Statements and Recommendations for Guided Bone Regeneration: Consensus Report of the Guided Bone Regeneration Symposium Held in Bologna, October 15 to 16, 2016

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Introduction: *In the past 10 years, long-term studies have demonstrated that guided bone regeneration (GBR) is a successful and reliable technique for vertical and horizontal ridge augmentation, but strict and rigorous protocols must be adopted.*

Material and Methods: *Because no reports have yet been published with statements and clinical recommendations for GBR, a closed meeting of all authors was organized to discuss this matter during a GBR symposium held in Bologna (Italy) in October 2016. The authors focused on the findings of systematic and narrative reviews, prepared before the meeting, covering aspects of the clinical management of GBR techniques. Successively, a discussion based on the scientific evidence and on the experts' opinions led to the formulation of statements, clinical recommendations, and implications for future research.*

Results: *To avoid complications and to optimize outcomes, the following factors should be considered by clinicians: patient selection; analysis of defect type; blood supply; antibiotic treatment; flap passivation; delayed implant placement; combination of autogenous bone and xenograft or allograft; rigorous fixation of membranes; removal after 6 to 9 months; analysis of complications; soft-tissue management; and high care in scarred sites and in esthetic areas.*

Conclusions: *The present consensus report reviewed the scientific evidence and provided specific guidelines and recommendations for clinical practice and the different approaches to GBR techniques to ensure surgical success and predictable outcomes. (Implant Dent 2019;00:1–12)*

Key Words: guided bone regeneration, bone augmentation, guidelines, statements, bone atrophy

Today, osseointegrated implants are widely used for the rehabilitation of edentulism with high success rates in terms of both function and esthetics. However, adequate quantity and quality of bone are required to achieve implant success.[1–9] In the past 10 years, short- and long-term studies have demonstrated that guided bone regeneration (GBR) is a successful, reliable technique for vertical and horizontal ridge augmentation, but strict, rigorous protocols must be adopted to avoid complications and to optimize outcomes.[1–9]

No reports have yet been published with statements and clinical recommendations for GBR. Therefore, during

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a GBR symposium held in Bologna, a closed meeting of all authors was organized to discuss this matter. The present consensus report is intended to review the scientific evidence and to provide specific guidelines and recommendations for clinical practice and the different approaches to GBR techniques to ensure surgical success and predictable outcomes.

The GBR therapeutic concept, a development of the guided tissue regeneration biological rationale as first proposed by Dahlin et al,[9] advocates the formation of secluded anatomical sites through the application of an occlusive membrane, thereby allowing for mechanical exclusion of undesirable soft tissue but allowing osteogenic cells to grow into the osseous defect.[10] All the principles and applications of GBR have been well described by Retzepi and Donos,[1] who summarized, from a biological point of view, the evolution of the GBR therapeutic concept over the past 2 decades, the evidence for GBR effectiveness, and the predictability of therapeutic application in critically sized maxillofacial defects. In this consensus meeting, any reconstructive surgical technique that involved the application of a nonresorbable or resorbable barrier, and a particulate bone graft, was considered to be a GBR technique. The barriers play 2 key roles: exclusion of nonosteogenic cells and space creation/maintenance.[11] Therefore, according to this definition, the authors considered that GBR included reconstructions using expanded polytetrafluoroethylene (e-PTFE) membranes, high-density PTFE (d-PTFE) membranes, titanium-reinforced high-density PTFE (Ti + d-PTFE) membranes, collagen membranes, and also regenerations using titanium meshes or plates covered by collagen sheets or resorbable membranes based on synthetic polymers, such as poly-D,L-lactide (PDLLA) devices (which may also be covered by collagen membranes)[12–18] (Figs. 1–3). As a consequence, no technique involving onlay or inlay graft placement or sinus lift was considered to reflect GBR. To a large extent, the applicability of augmentation procedures depends on the defect type. First, the regenerative potential, which is affected by defect morphology, vascularization, and cellularity, is the major factor influencing the choice of the surgical technique used to achieve effective new bone formation in the augmented area.

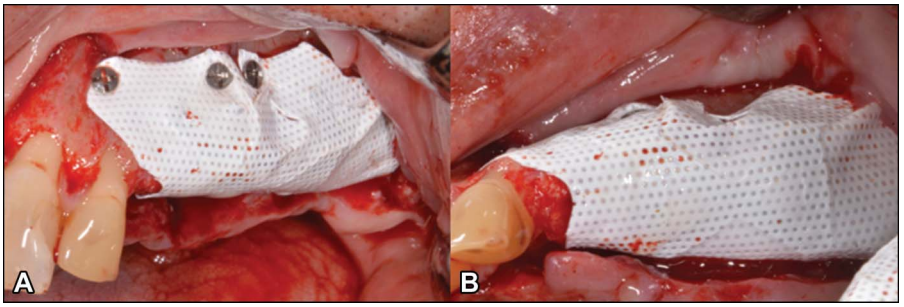

Fig. 1. A and **B**, Ti-reinforced membrane for maxillary augmentation—lateral and occlusal view, which shows the vertical regeneration line and distance from the adjacent teeth after fixation and stabilization.

