on a rat model evaluated eight different collagen membranes and found the increased degree of cross-linking to be directly related to prolonged biodegradation time, decreased tissue integration and foreign body reaction (181). Histological investigations showed that inflammatory cells are involved in the resorption process of cross-linked collagen membranes (21, 181). This may explain the increased frequency of mucosal dehiscence with impaired soft-tissue healing and wound infections that occurred in clinical trials (3, 14). In contrast, other preclinical and clinical studies showed promising results for cross-linked collagen membranes, exhibiting adequate tissue integration and successful bone regeneration that were similar, or even superior, to those achieved when using native collagen membranes (72, 149, 193, 223). Furthermore,

several studies revealed that the premature exposure of a cross-linked collagen membrane was followed by complete spontaneous secondary epithelialization without impaired bone regeneration (72, 74, 149). These contrasting findings indicate differences in the biological behaviors among the different types of cross-linked membranes.

The use of synthetic resorbable membranes made out of aliphatic polyesters such as polylactic acid, polyglycolic acid, trimethylcarbonate and their copolymers has been reported to be effective for guided bone regeneration procedures in experimental (60, 94, 206), as well as in clinical (133, 138, 200) studies. However, the use of these membranes may be subject to drawbacks such as inflammatory foreign-body reactions associated with their degradation products (223, 226). Some studies found a reduced defect fill when applying polylactic acid and polyglycolic acid membranes as opposed to e-PTFE membranes (132, 200, 204).

Form-stable polylactic acid/polyglycolic acid copolymer (PLGA) membranes, modified with *N*-methyl-2-pyrrolidone as a plasticizer, were recently evaluated in preclinical (112, 141, 151) and clinical (242) studies. PLGA membranes used for guided bone regeneration of large peri-implant defects appear susceptible to fracture when they are not supported by grafting material, indicating that the mechanical stability of the membrane is insufficient for this type of application (112). In combination with grafting material, PLGA performed similarly to native collagen. In a recent multicenter, randomized controlled trial, including 40 patients with peri-implant dehiscences, guided bone regeneration was performed using either PLGA membranes or titanium-reinforced e-PTFE membranes (187). At 6 months re-entry surgery, the mean vertical defect fill was 81% within the PLGA group and 96% within the e-PTFE group. Titanium-reinforced e-PTFE membranes were able to maintain the horizontal thickness of the regenerated region more effectively and developed fewer soft-tissue complications compared with PLGA membranes.

A new approach, aiming at simplifying the clinical handling, was taken with a synthetic *in-situ* polymerizing membrane made of polyethylene glycol (Fig. 1) (115, 135, 231). *In situ*, polyethylene glycol is degraded by hydrolysis with no acidic byproducts, which have been shown to trigger foreign-body reactions in the surrounding tissues (97, 231). Preclinical studies indicated that this material is highly biocompatible and cell-occlusive and allowed the formation of similar amounts of new bone compared with other types of materials, such as e-PTFE and polylactic acid

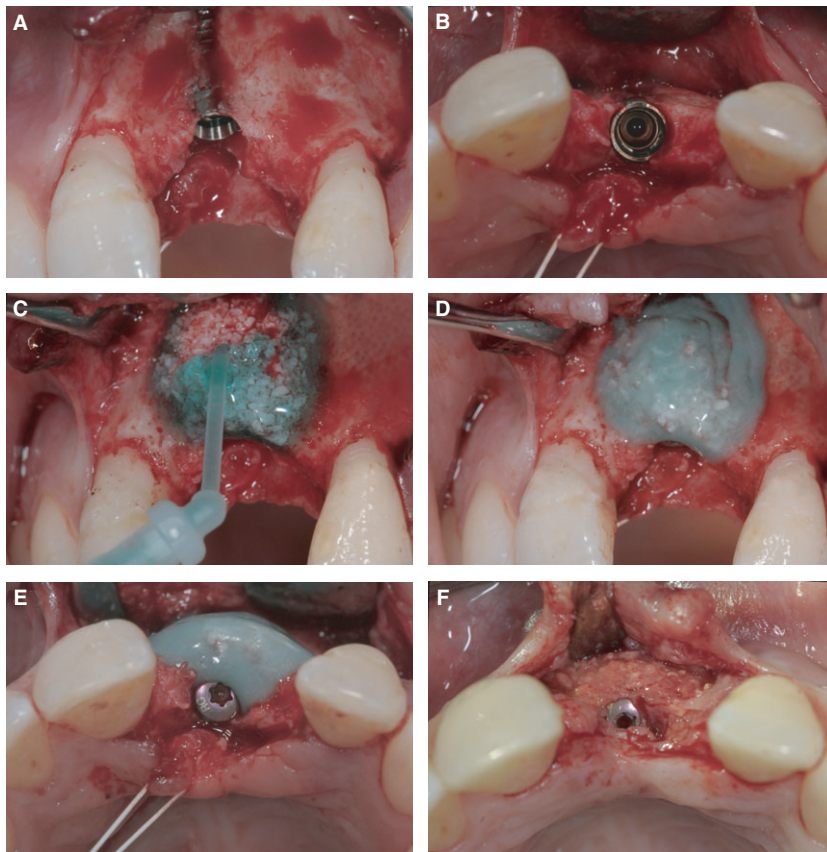


Fig. 1. (A, B) Dehiscence-type bone defect at an implant position 21. (C) The defect is treated by guided bone regeneration applying particulate bovine-derived bone mineral and synthetic hydrogel made of polyethylene glycol (D, E) *In-situ* polymerized polyethylene glycol membrane. (F) Re-entry surgery 6 months after implant placement.

(115, 215). In a randomized controlled trial, the polyethylene glycol membrane was as successful as native collagen membrane in terms of vertical defect repair of peri-implant osseous dehiscences (111). Moreover, in recent preclinical studies, polyethylene glycol membranes showed promising results for staged augmentation of challenging lateral ridge defects in terms of bone ingrowth and preservation of the ridge contours (142, 191, 214).

Bone grafts and bone-graft substitutes

Due to its potential osteogenic, osteoinductive and osteoconductive properties, autogenous bone has long been considered the ideal grafting material for bone augmentation procedures (26, 98). However, morbidity and complications related to the donor site, limited graft availability and unpredictable graft resorption are major limitations related to the use of autogenous grafts (41, 43, 107, 155, 183, 227, 233). To overcome these shortcomings, bone-graft substitutes have been developed as adjuncts to, or replacements for autografts in bone augmentation procedures.

Bone grafts and bone substitutes can be classified into four groups, according to their origin: autografts,

from the same individual; allografts, from another individual within the same species; xenografts, from another species; and alloplasts, synthetically produced (Table 2). Their application modality encompasses several forms for application, such as block, granular, moldable, injectable or *in-situ* hardening materials.

It has been claimed that grafts and bone-graft substitutes for guided bone regeneration need to fulfill the following requirements: biocompatibility; osteoconductivity; adequate mechanical support of the membrane to provide the volume for the regenerated bone; biodegradability; and replacement with the patient's own bone (77, 78, 103). Recent studies have suggested that a slow substitution may be advantageous for maintenance of the augmented volume (104, 105).

A multitude of xenografts, consisting of minerals derived from animals, corals or algae, are commercially available. The best-documented bone substitute used in implant dentistry, and currently accepted as the gold standard, is a deproteinized bovine-derived bone mineral (106). Biocompatibility and osteoconductivity of deproteinized bovine-derived bone mineral have been demonstrated in several preclinical studies (94, 120, 184). However, whether deproteinized bovine-derived bone mineral

Table 2. Grafting materials used for guided bone regeneration procedures

Graft material	Origin	Examples
Autograft	Patient's own tissue	Intra-orally or extra-orally harvested
Allograft	Tissue from individuals of the same species	Fresh-frozen bone, freeze-dried bone, demineralized freeze-dried bone
Xenograft	Tissue from other species	Bovine-, porcine-, equine-derived bone mineral
Alloplast	Synthetically produced material	Tricalcium phosphate, hydroxyapatite, hydroxyapatite/tricalcium phosphate composite, calcium phosphate cement, calcium sulfate, bioactive glass, polymers

is bioresorbable still remains controversial (19, 77, 148). The presence of cells with osteoclastic characteristics was interpreted as a sign of ongoing resorption of the deproteinized bovine-derived bone mineral bone-graft substitute (170). A recent clinical trial including 20 patients found deproteinized bovine-derived bone mineral particles unchanged and integrated in the bone 11 years after sinus floor augmentation (148). The clinical consequences of the rate and the pattern of resorption of deproteinized bovine-derived bone mineral in a given patient situation remain to be investigated.

Recently, several new bovine-, porcine- and equine-derived bone substitutes have been developed. Preclinical studies and clinical case series demonstrated that these materials are biocompatible and osteoconductive, and can be used as bone substitutes without interfering with the normal reparative bone process (30, 174, 175, 182, 189, 213).

