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REVIEW ARTICLE

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Complications in bone-grafting procedures: Classification and management

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1 | INTRODUCTION

Different bone-regenerative techniques have been proposed and tested for reconstructive surgery to deficient alveolar ridges to allow adequate bone for dental implant placement.[1-3] Depending on the architecture of the bone defect,[4,5] these regenerative interventions may have, as their main objective, lateral, vertical, or combined bone augmentation. Moreover, such regenerative interventions may be carried out simultaneously with implant placement in a prosthetically driven position or staged with the implant installation.[6,7]

A careful assessment and classification of the residual alveolar ridge is of paramount importance when selecting the most appropriate regenerative strategy and technology. Moreover, any bone-regenerative intervention in the jaws must be based on a set of fundamental biologic principles of wound healing, including primary wound closure, enhancement of cell delivery and differentiation, and protection of the initial wound stability and integrity.[8]

Among the different interventions reported in the scientific literature, the most frequently used are those based on the principles of guided bone regeneration using an autogenous bone graft or bone substitute as a scaffold material to fill the osseous defect together with a barrier membrane to prevent the ingrowth of epithelium and soft connective tissues into the defect.[8] Other frequently used bone-regenerative interventions are the use of autogenous block grafts to treat deficient ridges, and bone-grafting procedures, with the aim of preserving the dimension of the ridge. The latter are often associated with the placement of dental implants in fresh extraction sockets (in most of these clinical situations the morphology of the socket does not match with the implant diameter).[9]

Based on its origin, the graft can be autologous when it comes from the same patient, xenogenic when it has been retrieved from an animal, allogenic when it is obtained from the same species, and synthetic when it has been developed in a laboratory.

2 | BONE-REGENERATIVE TECHNIQUES

The purpose of this section is to review complications associated with the different bone-grafting and membrane procedures, rather than the procedures themselves.

2.1 | Biomaterials used as bone-replacement grafts

Different biomaterials, either natural or synthetic, have been used as bone-replacement grafts and, depending on their source, they have different biologic properties. Autologous grafts are the only ones with osteogenic properties, as they are capable of harnessing osteogenic cells within the bone graft.[10] Osteoinductivity is the capability of a graft to actively promote bone formation by facilitating colonization and the differentiation of osteoblasts.[11] Osteoconductivity is a characteristic of a scaffold (physical and chemical) that facilitates the colonization and ingress of new bone cells and angiogenesis via capillary ingrowth as a result of its three-dimensional structure.[12]

Autologous bone is still considered the gold standard as a bone-replacement graft because of its osteogenic, osteoinductive, and osteoconductive properties,[13] and it contains different cell lines with the ability to promote the formation and remodeling of new bone.[14] Different types of autologous bone grafts have been defined,[15-17] depending on several factors:

1. The architecture of the graft (cortical, cancellous, or cortico-cancellous).
2. Its embryonic origin (intramembranous or endocondral).
3. The source of donor site (intra-oral or extraoral).
4. The morphology of the graft (particulate or block).
5. The type of block (onlay, inlay, or veneer).

In defects of two or more bony walls, particulate bone grafts harvested from intra-oral sites are usually employed in combination with barrier membranes following the principles of guided bone regeneration. In large-flat or one-wall defects, mono-cortical block autografts are usually indicated because they can preserve and maintain the space more appropriately.[5] Autologous bone grafts, however, have important limitations in light of their limited availability, the sensitivity of the surgical techniques involved, the morbidity associated with harvesting the graft, and unpredictable graft resorption.[18,19] This has led to the search for other biomaterials as bone substitutes,[8] such as allogenic[20] or xenogenic blocks.[21,22]

The main indication for autologous bone blocks is horizontal ridge augmentation in situations where the alveolar ridge width does not allow for implant placement in an adequate position. The effectiveness of this technique has been evaluated in several systematic reviews, reporting cumulative success rates of > 90% and mean implant survival rates of 87%-97.8%.[1,3,23-26] Despite these good results, most studies also reported adverse events, the most frequent being graft exposure, pain, hemorrhage, infection, temporal paraesthesia, and hematoma.

Autologous bone blocks have also been used to restore the alveolar height, either in a staged or simultaneous approach.[27] The effectiveness of the technique has been evaluated in several systematic reviews, showing cumulative implant success rates of 59%-100% and implant survival rates of 76%-100%.[2,24,28,29] Despite this, there is a high frequency of reported complications associated with such vertical bone-regenerative procedures, like pain, swelling, nerve disturbances, graft/membrane exposure, and/or infection.[30] Most of the studies selected in these systematic reviews are, however, prospective case series carried out by highly skilled surgeons in special environments, which, combined with the anatomic difficulties of an atrophic alveolar site, makes the external validity and predictability of these procedures questionable, and hence the generalizability of this approach in daily clinical practice remains limited at this time.[2]

Besides autologous grafts, the use of xenogenic, allogenic, and synthetic biomaterials (including polymers, bio ceramics, composite biomaterials, or other synthetic biomaterials) as bone-replacement grafts in regenerative interventions in the craniomaxillofacial region has also been evaluated.[17,31]

2.2 | Barrier membranes for guided bone regeneration

The biologic rationale of guided bone regeneration is based on the use of barrier membranes to mechanically exclude the growth of rapidly growing epithelial cells and fibroblasts from the overlying connective tissues into the bone defect, hence allowing only cells with osteogenic potential originating from the bony walls to fill the defect.[32] The barrier membrane creates a secluded space that not only excludes soft tissue penetration, but also allows the stabilization of the blood clot and secondary colonization by osteogenic cells, leading to bone formation.[33,34] The materials used for membranes require specific physicochemical characteristics, such as:

- Biocompatibility.
- Structural integrity.
- Host tissue integration.
- Cell occlusivity.
- Space maintenance.
- Clinical manageability.[17,31,35-37]

In the regeneration of the alveolar ridge, either simultaneously with implant placement or using staged protocols, most of the membrane materials, either nonresorbable or resorbable, cannot withstand the pressure from the overlying soft tissues and collapse inside the defect, hence requiring a bone-replacement graft, used as a scaffold to maintain the space beneath the membrane. With this purpose, particulate autologous bone and/or bone substitutes are frequently used as graft materials,[38] and should ideally have adequate mechanical properties and slow resorption rates.[39,40]