The review showed that information on the characteristics of the initial bone defects was not comprehensively incorporated in most studies; the vertical and horizontal dimensions of the defects, if available, were reported quantitatively, either using descriptive terms or using the classification of Cawood and Howell.[19] The latter authors developed the following classification based on the number of surrounding bony walls: class "A" for 2-wall defects; class "B" for one-wall defects; and class "C" for defects with no surrounding walls. Nevertheless, the consensus was that the classification developed by Wang and Al-Shammari,[20] which involves the following 3 classes, was easier and more comprehensive: class "H" for horizontal defects; class "V" for vertical defects; and class "C" for combined defects. Each category is subdivided into small (<3-mm), medium (4- to 6-mm), and large (>7-mm) defects (Fig. 4). To investigate the role of recipient bed characteristics in terms of the success of augmentation procedures, future schemes might consider differences in revascularization between short and long defects. Moreover, there is a need to validate and standardize the definitions of initial bone defects when GBR techniques are used, as is also true for other augmentation procedures; to evaluate the susceptibility of different recipient sites to treatment; and to choose optimal materials and methods.

All the following guidelines should be read in the spirit that bone augmentation using nonresorbable or resorbable membranes may reduce complications and optimize clinical outcomes.

MATERIALS AND METHODS

Working Group and Consensus

The working group for the consensus consisted of competent, experienced clinicians who specialize in

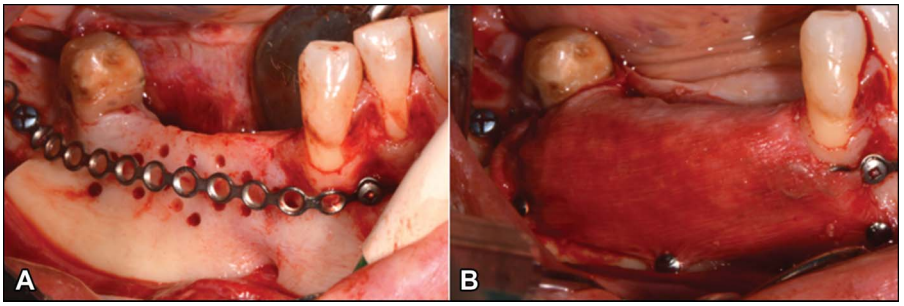

Fig. 2. A, Titanium osteosynthesis plate for space-making effect for mandibular augmentation: It was modeled following the horizontal regeneration curve, and it was fixed by means of 2 self-tapping titanium miniscrews. **B**, Native collagen membrane for cell-occlusive effect for mandibular augmentation: It was trimmed over the regeneration space, and it was fixed by means of titanium tacks.

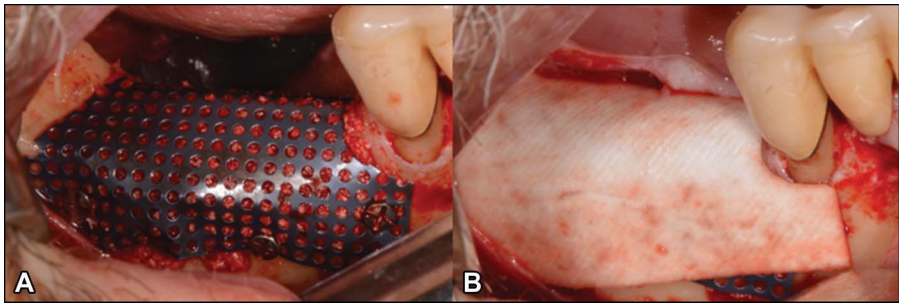

Fig. 3. A, Titanium mesh for space-making effect for mandibular augmentation: It was trimmed over the regeneration space following the vertical regeneration line and the horizontal regeneration curve; and it was fixed by means of self-tapping titanium miniscrews. **B**, Cross-linked collagen membrane for cell-occlusive effect for mandibular augmentation: It was trimmed over the regeneration space, and it was used to cover the titanium mesh.

GBR procedures and were speakers at the Second GBR symposium held in Bologna, Italy, on October 14 to 15, 2016.

First, the authors focused on the findings of systematic and narrative reviews, prepared before the meeting, covering aspects of the clinical management of GBR techniques. The following reviews formed the basis of this consensus: Retzepi and Donos; Rakhmatia et al; Clementini et al; Carbonell et al; Al-Nawas and Schiegnitz; Millinkovic et al; Lutz et al; and Keestra et al.[1–8]

Finally, an interactive discussion based on the scientific evidence and on the experts' opinions led to the formulation of statements, clinical recommendations, and implications for future research, to produce practice guidelines for GBR procedures on the following issues: patient selection; blood supply; antibiotic treatment; flap passivation; timing of implant placement; implant surface; barrier membranes; bone grafts; membrane fixation; timing of membrane removal; complications; soft-tissue management; GBR at scarred sites; and GBR in esthetic areas.

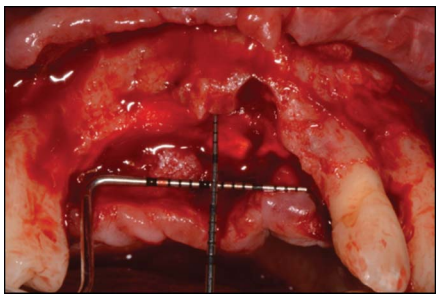

Fig. 4. Vertical and horizontal defect—Large class C defect: Interproximal bone peaks of the adjacent teeth are a key factor for a complete bone regeneration of the combined defect.