Deproteinized bovine-derived bone mineral is the best documented bone substitute for guided bone regeneration of dehiscence- and fenestration-type defects concomitant with implant placement (106). In contrast, there are only limited clinical data reporting on the application of deproteinized bovine-derived bone mineral in combination with resorbable membranes for bone augmentation before implant placement (74, 91, 240). In a clinical study, deproteinized bovine-derived bone mineral blocks and collagen membranes were applied to 12 patients to treat horizontal bone deficiencies before implant placement (Fig. 2) (91). After 9–10 months, in 11 of 12 patients the resulting bone volume was sufficient to allow implant placement in the prosthetically optimal position. It was therefore concluded that the procedure was effective for horizontal ridge augmentation. These results are in agreement with a preclinical study comparing autogenous bone blocks with deproteinized bovine-derived bone mineral blocks for lateral ridge augmentation, in which a similar increase of ridge augmentation was clinically mea-

sured in both groups (59). In fact, all sites treated with deproteinized bovine-derived bone mineral blocks for horizontal bone ridge augmentation appeared, clinically, to be suitable for implant placement. Histologically, however, several studies found that deproteinized bovine-derived bone mineral blocks were mainly embedded in connective tissue and only a moderate amount of new bone formation was observed in peripheral parts of the graft (8, 59, 189, 192). These results may explain the clinical finding that the deproteinized bovine-derived bone mineral blocks were firmly integrated within the surrounding host tissues and were mechanically stable, as observed at re-entry surgery (59, 91).

Examples of allografts include fresh-frozen bone, freeze-dried bone and demineralized freeze-dried bone. Their main limitation is derived from the risk of immunologic reactions and possible disease transmission as a result of their protein content (71). Successful use of freeze-dried bone and demineralized freeze-dried bone for bone augmentation concomitant to implant placement has been reported in clinical studies (76, 167). Furthermore, case series demonstrated that block allografts, in conjunction with placement of resorbable membranes, may be a viable treatment option for augmentation of atrophic alveolar ridges in two-stage implant placement procedures (117, 152, 153). During a recent clinical trial including 40 patients, the use of freeze-dried bone block allografts and collagen membranes for primary augmentation of anterior atrophic maxilla was evaluated (154). After 6 months, bone samples were harvested and 83 implants were placed. The histomorphometric analysis found the mean percentage of newly formed bone to be $33 \pm 18\%$ and of residual allograft to be $26 \pm 17\%$. The implant survival rate was 98.8% after a mean follow up of 48 ± 22 (range: 14–82) months. A previous systematic review concluded that clinical studies on allograft blocks included a relatively small number of interventions and implants without long-term follow-up periods

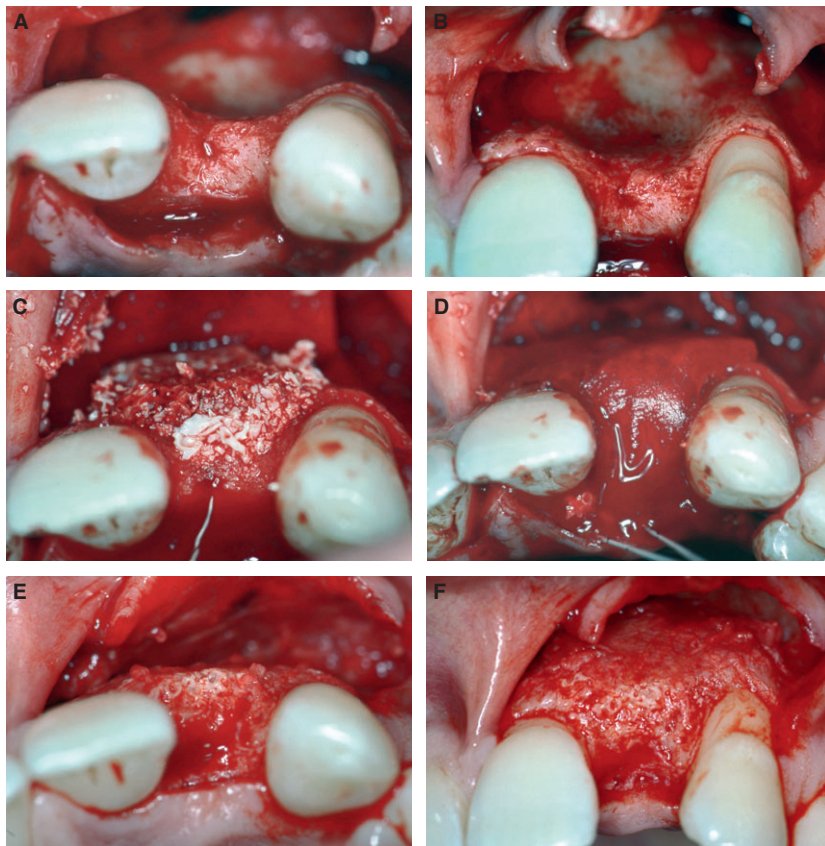


Fig. 2. (A, B) A horizontal ridge defect at an implant site 22. (C, D) A block of bovine-derived bone mineral is placed to support a resorbable collagen membrane. (E, F) At re-entry surgery 9 months later, the ridge volume is adequate for the placement of an implant in the prosthodontically ideal position.

and therefore implied that they do not provide sufficient evidence to establish the treatment efficacy relative to graft incorporation, alveolar ridge augmentation and long-term dental implant survival (228).

Alloplastic bone substitutes represent a large group of chemically diverse synthetic biomaterials, including calcium phosphate (e.g. tricalcium phosphate, hydroxyapatite and calcium phosphate cements), calcium sulfate, bioactive glass and polymers. These materials vary in structure and in chemical composition, as well as in mechanical and biological properties. Porous calcium phosphates have been under intense investigation for more than 20 years and constitute a high number of commercially available bone substitutes (13, 49). Hydroxyapatite is the main mineral component of natural bone and the least soluble of the naturally occurring calcium phosphate salts. It is therefore highly resistant to physiologic resorption (83). In contrast, tricalcium phosphate is characterized by rapid resorption and replacement with host tissue (12, 105). Although bone ingrowth regularly occurred into the area intended for regeneration, this ingrowth did not fully compensate for the resorption of the tricalcium phosphate, resulting in a reduction of the augmented volume (105).

Biphasic compounds of hydroxyapatite and tricalcium phosphate have been developed to combine the

features of space maintenance and bioresorption, allowing space for bone ingrowth (50, 104, 130). Preclinical studies using different experimental models provided histological evidence that particulate or moldable *in-situ* hardening hydroxyapatite/tricalcium phosphate shows osteoconductivity and resorption properties similar to those of deproteinized bovine-derived bone mineral (104, 142, 185, 191). In recent human controlled trials, hydroxyapatite/tricalcium phosphate and deproteinized bovine-derived bone mineral were found to produce similar amounts of newly formed bone for grafting of the maxillary sinus (42, 75). Another study compared hydroxyapatite/tricalcium phosphate and deproteinized bovine-derived bone mineral, in conjunction with collagen membranes, for guided bone regeneration of extraction sockets (137). After 8 months, the bucco-oral dimension of the alveolar ridge decreased by 1.1 mm in the hydroxyapatite/tricalcium phosphate group and by 2.1 mm in the deproteinized bovine-derived bone mineral group with a statistically significant difference. A randomized controlled trial found that hydroxyapatite/tricalcium phosphate performs similarly to deproteinized bovine-derived bone mineral for guided bone regeneration of peri-implant dehiscencies with respect to vertical defect reduction (220). Based on these findings, the combination of

hydroxyapatite/tricalcium phosphate for alveolar ridge augmentation holds some promise for the future. However, further long-term clinical studies are necessary to demonstrate its equivalence to deproteinized bovine-derived bone mineral.

Choice of material

There are an increasing number of different materials that can be used in bone augmentation procedures. However, most have not been sufficiently documented in clinical studies (64). In dehiscence- and fenestration-type defects, deproteinized granular xenografts and particulate autograft covered with native collagen or e-PTFE membranes are the best-documented augmentation materials (38, 106). These procedures may be considered as safe and predictable therapies for long-term performance of implants.

The use of resorbable membranes offers several advantages over nonresorbable membranes. These include: no need for membrane-removal surgery; simplification of methods; elimination of exposure of the regenerated bone; a wider range of surgical techniques possible at abutment connection; better cost-effectiveness; and decreased patient morbidity. Consequently, resorbable membranes are preferred, whenever possible, for the treatment of horizontal bone defects.

e-PTFE membranes have been demonstrated to lead to successful bone regeneration without the additional use of graft material (53, 108). Nevertheless, a combination of membrane and bone graft or bone substitute is generally recommended for guided bone regeneration procedures to provide adequate support of nonstable membranes and to enhance bone ingrowth into the defect.

In clinical studies, autogenous bone has not been demonstrated to promote better bone regeneration at dehiscence- and fenestration-type defects compared with some bone-substitute materials (38). In order to avoid additional morbidity associated with bone harvesting, the use of bone substitute materials is therefore recommended for bone regeneration at exposed implant surfaces.

