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Mechanisms of Guided Bone Regeneration: A Review

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Abstract: Post-extraction crestal bone resorption is common and unavoidable which can lead to significant ridge dimensional changes. To regenerate enough bone for successful implant placement, Guided Bone Regeneration (GBR) is often required. GBR is a surgical procedure that uses barrier membranes with or without particulate bone grafts or/and bone substitutes. There are two approaches of GBR in implant therapy: GBR at implant placement (simultaneous approach) and GBR before implant placement to increase the alveolar ridge or improve ridge morphology (staged approach). Angiogenesis and ample blood supply play a critical role in promoting bone regeneration.

Keywords: Bone regeneration, implant, ridge augmentation.

INTRODUCTION

Implant therapy to restore an edentulous site has gained more popularity in modern dentistry. Successful implant placement requires adequate alveolar ridge dimensions, which are essential to house the implant and provide esthetics and function.

Following tooth removal, the normal healing process takes place over approximately 40 days, starting with clot formation and culminating in a socket filled with bone covered by connective tissue and epithelium [1, 2]. Complete preservation and restoration of the original ridge volume after tissue remodeling would be ideal for future implant placement. Unfortunately, this is usually not the case. In fact, without further treatment, crestal bone resorption is common and unavoidable which can lead to significant ridge dimensional changes. These changes range from an average vertical bone loss of 1.5 to 2 mm and an average horizontal ridge width loss of 40 to 50% over six to twelve months healing [3-7]. Most of the dimensional changes occur during the first 3 months [4] and can continue over time, with as much as an additional 11% of volumetric bone loss during the following 5 years [8, 9]. Ashman showed that tooth extraction resulted in approximately 40% to 60% loss of bone height and width respectively within 2 to 3 years [10]. More often, greater bone resorption occurs in the horizontal plane than in the vertical plane, leading to more severe loss of alveolar width [5, 6, 11]. The presence of bone dehiscences or fenestrations during extraction may increase post-extraction alveolar remodeling, leading to an even more severe buccal concavity after healing [12].

To attempt to minimize or prevent post-extraction bone resorption and to preserve ridge integrity, it is recommended to place a space maintaining graft in the alveolus at the time of extraction. Various ridge preservation techniques and materials have been utilized [13-18].

GUIDED BONE REGENERATION

A lack of horizontal and/or vertical bone in implant sites may cause major clinical problems [19] and needs to be corrected prior to implant placement. To regenerate enough bone for successful implant placement, a ridge augmentation technique is often required.

One technique of ridge augmentation is Guided Bone Regeneration (GBR). GBR is a surgical procedure that uses barrier membranes with or without particulate bone grafts or/and bone substitutes. Osseous regeneration by GBR depends on the migration of pluripotential and osteogenic cells (e.g. osteoblasts derived from the periosteum and/or adjacent bone and/or bone marrow) to the bone defect site and exclusion of cells impeding bone formation(e.g. epithelial cells and fibroblasts) [20-23]. To accomplish the regeneration of a bone defect, the rate of osteogenesis extending inward from the adjacent boney margins must exceed the rate of fibrogenesis growing in from the surrounding soft tissue [24]. In a clinical situation, it is often hard to predict the efficacy of ridge augmentation. To ensure successful GBR, four principles need to be met: exclusion of epithelium and connective tissue, space maintenance, stability of the fibrin clot, and primary wound closure [25].

After GBR procedures, bone regeneration follows a specific sequence of events. Within the first 24 hours after a bone graft, the graft material/barrier created space is filled with the blood clot which releases growth factors (e.g., platelet derived growth factor) and cytokines (e.g., IL-8) to attract neutrophils and macrophages. The clot is absorbed and replaced with granulation tissue which is rich in newly formed blood vessels. Through these blood vessels, nutrients and mesenchymal stem cells capable of osteogenic differentiation can be transported and contribute to osteoid formation.

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Mineralization of osteoid forms woven bone [26], which later serves as a template for the apposition of lamellar bone [27]. This transformation of primary sponge work would eventually constitute both compact and reticular bone with mature bone marrow. These events occur 3 to 4 months post-surgery [28].