Patient Selection

Accurate evaluation of the medical history and personal features of each patient form the basis on which to evaluate whether GBR is possible and whether the results are predictable. Currently, the available evidence does not allow for the establishment of specific guidelines for the management of candidates for GBR procedures who have systemic disorders or local risk factors. To deliver successful GBR treatment, the working group recommended that pre-existing medical conditions and status must be strictly evaluated, noting primarily if any medical condition is controlled or uncontrolled and specifying its effect on the patient. Clinicians must be aware of all risk factors and lifestyle features that might interfere with (i) wound healing, (ii) the immune response, (iii) angiogenesis, and (iv) bone metabolism. The following general health conditions must be always evaluated before use of a GBR procedure to avoid complications or failure:

1. Smoking has been widely investigated in several studies as a risk factor for adverse implant outcomes and soft-tissue complications.[21] Smoking adversely affects angiogenesis and wound healing, reduces peripheral circulation, affects collagen production, impairs fibroblast function, and compromises neutrophil and macrophage function because cigarette smoke is toxic.[22,23] Smoking is not an absolute contraindication for implant placement. Most studies reported implant survival rates of 80% to 90% in smokers but an increased risk of implant loss and periimplantitis.[23] Therefore, it was recommended that GBR techniques be performed only on light smokers (<10 cigarettes per day).
2. Diabetes similarly affects the immune response and wound healing due to hyperglycemia and prolonged hypoxia, which may be caused by both insufficient perfusion and inadequate angiogenesis.[24] Little is known about the effect of diabetes on osseointegration or on the prognosis after dental implantation; most experimental studies have indicated that bone matrix formation and bone mineralization were very similar in controlled diabetic and nondiabetic animals, but the extent of bone-implant contact was lower than normal even in controlled diabetes.[25] Before GBR, it is mandatory to ensure long-term control of diabetes by monitoring the glycosylated hemoglobin (type A_{1c}) (HbA_{1c}) level (as the ratio of this hemoglobin to unglycosylated hemoglobin, expressed as a percentage). The HbA_{1c} value should be less than 7% (or 53 mmol/mol).
3. Patients at risk of medically related osteonecrosis of the jaw (MRONJ) because of antiresorptive and/or antiangiogenetic treatment require special consideration. These treatments also negatively affect wound healing and bone metabolism, inhibiting osteoclast and fibroblast activity, consequently reducing soft tissue and bone turnover, and compromising the vascular recipient site. Unfortunately, scant high-quality data are available indicating how to proceed in such patients. The following

recommendations are based on the American Association of Oral & Maxillofacial Surgeons (AAOMS) Position Paper[26,27] on MRONJ and a recent systematic review.[28] AAOMS position papers produced in 2009 and 2014 stated that GBR should be avoided in patients for whom intravenous treatment is immediately planned and in asymptomatic patients on intravenous or subcutaneous therapy for malignant diseases with intraosseous metastases. Also, based on the following time frame, GBR should be considered only with extreme care in patients taking oral drugs to treat osteoporosis and benign disease: patients taking oral bisphosphonates (BPs) for less than 4 years with no local risk factor may undergo implant surgery with or without a drug holiday; however, patients taking oral BPs for less than 4 years and concomitant corticosteroids, or those taking oral BPs for more than 4 years, should have a drug holiday of at least 2 months before surgery and 1 month after bone healing.[29]

Although clinical guidelines for compromised patients were thus suggested, the current literature does not address the details of GBR procedures appropriate for patients with the abovementioned conditions. There is a clear need for well-designed clinical trials focusing on compromised patients and disease-related variables that may influence the success of GBR.

Antibiotic Treatment

Bacterial infiltration into the area of bone augmentation is possible because of the porosity of barrier membranes. In terms of nonresorbable membranes, the high porosity (5–30 μm) of e-PTFE membranes increases the risk of early infection, whereas the low porosity (0.2–0.3 μm) of d-PTFE membranes lowers the risk. The use of nonresorbable membranes requires second-stage removal surgery, and, unlike the case for resorbable membranes, exposing the membranes to bacteria.[2] Currently, little evidence is available on whether antibiotics are required. However, to ensure infection-free healing, the following recommendation (relevant to the use of both resorbable and nonresorbable membranes) was made based on combined clinical experience.

Generally, as in all dental procedures in which significant oral bleeding and exposure to potentially contaminated tissue may occur, it is strictly recommended that GBR procedures should feature antibiotic prophylaxis (a loading dose 1 hour before surgery and postoperative long-course therapy with compress placement 3 times daily for 7 days).

The relationship between preoperative and postoperative antibiotic use during GBR procedures, and the GBR success rate is poorly documented in the current literature. Future research should focus on the best choice of antibiotic, the timing of administration, and dose. The effects of antibiotics on the predictability of GBR procedures remain to be explored. Moreover, it would be interesting to determine which pathogenic bacteria might adhere to GBR membrane barriers to ensure that the activity spectrum of the antibiotic is adequate. It was suggested that 2-g amoxicillin + clavulanic acid with 500-mg metronidazole should be given 1 hour before surgery, followed by 1-g amoxicillin + clavulanic acid every 8 hours for 7 days and 250-mg metronidazole every 8 hours for 4 days after surgery.

Flap Passivation

Flap passivation is critical in terms of tension-free closure of the surgical wound; this is the goal of primary healing.[11] Maintaining flap closure over a nonresorbable membrane is more challenging than in other augmentation procedures because PTFE membranes separate the bone graft from the overlying flap and the periosteal vascularization.[35] The consensus report drew on expert experience with various surgical techniques in terms of flap design and passivation affording tension-free primary closure. Different anatomical regions require different surgical techniques to achieve adequate flap passivation. In the mandible, free-tension closure is easier because it is possible to manage both the lingual and buccal flaps. The management of surgical flaps has been addressed by various authors, including Simion et al,[13] Buser et al,[32] Jovanovic et al,[36] and Tinti et al.[37,38] Recently, other authors[35,39–42] have described coronal advancement of mandibular lingual and buccal flaps placed during GBR surgery. In the maxilla, several flaps have been advocated, including a buccal rotational flap,[43] a coronally positioned palatal sliding flap,[44] a split palatal rotated flap,[45] and a palatal advanced flap[46]; the brushing technique[47] and the papilla shift technique[48] have also been described. Recently, Urban et al[49] proposed a scheme of flap design and passivation during GBR in the anterior maxilla. Four clinical conditions were defined as follows: (i) a shallow vestibule with a healthy periosteum; (ii) a deep vestibule with a healthy periosteum; (iii) a shallow vestibule with a scarred periosteum; and (iv) a deep vestibule with a scarred periosteum. The clinicians emphasized that correct flap design is