A recent systematic review divided the results of studies on augmentation of dehiscence- and fenestration-type defects according to the membrane used (106). For nonresorbable membranes the percentage defect fill was 75.7%, the percentage of cases with complete defect fill was 75.5% and the rate of mucosal dehiscence was 26.3%. When resorbable membranes were used, the corresponding values were

87%, 75.4% and 14.5%, respectively. The implant survival rates ranged from 92.9 to 100% (median 96.5%) with nonresorbable membranes and from 94 to 100% (median 95.4%) with resorbable membranes. It was concluded that the heterogeneity of the available data precludes clear recommendations regarding the choice of a specific membrane and a specific supporting material (106). In addition, comparative studies using different augmentation protocols were rarely found.

In a split-mouth prospective study, a total of 84 implants were placed into partially resorbed alveolar ridges (238). The resulting peri-implant defects were treated with deproteinized bovine-derived bone mineral covered either with a resorbable collagen membrane or with an e-PTFE membrane. After 4–6 months, a mean vertical bone fill was found, amounting to 92% in the collagen-treated defects and to 78.5% in the sites treated with e-PTFE. This difference was not statistically significant. Nonetheless, membrane dehiscences occurred more frequently within e-PTFE than within collagen membranes. Membrane dehiscences significantly reduced new bone formation in e-PTFE-treated sites but not in dehiscenced collagen-treated sites. A recent three-arm clinical trial evaluated the long-term outcome of implants placed simultaneously with guided bone regeneration using e-PTFE and collagen membranes and that of implants placed into pristine bone without the need for guided bone regeneration (109). After a mean follow-up of 12.5 years, 58 patients participated in the investigation, corresponding to 80.5% of the original study population. Resorbable collagen membranes and nonresorbable e-PTFE membranes exhibited similar results with respect to the implant survival rate, the interproximal marginal bone level and the peri-implant soft-tissue parameters. In another study, a cone-beam CT examination of implants that were treated using nonresorbable and resorbable membranes was performed 6–57 months after insertion of the abutment (147). The thickness of the buccal bone in the cervical region was significantly higher in the group treated with nonresorbable membranes. A recent multicenter randomized controlled trial compared titanium-reinforced e-PTFE with modified PLGA membranes for guided bone regeneration of dehiscence-type defects at implants (187). At re-entry surgery, 6 months after implant placement and guided bone regeneration, the e-PTFE membrane provided better maintenance of the horizontal thickness of the regenerated region.

Preclinical and clinical studies thus demonstrate that both resorbable and nonresorbable mem-

branes are successful for guided bone regeneration of peri-implant defects. Owing to the higher risk of complications and the increased surgical trauma, the use of e-PTFE membranes for the treatment of peri-implant defects is justified only when the volume stability of the region to be augmented is not provided by the adjacent bone walls (38, 106). The use of titanium-reinforced e-PTFE membranes and membrane-supporting materials is recommended for the treatment of such challenging defects.

In a recent systematic review, the results after horizontal ridge augmentations were divided according to whether a space-maintaining autogenous bone block was used as opposed to a particulate bone graft or a granular bone substitute material (106). In studies utilizing autogenous bone blocks, alone, or in combination with a membrane and/or a bone substitute material, the mean gain in ridge width was 4.4 mm, the complication rate was 3.8% and the percentage of cases that needed additional grafting was 2.8%. When no autogenous block graft was used, the corresponding values were 2.6 mm, 39.6% and 24.4%, respectively. These findings indicate that autogenous bone blocks, alone, or in combination with particulate bone substitute and/or membranes, are the most reliable and secure procedure for staged augmentation of large bone defects before implant placement (106, 119).

The use of membranes and bone substitutes, in conjunction with autogenous bone blocks, has been demonstrated, in preclinical and clinical studies, to reduce the resorption of the autogenous bone grafts (1, 4, 60, 118, 136, 224, 225). In a recent randomized controlled trial, patients were treated with autogenous bone blocks, either alone or covered with a xenograft and a collagen membrane (44). Four months later, the resorption for the autograft alone with respect to the initial width was 21% (0.89 mm) and for the autograft with collagen membrane and xenograft it amounted to 5.5% (0.25 mm). The difference between the groups was statistically significant.

e-PTFE membranes, in combination with bone grafts or bone substitutes, are a valuable treatment option for primary ridge augmentation. In horizontal ridge augmentations performed before implant placement, e-PTFE membranes were mainly used to cover granular grafting materials (37, 66, 74, 76, 168) and only seldom were they used to cover autogenous bone blocks (28, 29). For this clinical indication, the use of nonresorbable membranes presented less gain in ridge width, increased need for additional grafting procedures and higher complication rates, compared with the use of resorbable membranes or no membrane at all (106).

Despite the promising results of allogenic blocks, it is clear that more clinical evidence is needed for the use of bone substitutes, alone or in combination with resorbable membranes, for primary bone augmentation. When looking at materials recently introduced for guided bone regeneration, there is limited clinical documentation for the use of cross-linked collagen and polyethylene glycol membranes, and for synthetic and new xenogenic bone substitutes.

Long-term results

There is a high level of evidence that survival rates of dental implants placed simultaneously with, or after, bone augmentation are similar to survival rates of implants placed into pristine bone (61, 89, 106). The majority of studies providing internal controls found implant survival rates for a period between 1 and 5 years ranging from 95 to 100% at both augmented and control sites (17, 139, 164, 239, 241). In a recent prospective study, the survival rates, after a mean observation period of 12.5 years, for implants either placed simultaneously with guided bone regeneration or placed into native bone were 93% and 95%, respectively (109). The analysis of intra-oral radiographs within controlled studies did not reveal any difference of the interproximal marginal bone levels between implants placed into augmented sites and those placed into pristine bone (17, 109, 139, 241).

Although the high survival rates of implants placed in conjunction with bone augmentation are well documented, the long-term stability of the regenerated bone has been assessed in very few studies (38, 61). In addition, when bone defects are present at the time of implant placement, very little evidence is available that assesses the long-term outcome when comparing situations in which this defect was augmented with situations in which this defect was not augmented. In other words, in many situations it is currently impossible to conclude whether bone augmentations are needed in order to allow the long-term survival of implants.

In a recent study, implants placed immediately into extraction sockets were evaluated at 7 years of function using cone-beam computed tomography (18). At implant placement, infrabony defects and dehiscences were grafted with a xenogenic bone substitute and covered with a collagen membrane without over-augmenting the buccal bone plate. At the 7-year follow-up, in five out of 14 implant sites almost no buccal bone was radiographically detected, whereas, within the other nine implant sites, the buccal bone plate

covered the entire rough implant surface. Despite this difference, all implants exhibited clinically successful tissue integration. The mucosal margin was located 1 mm more apically within the group of implants without radiographically detectable buccal bone. Future research should determine the need for augmentation procedures for the long-term success of the implants. In addition, the long-term stability of the augmented bone should be assessed and monitored (121).

Clinical concept

Case evaluation and treatment planning

Analysis of the patient situation, identifying the objective of the therapy and assessing the risks involved, leads to the choice of treatment steps and of the materials. The primary aim of implant therapy is to provide the patient with a reconstruction and, hence, all clinical procedures need to be prosthodontically driven. A detailed preoperative prosthodontic diagnostics is essential for identifying the best treatment plan and achieving an optimal result of the therapy with dental implants.

Assessment of the risks related to implant therapy includes evaluation of the patient's condition, the soft tissue and the bone morphology. Patient's behaviors and systemic and local conditions, which may lead to impaired tissue healing, represent relative or absolute contraindications for implant placement and regenerative procedures. An intact and well-dimensioned soft tissue, allowing tension-free coverage of the augmented region, is a prerequisite for successful bone regeneration. In situations where the quantity or quality of mucosa at the implant site is inadequate, augmentation of the soft tissue may be indicated before performing the bone regeneration procedure. In addition, in areas of esthetic priority, the appearance of the soft tissue determines whether or not the result of the reconstructive therapy is esthetically pleasing. When evaluating the soft-tissue condition, the following aspects are assessed: the presence and extent of soft-tissue defects; gingival biotype; level of the soft tissue at the teeth neighboring the gap; the amount of keratinized mucosa; and the presence of invaginations, scars, discolorations and pathologies in the mucosa at the site to be augmented. The clinical and radiographic examination of the bone at the implant site includes assessment of the bone defect morphology, the mesio-distal size of the edentulous area and the bone level at the teeth adjacent to the gap.

The decision regarding the optimal bone augmentation protocol and the selection of materials is primarily based on the defect morphology and on whether or not the ridge contour needs to be augmented. Based on this, a classification of bone defects has been developed, aiming to simplify the decision-making process regarding choice of the strategy for bone augmentation (Fig. 3, Table 3). Bone augmentations can be performed simultaneously with (combined approach) or prior to (staged approach) implant placement. The combined approach is preferred, whenever permitted by the clinical situation, as this approach results in decreased patient morbidity, treatment time and costs.

