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Invited Review

Guided Bone Regeneration: biological principle and therapeutic applications

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Abstract

The Guided Bone Regeneration (GBR) treatment concept advocates that regeneration of osseous defects is predictably attainable via the application of occlusive membranes, which mechanically exclude non-osteogenic cell populations from the surrounding soft tissues, thereby allowing osteogenic cell populations originating from the parent bone to inhabit the osseous wound. The present review discusses the evolution of the GBR biological rationale and therapeutic concept over the last two decades. Further, an overview of the GBR research history is provided with specific focus on the evidence available on its effectiveness and predictability in promoting the regeneration of critical size cranio-maxillo-facial defects, the neo-osteogenesis potential and the reconstruction of atrophic alveolar ridges before, or in conjunction with, the placement of dental implants. The authors conclude that future research should focus on (a) the investigation of the molecular mechanisms underlying the wound healing process following GBR application; (b) the identification of site and patient related factors which impact on the effectiveness and predictability of GBR therapy and (c) the evaluation of the pathophysiology of the GBR healing process in the presence of systemic conditions potentially affecting the skeletal system.

Guided bone regeneration (GBR) was introduced as a therapeutic modality aiming to achieve bone regeneration, via the use of barrier membranes (Dahlin et al. 1988). The concept of creating a secluded anatomic site with the aim to promote healing was first introduced 50 years ago, when cellulose acetate filters were experimentally used for the regeneration of nerves and tendons (Bassett et al. 1956; Ashley et al. 1959). Murray et al. (1957) reported new bone formation beneath plastic cages adapted over decorticated femoral defects in the dog. Subsequent animal studies reported enhanced osseous healing of rib, radial bone and femoral bone defects via the application of cellulose acetate and Millipore filters (Hurley et al. 1959; Rüedi & Bassett 1967). In the craniofacial region, successful results have also been reported following the placement of mechanical barriers over jawbone defects in rabbits (Kahnberg 1979) and over cranial defects in rats (Melcher 1969). These experimental studies provided significant evidence that bone regeneration is significantly enhanced when the invasion of soft tissue into osseous defects is mechanically impeded. However, in these early studies, most authors attributed the success of the barriers to the preservation and protection of the blood clot rather than to the colonisation of the secluded space created by osteogenic cell populations.

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In the mid 1980s, the Guided Tissue Regeneration (GTR) principle was introduced, according to which, regeneration of a certain type of tissue is achieved when cells with the capacity to regenerate the particular type of lost tissue are allowed to populate the defect during healing (Nyman et al. 1982; Gottlow et al. 1984). The GBR treatment concept was developed on the basis of the GTR principle. Hence, the GBR biological rationale advocated the mechanical exclusion of undesirable soft tissues from growing into the osseous defect, thereby allowing only osteogenic cell populations derived from the parent bone to repopulate the osseous wound space (Dahlin et al. 1988; Hämmerle et al. 1995).

The scope of this narrative review is to present the evolution of the GBR treatment principle over the last 22 years and the evidence on the GBR effectiveness and on the predictability of its various therapeutic applications.

GBR therapeutic protocol

The GBR therapeutic protocol involves surgical placement of a cell occlusive membrane facing the bone surface, in order to physically seal off the skeletal site in need for regeneration (Dahlin et al. 1988). Furthermore, the membrane creates and maintains a secluded space, thus providing an environment to the osteoprogenitor cells, which is permissive for recruitment and proliferation of osteoprogenitor cells, differentiation along the osteoblastic lineage and expression of osteogenic activity (Linde et al. 1993; Karring et al. 1993).

Various non-resorbable and resorbable membrane materials have been used in experimental and clinical studies in the context of GBR treatment. The desirable characteristics of barrier membranes utilised for GBR therapy include biocompatibility, cell occlusion properties, integration by the host tissues, clinical manageability and space making ability (Karring et al. 1993). Expanded polytetrafluorothylene (e-PTFE) has been the most frequently used material for periodontal and bone regeneration. e-PTFE is a chemically stable and biologically inert polymer, featuring a porous structure and flexible form. It resists microbiological and enzymatic degradation and does not elicit immunologic reactions (Becmeur et al. 1990). e-PTFE membranes have been widely applied in periodontal and bone regeneration, because it was documented that their use predictably leads to successful GBR treatment results (Hämmerle & Jung 2003).