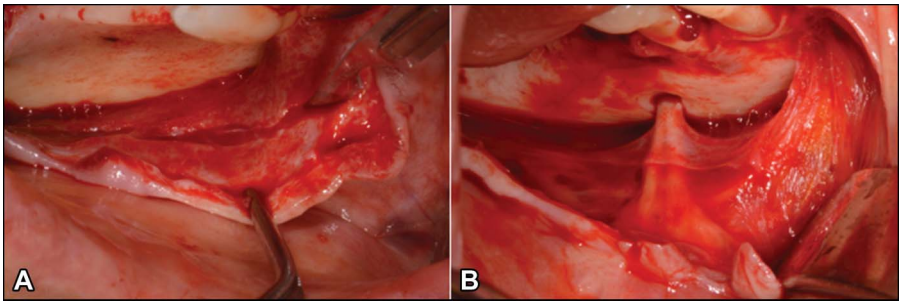

Fig. 5. A, Passivation of the buccal flap: A superficial incision of the periosteum allows to release and to mobilize perfectly the buccal flap in healed sites, while scared sites require a deep dissection. **B**, Periosteal incisions and connective tissue dissection around mental nerve: Isolation and protection of mental nerve is a key factor to avoid neurological damages.

critical when using the above-mentioned surgical techniques (Fig. 5).

Although GBR procedures may be very successful when surgical flap management is good, the scant available data are based on case series, retrospective studies, and a small number of prospective works. Further studies are needed.

Blood Supply

An adequate blood supply is mandatory for bone formation and maturation throughout the specific stages of osteogenesis.[30] To ensure successful GBR, the "PASS" principles, as described by Wang et al,[11] should always be met: primary wound closure (P), angiogenesis (A), space maintenance (S), and stability of the biomaterial (S). A strong relationship is evident between newly formed blood vessels and de novo bone formation.[31] Cortical bone perforation and bone decortication are key features of GBR. These afford communication with the marrow space and allow bleeding into the defect area, enhancing healing both by promoting bleeding and allowing progenitor cells and blood vessels to attain the bone-grafted site more readily.[32] In terms of bone marrow penetration, 2 narrative reviews[30,33] have created controversy regarding whether cortical perforation accelerates or reduces bone regeneration. However, some studies found that bone regeneration can develop even from a nonperforated cortical layer.[34] The literature lacks data on the appropriate diameter of holes made in bone, their spatial configuration, or the extent of the area that should be decorticated in terms of the size of the GBR-treated site. The consensus group opinion, based on available data and personal surgical experience, stressed the importance of an adequate blood supply for the formation of blood clots; the release of growth factors, such as platelet-derived growth factor and bone morphogenetic protein; the diffusion of extracellular nutrients; neoangiogenesis and bone graft revascularization; recruitment of osteoprogenitor cells; and drug delivery.

Implant Surface

Many studies have adduced evidence supporting a positive relationship between the bone-to-implant contact area and surface roughness. Indeed, rougher surfaces (thus, with higher surface areas) afford much better mechanical stability; promote stabilization of blood clots; stimulate differentiation, growth, and attachment of bone cells; and increase mineralization.[53] The bone response was influenced by implant surface topography (the roughness value [Sa]). Smooth (Sa $<$ 0.5 mm) and minimally rough (Sa $=$ 0.5–1 mm) surfaces exhibited weaker bone responses than rougher surfaces. Moderately rough (Sa $=$ 1–2 mm) surfaces were associated with stronger bone responses than were very rough surfaces (Sa $>$ 2 mm).[54] As GBR with simultaneous placement of implants with machined surfaces can trigger formation of a zone of dense connective tissue between the implant and the newly formed bone, the formation of even considerable amounts of bone following vertical ridge augmentation with GBR, and implantation, did not predict implant osseointegration.[55] To enhance osseointegration, a simultaneous approach should always use rough-surfaced implants. Similarly, as newly formed bone is not always well organized or highly mineralized in the augmented areas, it is sensible to place implants with rough surfaces to improve osseointegration and bone-to-implant contact. The working group recognized a possible risk of peri-implantitis attributable to the rough implant surface during long-term follow-up, but further data are needed to discourage the use of such implants in augmented areas.

Timing of Implant Placement

In terms of implantation timing, the systematic review performed by Clementini et al[3] explored the success rates (criteria for which had been previously defined by Albrektsson[50] and adapted by Buser[51]) of immediate and delayed implantation following ridge augmentation. Seven GBR studies were included; the mean success rate of implantation using a simultaneous approach was 87.7% (range 61.5%–100%); similarly, the mean success rate using a staged approach was 86.4% (range 75%–98.3%). In terms of implant survival, similar results were observed (98.9% and 100% for immediate and delayed implants, respectively). As the cited review evaluated only prospective and retrospective studies and as the postloading follow-up was often short, no evidence-based conclusions can be drawn. Thus, the choice of a simultaneous or a staged approach must reflect the preference of the clinician (Fig. 6). Based on the experience of the consensus group, a staged approach affords many advantages: reduction in operative time; no need for primary stability; better vascularization of the bone graft; a more predictable marginal bone level; more prosthetic guidance in terms of implant placement; and the possibility of further bone augmentation using connective tissue. However, a simultaneous approach allows for assessment of native bone; implant-guided bone augmentation; and better stabilization