In the case of intra-alveolar defects and peri-implant dehiscences, in which the volume stability of the region to be augmented is provided by the adjacent bone walls, a bioresorbable membrane, in combination with a particulate bone substitute, represents the treatment of choice. Where the volume stability of a peri-implant dehiscence-type defect is not provided by the adjacent bone walls, an e-PTFE membrane and particulate bone substitute are used. The staged approach is chosen when large bone defects are present that, either preclude anchorage of the implant in the prosthodontically correct position or result in an unfavorable appearance of the soft tissue due to the lack of hard-tissue support. In such situations the alveolar ridge is first augmented and, after the appropriate healing time, the implant is placed in the prosthodontically correct position.

Ridge preservation

The alveolar ridge undergoes a significant remodeling process following tooth removal. In a recent systematic review it was described that during the 6 months after tooth extraction, the mean width reduction of the alveolar ridge is 3.8 mm and the mean height reduction is 1.2 mm (209). These hard- and soft-tissue changes may affect the outcome of treatment with implants, either by limiting the bone volume needed for anchorage of the implant or by compromising the esthetic result regarding the appearance of the soft tissue at the final implant-supported reconstruction.

When implant placement is planned at a time point after the tooth extraction, it may be advisable to perform a ridge preservation procedure to counteract the subsequent reduction of the ridge dimension. This may simplify the subsequent implantation procedure and reduce the need for hard- and soft-tissue regeneration. There are, however, no data available

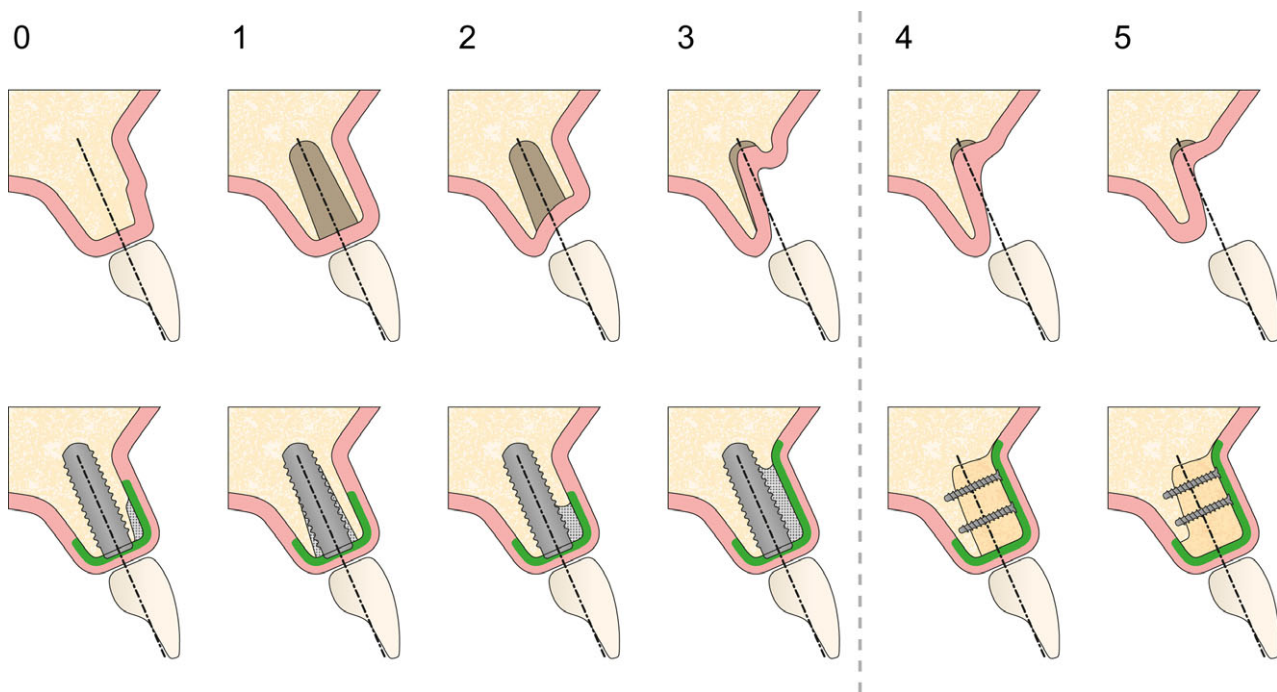


Fig. 3. Schema displaying bone defect Classes 0–5 and the corresponding bone augmentation procedures.

Table 3. Classification of bone defects

Bone defect	Description
Class 0	Site with a ridge contour deficit and sufficient bone volume for standard implant placement
Class 1	Intra-alveolar defect between the implant surface and intact bone walls
Class 2	Peri-implant dehiscence, in which the volume stability of the area to be augmented is provided by the adjacent bone walls
Class 3	Peri-implant dehiscence, in which the volume stability of the area to be augmented is not provided by the adjacent bone walls
Class 4	Horizontal ridge defect requiring bone augmentation before implant placement
Class 5	Vertical ridge defect requiring bone augmentation before implant placement

regarding the benefit of ridge preservation procedures on the long-term outcomes of implant therapy.

The techniques aimed at ridge preservation encompass two different approaches: maintain the ridge profile; or enlarge the ridge profile (84). Recent systematic reviews concluded that these techniques cannot prevent physiological bone resorption after tooth extraction, but they may aid in reducing bone dimensional changes (211, 221). A meta-analysis of the literature found 1.4 mm less reduction of the ridge width and 1.8 mm less reduction of the ridge height after applying ridge preservation procedures in comparison with untreated control sites (221). The scientific evidence does not provide clear guidelines regarding the surgical procedure or the type of biomaterial to be used for ridge preservation (221). Positive effects have been observed resulting from procedures

involving flap elevation, the use of a grafting material and/or a barrier membrane, and the achievement of a wound closure. It remains, however, unclear which is the most adequate technique for achieving a wound closure. Disadvantages of the current ridge preservation procedures include the postponement of implantation, as well as the costs of the treatment. When flaps are raised to enlarge the ridge contour, achieving primary wound closure becomes increasingly difficult. Moreover, such surgical procedures cause additional patient morbidity.

An approach has been developed with the aim of achieving optimal soft-tissue conditions at the time of implant placement (113, 125, 126). Following tooth extraction, a bone substitute is placed into the extraction socket. Subsequently, a soft-tissue graft is harvested from the palate and sutured against the

soft-tissue margins of the extraction socket, thus covering the grafting material. Preclinical studies investigating this method have demonstrated uneventful graft integration and beneficial effects in terms of maintenance of the ridge contour (67, 68). In a prospective clinical study including 20 patients in need of tooth extraction, soft-tissue grafts were applied to seal the extraction socket that was filled with deproteinized bovine-derived bone mineral (113). Six weeks later, the grafts had healed very well, as indicated by 99.7% integration of the soft-tissue graft area. In addition, the color match with the surrounding tissues was excellent, as the mean color difference between the graft and the adjacent tissues did not reach the threshold value for distinction of the intra-oral color by the human eye. The technique presented achieved the desired aim, namely to optimize the quality and the quantity of soft-tissue for early implant placement at around 6 weeks after tooth extraction. Early implant placement (Type 2 placement), combined with bone regeneration, can then be performed under optimized soft-tissue conditions (86). Due to the effort and the costs needed to perform this treatment, it is mainly indicated in esthetically sensitive situations.

Contour deficit: Class 0

This situation occurs when an implant can be placed in a prosthetically correct position within the bony envelope but a bone augmentation procedure is indicated to improve the contour of the ridge. This is often the case in esthetically sensitive sites with a healed alveolar ridge (Type 4 placement) (86). As a result of post-extractive ridge resorption, such sites generally present a reduced dimension of the alveolar ridge. The guided bone regeneration procedure with a resorbable membrane and particulate bone substitute, described for Class 2 dehiscence-type defects, is performed in these situations.

Intra-alveolar defect: Class 1

Class 1 defects are characterized by gaps between the implant surface and the intact bone walls. Owing to the resorptive processes starting immediately following extraction of the tooth, Class 1 defects are mostly limited to situations where immediate implant placement is performed (Type 1 placement) (86). In some situations the bone walls of the socket may still be intact at a later time point, when implants are placed following soft-tissue healing (Type 2 placement).

After implant placement, the site is analyzed and one of the following strategies for the management of Class 1 defects is selected: (i) no guided bone regeneration; (ii) guided bone regeneration of the residual socket; or (iii) guided bone regeneration of the residual socket and over-augmentation of the buccal bone wall.

Data from different preclinical experiments suggest that the horizontal dimension of the gap between the bone and the implant is of critical importance for spontaneous osseous healing of this defect. The results indicate that wider gaps lead to less favorable histological outcomes (2, 57, 171). For implants placed in sockets immediately after extraction, both preclinical and clinical studies show that spontaneous bone fill, without the use of grafting materials, occurs in the peri-implant marginal defects when the horizontal defect size is 2 mm or less (9, 47). Other animal and human studies concluded that the placement of grafting material filling the marginal infrabony defects around implants, that were placed in the sockets immediately after tooth extraction, contributes to a more complete resolution of the defect and preservation of the alveolar process (7, 31, 32, 36, 46). However, even when guided bone regeneration of peri-implant intra-alveolar defects is performed, considerable resorption of the alveolar ridge may occur after immediate implant placement (7, 18, 32).