Several systematic reviews have evaluated the efficacy of guided bone-regeneration approaches combining bone grafts and barrier membranes, mainly applied simultaneously with implant placement for the treatment of dehiscence- and/or fenestration-type defects. These procedures have demonstrated high implant survival and success rates (80%-100%),[1,3,7,16,41-44] with comparable results with implants placed in nonregenerated bone,[45] and with a weighted mean defect height reduction of 4.28 (3.69-4.88) mm.[3,41]

When guided bone regeneration was used in a staged manner prior to implant placement and aiming for horizontal ridge augmentation, the success rates of the procedure and implant survival were also high (> 90%) in most studies.[1,3,41,43] While no differences in terms of bone gain and implant survival have been reported when comparing guided bone regeneration with onlay bone grafting,[44,46] the results from a recent meta-analysis reported higher bone width gain for the combination of a particulate xenograft plus autologous bone and a resorbable membrane (5.68 ± 0.68) compared with autologous bone blocks (4.26 ± 0.23 mm).[3]

When used for vertical ridge augmentation, simultaneously with, or prior to implant placement, guided bone regeneration was shown to be effective in terms of vertical bone gain (2-8 mm), implant survival (92.1%-100%), and success rates (76.3%-97.5%),[2,47] as well as long-term maintenance of the regenerated bone.[29]

Although bone regeneration using barrier membranes is often successfully achieved in clinical practice, some problems remain and need to be resolved to increase its predictability. The most frequently encountered complications with guided bone regeneration include partial or total collapse of the barrier membrane resulting in incomplete bone regeneration, and exposure of the membrane because of soft tissue dehiscence, resulting in local infection.[48]

3 | SPECIFIC PROCEDURE-RELATED COMPLICATIONS

3.1 | Bone blocks

3.1.1 | Complications associated with either horizontal or vertical bone-augmentation interventions

Complications related to lateral and vertical bone-augmentation procedures using bone block grafts mainly involve soft tissue dehiscences, infections, bone fractures, graft encapsulation by soft tissues, and neural damage.[22,49,50] Risk factors associated with the incidence of these complications include age (> 40 years), smoking, a history of periodontitis, and bone defects requiring more than one implant.[22,51]

The most common complication is the occurrence of soft tissue dehiscence leading to graft exposure and subsequent contamination of the bone graft and/or membrane, which usually results in impaired regenerative outcomes and frequent loss of the bone graft.[21,22,52-56] These soft tissue dehiscences are usually encountered together with edema or ecchymosis (Figure 1). The incidence of this reported complication (exposure) ranges from 0% to 70% depending upon whether or not a barrier membrane was used and whether the objective of the regenerative procedure was horizontal or vertical augmentation.[21,22,52-57] Postoperative graft infections may arise as a result of intra-surgical contamination or as a consequence of secondary contamination resulting from soft tissue dehiscence and exposure to the oral environment. A recent publication evaluating the safety and performance of xenogeneic bone blocks for lateral bone augmentation proposed a classification for soft tissue dehiscence depending upon the timing of the dehiscence relative to the surgery (Table 1).[22] Management of these complications is primarily governed by the type of soft tissue deficiency, the amount of exposed bone graft, and whether or not a concomitant acute infection is present.

The authors of the current review have also proposed a classification of complications based upon the amount of graft exposure and the presence of a concomitant infection (Table 2). This classification of complications, with specific recommendations for their management, follows below.

Complication class 0

In this clinical situation there is adequate healing of the soft tissues without signs of infection, but neural complications are present, either in the mandible (alveolar, mental, incisal, or lingual nerves) or in the maxilla (infraorbital nerve). These nerve impairments are a consequence of direct nerve injury, either with a blade during the releasing incisions, or by direct trauma during bone-graft harvesting or with implant placement, and may result in temporary or permanent neuronal damage and associated neurological symptoms.[24,58,59] A recent systematic review analyzing nerve injuries during oral surgery revealed that 13% and 3% of patients experienced short-term (< 10 days) and long-term (>1 year) altered sensation, respectively, with a pooled recovery rate within 6 months of surgery of 80%.[60] One high-risk area is the chin. When bone grafts are harvested from this region, the incidence of paraesthesia in the lower incisor area

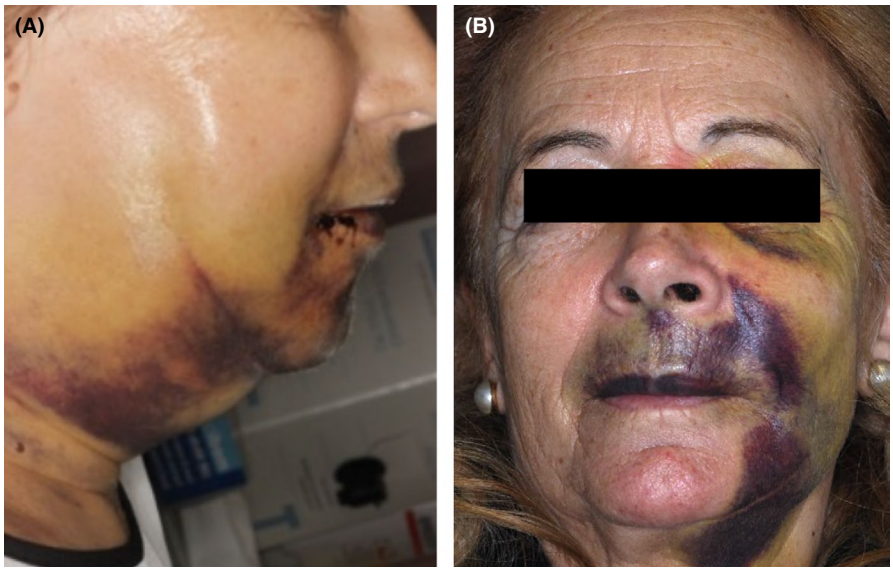

FIGURE 1 A, Postoperative situation 4 d after an extensive bone-augmentation procedure in the mandible. Significant edema and erythema were present. B, Postoperative situation 7 d after bone-regenerative procedure in the maxillary left quadrant. Note remarkable ecchymosis that has shifted to the lower third of the face

TABLE 1 Classification for soft tissue dehiscence depending upon the timing of the dehiscence relative to the surgery

Complication	Description
Class 0	No dehiscence
Class 1	From augmentation to 4 wk of healing
Class 2	From 4 wk to implant placement at 26 wk
Class 3	From implant placement to implant abutment connection
Class 4	From implant abutment connection to implant loading