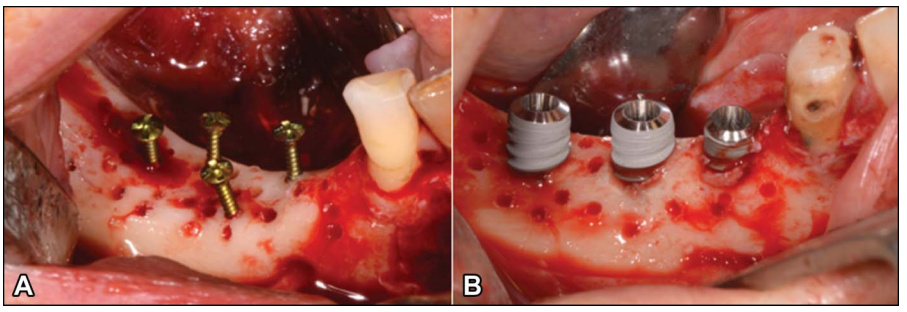

Fig. 6. A, Tenting screws for space-making effect—GBR-delayed approach: The primary aims are to support the membrane, to stabilize the bone graft, and to assess the vertical and horizontal augmentation. **B**, Simultaneous implants—GBR immediate approach: An ideal 3-dimensional implant placement based on a prosthetically guided planning allows to optimize the anatomical profiles of restoration.

of the barrier membrane, bone graft, and blood clots. However, if healing complications occur, use of this approach can lead to lack of bone regeneration around the implant or complete implant failure related to immediate implant placement into avascular bone.[52] Finally, the presence of a bone volume ensuring implant stabilization is critical to the achievement of good primary stability and consequent implant osseointegration.

Barrier Membrane

Rakhmatia[2] indicated that the barrier membrane must have 5 characteristics: biocompatibility, the ability to maintain a space for ingrowth, the capacity to exclude cells, tissue integration, and clinical manageability.[56] Generally, the membranes used in GBR are divided into 2 groups, resorbable and nonresorbable. The biomaterials used all have certain advantages and disadvantages, as discussed in several reviews.[1,2,4,58]

1. Nonresorbable membranes include PTFE, both expanded PTFE (e-PTFE) and high-density PTFE (d-PTFE) membranes. Both membranes can be titanium-reinforced (Ti + e-PTFE and Ti + d-PTFE, respectively). d-PTFE membranes are made from high-density PTFE with a submicron (0–2 μm) pore diameter. Bacterial infiltration into the bone augmentation site is thus eliminated, protecting the underlying graft material and/or the implant. The membrane presents a uniformly flat surface,-minimizing the attachment of cells and fibers. In Ti + PTFE membranes, a titanium frame is trimmed and shaped to create additional space for bone growth, allowing the membrane to be shaped to fit a variety of defects without rebounding, thus affording additional stability in instances of large, non–space-maintaining osseous defects. Titanium reinforcement maintains a large protected space for blood clot formation and bone graft stabilization.[30,47] No clinical or histological differences in terms of vertical bone gain around implants were observed when the GBR procedures featured the use of either e-PTFE or d-PTFE membranes. d-PTFE membranes are easier to remove (and possibly manage), perhaps supporting their use for vertical ridge augmentation of atrophic ridges during GBR. However, further clinical and histological studies are necessary to confirm such findings and to evaluate the long-term results in terms of implant survival and the stability of vertically augmented bone.
2. The most common resorbable membranes are based on collagen, and both native collagen membranes and cross-linked collagen membranes are available. Native collagen membranes are resorbed through enzymatic degradation by collagenases/proteases and enzymes secreted by macrophages/polymorphonuclear leukocytes.[59,61] Although resorbable materials simplify surgical protocols, their unpredictable degradation rates compromise the control of barrier function. If resorption is rapid, the consequential loss of strength renders their space-making and cell-occlusive effects unpredictable. To improve membrane mechanical and biodegradative stability, various cross-linking methods have been introduced.[58] Cross-linked collagen membranes are more stable over time, affording cell-occlusive effects that last longer than those of native collagen membranes. However, the chemical modifications reduce biocompatibility, increasing the risk of postoperative complications.[62] Over the past few years, several studies have shown that it is possible to achieve vertical and/or horizontal bone augmentation using different surgical techniques based on resorbable membranes.[63–67] Merli et al[66–70] reported bone augmentation outcomes after the use of both resorbable and nonresorbable membranes. Both techniques were effective, affording similar vertical bone gains, but both were associated with complications. Moreover, vertically regenerated bone was successfully maintained after functional implant loading.

Although various nonresorbable and resorbable barrier membranes have been developed and extensively investigated, more work is needed to develop the "ideal" membrane for clinical applications. Research should explore the efficacy and efficiency of bone augmentation using different types of membrane. It has been suggested that PTFE membranes should serve as the gold standard when comparing results obtained using new materials.[1,62] The working group suggested that it was important to carefully evaluate the defect type and size when choosing the most appropriate membrane. The authors suggested that resorbable membranes be used for horizontal augmentation and (potentially) vertical augmentation of small defects but that nonresorbable membranes should be used for vertical augmentation of large defects. The benefit/risk ratio and the predictability of the GBR outcome should always be evaluated when choosing the optimal treatment.