Therefore, for Class 1 defects the decision regarding the need for, and the extent of, guided bone regeneration is based on the horizontal dimension of the intra-alveolar defect and the need for augmentation of the ridge contour. In posterior sites the guided bone regeneration procedure primarily aims to resolve the peri-implant osseous defect (Fig. 4). In anterior sites the therapy is also directed at increasing the buccal contour to achieve a pleasing appearance of the peri-implant soft tissues (Fig. 5). Based on this, the following procedure is recommended (Table 4). The mucoperiosteal flap is elevated in order to gain access for implant placement and to obtain an adequate overview of the surrounding bone. In posterior sites in which the residual gap between the implant and the wall of the socket is <1–2 mm, a guided bone regeneration procedure is generally not needed for successful tissue integration and defect healing. In contrast, if the horizontal defect dimension exceeds 1–2 mm, bone substitute is applied in the infrabony defect and covered with resorbable membrane (Fig. 4). In esthetically sensitive areas, a vertical-release incision is placed in order to gain adequate approach to the buccal bone. Subsequently, a bone

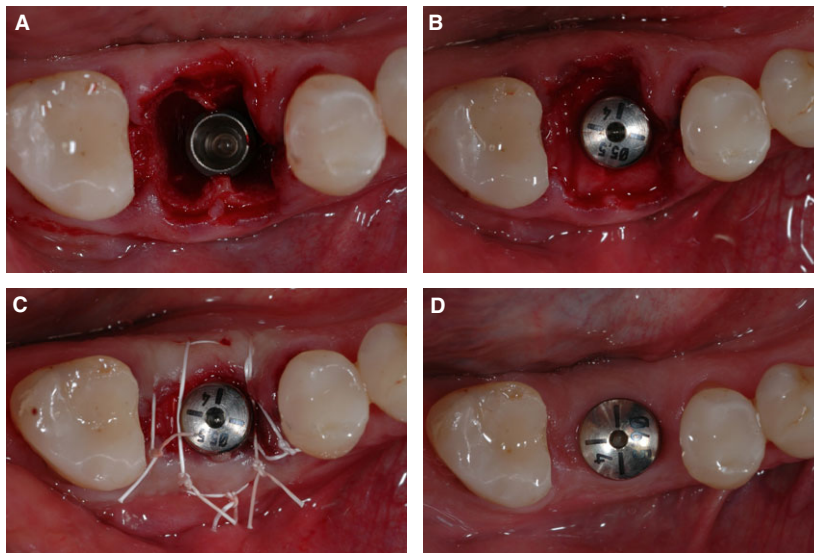


Fig. 4. (A) Intra-alveolar defect (Class 1) at an implant position 46. The distance between the implant surface and the bone walls exceeds 2 mm. (B) Guided bone regeneration by applying particulate bone substitute into the residual socket and covering the grafted area with a resorbable collagen membrane. (C) The flaps are adapted and sutured to allow transmucosal healing of the implant site. (D) Clinical situation 4 months after implant placement.

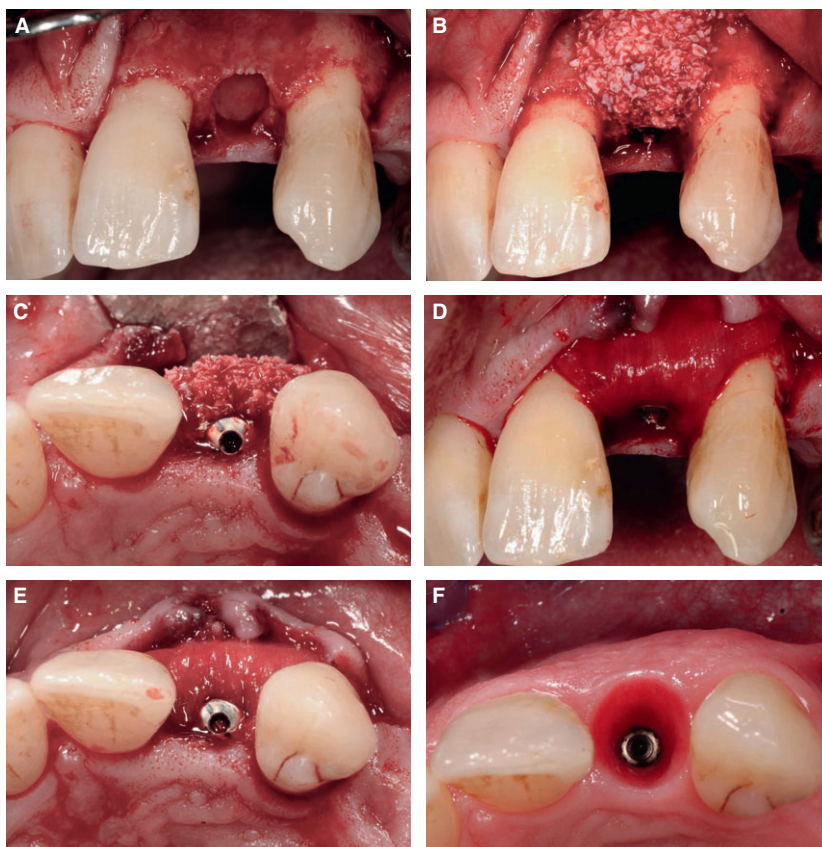


Fig. 5. (A) Extraction socket at position 22 with intact bone walls. (B, C) Guided bone regeneration of an intra-alveolar Class 1 defect by application of particulate bone substitute into the residual socket and over the buccal bone. (D, E) A resorbable collagen membrane is adapted to cover the grafted area and fixed by attaching the membrane around the healing abutment. (F) Clinical situation 8 months after implant placement.

Table 4. Guided bone regeneration for Class 1 defects

Site	Guided bone regeneration procedure
Esthetically non-sensitive site	
HDD < 1–2 mm	No guided bone regeneration
HDD > 1–2 mm	Application of bone substitute into the intra-alveolar defect and coverage with resorbable membrane
Esthetically sensitive site	Application of bone substitute into the intra-alveolar defect and over the buccal bone wall and coverage with resorbable membrane

HDD, horizontal defect dimension.

substitute is applied into the residual socket and over the buccal bone (Fig. 5). The resorbable membrane is adapted to extend 2 mm beyond the grafted area. If needed, the membrane is stabilized using resorbable pins made of polylactid acid and/or the implant cover screw. Thereafter, the flap is adapted and sutured to allow submucosal or transmucosal healing of the implant site.

The clinical outcomes of the submerged and the transmucosal healing modes for implants placed in fresh extraction sockets were compared in a recent multicenter randomized controlled trial (45). After 1 year, there were no differences between the treatment groups in the survival rate, the marginal bone loss and the recession of the mid-buccal mucosa and of the interproximal papillae. However, in the submerged group, 1 mm more loss of the width of keratinized mucosa was observed in comparison with the transmucosal group. This finding was explained by the fact that, in the submerged group, the flap was coronally repositioned to reach primary wound closure. This procedure probably caused coronal displacement of the mucogingival junction, which led to the reduced width of keratinized mucosa at the buccal aspect. In the event of partial or complete loss of the buccal bone wall of the socket at the time of implant placement, the procedure described for dehiscence-type defects is performed.

Dehiscence-type defect: Class 2

Class 2 defects are characterized by peri-implant dehiscences, in which the volume stability of the area to be augmented is provided by the adjacent bone walls. Dehiscence of the buccal bone is the most frequently encountered situation needing bone regeneration at implants. A large number of preclinical and clinical studies demonstrated that dehisced implant surfaces successfully osseointegrate following combined guided bone regeneration procedures (123, 165, 166, 230, 234).

After implant placement, analysis of the dehiscence-type defect is performed and the decision regarding the need for augmentation of the ridge contour is taken. In posterior sites, which generally do not require augmentation of the ridge contour, a bioresorbable membrane in combination with particulate bone substitute is the treatment of choice (Fig. 6). Similarly, in esthetically sensitive sites, in which the volume stability of the bone defect is provided by the adjacent bone walls, a bioresorbable membrane in combination with particulate bone substitute is the treatment of choice (Fig. 7).