GRAFTING MATERIALS

Bone regeneration can be accomplished through three different mechanisms: osteogenesis, osteoinduction, and osteoconduction. Osteogenesis is the formation and development of bone, even in the absence of local undifferentiated mesenchymal stem cells. Osteoinduction is the transformation of undifferentiated mesenchymal stem cells into osteoblasts or chondroblasts through growth factors that exist only in living bone. Osteoconduction is the process that provides a bio-inert scaffold, or physical matrix, suitable for the deposition of new bone from the surrounding bone or encourage differentiated mesenchymal cells to grow along the graft surface [29].

The primary types of bone graft material are autogenous bone, allografts, xenografts and alloplasts. All grafting materials have one or more of these three mechanisms of action. The mechanisms by which the grafts act are normally determined by their origin and composition. Autogenous bone harvested from the patient forms new bone by osteogenesis, osteoinduction, and osteoconduction. Allografts harvested from cadavers have osteoconductive and possibly osteoinductive properties, but they are not osteogenic. Xenografts/ alloplasts are typically only osteoconductive.

BONE AUTOGRAFT

An autograft is tissue transferred from one location to another within the same individual. Common areas from which autogenous bone can be harvested include extraoral sites such as the iliac crest or tibial plateau; and intraoral sites such as the mandibular symphysis, maxillary tuberosity, 8- to 12-weeks post-extraction healing sites[30], ramus, tori or exostoses [29]. Autogenous bone can be harvested as block autograft or particulate graft. High or slow speed handpieces, chisels, trephines, piezosurgical instruments, rongeurs, or bone scrappers may be used to harvest bone from donor sites. Grafted autogenous bone can be trabecular (cancellous), cortical or corticotrabecular. In general, cancellous bone has more osteogenic potential than cortical bone due to presence of hematopoietic marrow and a greater amount of pleuripotential cells in cancellous bone [31]. Cortical graft has fewer surviving osteogenic cells but provides the most bone morphogenetic protein (BMP) [32]. BMP differentiates host mesenchymal cells into osteoblasts. In addition, BMP provides more resistance to the graft structure resorption, which impedes soft tissue in-growth but also may prolong the time needed for blood vessels to infiltrate the graft [32-34]. Corticotrabecular block grafts can be shaped and trimmed to fit the recipient bed, and the trabecular part is placed to face the recipient bed.

The optimal donor site depends on the volume and type of regenerated bone needed for the specific case. The posterior iliac crest provides the greatest amount of bone - up to 140 mL, the anterior iliac crest up to 70 mL, and 20-40 mL from the tibial plateau. Intraoral sites provide up to 5-10 mL from the ascending ramus, up to 5 mL from the anterior mandible, up to 2 mL from the tuberosity, and varying amounts from bone shavings or exostoses or through the use of suction traps [35]. Different particle size of autogenous bone can be obtained with different harvesting techniques. Autogenous bone can be obtained by high speed burs, low speed burs, hand chisels and bone blending, Particle size of bone blend (cortical or cancellous bone that is procured with a trephine or rongeurs, placed in an amalgam capsule, and triturated to the consistency of a slushy osseous mass) is approximately 210 × 105 um. Grafts obtained with high and low speed burs have a particle size of roughly 300 to 500 um, while hand-chiseled bone chips have the largest and least uniform particle size of 1559 × 783 um [36]. Autogenous bone is highly osteogenic and is considered as the gold standard of grafting materials. Autogenous bone provides proteins, bone-enhancing substrates, minerals, and vital bone cells to the recipient site, which enhance the overall success of the grafting procedure, resulting in high success rates [29, 37, 38]. However, there are downsides associated with autogenous bone: 1) the necessity of harvesting from a secondary surgical site and the possible resultant patient morbidity; 2) possible root resorption and ankylosis with the use of fresh iliac bone graft when placed near the roots [39, 40]; and 3) the difficulty of obtaining a sufficient amount of graft material, especially from intraoral sites. These limitations led to the development of allografts and alloplasts as alternative or supplemental grafting materials.