Bone Grafting

Autogenous bone (AB) is highly osteogenic and is considered to be the gold standard for use in bone regeneration procedures, providing proteins, bone-enhancing substrates, minerals, and vital bone cells to the recipient site, enhancing the overall process of grafting, and affording high success rates.[71,72] Many authors mix AB with various grafting materials to impart the scaffolding properties of a xenograft to the osteogenic and osteoinductive properties of the autogenous graft; also, bone allografts are an alternative material to improve osteoinductive properties of bone grafts.[30] In terms of xenografts, the most used biomaterial is the deproteinized bovine bone mineral graft (DBBM) that is applied as osteoconductive scaffold enhancing bone tissue repair and growth.

Several studies have sought to define the appropriate mixture for bone grafting: Successful vertical ridge augmentation has been reported when using a 1:1 (wt/wt) combination of DBBM and AB chips and a PTFE membrane.[39,73] Furthermore, the use of AB mixed with DBBM and a natural collagen (resorbable) barrier membrane to treat horizontally deficient alveolar ridges (using a GBR technique) was successful.[40,74] Most studies on lateral and vertical ridge augmentation used bone substitutes either alone or in combination with AB, affording gains in the lateral dimension of 3.6 to 5.6 mm and in the vertical dimension of 2.0 to 5.6 mm.[71] In a more recent review,[5] the authors reported the mean implant survival rates of 97.4% when bone substitutes (bone substitute materials [BSM]) were used, of 98.6% when AB was used, and of 100% when a combination of BSM and AB was used. Meta-analysis was not possible because of interstudy heterogeneity and missing data; the authors concluded that the implant survival rate seemed to be independent of the biomaterial used for ridge augmentation. However, further studies are required.[64,65,75,76] Currently, given the lack of evidence pertaining to the best choice of the bone graft for regeneration of bone defects, the authors recommended the following: when horizontal ridge augmentation is planned, an allograft or xenograft can be used alone without AB, but it should be covered by a cell-occlusive membrane; when vertical ridge augmentation is planned, a xenograft or allograft mixed with AB should be used, in association with a cell-occlusive membrane and a space-maintaining device; generally, autogenous particulate bone should always be used to treat progressively larger defects, especially when the defects and/or patients exhibit reduced osteogenic potential (Fig. 7).[77] There is no clear evidence showing that any specific bone graft combination is superior to others in terms of vertical or horizontal augmentation. To improve decision-making, more randomized controlled studies yielding clinical, radiographic, and histological evidence are required.

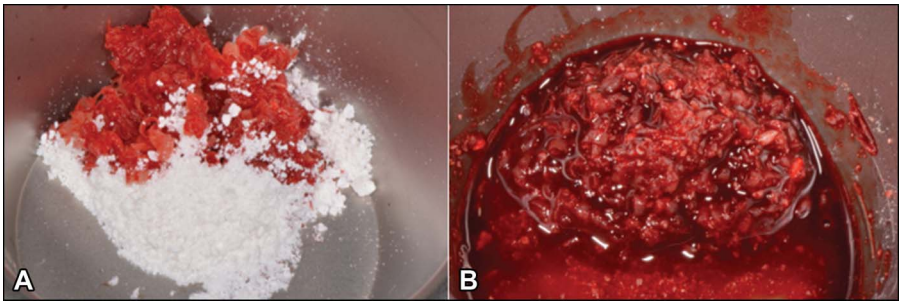

Fig. 7. A, Mixture 50:50 AB and xenograft: If bone allograft is not available, osteogenetic, osteoinductive, and osteoconductive effects can be achieved using the above-mentioned mixed bone graft. **B**, Peripheral venous blood and bone graft: It allows to add in the regeneration space blood cells, nutrients, and drugs, such as antibiotics.

Membrane Fixation

The key to successful regeneration is avoidance of bone graft micromovement by virtue of the stability afforded by the barrier membrane.[11] Adequate stability and minimal stress are required to allow for bone formation, as formation of the new vascular network is highly sensitive to mechanical conditions. It has been shown *in vivo* that new bone formation is more rapid and more organized in rigidly fixed defects featuring plate osteosynthesis, covered with resorbable collagen membranes, than in nonrigidly fixed defects.[57,78] Furthermore, in a randomized controlled trial comparing resorbable with nonresorbable membranes used during GBR to place implants in osseous defects, significant postoperative complications developed when the barrier membranes lacked adequate fixation after initial surgery.[63] There is scant available data, but the tendency revealed by earlier studies and expert opinion favors stabilization of the membrane *per se*; osteosynthesis screws and/or titanium pins should be placed on both the buccal and lingual/palatal sides to fix the barrier membrane and stabilize the graft even if screw or pin removal requires an additional surgical procedure. No information is yet available regarding how new bone develops and matures when various fixation methods are used; future research in human subjects should explore the optimal fixation method for adequate bone regeneration (Fig. 8).

Timing of Membrane Removal

Nonresorbable membranes must remain in place, completely covered by soft tissue, for a period of time sufficient to allow for bone regeneration and maturation, and they then must be removed through a second surgery. Similarly, resorbable membranes must remain submerged during healing before any re-entry surgery. The lack of useful data renders the timing of membrane removal controversial. A