Subsequent to implant placement, the cortical bone around the dehiscence defect is perforated to allow earlier vascularization and thus to improve bone repair (179). A particulate bone substitute material is applied onto the exposed implant surface and a resorbable membrane is shaped and adapted to extend 2 mm beyond the defect margins (Figs 6 and 7). It is important to bear in mind that particulate grafting material, in combination with a resorbable membrane, does not provide complete volume stability. During healing, compressive forces at the site to be regenerated may result in membrane collapse and displacement of parts of the grafting material (140, 190, 207, 236). A small over-augmentation of the dehiscence defect by placement of some additional bone substitute material is therefore recommended when applying this procedure. For adequate stabilization of the area to be augmented, additional fixation of the membrane is recommended by using resorbable pins, by attaching the membrane around the implant or healing cap, or by a combination of both. Thereafter, the flap is adapted and sutured to allow submucosal or transmucosal healing of the implant site. No scientific evidence is available on whether or not adding autogenous bone to the bone substitute will lead to more successful clinical results. In numerous clinical studies it has been demonstrated that the application of bone substitute alone, together with a barrier membrane, leads to successful bone coverage of previously dehisced implant surfaces (85, 93, 149). An adjunct of autogenous bone to the bone substitute can therefore be considered unnecessary for the successful treatment of dehiscence-type defects. As scientific data are lacking on the influence of guided bone regeneration on the survival and the success rates of implants, a statement on the need for guided bone regeneration in cases of small bone dehiscences cannot be made (38, 61). However, augmentation of buccal bone defects may play an important role as far as the esthetic outcome of the rehabilitation is concerned.

It has been demonstrated clinically that guided bone regeneration of peri-implant defects, in conjunction with transmucosal healing, is a successful procedure with a high degree of defect repair (24, 87, 93, 127). A multicenter randomized controlled trial compared the submerged and the transmucosal healing modalities at single-crown two-piece implants placed in the anterior maxilla and mandible (90). The implants were placed as Type 2, Type 3 or Type 4 implant-placement procedures (86). Guided bone regeneration of peri-implant bone defects was performed in 42% of the patients. One-hundred and twenty-seven subjects completed the 1-year

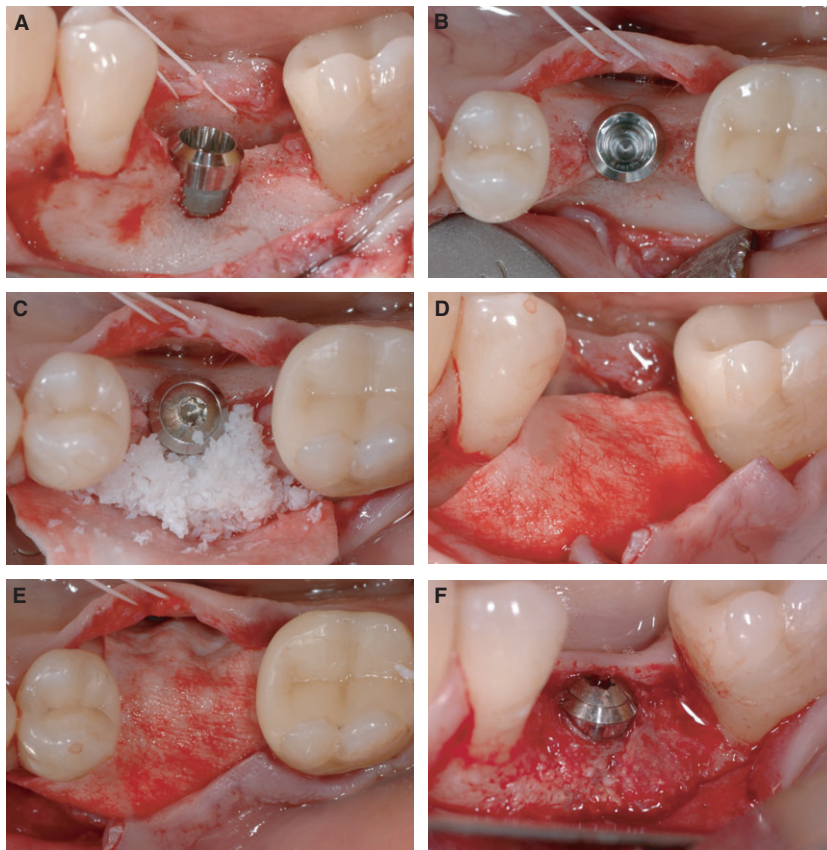


Fig. 6. (A, B) Dehiscence of the buccal bone at an implant position 36. The defect is treated by guided bone regeneration, applying (C) particulate bovine-derived bone mineral and (D, E) a resorbable collagen membrane. (F) At re-entry surgery 6 months later, the initially exposed implant surface is covered by newly formed bone.

examination. It was concluded that the submerged and the transmucosal healing modes achieved similar outcomes with regard to implant survival, interproximal bone level, soft-tissue parameters and patient satisfaction. These results were confirmed by other recent randomized controlled trials, which found equivalent clinical performances for submerged and transmucosal healing modes (34, 35, 62, 63, 208). Nevertheless, in the following clinical situations the submerged healing mode may be desirable: when the implant does not exhibit optimal primary stability; when it cannot be excluded that a removable mucosa-supported provisional denture could transmit excessive forces onto the healing abutment; and in cases where surgical corrections of the soft tissue following the implant placement are planned.

Dehiscence-type defect: Class 3

Class 3 defects are characterized by peri-implant dehiscences, in which the volume stability of the area to be augmented is not provided by the adjacent bone walls. In situations requiring optimal support of the peri-implant soft tissue, the use of titanium-reinforced e-PTFE membranes, in combination with a particulate bone substitute, is recommended for the treatment of Class 3 defects (Fig. 8).

The clinical protocol for guided bone regeneration at Class 3 defects includes the following steps: perforation of the cortical bone around the dehiscence defect; application of particulate bone substitute; and adaptation of a titanium-reinforced e-PTFE membrane over the bone dehiscence without over-building the area (Fig. 8). The use of titanium tacks is recommended to provide adequate adaptation and stabilization of the membrane. A resorbable membrane may be applied over the e-PTFE membrane with the aim of facilitating spontaneous wound healing in the event of soft-tissue dehiscence. Thereafter, the flap is adapted and sutured to allow submerged healing of the regeneration site.

As premature exposure of e-PTFE membranes often leads to infectious complications and failure of guided bone regeneration, attention should be paid to achieve complete and tension-free soft-tissue coverage at the regenerated area (38, 106). In cases where the mucosal quantity and/or quality in the defect area are deemed deficient, a soft-tissue grafting procedure may be indicated before implant placement.

The staged guided bone regeneration approach has been claimed as advantageous for achieving successful outcomes of bone augmentation at peri-implant dehiscences. In a recent preclinical study, the staged and the combined approaches showed

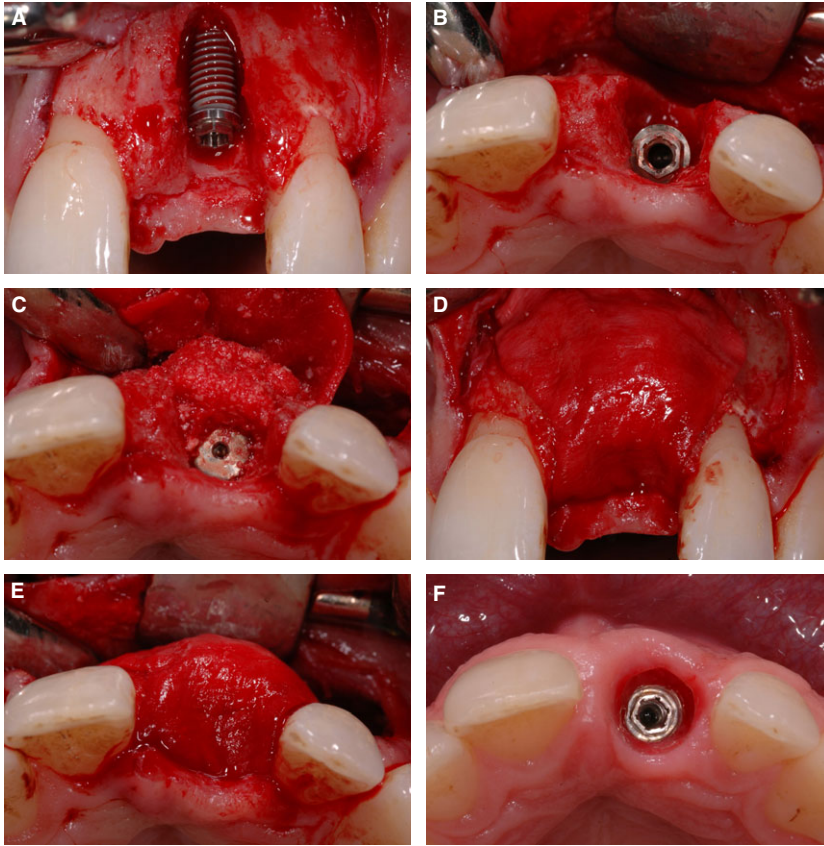


Fig. 7. (A) Dehiscence-type defect (Class 2) at an implant position 21. (B) The volume stability of the region to be augmented is provided by the adjacent bone walls. (C) Bovine-derived bone mineral containing collagen is applied onto the exposed implant surface. (D, E) A resorbable collagen membrane is adapted to extend beyond the defect margins and fixed by two resorbable polylactide pins placed in the apical region. (F) Clinical situation 9 months after implant placement.

similar implant osseointegration levels over time (10). However, the histological analysis found slightly better vertical bone fill for the staged approach compared with the combined approach at 8 and 16 months. Another histological study in a dog model concluded that the combined approach is preferable to the staged approach in terms of alveolar crest maintenance (5). A prospective cohort study including 45 patients reported that implant placement combined with, or staged after bone augmentation resulted in predictable treatment outcomes at 3 years of function (39). Owing to the lack of prospective controlled clinical trials, there is no clear evidence regarding the influence of the timing of augmentation procedures on the outcome of guided bone regeneration at peri-implant bone defects (61, 216).