BONE ALLOGRAFTS

Allografts consist of tissue transferred from one individual to another genetically dissimilar individual of the same species. The main benefit of allograft bone is the avoidance of a secondary donor site, reduced surgical time, decreased blood loss, decreased host morbidity and unlimited supply of graft material. However, allografts are not osteogenic and bone formation usually takes longer and results in less regeneration than autogenous grafts. With allografts, concerns have been raised regarding the possibility of disease transmission through grafting; however, with meticulous donor screening and specimen processing, the risk is extremely low [41]. Freeze-drying and the Tutoplast® process are two commonly used sample processing methods that can further reduce the risk of disease transmission [42, 43]. Freeze-dried bone can be used in two forms, demineralized freeze-dried bone allograft (DFDBA) or mineralized freeze-dried bone allograft (FDBA). Since FDBA is mineralized, it elicits slower resoprtion than DFDBA and provides an osteoconductive scaffold when implanted in mesenchymal tissues. For DFDBA, the demineralization process removes the mineral phase of the graft which can expose the underlying bone collagen and possibly bone growth factors like BMPs [44-46]. Because of this, DFDBA may have a higher osteoinductivity than FDBA [44-46]. However, this osteogenic potential depends on the quality and quantity of the bone matrix in the graft material. Most commercial bone banks do not verify the presence or activity of BMPs in DFDBA nor the ability of DFDBA to induce new bone. Schwartz *et al.* [47]

found that DFDBA from different tissue banks had a variety of shapes and sizes as well as considerably variable osteoinductive potential which seemed to be age-dependent, with stronger potential from younger donors. Even from the same tissue bank, different batches may have different clinical results. This may partially explain why Rummelhart found similar clinical results between DFDBA and FDBA for osseous regeneration [48]. The size of the grafting particulates also matters. The most appropriate particle size was found to be 100- 400 um [36, 49]. It was suggested that these small particles may enhance osteogenesis compared to larger particles (1000 - 2000 um) due to enlarged surface area and ideal pore size between particles which allow for increased vascularization and osteogenesis to occur. Particles that are too small may get resorbed too fast for bone formation. Particles that are too large may hinder vascularization and may be sequestered [50].

Considering the different biological and mechanical properties, different grafting materials are often combined to optimize the environment for the regeneration of vital bone. If rapid osteoinduction is desired while still retaining the space making benefits and increased mineral density associated with mineralized allograft, FDBA can be combined with DFDBA or autogenous bone. With such a combination, one may take advantage of the presumed osteoinductivity and more rapid turnover time of the demineralized or autogenous graft combined with the prolonged turnover time and higher density achieved with the mineralized allograft tissue. Sanders *et al.* (1983) compared the clinical effects of FDBA alone and the composite FDBA/autogenous bone graft in the treatment of periodontal defects and found a greater success rate of the composite grafts [51].

BONE XENOGRAFTS AND ALLOPLASTS

Xenografts are tissue grafts obtained from a species other than the host species. The representative xenograft materials are natural hydroxyapatite (HA) and deorganified bovine bone (anorganic bone matrix or ABM). These graft materials are inert osteoconductive filler material, which serves as a scaffold for new bone formation. Natural hydroxyapatite is extracted from animal bones. It has the three-dimensional microstructure of natural bone and is highly biocompatible to adjacent hard and soft tissues. ABM is an inorganic bone of bovine origin. It is a carbonate containing apatite with crystalline architecture and a calcium/phosphate ratio similar to that of natural bone mineral in humans. With time, ABM graft material becomes integrated into the human bone and is slowly replaced by newly formed bone. However, the remodeling process takes a long time and reports have shown the bovine graft present even after 18 months [52-55]. Human biopsies after sinus augmentation confirm that particles of bovine-derived bone substitutes can still be found up to 10 years postoperatively [56]. Disadvantages of xenografts are the increased risk of a host-immune response, brittleness and easy migration [29, 57]. Xenografts appear to incorporate into natural bone, but their low resorption rate may negatively impact the healing of the grafted site and compromise the mechanical and biological properties of the regenerated bone.

Alloplasts are an inert synthetic graft material. The most commonly used alloplast materials are calcium carbonate, calcium sulfate, bioactive glass polymers and ceramic materials, including synthetic hydroxyapatite and tricalcium phosphate (TCP). The mechanism of action of these materials is strictly osteoconduction. They provide a scaffold for enhanced bone tissue repair and growth.

The use of autografts, allografts, xenografts, or alloplasts, alone or in combination, should be based on the individual's systemic healing capacity, the osteogenic potential of the recipient site, and the time available for graft maturation. Due to the absence of definitive conclusions as to the relative efficacy of xenografts and alloplasts in the management of periodontal defects, they are recommended to be combined with allografts for small defects in healthy patients. Autogenous bone should be added for progressively larger defects, especially for defects and/or patients with lower osteogenic potential. Additionally a barrier membrane should be utilized for better results [29, 58].