TABLE 2 Classification of healing complications with bone blocks

Complication	Description
Class 0	Adequate soft tissue healing with neurological disorder
Class 1	Small graft exposure (≤ 5 mm) without signs of infection (– suppuration)
Class 2	Large graft exposure (> 5 mm) without signs of infection (– suppuration)
Class 3	No graft exposure with signs of infection (abscess +/– suppuration)
Class 4	Small graft exposure (≤ 5 mm) with signs of infection (+ suppuration)
Class 5	Large graft exposure (> 5 mm) with signs of infection (+ suppuration)

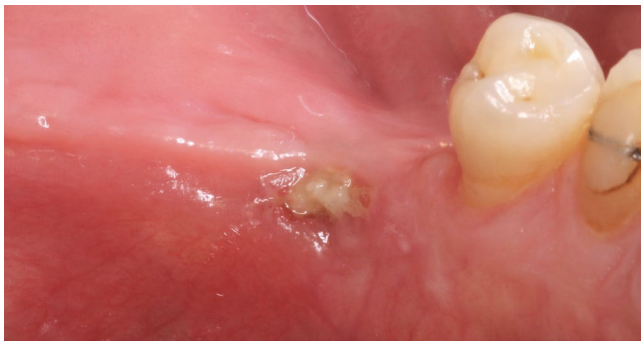

FIGURE 2 Complication type class 1. Note minimal exposure (< 5 mm) of the block graft close to the incision line

amounts to 29% of all the patients receiving surgery,[61] whereas 51% experienced permanent decreased sensitivity in the skin.[59] An alternative intra-oral bone area for harvesting is the ascending ramus of the mandible, which has been associated with lower levels of morbidity and complications,[62] although this area may have limitations with regard to the amount of bone volume and technical difficulties in harvesting the bone blocks.[63,64] A recent analysis of a cohort of 279 patients treated with autologous bone grafts for delayed implant placement reported 7% of mental nerve hypoesthesia after block harvesting and a 2.6% infection rate of the donor site.[51]

The most appropriate management of complications with block bone grafts is their prevention through a meticulous preoperative assessment of the anatomic structures using three-dimensional imaging techniques and the assurance of safety margins during the surgery itself. Minor neural complications should be closely monitored with regular follow-up to monitor their evolution.[65]

When a sensory disturbance occurs, mapping of the affected areas using a sharp instrument is helpful in evaluating the evolution in the sensory defect.[66] Management options for these complications include the removal of the implant in cases of proximity to the inferior alveolar nerve canal, administration of corticosteroid medications in cases of severe nerve damage to help reduce inflammation, and prescription of B-group vitamins to promote faster nerve regeneration.[67]

Class 1 complications

This type of complication describes minor graft exposures (≤ 5 mm in diameter) without signs of infection (there is no marked inflammation or suppuration) (Figure 2). The cause is usually attributable to flap dehiscence during the early stages of healing (from surgery to 1 month postoperatively) or when there is a soft tissue opening over the bone graft after a delayed period of healing (after 1 month and before implant placement).[68] In the literature, the incidence of such small perforations range from 21.4% in lateral bone-augmentation procedures using xenogenic bone blocks[22] to 37.5% using autologous bone blocks combined with deproteinized bovine bone mineral and a native collagen membrane,[53,69] or to 33.3% with allogenic bone blocks covered with deproteinized bovine bone mineral and a native collagen membrane,[54] or to 25% with allogenic bone blocks alone.[70] These types of dehiscence defect are usually treated by removing the exposed portion of the graft with a surgical bur under copious irrigation combined with application of local antiseptics (mouthrinses and/or gels), thus allowing the soft tissues to heal by secondary intention over a 2-4 week period.[21,22,53,54,69,70] Despite the possible loss of bone-graft volume, implant placement or the success rate of the procedure is not normally jeopardized.

Class 2 complications

This type of complication occurs when a large portion of the graft is exposed (> 5 mm in diameter), but still without evident signs of infection (no marked inflammation and/or suppuration) and with

healthy surrounding soft tissues. This complication is usually caused by lack of tension-free flap closure during postoperative healing or by excessive pressure to the soft tissues covering the bone graft during healing, in large augmented areas (Figure 3A-D). The suggested management of these situations is to reduce the exposed graft area using a bur, as previously described. In large areas, where soft tissue secondary intention healing is unlikely to occur, an autologous soft tissue graft may be necessary, with the primary objective of attaining closure of the wound.[56,71] In cases where the graft cannot be covered by soft tissue, its removal should be considered, effectively resulting in failure of the regenerative procedure.

Class 3 complications

This type of complication arises when there is a significant infection, but without signs of graft exposure (Figure 4). Its cause may be related to bacterial colonization during the augmentation procedure or to a postoperative infection through the incision lines or the neighboring teeth. Its incidence is reported to be low in most studies (< 10%).[13,56,72,73] To manage these complications, high doses of systemic antibiotics, together with the application of local antiseptics, have been recommended. In some cases a surgical approach is required to drain the infection and resolve the abscess.[13,52] If the infection persists, graft removal should be considered, with the consequent failure of the regenerative procedure.

Class 4 complications

This type of complication occurs when there is a small graft exposure (≤ 5 mm in diameter) with clear signs of infection (presence of suppuration), usually accompanied by pain, swelling, redness, fever, and/or pus.[13,22,52,74] Its cause is usually a result of flap and secondary infection of the flap during early healing or secondary infection creating a soft tissue fistula. A recently published case series reported a low incidence rate of these infections (4.4%).[22] Again, this complication may be managed by remodeling the exposed graft and applying adjunct systemic antibiotics and local antiseptics, thus allowing the soft tissues to heal by secondary intention within 2-4 weeks.[22,53] If the infection persists, a portion of, or even the entire graft, should be removed.

Class 5 complications

This type of complication arises when there is a large graft exposure (> 5 mm in diameter) together with signs of infection (presence of suppuration) (Figure 5). It is the least frequent complication (1%-10%), with a paucity of reports available in the literature.[13,52,75] Factors associated with this complication include the presence of micro-movements of the graft or the use of nonautogenous block grafts with defective vascularization.[52,57,76] When this complication arises, the graft should be completely removed and high-dose systemic antibiotics prescribed combined with topical antiseptics, allowing the soft tissues to heal for at least 8-12 weeks before any further attempt at bone augmentation.