The non-degradable barrier membranes do not undergo solubilisation when placed in the living body, hence they require a second surgical intervention in order to be removed. This disadvantage led to the development of biodegradable membrane devices. Several biodegradable materials have been tested with varying success in periodontal and/or bone regeneration, including collagen type I, polyurethane, polyglactin 910, polylactic acid, polyglycolic acid, polyorthoester and different copolymers of polylactic and polygalactic acid (Sandberg et al. 1993; Zellin et al. 1995; Brunel et al. 1998). When inserted in an aqueous environment, such as a biological system, the biodegradable polymers undergo four stages of degradation, namely hydration, strength loss, loss of mass integrity and solubilisation via phagocytosis. The time length of each stage and the overall degradation rate depend on the nature of the polymer, the pH, the temperature, the polymer crystallisation degree and the membrane volume (Warrer et al. 1992; Hämmerle & Jung 2003). It may be therefore concluded that the barrier function duration is not strictly controlled and that the resorption process may possibly interfere with the wound healing and bone regeneration process. Therefore, although the launch of bioresorbable membranes eliminated the need for membrane removal surgery, thus simplifying the surgical protocols and improving the cost-effectiveness, it has been suggested that the e-PTFE membranes should serve as the gold standard for comparing the results obtained via the use of new materials (Hämmerle & Jung 2003).

Treatment of critical size osseous defects

Maxillofacial defects

Dahlin et al. (1988) were the first to apply the GBR principle for the treatment of standardised, 5 mm in diameter, transmandibular defects in rats. Six weeks postoperatively, the test sites, which had been covered with expanded e-PTFE membranes, had healed completely with bone, whereas the sham-operated controls presented fibrous tissue non-union, due to connective and/or muscular tissue invasion in the wound area. In a subsequent experimental study, a similar model of mandibular critical size defects in rats was used in order to evaluate the GBR treatment efficacy following application of resorbable membranes. The authors reported gradual regeneration of the mandibular bone from 15 to 180 days postoperatively, whereas new bone formation in the non-GBR-treated control sites ceased after 1 month of healing (Kostopoulos et al. 1994). The efficacy of the application of either non-resorbable or resorbable barrier membranes for the treatment of critical size maxillary and mandibular defects has been further documented in various experimental models in rats (Sandberg et al. 1993; Bartee & Carr 1995; Zellin et al. 1995; Matzen et al. 1996; Zahedi et al. 1998; Ohnishi et al. 2000), rabbits (Mundell et al. 1993; Mooney et al. 1996; Lundgren et al. 1998), dogs (Schenk et al. 1994; Simion et al. 1999) and monkeys (Dahlin et al. 1990).

Calvarial defects

A further series of animal experimentation studies have provided evidence that GBR treatment predictably ensures bone regeneration in critical size osseous defects in the calvarial bones in rats (Bosch et al. 1995; Donos et al. 2004), rabbits (Hämmerle et al. 1992; Hämmerle et al. 1995; Marouf & El Guindi 2000) and monkeys (Petit & Ripamonti 1994) (Fig. 1). Complete bone regeneration of calvarial defects is predictably achieved via double membrane placement covering both the inner and the outer aspect of the defect (Lundgren et al. 1992; Bosch et al. 1995). On the contrary, incomplete occlusion of the surrounding intracranial (dura) and extracranial soft tissues has been associated with impaired bone formation (Verna et al. 2002). Furthermore, collapse of the membrane into the osseous defect leads to diminished space availability for bone regeneration, thus limiting the amount of new bone formation (Lundgren et al. 1998; Wiltfang et al. 1998).