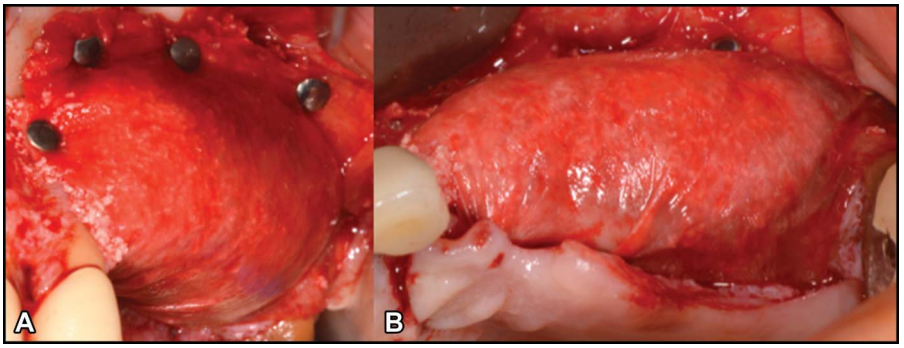

Fig. 8. A and **B**, Fixation of collagen membrane with titanium pins—frontal and lateral view, which shows the vertical regeneration line and distance from the adjacent teeth after fixation and stabilization with titanium tacks. Titanium tacks must seal the regeneration space with a perfect closure of the membrane. Horizontal augmentation overbuilds the alveolar ridge profile.

recent systematic review[6] found that membrane removal should occur 2 to 8 months and 3 to 10 months after horizontal augmentation with simultaneous and nonsimultaneous implant placement, respectively. After vertical augmentation, the healing times were 4 to 12 months and 6 to 12 months, respectively. No specific guidelines were available because of high inter-study heterogeneity. The working group recommended the following: after lateral GBR augmentation, a healing period of at least 6 months seems to be sufficient if BSM with or without AB is used; if simultaneous implants are placed, re-entry surgery can be performed after 4 to 6 months; after vertical GBR augmentation, a healing period of 6 to 12 months is required before membrane removal when either simultaneous or delayed implants are placed. More research is required. Most included studies had limitations; the treatments used different types of nonresorbable membranes and different bone graft materials in several clinical situations. No clear surgical conclusions could be drawn.

Healing Complications

The use of a barrier membrane is a sensitive procedure and is not lacking in complications. In terms of nonresorbable membranes, most reports address complications associated principally with premature exposure of the membrane to the oral environment; this reduces the level of regenerating tissue under the barrier.[6,79,80] Rocchietta et al[79] systematically reviewed vertical ridge augmentations with nonresorbable membranes that encountered various complications (in 0%–45.5% of patients). In terms of clinical practice rather than evidence-based medicine, a recent classification of complications associated with the use of nonresorbable grafts has been described by Fontana et al.[52] Complications occurring during healing are first classified based on their nature and then on the time of membrane exposure and infection status: class I, early exposure with a fenestration smaller than 3 mm, without any purulent exudate; the membrane should not be removed immediately but rather left in place for a maximum of 1 month with topical application of 0.2% (wt/vol) chlorhexidine gel twice daily and careful follow-up; class II, early exposure with a fenestration larger than 3 mm, without any purulent exudate; the membrane must be immediately removed to avoid any interference with the healing process, even if, in most patients, the underlying bone is not compromised; class III, early exposure associated with a purulent exudate; the membrane must be removed immediately and the underlying infected particles and inflammatory tissue curetted; and class IV: formation of an abscess in the regenerative area without exposure of the membrane; membrane removal is required immediately, with curettage of the graft and local antibiotic washing.

All complications developing after 3 months are considered to reflect late exposure and, despite the absence of infection, the membrane must be removed immediately. However, the classification refers to situations where e-PTFE membranes are used; d-PTFE membranes may require different management if healing complications develop.[52] The working group supported this classification and management of healing complications after GBR using nonresorbable membranes. Similar approaches could be used to evaluate and treat complications developing after GBR using titanium meshes or resorbable membranes (Fig. 9).

Soft-Tissue Management

A matter of concern in implant dentistry is the role played by keratinized tissue (KT) and the influence thereof on periimplant tissue health. It has been shown that reduced alveolar bone height will result in loss of KT because of the shorter distance between the mucogingival line and the bone crest.[81] Wennstrom et al[82] explored whether KT was required to maintain periimplant tissue stability and health. The available data do not indicate any correlation between the lack of an "adequate" KT dimension and a higher plaque score or a higher gingival inflammation score. The evidence suggests that, with good oral hygiene, periimplant soft-tissue health can be maintained irrespective of the presence/absence of keratinized mucosa around the implant. Ultimately, owing to the lack of available data and methodological limitations, no conclusion can be drawn about the association between the amount (or presence) of KT and changes in marginal bone levels or implant loss.[63–64]

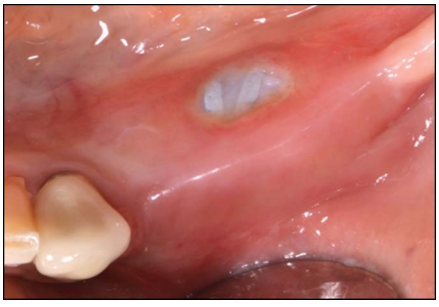

Fig. 9. Late exposure of PTFE membrane without suppuration—Class II: Clinical view shows no infection or soft-tissue inflammation. It is recommended to check the exposure every week until 6 to 9 months, if possible.

Despite the lack of evidence for any correlation between the amount of KT and marginal bone loss, some studies found that KT thickness and width played roles during the establishment of the required biological dimensions of the soft-tissue barrier during the first 6 to 12 months after implant restoration.[85,86] In addition, Lutz et al[7] reported on studies exploring the relationship between the position of the soft-tissue margin and the level of the crestal bone after GBR procedures; these confirmed the maintenance of the soft-tissue profile over time.[87,88]

Basically, several different methods can be used to improve soft tissues around implants: an apically positioned flap plus a free gingival graft and a connective tissue graft (CTG); a coronally advanced flap plus a CTG; and collagen matrices with apical or coronal flaps.[89–92] The surgical technique used and the treatment timing depend on various factors, such as the anatomical area, the gingival biotype, and/or esthetic expectations.[93]

Given the suggested advantages afforded by "adequate" periimplant soft tissue, the consensus group recommends that the KT width should be > 2 mm around implants placed in augmented sites to (i) prevent early

marginal bone loss, (ii) facilitate oral hygiene procedures, and (iii) improve plaque and gingival inflammation scores over time. Both medium- and long-term (5–10-year) studies are needed to explore the effects of soft-tissue augmentation on the stability of periimplant soft and hard tissues as well as on esthetic- and patient-related outcomes.