3.1.2 | Prevention of complications associated with the use of bone blocks

When using horizontal and/or vertical bone-augmentation procedures, either simultaneous or staged with implant placement, prevention of complications should be based on surgical experience and the planning and execution of a meticulous surgical approach.[5,8,24,77]

Patient preparation prior to surgery is critical, with special focus on the control of patient-related risk factors, such as smoking or glycemic control and the presence of active periodontal disease, and its careful management before the regenerative procedure is critically important. When planning the regenerative procedure, appropriate three-dimensional planning should allow the study of important anatomic structures and guide the surgical procedure design (Figure 6A-D). It is also important to properly assess the available bone volume, to determine whether the donor site will offer sufficient bone to restore the defect. Similarly, the surgeon should be aware of the location of the basal bone to reduce the risk of fractures.

During the surgical procedure when harvesting the autologous bone blocks, special precautions should be taken to avoid damage to the alveolar nerve or to the nerve bundles at the apices of teeth.[56,63,69,78] A publication form 2017 recommended the use of computer-guided surgery to obtain mandibular bone blocks, thus reducing the risk of any neuronal complications.[79]

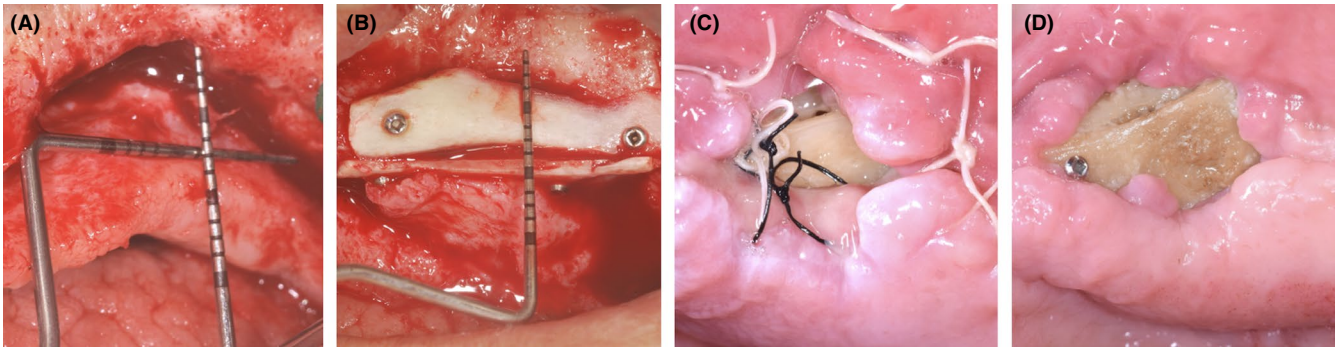

FIGURE 3 A, 7 mm vertical bone defect in the maxilla. B, Bone augmentation is performed using laminated sections of autologous bone from the ramus. C, 10 d after surgery a class 2-type complication is encountered. Note large exposure (> 5 mm) without the presence of concomitant infection. D, Clinical view after suture removal

Prior to placing the graft cortical bone, perforations are recommended at the recipient site to improve vascular and cellular supply to the grafted area.[80-82] When placing the block graft it should be in intimate contact with the underlying bone bed, which may be enhanced by meticulous trimming to improve its adaptation, and by supplemental fixation using miniscrews, thus avoiding any micromovement during healing. Where there is a discrepancy between the bone defect and the graft, the resulting dead space should be filled with particulate bone, either autologous or a bone substitute. Complete coverage of the grafted area with a tension-free flap, closed with meticulous suturing, is essential. This is usually carried out with adequate periosteal release and tension-free suturing. Appropriate antibiotic coverage preoperatively and postoperatively is usually undertaken together with topical application of chlorhexidine until the sutures are fully removed 1-2 weeks postoperatively.

The use of computer aided design-computer aided manufacturing technology to obtain customized blocks from synthetic materials[83] or by milling from a block[84] have significantly reduced patient morbidity, although results on their efficacy are still lacking.

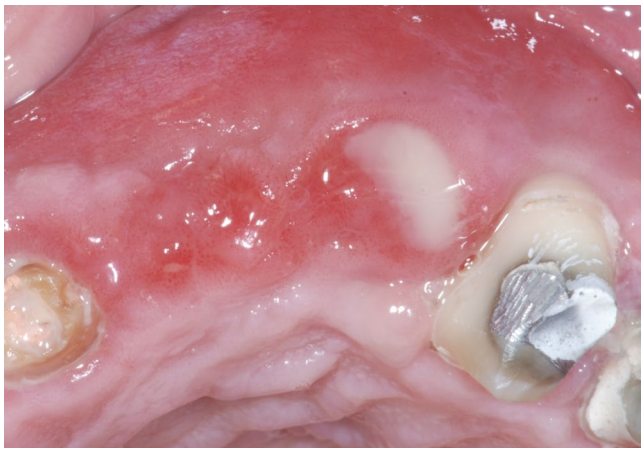

FIGURE 4 Class 3 type complication. Two months after surgery the patient presented with postoperative infections, as evidenced by the presence of suppuration without signs of graft exposure

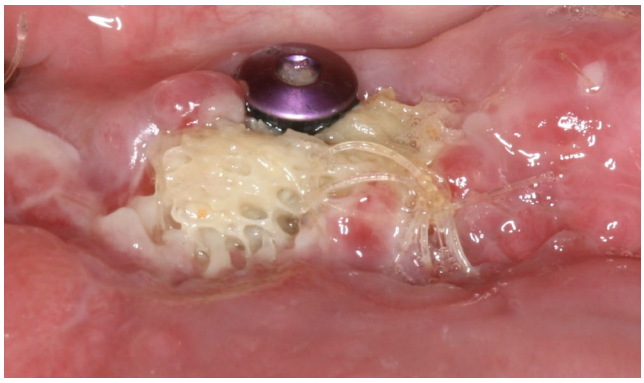

FIGURE 5 Class 5 type complication. Note that there is a large graft exposure (> 5 mm) with concomitant signs of postoperative infection

3.2 | Guided bone regeneration

3.2.1 | Complications associated with either horizontal or vertical bone-augmentation interventions

The complications associated with these interventions are usually related to exposure of the barrier membrane, which may impair the outcome of the regenerative procedure, because the exposed membrane immediately becomes contaminated with bacteria from the oral environment.[85,86] When using non-resorbable membranes, early bacterial contamination usually results in postsurgical infections and usually demands the early removal of the barrier membrane.[87] Exposure of resorbable membranes, however, usually results in their rapid resorption, with the possibility of secondary epithelialization and uneventful healing.[88] A published systematic review evaluated the impact of complications, such as membrane exposure, on the outcome of guided bone-regeneration procedures.[77] In the simultaneous approach, the meta-analysis reported a significantly higher defect reduction when the membrane was not exposed (weighted mean difference = 1.01 mm). The same results were observed for the staged approach, with significantly higher bone width gain in nonexposed cases (weighted mean difference = 3.10 mm). Similar findings have been reported in other reviews.[85,89]

The rate of soft tissue complications following guided bone regeneration has been reported to range from 0% to 45%.[90] Based on the 15 publications included in this review, the weighted complication rate was 16.8%, and included:

- Exposure of the membrane.