In a prospective clinical study including 16 patients, peri-implant dehiscences at single implants were augmented using e-PTFE membranes and deproteinized bovine-derived bone mineral (186). The labial gain of peri-implant tissue obtained by guided bone regeneration and soft-tissue augmentation was assessed using a new method for volumetric measurements. Implant placement with simultaneous guided bone regeneration using e-PTFE membranes resulted in a gain of labial volume in all cases. In the

majority of patients treated, the gain of peri-implant tissue in the labial direction ranged from 1 to 1.5 mm and remained stable to a high degree within the first year after crown insertion. The guided bone regeneration procedure contributed more to the volume gain than did the soft-tissue grafting.

Horizontal defect: Class 4

Class 4 defects are characterized by reduced ridge width precluding the primary stability of the implant in the prosthodontically correct position. In such situations, the staged approach for bone regeneration and implant placement is chosen (Fig. 9). Autogenous bone blocks, alone, or in combination with bone substitute and/or collagen membranes, are the most reliable and successful procedures for staged augmentations of large bone defects before implant placement (106, 119).

The clinical procedure for primary horizontal ridge augmentation starts with the preparation of the site to be augmented. After elevation of the mucoperiosteal flap, the cortical bone at the recipient bed is perforated in order to allow earlier vascularization and to improve integration of the bone block (58, 65, 169). Subsequently, the autogenous bone block is harvested, adapted to achieve

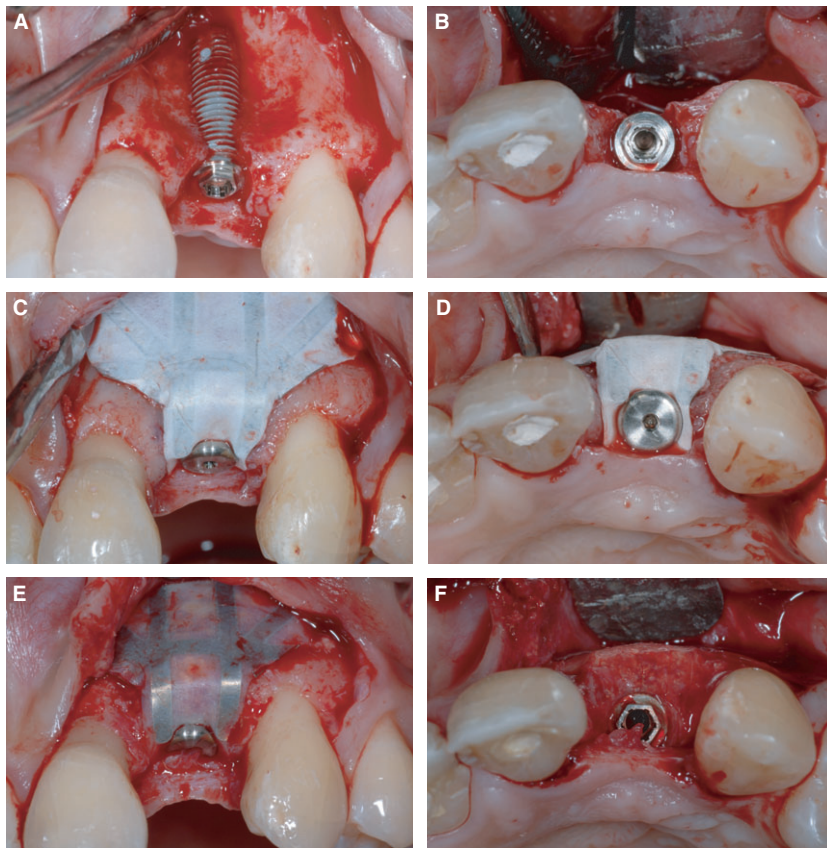


Fig. 8. (A, B) Dehiscence-type defect (Class 3) at an implant position 22. (C, D) The defect is treated by guided bone regeneration applying particulate bovine-derived bone mineral and an expanded polytetrafluoroethylene titanium-reinforced membrane. (E) Six months later, the flap is raised to gain access for the membrane removal. (F) Note the substantial volume of the newly formed bone.

intimate contact between the graft and the bone at the recipient site and rigidly fixed with metal screws (Fig. 9). To reduce its resorption, the bone block is covered with particulate bone substitute and a resorbable membrane (4, 44, 136). The donor defect in the chin region is filled with bone substitute and covered with a resorbable membrane, in order to enhance bone repair (188). The flap is coronally advanced by periosteal release, adapted and sutured to allow a tension-free primary closure at the augmented site. A healing time of 4–6 months before the second surgical intervention for placement of the implants is commonly accepted (4, 44).

Several techniques for harvesting autogenous bone blocks from intra- and extra-oral donor sites have been described in the literature (134, 145). For the treatment of localized jaw defects, intra-oral sites generally offer a sufficient amount of bone (41, 102, 124, 146). Intra-oral sites for the harvesting of bone blocks encompass the chin and the retromolar mandibular region, including the mandibular ramus. When selecting the site for intra-oral autogenous bone harvesting, the amount of bone needed for grafting and the risk of complications should be considered. The chin generally offers a larger bone volume for harvesting compared with

the retromolar mandibular area (43). However, large interindividual variability exists regarding the amount of bone that can be harvested, and this is determined by the location of anatomical boundaries such as teeth, blood vessels and nerve bundles (48). Postoperative complications related to the harvesting of bone include pain, wound dehiscences, pulp necrosis of teeth and temporary and permanent neurosensory disturbances (43, 155, 173, 227, 232). It has been reported that autogenous bone harvesting from the chin region is related to increased postoperative morbidity and number of complications, in comparison with autogenous bone harvesting from the retromolar region (40, 43, 173). This may be explained by the presence of blood vessels and nerve bundles in the anterior mandible (131, 212). In a recent cone-beam CT examination, bone canals in the anterior mandible were found in 86% of the patients examined (178). Owing to the potentially lower risk of complications, the retromolar mandibular area is, whenever possible, the preferable site for intra-oral harvesting of autogenous bone blocks. Cross-sectional diagnostic imaging may enhance the ability to assess the topography and dimension of bone available for grafting (96).

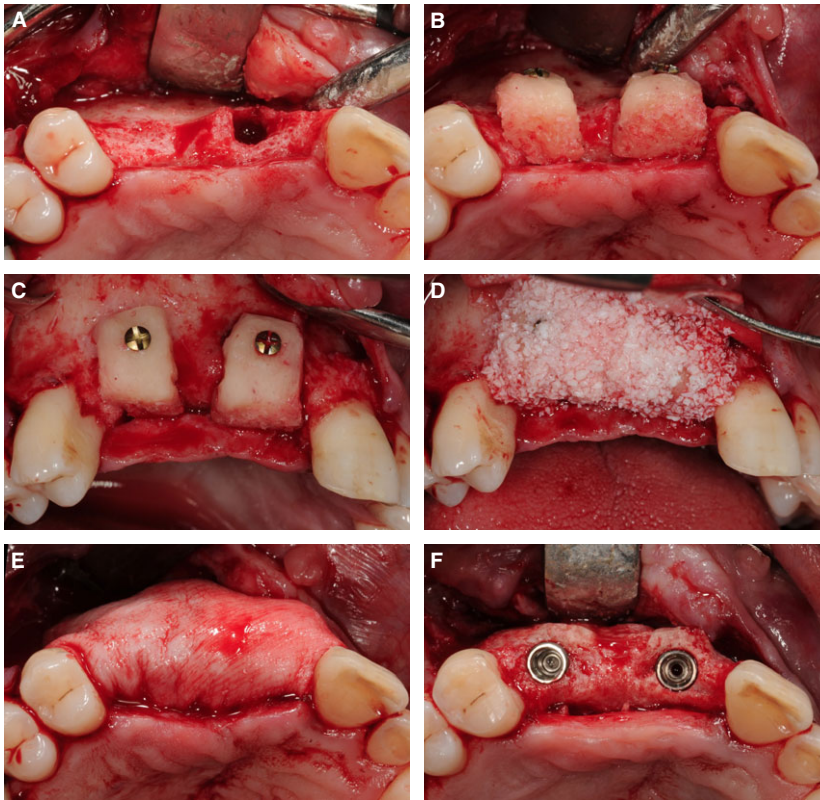


Fig. 9. (A) A horizontal and vertical ridge defect (Class 5) in a maxillary front. (B, C) Two autogenous bone blocks harvested from the chin are adapted to the recipient sites and rigidly fixed with metal screws. (D, E) The bone blocks are covered with particulate bovine-derived bone mineral and a resorbable collagen membrane. (F) Placement of the implants at positions 11 and 13, 6 months after primary bone augmentation (staged approach).

e-PTFE membrane, in combination with particulate deproteinized bovine-derived bone mineral, is a well-documented alternative procedure for primary ridge augmentation, permitting drawbacks related to the harvesting of autogenous bone to be avoided (106). Compared with the use of autogenous bone blocks, this procedure appears to permit less gain in ridge width and to be associated with an increased need for additional grafting and a higher complication rate.