In summary, bone regeneration occurs predictably following GBR application in

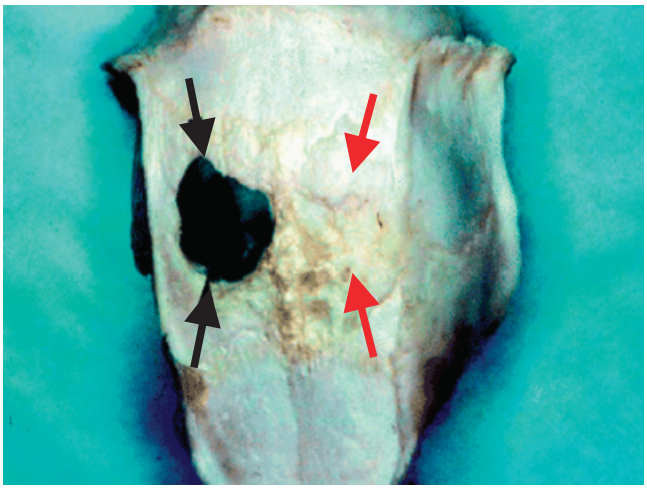

Fig. 1. Healing of GBR and non-GBR treated, critical size, rat calvarial defects following a healing period of 4 months. The left defect (untreated control; black arrows) demonstrates that only minimal healing has occurred. The right defect (red arrows) was treated by GBR using intracranially and extracranially placed occlusive membranes, thus leading to complete regeneration (modified by Donos et al. 2004).

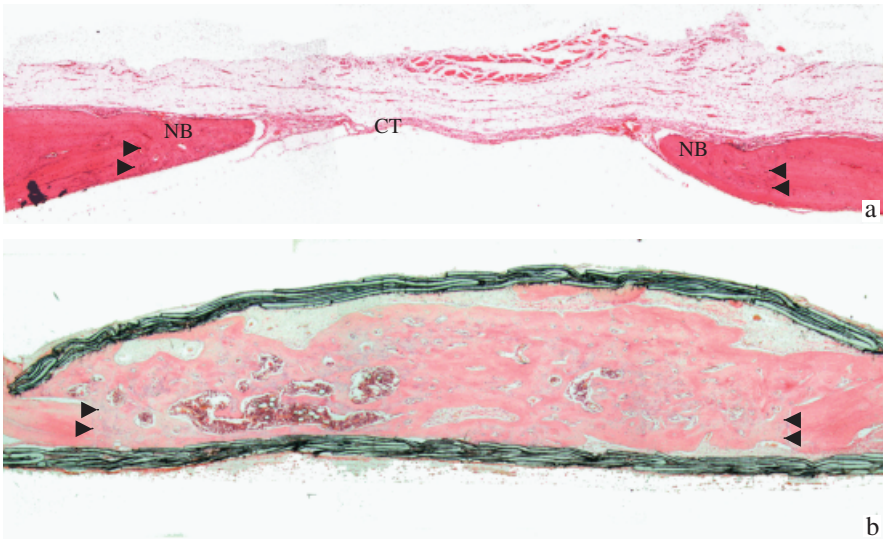

Fig. 2. Photomicrographs of non-GBR and GBR-treated critical size calvarial defects at 60 days of healing. (a) non-GBR-treated specimen. Minimal apposition of new bone adjacent to the original defect borders is observed. The major part of the defect is occupied by dense connective tissue with collagen fibres orientated parallely to the long axis of the defect. (b) GBR-treated specimens. Complete osseous union has occurred; the newly formed bone has largely remodelled into lamellar bone especially at the peripheral areas of the defect. The original defect borders are demarcated by the black arrowheads. NB, new bone; CT, connective tissue. Original magnification × 100. Stained with H&E. (Retzepi 2009).

critical size maxillofacial and calvarial defects. This is achieved via a standard, basic pattern of bone formation process, which resembles closely bone development and growth during intramembranous ossification (Schenk et al. 1994; Retzepi 2009) (Fig. 2).