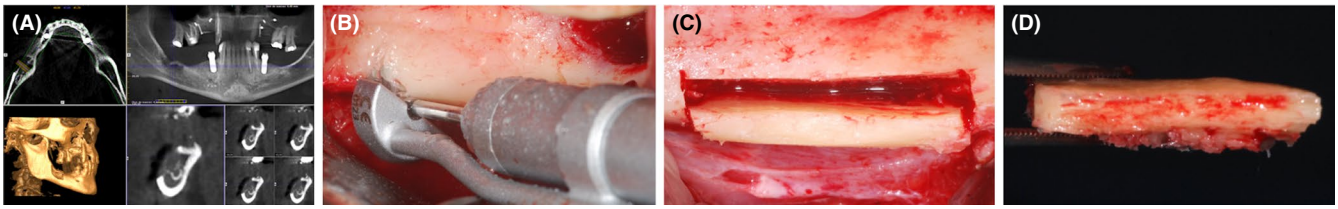

FIGURE 6 A, Three-dimensional analysis of the ramus area where the graft will be harvested. B, Care is taken during graft harvesting to avoid the laceration of or injury to the adjacent soft tissues. C, Bone osteotomies performed prior to graft harvesting. D, Clinical view of the ramus graft

- Soft tissue dehiscence.
- Acute infections or abscesses.

In the current review, complication rates appeared to be related to the choice of the regenerative material, in particular the barrier membranes, as depicted in Tables 3 and 4. This is in agreement with a recent systematic review conducted by Thoma et al,[91] which reported average exposure rates of 16.83%, 22.64%, 39.43%, and 29.3% for resorbable noncross-linked collagen membranes, cross-linked membranes, synthetic membranes, and nonresorbable expanded politetrafluoroetylene membranes, respectively.

Exposure of the barrier material

Expanded polytetrafluoroethylene barrier membranes have been extensively and successfully used in bone-augmentation procedures for more than 3 decades.[49,92-96] The incidence rate of soft tissue complications associated with their use has been reported at around 20%,[97] although this incidence is diverse, ranging from 17%-25%[93,98] to 12%-14% when strict surgical and postoperative protocols have been applied.[99,100] This complication leads to contamination of the expanded polytetrafluoroethylene membrane and frequent infection of the tissues above and under the membrane,[86,101-103] and requires early membrane removal, resulting in impaired bone regeneration.[48,87,104,105] If the membrane exposure is small (≤ 3 mm), removal of the exposed portion of the membrane, together with continuous weekly monitoring of the patient and topical application of antiseptics, such as clorhexidine, may allow for the healing of the wound without the need for complete membrane removal.[106] When membrane removal is indicated, a minimum of 4-6 weeks in situ is often necessary to promote the proper barrier function for bone regeneration.[107] However, open membrane exposure and the ensuing infection will frequently lead to early removal of the membrane (Figure 7A-G).[108]

To minimize the incidence of complications, alternatives to the expanded polytetrafluoroethylene membranes, such as dense polytetrafluoroethylene, have been proposed, as they have a smaller pore size (0.2-0.3 vs 0.5-30 μm), and therefore provide greater resistance to bacterial penetration.[109] Another alternative is the use of titanium meshes, especially in cases requiring vertical bone augmentation,[68,110] where a low incidence of postoperative infection and exposure has been reported.[111] However, the use of titanium meshes has been associated with highly diverse complication rates ranging from 50%[112,113] to 5%,[114,115] and once exposed, the ensuing bone regeneration is heavily compromised (Figure 8A,B).[111,114]

Resorbable membranes were introduced to overcome these complications.[116] Clinical trials have compared non-resorbable with resorbable barrier membranes, reporting incident exposure rates of 24.4% and 16.3%, respectively.[112] At 6 weeks, all the dehiscence lesions remained in the expanded polytetrafluoroethylene group, while only 9% remained in the collagen group.

The rapid degradation of collagen membranes usually occurs once they are exposed to the oral cavity, mainly as a result of enzymatic degradation and the activity of the oral flora.[88,117-119] This is indeed one of the most important advantages of these membranes, because once resorbed there is a spontaneous healing of the oral mucosa occurs (Figure 9A,B).[98,120] In barrier membranes made of collagen, degradation times depend on its structure and the method of processing.[121-124] Cross-linking of the collagen contributes to a prolonged barrier function effect,[125-128] although the chemical process may affect its behavior.[129] Two clinical studies have reported an increased rate of soft tissue complications and postsurgical infections when using an experimental cross-linked collagen membrane.[130,131] Conversely, using a ribose cross-linked collagen membrane, Friedmann et al reported improved regenerative outcomes compared with noncross-linked collagen membranes, even in the presence of dehiscence defects.[132]

Although the incidence rates of exposures associated with naturally derived membranes vary significantly in the scientific literature (Table 4), in most studies this event was not associated with further treatment, other than the use of antiseptics such as chlorhexidine.[100,131]

The use of synthetic resorbable membranes in guided bone regeneration, mainly based on aliphatic polyesters, has proven effective in experimental investigation[133-135] and in clinical studies.[136-138] However, when these membranes are exposed, it may take up to 4 weeks before they completely degrade, which increases the incidence of local infections and the requirement for removal of the exposed part of the membrane.[86,101,139,140]

Exposure of particulated bone grafts

Particulated bone grafts may also be exposed to the oral environment and contaminated by oral bacteria,[141,142] particularly in cases aiming for socket preservation when the socket opening is not adequately closed.[143] Exposure of the graft particles often leads to superficial soft tissue encapsulation and bacterial contamination.[144-146] There is limited evidence for the effect of particulate bone exposure on horizontal bone-augmentation procedures. However, it may be assumed that in cases of early membrane exposure, the particulate bone graft may also end up being exposed to the oral cavity, and the most superficial parts of the particulate graft could therefore become embedded in the soft tissue. These encapsulated graft particles can be curetted away, and antibacterial mouthrinses or gels applied over the area to speed up healing.