BARRIER MEMBRANES

Guided tissue regeneration is a barrier technique used for the treatment of periodontal bone defects. Guided bone regeneration is used to enhance bone growth of the alveolus for implant placement and around peri-implant defects [59, 60]. Studies by Dahlin *et al.* showed that if a barrier membrane was placed in direct contact with the surrounding bone surface and a space was created, only cells from the neighboring bone or bone marrow can migrate into this bone defect, without in-growth of competing soft tissue cells from the overlying mucosa [61]. There may be additional benefits to the use of a membrane, such as protection of the wound from mechanical disruption and salivary contamination. A barrier membrane should satisfy the following conditions: tissue adhesion without mobility, block soft tissue in-growth, east to use, maintains a space, and biocompatibility. Currently, barrier membranes are of two types, non-resorbable and resorbable.

NON-RESORBABLE MEMBRANES

Expanded Polytetrafluoroethylene

Expanded polytetrafluoroethylene (e-PTFE) was originally developed in 1969 and it became the standard for bone regeneration in the early 1990s [62-66]. The e-PTFE membrane is sintered with pores between 5 and 20 μm in the structure of the material. The most popular commercial type of e-PTFE was Gore-Tex®.

The e-PTFE membrane acts as a mechanical hindrance. Fibroblasts and other connective-tissue cells are prevented from entering the bone defect so that the presumably slower-migrating cells with osteogenic potential are allowed to repopulate the defect. An animal study performed by Dahlin *et al.* [20] used e-PTFE membranes to cover surgically-created standard size bone defects in the mandibular angles of rats and found that the e-PTFE membrane excluded soft tissue and accelerated bone healing (3-6 weeks) while no healing was achieved in the non-membrane control group

even after an observation period of 22 weeks. Similar results were found in monkeys with through-and-through maxillary and mandibular surgically-created bone defects. It was found that osteogenesis was able to occur without interference from other tissue types in the e-PTFE barrier group after a healing period of 3 months compared to incomplete bone healing with various degrees of connective tissue in-growth in the control group [62]. The biologic principle of osteopromotion by exclusion has proved to be predictable for ridge enlargement or defect regeneration [67].

The e-PTFE membrane has been shown to produce bone predictably in localized bony defects around implants with or without bone grafts [68, 69]. In an experimental rabbit study [21], partially exposed implants were covered with an e-PTFE barrier membrane on the experimental side; on the contralateral side, the flap was closed without a membrane. Results revealed that on the experimental side, all exposed screw threads were covered with new bone, but little bone regeneration was observed on the control side (mostly connective tissue was gained). Another multicenter study in humans applied an e-PTFE membrane to cover the dehiscence or fenestration bone defects around implants to facilitate bone regeneration. This study showed the average osseous defect was reduced from 4.7 mm to 1.1 mm on re-entry, which they believed was due to the use of barrier membranes for GBR [70]. Additionally the efficacy of e-PTFE barrier membranes to preserve and regenerate bone around implants placed in fresh extraction sockets were also validated in several other studies [22, 71, 72].

High-Density Polytetrafluoroethylene

In time clinicians discovered e-PFTE exposed to the oral cavity resulted in migration of micoorganisms through the highly porous membrane. The average pore size of 5 to 20 μm and the diameter of pathogenic bacteria generally less than 10 μm, migration of microoraganisms through the highly porous e-PTFE membrane at exposure is a common complication. To address this problem, a high density PTFE membrane (d-PTFE) with a nominal pore size of less than 0.3 μm was developed in 1993, the most popular Cytoplast®. The increased efficacy of d-PTFE membranes in guided tissue regeneration has been proven with animal and human studies [73, 74]. Even when the membrane is exposed to the oral cavity, bacteria is excluded by the membrane while oxygen diffusion and transfusion of small molecules across the membrane is still possible. Thus, the d-PTFE membranes can result in good bone regeneration even after exposure [75, 76]. Because the larger pore size of e-PTFE membranes allows tight soft tissue attachment, it usually requires sharp dissection at membrane removal. On the contrary, removal of d-PTFE is simplified due to lack of tissue ingrowth into the surface structure [77].

Bartee [78] reported that the use of d-PTFE is particularly useful when primary closure is impossible without tension, such as alveolar ridge preservation, large bone defects, and the placement of implants immediately after extraction. In those cases, d-PTFE membranes can be left exposed and thus preserve soft tissue and the position of the mucogingival junction. Using d-PTFE membranes may enhance healing, since there may be no need for extensive releasing incisions to obtain primary closure can compromise the blood supply and eliminate keratinized tissue, using d-PTFE membranes may enhance healing [73, 78, 79].