Neo-osteogenesis

A series of animal studies have demonstrated that neo-osteogenesis, i.e. *de novo* bone formation beyond the genetically determined skeletal envelope, can be predictably achieved via application of the GBR principle. Schmid et al. (1991) reported substantial new bone formation under a titanium mesh covered with e-PTFE membrane, securely adapted over the rabbit calvarium. Further studies have demonstrated significant neogenetic bone formation beyond the anatomic skeletal borders, in the secluded space created via "dome" or "capsule" shaped membrane barriers fixed on the calvarial bone (Linde et al. 1993; Lundgren et al. 1995; Zellin & Linde 1996; Hämmerle et al. 1997), the tibia (Hjörting-Hansen et al. 1995) and the mandibular ramus (Kostopoulos et al. 1994; Kostopoulos & Karring 1994; Donos et al. 2005a). Experimental neogenetic bone formation has been predictably achieved via application of a wide variety of barrier materials, including e-PTFE capsules (Kostopoulos et al. 1994; Kostopoulos & Karring 1994; Mardas et al. 2003), e-PTFE membranes supported by a titanium framework (Hjörting-Hansen et al. 1995), titanium domes (Lundgren et al. 1995; Slotte & Lundgren 2002), resorbable domes made of polylactic acid (Hämmerle et al. 1997; Schmid et al. 1997) and silicone domes (Slotte & Lundgren 1999).

The healing period following GBR application is a critical factor affecting the amount of experimental neogenetic bone formation. Kostopoulos et al. (1994) demonstrated augmentation of the mandibular bone beyond its original anatomic borders leading to a five to sixfold increase of the mandibular ramus width after 120 days of healing, following the application of hemispherical Teflon capsules adapted over the lateral surface of the mandible. The authors further reported that significant augmentation of the mandibular bone occurred gradually from 7 to 60 days, whereas limited further increase was observed from 60 to 120 days of healing. A subsequent study using the same experimental model demonstrated that the newly formed bone beyond the skeletal envelope remained stable in the long-term following removal of the GBR device (Lioubavina et al. 1999).

It is well established that the structural integrity of the barrier material and the sufficient adaptability of its borders to the parent bone constitute prerequisites for predictable new bone formation via GTR, in order to ensure occlusiveness against cellular invasion (Kostopoulos & Karring 1994). It has been however suggested that the application of barrier materials with increased porosity may enhance neogenetic bone formation via GTR (Linde et al. 1993) On the contrary, Schmid et al. (1994) suggested that membrane permeability does not constitute a prerequisite for guided bone formation, based on observations of

neogenetic bone generated after 8 months of healing in secluded chambers on the rabbit calvarium, irrespective of whether the chambers were sealed off by cast titanium or e-PTFE membranes. Zellin & Linde (1996) and Lundgren et al. (1998) reported however, that the placement of barriers with a porosity >25 μm, significantly enhanced new bone formation during the initial healing period, compared with non-porous barriers or membranes with reduced porosity. However, after 12 weeks of healing, similar amounts of neogenetic bone were observed in all types of barrier membranes and, as such, the authors concluded that increased barrier porosity may promote the early osteogenic rate, but not the final amount of neogenetic bone formed. Finally, Rompen et al. (1999) provided evidence that perforations of the cortical bone, which allowed bleeding from the marrow spaces, in combination with peripheral blood delivery in the secluded space may also promote significantly neogenetic bone formation via GBR.

Hämmerle et al. (1996) provided evidence that production of significant amounts of new bone beyond the genetically determined skeletal borders is feasible via GBR application in humans. The experimental protocol was designed with a view to obtain specimens of both regenerated and newly formed mandibular bone. The authors placed hollow titanium cylinders covered with e-PTFE membranes in the retromolar areas of healthy volunteers. The titanium devices were partly submerged by 1.5–2 mm in the jawbone, whereas the remaining 2–2.5 mm surpassed the level of the mandibular border. The specimens harvested following <3 months of healing were almost entirely composed of soft tissue. After 4 months of healing however, increasing amounts of mineralised tissue were observed. New bone formation beyond the skeletal border occurred after a healing period of 6 months, thereby altering the genetically determined original mandible configuration of the mandibular bone.

Socket preservation

The application of GBR has been advocated for the promotion of new bone formation and for the preservation of the volume and contour of the alveolar ridge following tooth extraction.