Postoperative infections in guided bone regeneration

Other than membrane or graft exposure, the reported rates of postoperative infections after guided bone-regeneration augmentation procedures range from 2% to 11%.[56] This rate increases as surgical intervention becomes more aggressive and demanding (eg, in vertical bone-augmentation procedures).[147,148] Similarly, the biomaterial selected may also affect the incidence of postoperative infections,

TABLE 3 Membrane exposure in prospective studies with guided bone-regenerative procedures and a minimum of 10 patients utilizing nonresorbable barrier membranes

Author (year)	Study	Defect	Number of patients	Number of implants	Membrane (test)	Membrane (control)	Staged/simult	% of membrane exp.	Description of other complications
Nonresorbable e-PTFE membranes									
Jovanovic et al (1992)	PCS	DEH	11	19	ePTFE(GTAM)		Simult	21.05%	1 fistula with purulent drainage. 5 implants partial bone fill
Becker et al (1994)	PCS	IMI	49	49	ePTFE(GTAM)		Simult	40.81%	3 failed implants (6.1%). 20 MB early removed
Simion et al (1994)	PCS	IMI/HOR	10	NR	ePTFE(GTAM)		Staged/simult	50%	No other complications reported
Dahlin et al (1995)	CCT	DEH/FEN	45	55	ePTFE(GTAM)		Simult	10.9%	4 implant failures (7.4%)
Buser et al (1996)	RCT	HOR	40	66	ePTFE(GTAM)		Staged	2.5%	2 patients compromised healing with encapsulation
Zitzmann et al (1997)	RCT	DEH/FEN	25	84	ePTFE(GTAM)	Native colagen	Simult	24.4% (NR) /16.3% (R)	2 implant failures NR group
Lorenzoni et al. (1998)	CCT	DEH/FEN	82	129	Ti-reinforced	GTAM/Biofix	Simult	47%/22% (GTAM)/50% (R)	Infections in Biofix membranes
Chiapasco et al (1999)	CCT	HOR	15	30	ePTFE(GTAM)		Staged	13.3%	2 sites with compromised regeneration
Carpio et al (2000)	RCT	FEN	48	34	ePTFE(GTAM)	Native colagen	Simult	12.5% (NR)/8.7% (R)	Implant exposures and soft tissue dehiscences
Simion et al (2004)	PCS	VER	14	38	Ti-reinforced e-PTFE		Staged/simult	12.5%	3 implant failures associated with MB exposure
Chiapasco et al (2004b)	CCT	VER	11	25	Ti-reinforced e-PTFE		Staged/simult	27.27%	2 paresthesias secondary to chin grafts and 1 infection
Blanco et al (2005)	CCT	DEH/FEN	19	26	ePTFE(GTAM)		Simult	11.53%	No other complications reported
Canullo et al (2010)	CCT	VER	20	42	Ti-reinforced e-PTFE		Simult	5%	Significant peri-implant bone loss over time
Naenni et al (2016)	RCT	DEH	27	27	Ti-reinforced e-PTFE	Native colagen	Simult	14% (NR)/30% (R)	25% presented inflammed tissues 6 months post-operative
Nonresorbable d-PTFE membranes									
Ronda et al (2013)	RCT	VER	23	78	Ti-reinforced d-PTFE	Ti-reinforced e-PTFE	Staged	0%	3 paresthesias. Detach mylohyoid
Urban et al (2014)	PCS	VER	19	NR	Ti-reinforced d-PTFE		Staged	0%	No other complications reported
Herzberg (2017)	PCS	VER	10	10	Ti-reinforced d-PTFE		Staged	0%	1 implant experienced bone loss

TABLE 3 (Continued)

Author (year)	Study	Defect	Number of patients	Number of implants	Membrane (test)	Membrane (control)	Staged/simult	% of membrane exp.	Description of other complications
Titanium mesh-osteosynthesis plates									
Von Arx et al (1996)	PCS	HOR	20	28	Micro Ti-Mesh		Staged	50%	One infection. Sensory disturbances
Von Arx et al (1999)	PCS	DEH/FEN	15	20	Micro Ti-Mesh		Simult	5%	Graft failure associated to exposure
Maiorama et al (2001)	PCS	DEH/FEN	14	59	Ti-Mesh		Staged	14.2%	No other complications reported
Artzi et al (2003)	PCS	VER	10	26	Ti-Mesh		Staged	20%	No other complications reported
Rocuzzo et al (2004)	PCS	VER	18	37	Ti-Mesh		Staged	17.3%	5 temporary paresthesias
Merli et al (2006)	CCT	VER	19	29	Osteosynt plates	Ti-reinforced e-PTFE	Simult	25%/9.09% (test)	No other complications reported
Proufasefs et al (2006)	PCS	HOR/VER	17	38	Ti-Mesh		Staged	35.29%	Persistent pain, prolonged hypestesia
Merli et al (2007)	CCT	VER	22	77	Osteosynt plates	Ti-reinforced e-PTFE	Simult	9.09%/9.09%	3 abscesses in test group. 3 fistulas control
Rocuzzo et al (2007)	CCT	VER	12	NR	Ti-Mesh		Staged	33.3%	Temporary paresthesia
Pieri et al (2008)	PCS	VER	16	44	Ti-Mesh		Staged	5.3%	Temporary dysesthesia
Torres et al (2010)	RCT	HOR/VER	30	97	Ti-Mesh-PRP	Ti-Mesh	Staged	0% (test)/13.04%	All exposures in control. 1 graft, 1 IMP failure in control

Abbreviations: C, control; CCT, controlled clinical trial; DEH, dehiscence; dPTFE, dense politetrafluoroetylene; ePTFE, expanded politetrafluoroetylene; FEN, fenestration; GTAM, gore-tex augmentation membrane; HOR, horizontal; IMI, immediate implant; IMP, implant; MB, membrane; membrane exp, membrane exposure; NR, non-resorbable; PCS, prospective case series; PRP, platelet-rich plasma; R, resorbable; RCT, randomized controlled trial; simult, simulateneous; T, test; Ti-Mesh, titanium mesh; Ti-reinforced, titanium reinforced; VER, vertical.