In contrast, only limited clinical data are available reporting the successful use of particulate or block deproteinized bovine-derived bone mineral in combination with resorbable membranes for bone augmentation before implant placement (74, 91, 240). Healing times ranging from 7 to 10 months have been recommended when using deproteinized bovine-derived bone mineral without autogenous bone for various bone augmentation procedures (74, 77, 91, 219). Recent clinical case series demonstrated that block allografts, in conjunction with the placement of resorbable membranes, represent a viable treatment option for augmentations of atrophic alveolar ridges in a two-stage implant-placement procedure (117, 152, 154). More clinical evidence is needed to recommend the use of bone substitutes and resorbable membranes for horizontal bone augmentation.

Vertical defect: Class 5

Class 5 defects are characterized by reduced ridge height. Vertical ridge augmentation is indicated in situations in which the remaining amount of vertical bone is insufficient for anchorage of the implant or in which an unfavorable appearance of the soft tissue is expected owing to the lack of hard-tissue support. This procedure is performed using the staged approach for bone augmentation and implant placement. Similarly to horizontal ridge augmentation, autogenous bone block, alone, or in combination with bone substitute and/or collagen membrane, is the treatment of choice for vertical ridge defects (106, 119). When performing vertical ridge augmentation, the autogenous bone block is partially or completely fixed on the coronal surface of the alveolar ridge in order to augment the bone height. Apart from that, the same clinical procedure is performed as described for horizontal augmentations with autogenous bone blocks (Fig. 9). The rate of soft-tissue complications appears to be considerably higher for vertical ridge augmentations than for horizontal augmentations (177). This may be because a tension-free primary wound closure is more difficult to achieve as a result of the increased volume to be covered. The clinical use of bone-substitute

materials for the regeneration of vertical ridge defects is not sufficiently documented (106, 119).

Current research trends

The aim of the current research in bone augmentation procedures is to develop more effective strategies that promote the body's ability to regenerate lost tissues, to increase treatment predictability and to reduce surgical invasiveness. Major efforts in this research field are focusing on growth and differentiation factors and their delivery systems. One aim is to identify bioactive molecules that regulate wound and tissue regeneration and apply them to induce bone growth in the area to be regenerated. In order to deliver these molecules in therapeutically suitable concentrations at the site of regeneration, biomaterials with adequate mechanical properties and the capacity to release these factors with tailor-made kinetics are needed.

Growth factors and carrier systems

Research has been directed toward growth factors, aiming at overcoming the long treatment time and the limited predictability of bone regeneration of extensive bone defects (176, 218). Various growth factors, including bone morphogenetic proteins, growth and differentiation factors, platelet-derived growth factor, vascular endothelial growth factor, insulin-like growth factor, peptides of the parathyroid hormone and enamel matrix derivative, have been evaluated for bone regeneration procedures.

A recent systematic review assessed the preclinical and human studies regarding the clinical, histological and radiographic outcome of the use of growth factors for localized alveolar ridge augmentation (114). Different levels and quantity of evidence were available for the growth factors evaluated, revealing that bone morphogenetic protein-2, bone morphogenetic protein-7, growth and differentiation factor-5, platelet-derived growth factor and parathyroid hormone may stimulate local bone augmentation to various degrees. In six clinical studies, bone morphogenetic protein-2 positively affected the outcome of local bone augmentation, with increasing effects for higher doses (20, 22, 23, 69, 99, 110). It was therefore concluded that clinical data support the use of bone morphogenetic protein-2 in the promotion of bone healing for socket preservation, sinus floor elevation and horizontal ridge augmentation (114). Recent case series clinically and histologically

demonstrated the effectiveness of platelet-derived growth factor for the treatment of alveolar ridge defects in humans (56, 150, 202, 203). Future controlled clinical trials are required to demonstrate the outcomes of growth factor-mediated regeneration of alveolar ridge defects. Follow-up studies examining implants placed in these augmented areas are needed to determine the long-term success of this combined therapy in bone augmentation procedures.

The regenerative potential of growth and differentiation factors is dependent on a carrier material that serves as a delivery system and as a scaffold for cellular ingrowth (100, 197). Various carrier materials for the delivery of growth factor, including collagen, hydroxyapatite, tricalcium phosphate, allografts, deproteinized bovine-derived bone mineral, polylactic acid, polyglycolic acid and polyethylene glycol, have been evaluated for use in bone regeneration procedures (222). The ideal carrier, which should be able to provide space for bone regeneration, allow cell ingrowth and provide controlled release of bioactive molecules, has not yet been discovered. Research should address the questions regarding the clinically effective doses required, the properties of an ideal carrier material and the optimal release kinetics for the clinical applications of growth factors (216).

Bone substitutes

New bone substitute materials have been developed with the aim of simplifying the clinical steps of bone-augmentation procedures. These include injectable forms of calcium phosphate cement and moldable synthetic hydroxyapatite/tricalcium phosphate coated with PLGA and modified with *N*-methyl-2-pyrrolidone as plasticizer (6, 185). Both materials exhibit a self-setting process to a hard mass following contact with blood or saline. The use of such products may offer the following clinical advantages: more efficient *in-situ* application; improved mechanical retention of bone substitute within the defect; and enhanced volume stability of the regenerated area. Consequently, the use of devices for mechanical stabilization of the regenerated area, such as titanium-reinforced membranes and stabilization pins, may potentially decrease.

Currently, there are no clinically well-documented alternatives to autogenous bone blocks for the grafting of larger defects. An equine-derived block of bone mineral containing collagen was recently introduced for primary ridge augmentations at large

defects (70, 189). This material showed good clinical handling and high biocompatibility. Two preliminary preclinical trials using prototypes of this type of block material reported an invasion of connective tissue with limited bone formation (70, 201). In contrast, in another preclinical study, the prototype equine-derived scaffold exhibited high osteoconductive properties, as indicated by pronounced bone ingrowth and graft integration at the recipient sites (189). At the same time, the graft material was characterized by an active cell-mediated degradation. It was speculated that these contrasting findings might be explained by different physiochemical properties of the material prototypes.

A technique has recently been described for three-dimensional printing of a bone substitute block made of synthetic calcium phosphate (79). A preclinical study evaluated the use of such synthetic block graft for vertical ridge augmentation (217). The blocks were easy to handle and sufficiently stable to allow rigid fixation onto the host bone, using metal screws. Histological evaluation revealed a high degree of bone ingrowth and no signs of a foreign-body reaction. The amount of new bone within the graft was similar to that reported in previous studies applying established bone augmentation procedures (11, 19, 33). Although it is too early to draw clinical conclusions, it will be interesting to observe the development of these modern techniques.

Outlook into the future

Future developments in bone regeneration procedures will aim at simplifying the clinical handling and influencing the biologic processes.

New materials should allow optimal cell ingrowth and present adequate mechanical properties sufficient to maintain space for bone regeneration. To simplify clinical handling, no membranes or procedures for mechanical fixation should be needed. The use of synthetic bone substitutes would eliminate the risk of disease transmission and immunologic reactions potentially inherent to the use of nonsynthetic materials. In turn, this would result in lower morbidity of surgical procedures compared with the transplantation of autogenous tissue. Customized devices for bone regeneration, produced using three-dimensional imaging and computer-aided design/computer-aided manufacturing technologies, could represent a very efficient new process for treatment.

From a biological point of view, application of growth and differentiation factors may induce faster

growth of bone into the area to be regenerated, thus reducing the healing time and treatment efforts of extended bone defect volumes. Modification of the biomaterial surface, achieved by coating with cell-adhesion molecules or nanoparticles, may lead to more desirable tissue responses. The incorporation of antimicrobial substances might minimize the influence of bacterial contamination at the regenerated site. Additional efforts of future research should focus on understanding the regulation of gene expression and the molecular features of the bone regeneration process. Cell-based tissue engineering and gene-delivery therapy represent new therapeutic strategies that have the potential to overcome several shortcomings associated with the existing bone regeneration techniques.

Conclusions

- There is a large body of evidence demonstrating the successful use of guided bone regeneration to regenerate missing bone at implant sites with insufficient bone volume.
- Many of the materials and techniques currently available for bone regeneration of alveolar ridge defects were developed many years ago. Recently, various new materials and techniques have been introduced. The limited number of comparative studies does not provide sufficient evidence to select the most appropriate procedure.
- The influence of guided bone regeneration on implant survival and success rates, and the long-term stability of the augmented bone, remain unknown.
- The presented classification of bone defects is meant as a basis on which to create the decision-making process regarding the choice of strategy for bone augmentation.
- There is active research in different areas focusing on simplification of clinical handling and on the development of more effective strategies to promote the body's ability to regenerate lost tissues.

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