Lekovic et al. (1997) demonstrated that the application of non-resorbable membranes in fresh extraction sites significantly promoted vertical bone fill and reduced vertical bone height loss. The same research group reported similar results following the application of resorbable polylactide–polyglycolide membranes in extraction sites, with the additional benefit of reduced risk of infectious complications due to membrane exposure. Vance et al. (2004) also reported that the application of resorbable barriers without bone grafting procedures can reduce alveolar ridge resorption following tooth extraction.

Several studies provided histological evidence of new bone formation in extraction sockets following application of barrier membranes in combination with bone grafts of allogeneic (Brugnami et al. 1996; Smukler et al. 1999) and xenogeneic (Carmagnola et al. 2003; Molly et al. 2008) origin. In a randomised-controlled clinical study, Iasella et al. (2003) demonstrated that the application of collagen barrier membranes with freeze-dried bone allograft (FDBA) was associated with significantly reduced post-extraction resorption compared with unaugmented socket sites. Another recent randomised-controlled clinical trial indicated that the application of porcine cortico-cancellous bone in combination with collagen membranes was associated with significantly reduced horizontal absorption and with less vertical bone height loss compared to non-GBR-treated alveolar sockets (Barone et al. 2008). Froum et al. (2004) reported that the application of acellular dermal matrix was associated with reduced rate of infectious complications related to membrane exposure compared with e-PTFE application in combination with hydroxyapatite or inorganic bovine bone mineral for socket preservation purposes. However, in a more recent clinical and histological trial, Fotek et al. (2009) reported similar results following either e-PTFE or acellular dermal matrix application in combination with mineralised bone allograft, in spite of the more frequently observed premature exfoliation of the e-PTFE membranes.

In conclusion, the application of the GBR principle can significantly reduce the loss of alveolar bone volume in extraction sites. It should be noted however, that the available evidence supports the use of membranes alone or in conjunction with bone grafting materials for socket preservation purposes, but not the mere application of bone grafting materials, as they may actually interfere with the normal osseous healing process (Becker et al. 1998).

Alveolar ridge augmentation before implant placement

GBR has been experimentally applied for regeneration of alveolar ridge defects before implant placement. Seibert & Nyman (1990) demonstrated successful reconstruction of surgically created bucco-lingual defects in the alveolar ridge of dogs after 90 days of healing, with newly formed bone filling the space created by Teflon barrier membranes. Furthermore, Smukler et al. (1995) reported that the application of barrier membranes in Class III ridge defects led to a mean augmentation by 3.31 mm. In a different experimental setting, Buser et al. (1995) placed non-submerged implants in mandibular bone, which had been regenerated via membrane placement 6 months earlier. Based on histological analysis, the investigators reported that the placement of titanium implants stimulated the maturation and preservation of the regenerated mandibular bone.

Several case reports and clinical studies provided evidence on the potential of GBR treatment to augment atrophic alveolar ridges before implant placement in humans (Nyman et al. 1990; Buser et al. 1995) and on the long-term stability of the results achieved (Buser et al. 1996). Buser et al. (1990) reported a mean gain of 1.5–5.5 mm in new bone formation 6–10 months following GBR application. Lang et al. (1994) performed a retrospective clinical study, with the aim to assess the efficacy of non-resorbable barrier membranes in reconstructing deficient alveolar ridges of various configurations. Re-entry procedures performed following 6–8 months of healing, demonstrated that the regenerated alveolar bone filled 90–100% of the maximum volume of the available space for regeneration. However, in cases where the occurrence of complications related to membrane exposure or infection mandated earlier membrane removal, the new bone formation potential was significantly compromised. A recent systematic review

reported that the success rate of GBR application for staged lateral ridge augmentation, measured as the achievement of adequate ridge dimensions for implant placement, ranged from 87% to 95% during an observation period of 22.4 months to 5 years post-loading (Donos et al. 2008).