Walters *et al.* [80] reported that in a randomized study of GBR involving 14 patients, d-PTFE membranes achieved similar results as e-PTFE membranes with regard to vertical bone regeneration and soft tissue healing and no statistically significant difference was found between d-PTFE and e-PTFE membranes in the treatment of class II furcation defects in humans [81].

Titanium Mesh

Guided bone regenerative membranes can help in treating moderate to severe osseous defects, but the inherrent physical property of the membrane to collapse towards the defect due to the pressure of the overlying soft tissues (thus reducing the space required for regeneration) makes the overall amount of regenerated bone questionable. The use of titanium mesh which can maintain the space can be a predictable and reliable treatment modality for regenerating and reconstructing a severely deficient alveolar ridge [82-84].

The main advantages of the titanium mesh are that it maintains and preserves the space to be regenerated without collapsing and it is flexible and can be bent. It can be shaped and adapted so it can assist bone regeneration in non-space-maintaining defects. Due to the presence of holes within the mesh, it does not interfere with the blood supply directly from the periosteum to the underlying tissues and bone-grafting material. It is also completely biocompatible to oral tissues [84, 85].

Titanium mesh can be used before placing dental implants (staged approach) to gain bone volume or in conjunction with dental implant placement (non-staged approach).

Titanium-reinforced PTFE

The e-PTFE membrane and d-PTFE membrane are also available as titanium-reinforced e-PTFE or d-PTFE. The embedded titanium framework allows the membrane to be shaped to fit a variety of defects without rebounding and provides additional stability in large, non-space maintaining osseous defects.

An experimental study in five beagle dogs compared the osteopromotive performance of titanium-reinforced e-PTFE membranes to that of standard e-PTFE membranes and no membrane (control) in large dehiscence and supracrestal bone defects around dental implants placed in the mandibular alveolar process [86]. The histology examination of the sections after a healing period of 6 months demonstrated large amounts of newly formed bone beneath both types of barrier membranes, with a superficial layer of connective tissue. The control sites without membrane placement revealed minimal supracrestal bone formation. The titanium-reinforced e-PTFE membranes showed evidence of increased alveolar ridge width compared to e-PTFE membranes and control sites. The authors concluded that the reinforcement of e-PTFE membrane with titanium were able to maintain a large, protected space for blood clot stabilization without the addition of bone grafts and provided superior preservation of

the original form of the regenerated ridge during the healing period.

Disadvantages of Non-resorbable Membranes

Although clinical and experimental studies have shown excellent treatment results using non-resorbable membranes in GTR and GBR procedures [62-66, 87, 88], there are certain complications of using non-resorbable membranes. Primary soft tissue closure over the membrane is a vital clinical step that usually contributes to the success of the grafting procedure. However, wound dehiscence because of incomplete coverage or gingival recession during the healing processes is a common finding with usage of non-resorbable membranes [89-93]. Early exposure of barrier membranes to the oral environment and subsequent bacterial colonization can necessitate premature retrieval of the membranes [94, 95]. Wound infection following the exposure of e-PTFE membranes can compromise the results of grafting [24, 96-98]. Simion *et al.* [92] reported that bone gain around dental implants placed in fresh extraction sockets was significantly less when the membranes were exposed than when membranes were not exposed. Another major disadvantage of non-resorbable membranes is the need for a second surgery to remove the bio-inert membrane [69]. This entails discomfort and increased costs for the patients, as well as the risk of losing some of the regenerated bone, because flap elevation results in a certain amount of crestal bone resorption [99, 100]. Lastly, due to the rigidity of the non-resorbable membranes, extra stabilization of the membrane with miniscrews and tacks are often required.

Resorbable Membrane

Currently there are two kinds of resorbable membranes: polymeric and collagen derived from different animal sources. The advantages of bioresorbable membranes include, the elimination of the need for membrane removal, greater cost-effectiveness and decreased patient morbidity [60].