GBR to Treat Scarred Sites

Fibrous scars and soft-tissue defects may be caused by previous surgical attempts or implant failures. Such conditions require careful management during GBR procedures to avoid further failure caused by early exposure or infection. Recently, Urban et al[49] developed a classification based on 4 clinical scenarios and proposed different techniques for the management of surgical flaps. The classification considers the depth of the vestibule (deep/shallow) and the integrity of the periosteum (native/scarred). The authors suggested that, depending on the soft-tissue type, the following procedures might be appropriate: remote or safety flap placement; periosteal incision; separation of elastic fibers; periosteoplasty; muscle-releasing incision; papillary shifting; and double-layer suturing.

GBR to Treat Esthetic Sites

The greatest challenge in the esthetic area is to establish harmony, balance, and continuity of the soft tissue between implants and the adjacent natural teeth. All GBR procedures change the soft-tissue relationships, and achievement of optimal esthetics is very challenging. Many authors have proposed various protocols for the surgical management of bone defects in the anterior maxilla or mandible.[94–98] To overcome the drawbacks of bone augmentation, such as loss of vestibular depth, reduction in KT, and gingival scarring, flap design should be first based on the bone defect and soft-tissue conditions, and a soft-tissue graft should be placed to create a positive gingival architecture between implants.[99] Given the absence of evidence-based data, the working group suggests the use of the following protocol to reduce the risk of failure and to optimize the esthetic outcomes: GBR employing resorbable membranes should be used for horizontal augmentation of small defects; GBR employing nonresorbable membranes or titanium meshes should be used for horizontal augmentation of large defects and for vertical augmentation; staged implant placement and submerged implant healing with soft-tissue augmentation; reentry surgery with or without soft-tissue augmentation and esthetic periimplant plastic surgery (Fig. 10).

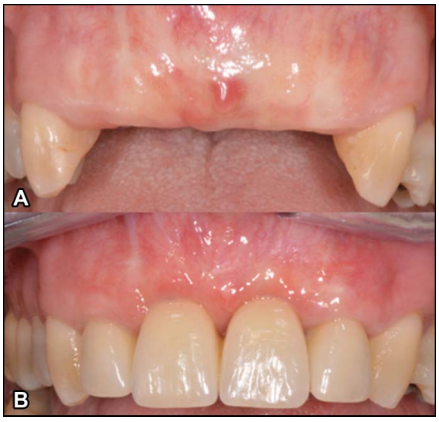

Fig. 10. A, Vertical and horizontal bone augmentation in the esthetic area—soft-tissue healing: The vertical regeneration line is perfectly straight. The mucogingival junction appears normal and papilla levels seem to be perfectly maintained. **B**, Implant-prosthetic rehabilitation in the esthetic area—definitive restoration: Prosthetic restoration must combine (i) a conditioning of the soft tissues, (ii) anatomical profiles, and (iii) a functional occlusion.

CONCLUSIONS

GBR is a predictable technique for bone augmentation. It allows for the correction of vertical and horizontal defects, ensuring an adequate bone volume for osseointegrated implants. Clinicians should always consider the key factors for success in GBR, including patient and defect analysis, blood supply, flap passivation, membrane fixation, and primary closure. The timing of healing should always be greater than 6 months, and 9 months for healing is recommended for severe defects. Soft-tissue management seems to be another important factor for long-term success. Esthetic sites and scarred sites require more experience and more surgical skill because of the higher risk of failure.

DISCLOSURE

The authors claim to have no financial interest, either directly or indirectly, in the products or information listed in the paper.

APPROVAL

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ROLES/CONTRIBUTIONS BY AUTHORS

A. Cucchi: Director of consensus meeting, speaker about "Rational choice between short implants and different surgical technique of vertical bone regeneration," property of images, manuscript preparation, manuscript editing, and revision. A. Chierico: Speaker about "Rational choice between short implants and different surgical technique of vertical bone regeneration," manuscript preparation, and manuscript editing. F. Fontana: Speaker about "Classification and management of complications in guided bone regeneration" and manuscript editing. F. Mazzocco: Speaker about "Solution for simplification of regenerative procedures" and manuscript editing. C. Cinquegrana: Systematic revision of reviews, manuscript preparation, and manuscript editing. F. Belleggia: Speaker about "Influencing key factors for choice of biomaterials and protocols for management of expositions." P. Rossetti: Speaker about "Advantages and disadvantages of GBR for dental office." C. Maria Soardi: Speaker about "Guided bone regeneration as mini-invasive surgery." M. Todisco: Speaker about "Guided bone regeneration to achieve function and esthetics." R. Luongo: Speaker about "Alveolar ridge preservation and augmentation." L. Signorini: Speaker about "Bone regeneration of the posterior maxilla: GBR or MSL?". M. Ronda: Speaker

about "Long-term prognosis of implants placed in vertically augmented bone." R. Pistilli: Speaker about "The role of maxilla-facial surgeon in the reconstruction of atrophic jaws," manuscript editing, and revision.

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