Immediate implant placement in fresh extraction sockets

Warrer et al. (1991) demonstrated histologically that GBR treatment via application of non-resorbable e-PTFE membranes around implants placed immediately in fresh extraction sockets promoted peri-implant bone regeneration and osseointegration, compared with the non-GBR-treated control sites in monkeys. These preliminary results were supported by a similar experimental study using e-PTFE membranes in implants immediately placed in fresh extraction sockets in dogs (Gotfredsen et al. 1993) and confirmed by subsequent *in vivo* studies utilising biodegradable membranes (Brunel et al. 1998).

A series of clinical studies have documented that non-resorbable and resorbable barrier membranes alone (Nyman et al. 1990; Lang et al. 1994; Hämmerle & Karring 1998) or in combination with allografts (Rosen & Reynolds 2001; Fugazzotto 2006) or xenografts (Hämmerle & Lang 2001; Juodzbalys et al. 2007) can be successfully applied in combination with two- or one-stage implants placed in fresh extraction sockets and promote new bone formation and bone to implant contact. A prospective multicenter clinical study demonstrated significantly more bone formation in sites, where immediate implant placement was combined with uncomplicated application of membranes, compared with sites, which necessitated early membrane removal (Becker et al. 1994). A randomised-controlled clinical trial by Chen et al. (2005) has indicated that the application of occlusive membranes around immediately placed, transmucosal implants in maxillary anterior extraction sites, which presented dehiscence defects, was associated with significantly reduced horizontal resorption of the buccal bony plate compared with the non-GBR-treated controls (66.6% vs. 37.7%). The clinical data are in accordance with histological reports indicating that the use of either non-resorbable or resorbable membranes in humans promoted bone regeneration and osseointegration of immediately placed implants (Simion et al. 1996). Furthermore, two randomised-controlled clinical trials have provided results favouring the combined application of resorbable membranes and xenografts compared with the application of membranes only for the promotion of peri-implant bone formation around implants placed in fresh extraction sockets (Cornelini et al. 2004; Chen et al. 2007).

Alveolar ridge width augmentation in combination with implant placement

Dahlin et al. (1989) were the first to provide evidence to support the effectiveness of GBR in promoting peri-implant bone formation, following application of e-PTFE membranes around exposed threads of implants inserted in rabbit tibiae. Becker & Becker (1990) also conducted a histological study, which assessed the GBR potential to treat exposed threads of implants placed in dog mandibles. They reported a mean increase of 1.37 mm in bone height for the GBR-treated test sites, vs. 0.23 mm for the sham operated controls.

A controlled clinical study confirmed that GBR treatment can be used for the reconstruction of peri-implant osseous defects, as evidenced by significant new bone formation in fenestration sites treated with e-PTFE membranes compared with non-treated controls (Dahlin et al. 1991). Further case series (Jovanovic et al. 1992; Lundgren et al. 1994; Dahlin et al. 1995; Simion et al. 1996; Mayfield et al. 1997; Lorenzoni et al. 2002) and controlled clinical studies (Mayfield et al. 1998; Zitzmann et al. 2001) documented clinically, radiographically and histologically that the GBR procedure may successfully promote bone formation in dehiscences and fenestrations around one and two-stage implants. However, most of the above studies reported that early exposure of the barriers correlated with compromised potential of the GBR treatment to regenerate peri-implant bone defects. In a recent systematic review, Chiapasco & Zaniboni (2009) reported that in 20% of the cases of GBR application for the treatment of dehiscences and fenestrations, e-PTFE membranes presented early exposure and/or infectious complications. However, 63–100% of defect coverage was achieved in spite of the e-PTFE membrane exposure. In the case of collagen and polylactic-polyglycolic acid biodegradable membranes, acceptable coverage of the initial defects occurred in the majority of the cases reported by the reviewed studies and, on average, 95% coverage of the initial defect was achieved.