TABLE 4 Membrane exposure in prospective studies with guided bone-regenerative procedures and a minimum of 10 patients utilizing resorbable barrier membranes

Author (year)	Study	Defect	Number of patients	Number of implants	Membrane (test)	Membrane (control)	Staged/simult	% of membrane exp.	Description of other complications
Resorbable collagen native membranes									
Tawil et al (2001)	RCT	DEH	17	18	Native collagen		Simult	11.76%	No other complications reported
Hammele and Lang (2001)	PCS	DEH	10	10	Native collagen		Simult	0%	1 infection. 1 superfical tissue necrosis
Hammerle et al (2007)	PCS	HOR	12	15	Native collagen		Staged	0%	1 patient no bone gain and biomaterial encapsulation
Urban et al (2013)	PCS	HOR	25	76	Native collagen		Staged	0%	1 abscess with minimal bone gain
Van Assche et al (2013)	RCT	DEH	14	28	Native collagen Hydroxyapatite/β-Tricalcium phosphate	Native collagen +XEN	Simult	14.28% (test)/7.14%	No other complications reported
Cardaropoli et al (2013)	PCS	VER	20	25	Native collagen		Simult	0%	No other complications reported
Resorbable collagen cross-linked membranes									
Friedmann et al (2002)	RCT	HOR	27	NR	Ribose cross-linked	ePTFE(GTAM)	Staged	64.28% (test)/71%	1 site infection and total graft failure (control)
Moses et al (2005)	CCT	DEH	41	73	Ribose cross-linked		Simult	39%	No other complications reported
Llambés et al (2007)	PCS	VER	11	32	Ribose cross-linked		Simult	0%	2 perforations of the mucosa by implant and 1 IMP failure
Becker et al (2009)	RCT	DEH	49	49	Experimental cross-linked	Native collagen	Simult	35% (test)/7.69%	4 wound infections (3 T, 1 C)
Beitlitum et al (2010)	CCT	HOR/VER	50	106	Ribose cross-linked		Simult/staged	24%	12.5% temporary paresthesia. 34% needed regrafting
Friedmann et al (2011)	RCT	DEH/FEN	37	73	Ribose cross-linked	Native collagen	Simult	23.5% (test)/20%	Sites with exposed membranes needed regrafting
Resorbable synthetic membranes									
Mayfield et al (1997)	PCS	DEH/FEN	11	17	PLA/PGA		Simult	0%	No other complications reported
Lorenzoni et al (1998)	CCT	DEH/FEN	82	129	PGA	ePTFE(GTAM)/ ePTFE(TR-GTAM)	Simult	50% (test)/22% (GTAM)/47%	No other complications reported
Jung et al (2009)	RCT	DEH	39	39	PEG	Native colagen	Simult	47.36% (PEG)/22.2%	4 patients (2 T, 2 C) presented postop. pain
Urban et al (2011)	PCS	HOR	22	58	PLA/PGA		Staged	0%	No other complications reported
Schneider et al (2014)	RCT	DEH	40	40	Mod-PGA	Ti-reinforced e-PTFE	Simult	26.3% (test)/9.5%	1 peri-implant infection and 1 failure of augmentation after exp.

Abbreiations: C, control; CCT, controlled clinical trial; DEH, dehiscence; ePTFE, expanded politetrafluoroetylene; FEN, fenestration; GTAM, gore-tex augmentation membrane; HOR, horizontal; IMP, implant; membrane exp, membrane exposure; mod-PGA, modified poliglycolic acid; PCS, prospective case series; PEG, polyethylene glycol; PGA, poliglycolic acid; PLA, polilactic acid; RCT, randomized controlled trial; simult, simulateneous; T, test; TR-GTAM, titanium-reinforced gore-tex augmentation membrane; VER, vertical; XEN, bone xenograft.

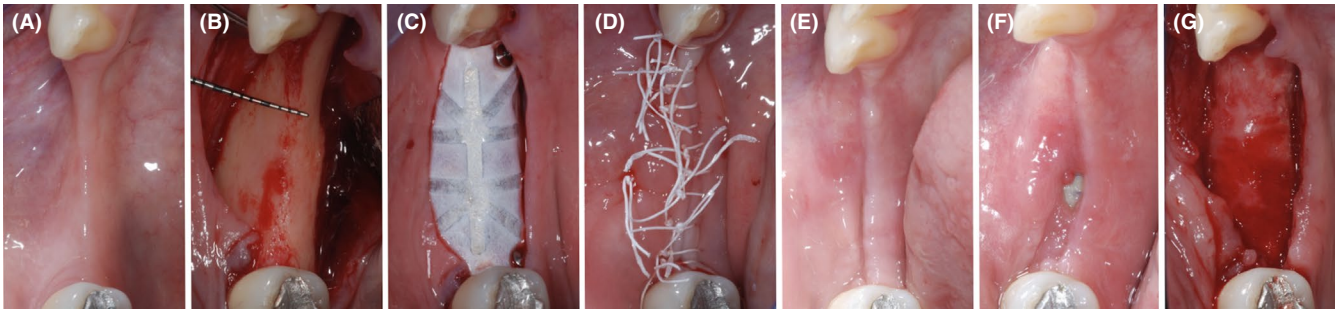

FIGURE 7 Treatment sequence of a guided bone-augmentation procedure performed with a nonresorbable expanded polytetrafluoroethylene barrier membrane. A, Preoperative image. B, Horizontal defect dimensions. C, Membrane fixation. D, Suturing by means of non-resorbable expanded polytetrafluoroethylene sutures. E, At the 4-wk follow-up, there is primary closure. F, At the 10-wk follow-up, there was a late exposure. Topical application of antiseptics was prescribed and it was monitored weekly. G, Three months after the intervention, the membrane is removed. Note how in the area of exposure the regeneration has been impaired

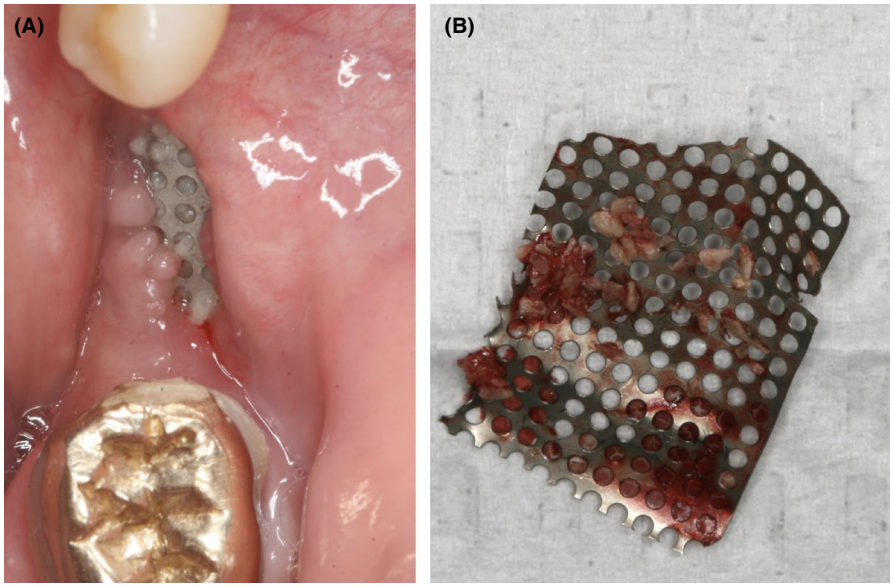

FIGURE 8 A, Exposure of a titanium mesh at the 3-wk follow-up stage. B, Mesh removal 2 wk later