Overall, there are no randomised-controlled clinical trials providing direct evidence that the application of GBR therapeutic modalities for the treatment of peri-implant dehiscences and fenestrations promotes the implant survival rate or success rate (Esposito et al. 2008). Two systematic reviews have reported that the survival rates of GBR-treated implants amounted to 95.5% (Aghaloo & Moy 2008) and 95.7% (Chiapasco & Zaniboni 2009). It should be noted however that no distinction between studies reporting on immediate or delayed implant placement was made in these systematic reviews. Further, Chiapasco & Zaniboni (2009) reported that the success rate of GBR-treated implants has been interrogated in only two studies and amounted to 96.1% (Blanco et al. 2005) and 90% (Juodzbalys et al. 2007), according to the criteria by Albrektsson et al. (1986). A systematic review by Donos et al. (2008) investigated the success rate of the GBR procedure for lateral ridge augmentation and reported that the GBR success rate expressed as complete coverage of the exposed implant surface ranged from 71.4 % to 100% for observation periods ranging from 12 months to 5 years.

Alveolar ridge height augmentation in combination with implant placement

Kostopoulos & Karring (1994) demonstrated histologically a significant increase of the mandibular height in rats, 6 months following application of resorbable membranes closely adapted to the inferior border of the rat mandible and supported via titanium microimplants. These observations are in accordance with a recent study utilising the rat model, which reported a significant increase of the vertical height beyond the genetically determined mandibular envelope following application of titanium reinforced e-PTFE membranes in combination with rough surface titanium microimplants (Retzepi et al. 2010) (Fig. 3). A series of *in vivo* studies in the rat model have also reported increased vertical height

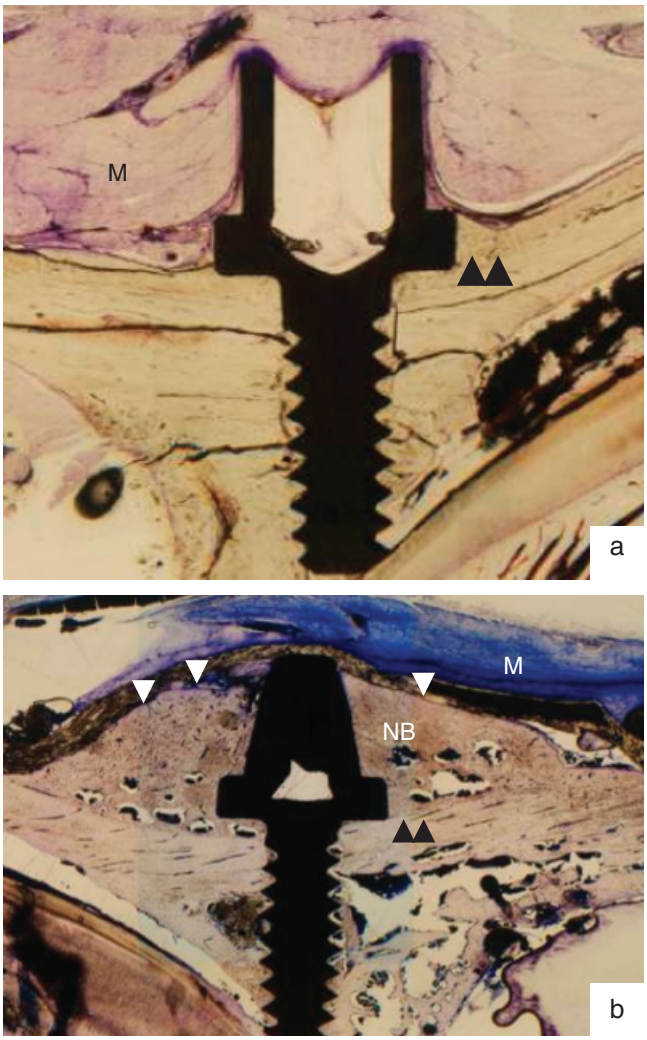

Fig. 3. De novo bone formation on the rat mandible following guided bone regeneration (GBR) application in combination with microimplant placement following a healing period of 90 days. (a) Microphotograph of non-GBR-treated control site. Direct bone-to-implant contact is observed between the mandibular bone and the threaded part of the microimplant. Limited new bone formation is evident adjacent to the stopper ring of the implant (black arrowheads). The non-threaded part of the microimplant is surrounded by muscular (M) tissue; (b) microphotograph of GBR-treated test site. The space outlined by the implant surface, the membrane (white arrowheads) and the original inferior mandibular border (black arrowheads) is completely filled with newly formed bone (NB). The non-threaded implant surface is osseointegrated with the newly formed bone. Original magnification × 40. Stained with toluidine blue (Retzepi et al. 2010).

of mandibular bone following combined application of e-PTFE membranes, titanium microimplants and autogenous ischiac (Donos et al. 2002a, 2005b) or mandibular bone grafts (Donos et al. 2002b), as well as following combined treatment with resorbable membranes, microimplants and autogenous ischiac bone grafts (Donos et al. 2002c).

Alveolar ridge height augmentation in combination with implant placement has also been documented in preclinical studies using larger animal models. Jovanovic & Nevins (1995) reported vertical augmentation of the mandibular process via application of e-PTFE membranes around supracrestally placed implants in dogs. Supracrestal new bone formation amounted to 1.82 ± 1.04 and 1.9 ± 0.3 mm following use of titanium re-inforced and standard e-PTFE membranes respectively. Subsequent *in vivo* studies in the dog model reported a mean vertical gain of 1.91–3 mm in the mandibular bone of dogs following combined placement of titanium reinforced e-PTFE membranes with autogenously or allergenic bone (Jensen et al. 1995; Renvert et al. 1996).

Simion et al. (1994) provided clinical evidence on the effectiveness of the GBR technique in promoting bone augmentation in non-space maintaining vertical defects with simultaneous implant placement. They reported that the histological mean gain in bone height was 4 mm, whereas the direct contact between the regenerated bone and the implant surface averaged 45% after 9 months of healing following titanium reinforced e-PTFE membrane application. Subsequent clinical and histological studies supported that vertical ridge augmentation in conjunction with implant placement can be achieved via the use of e-PTFE membranes combined with autologous bone chips or DFDBA (Tinti & Parma-Benfenati 1998; Parma-Benfenati et al. 1999; Simion et al. 2007).

An initial systematic review on available clinical studies has concluded that GBR procedures can be successful in attaining vertical augmentation of the alveolar ridge (Esposito et al. 2006). Rocchietta et al. (2008) recently performed a systematic review of studies reporting on the GBR efficiency in vertical bone augmentation. The review identified only two randomised-controlled clinical trials (Chiapasco et al. 2004; Merli et al. 2006) and two case series studies (Parma-Benfenati et al. 1999; Simion et al. 2007), whereby the treatment included the application of titanium reinforced e-PTFE membranes or osteosynthesis plates covered by resorbable membranes, in combination with autogenous bone particles alone or mixed with allogeneic bone graft. When case studies were also included in the outcome report, the authors suggested that the vertical bone gain varied from 2 to 8 mm in the various studies, although no meta-analysis was performed. It should be further noted that the complications rate varied significantly rising up to 45.5%.

In conclusion, although there is histological evidence supporting the ability of the GBR principle in promoting vertical bone augmentation in combination with implant placement, the available clinical research on the predictability of the technique is limited at present.

Conclusions

GBR can predictably lead to regeneration of critical size maxillofacial and calvarial defects and to *de novo* bone formation via a synchronised progression of events

recapitulating intramembranous ossification. In addition, the available preclinical and clinical evidence suggests that GBR constitutes a successful therapeutic approach for the treatment of peri-implant bone defects and for the preservation of the dimensions and the configuration of the alveolar socket following tooth extraction. Furthermore, lateral and vertical bone augmentation of atrophic alveolar ridges before or in conjunction with implant placement can be achieved via GBR application, albeit with varying degrees of success.

Carefully designed clinical studies with sufficient statistical power would be instrumental in elucidating the impact of site and patient related factors on the effectiveness and predictability of the GBR treatment. Ultimately, the goal would be to optimise the case selection process and to introduce guidelines in terms of developing the GBR therapeutic protocol. Furthermore, preclinical and clinical trials investigating the physiology and pathophysiology of the healing process following GBR application at the molecular level are warranted, with a view to develop and implement novel therapeutic strategies, e.g. tissue engineering, drug delivery and/or gene therapy aiming to promote the bone formation and regeneration potential following GBR treatment.

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