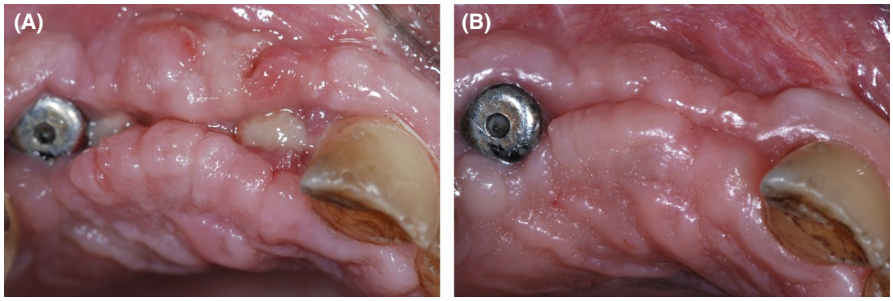

FIGURE 9 A, Membrane exposure with a resorbable collagen membrane (native collagen) at the 3-wk follow-up stage. B, At the 3-mo follow-up stage, the wound area appears closed with no signs of inflammation

with nonresorbable barrier membranes having a greater incidence.[93,149] The management of postoperative infections frequently involves the reopening of the site, retrieval of the barrier membrane and biomaterial under copious irrigation, prescription of systemic antibiotics, and possibly a requirement to repeat the regenerative procedure.[150]

Sensory disturbance

Sensory disturbances (anesthesia, paresthesia, or dysesthesia) have also been associated with guided bone-regeneration procedures and, similar to the use of bone blocks, are often related to damage of the sensory nerves adjacent to treatment areas, mainly when dental implants are placed in conjunction with the regenerative procedure

or when periosteal releasing incisions are made to ensure passivity of the flap.[151] The incidence specifically associated with guided bone regeneration is rare and is frequently associated with minimal sensory disturbance, which resolves spontaneously 3-4 months postoperatively.[152] Management should be similar to that described earlier associated with the use of bone blocks.

Requirement for further augmentation procedures

The need for further bone-augmentation procedures following guided bone regeneration can be considered a minor complication because it implies that the bone-augmentation procedure was unable to provide enough bone volume for adequate implant placement. A requirement for regrafting procedures was observed in seven of the 40 studies included in a recent systematic review and ranged from 0% to 23.5% of treated sites.[153] It must be acknowledged that, in staged guided bone-regeneration procedures, the need for regrafting depends heavily on the extent and anatomy of the defect, and on the desired implant diameter planned. Simultaneous approaches may offer a more objective view regarding the outcome of guided bone-regeneration procedures because the aim is to completely cover the exposed implant surface. The percentage of defect resolution varies significantly in the available literature. While some studies have reported a defect resolution of > 90% with the combination of collagen membrane and xenograft,[139,154] other studies reported percentages that ranged from 60% to 75% with similar approaches.[99,105]

3.2.2 | Prevention of complications associated with guided bone-regeneration procedures

The first step to prevent complications is adequate patient selection. Systemic diseases may affect the patient's wound-healing capability, mainly in those patients with diabetes and osteoporosis.[155,156] Uncontrolled glycemia in patients with diabetes affects the early stages of bone regeneration, and these patients have shown impaired potential for intramembranous and endochondral ossification.[157-159] Despite these findings, however, clinical results of regenerative procedures performed in patients with diabetes have demonstrated positive outcomes, which reinforces the importance of prevention.[160,161]

Cigarette smoking and nicotine have also shown a deleterious effect on bone healing and osseointegration.[162,163] Investigations evaluating the impact of smoking on the prognosis of implant therapy have reported a significantly enhanced risk for implant failure among smokers when implants were placed in combination with augmentation procedures (odds ratio 3.61).[164] The negative effect of smoking may not only affect the bone, but also the healing of the soft tissues.[165] Experimental investigations have also proven that smoking cessation may partially revert the negative effects previously described in bone healing.[166,167]

Reduction of surgical complications is also related to the selection of the surgical procedure, because their incidence is directly related to the severity of the bone defect. This is more evident when there is a need for vertical regeneration, as these surgical procedures are technique sensitive and adequate healing requires optimal patient management.[168] Such procedures should only be undertaken by surgeons with the appropriate training and experience in such techniques. To reduce the risk of postoperative complications, it is important that the regenerative biomaterials are carefully stabilized and appropriately covered by the soft tissues, which requires adequate flap management and precise suturing.[169-171] Finally, a strict aseptic protocol should be established to minimize the incidence of postoperative infections. Although there is limited information on the benefit of systemic antibiotics in reducing complications following bone-regenerative procedures, postoperative antibiotics are usually prescribed empirically, because of the possibility of contamination of the biomaterials employed. With regard to the method of provisionalization, fixed provisional restorations have been shown to achieve superior regenerative outcomes compared with removable prostheses, as the latter may impinge on the treated area and hinder regenerative outcomes.[172]

The use of specific surgical techniques through minimally invasive approaches such as tunneling has been advocated to reduce the risk of flap dehiscence, but clinical evidence is currently limited.[173-175] Similarly, the use of biologics, mainly platelet aggregates, has been advocated to promote soft tissue healing and minimize the incidence of membrane exposure,[111] although the added value of these procedures is still a matter of controversy.

4 | SUMMARY AND CONCLUSIONS

Bone-augmentation procedures have been shown to be highly predictable interventions when evaluating bone gain and implant survival, irrespective of the material used or the type of intervention. Nevertheless, all these are technique-sensitive procedures subject to different degrees of complications, which appear to arise more frequently in advanced defects, such as those with a vertical component. Because complications may jeopardize the success of the procedure and can even have implications for the patient's quality of life, their prevention should be one of our main objectives when treating bone deficiencies. It is therefore recommended that whenever possible clinicians choose procedures that have a lower degree of complications and employ less invasive surgical interventions. It is also essential to acquire the necessary skills and experience to treat more demanding cases and to understand how to treat the complications that may arise, in case they occur.

CONFLICT OF INTEREST

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

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