Polymeric Membranes

Polymeric membranes are valuable in preserving alveolar bone in extraction sockets and preventing alveolar ridge defects, as well as ridge augmentation around exposed implants. Polymeric membranes are made up of synthetic polyesters, polyglycolides (PGAs), polylactides (PLAs), or copolymers. These synthetic materials can be predictably reproduced in almost unlimited quantities. A clinical advantage of PGA, PLA, and their copolymers is their ability to be completely biodegraded to carbon dioxide and water *via* the Krebs cycle, thus they do not need to be removed at a second surgery [101].

Lekovic *et al.* [7] evaluated the clinical effectiveness of a resorbable membrane made of PGA and PLA copolymers in alveolar ridges preservation. Results at 6 months re-entry showed that use of a bioresorbable membrane presented with significantly less loss of alveolar bone height, less horizontal resorption of the alveolar bone width, and more internal socket bone fill, compared to non-membrane controls. Simon *et al*. designed a study to evaluate whether the amount of osseous structure 4 months postoperatively after GBR was significantly less than the amount surgically created and if this change was uniform over the area treated using polyglactide membrane over DFDBA for ridge preservation in nineteen extraction sites of 10 patients. The results after 4 months showed a significant loss in the alveolar width (ranging from 39.1 % to 67.4%) and height (14. 7% in the center of the edentulous area but ranged from 60.5% to 76.3% 3 mm mesial and distal to the midpoint) [102].

Although these polymeric membranes are usually biodegradable, their usage has been associated with inflammatory reactions in the body [103]. Either fibrous encapsulation or inflammatory cell infiltrate (multinucleated giant cells, macrophages, polymorphonuclear leukocytes etc.) can be present around the embedded membrane [104].

Premature membrane exposure to the oral cavity was studied by Simion *et al.* [105]. They found that, once exposed, PLA/PGA membranes started to resorb almost instantly, and the resorption process last for 3-4 weeks. As a result, this could lead to spontaneous healing and closure of the wound. On the other hand, a degradation process that is too fast could reduce the barrier function time and the space-making ability of the membrane, which could negatively affect the outcome of bone regeneration.

Collagen Membranes

Most of the commercially available collagen membranes are developed from type I collagen or a combination of type I and type III collagen. The source of collagen comes from tendon, dermis, skin or pericardium of bovine, porcine or human origin [59]. There are several advantages of collagen materials for use a barrier membrane to include: hemostasis [106], chemotaxis for periodontal ligament fibroblasts [107] and gingival fibroblasts [108], weak immunogenicity [109], easy manipulation and adaption, a direct effect on bone formation [110], and ability to augment tissue thickness [111]. Hence, collagen material appears to be an ideal choice for a bioresorbable GTR or GBR barrier.

Collagen is degraded through the enzymatic activities of macrophages and polymorphonuclear leukocytes to carbon dioxide and water [112, 113]. Von Arx and Buser reported the rapid degradation of non-cross-linked collagen membranes following exposure to the oral cavity to be an advantage in horizontal ridge augmentation procedures [114] since spontaneous re-epthelialization can occur within 2 to 4 weeks and no secondary surgery is necessary for their removal. Several physical or chemical cross-linking methods, such as ultraviolet light, hexamethylene diisocyanate (HMDIC), glutaraldehyde (GA), diphenylphosphorylazide (DPPA), formaldehyde (FA) plus irradiation and enzymatic cross-linkage have been used to modify the biomechanical properties of the collagen fibers. Studies have shown that cross-linking is associated with prolonged biodegradation [104, 115] as well as reduced epithelial migration, decreased tissue integration [115], and decreased vascularization [116]. The higher the degree of cross-linking, the longer the resorption rate [115]. Because prototype cross-linking makes the collagen membrane resorb slower severe inflammation and resorption of the grafted area has been reported.

Collagen membranes have been widely utilized in bone regeneration procedures. In a rabbit study by Colangelo *et al.*, a type I highly cross-linked collagen membrane was found to associated with a nearly complete continuous layer of lamellar bone with osteoblastic activity after 30 days compared to only fibrous connective tissue in the non-membrane control group [117]. Chung *et al.* [118] evaluated a cross-linked type I collagen membrane in GTR in 10 patients and reported mean gains in probing attachment of 0.56 ± 0.57 mm and bone defect fill of 1.16 ± 0.95mm. Blumental *et al.* [119] combined demineralized bone-collagen gel with collagen membrane barriers and achieved satisfactory intrabony bone fill results in humans. Collagen membranes can also be used for regeneration in periodontal furcation defects [120- 122].

Collagen membranes can also be used around implants. In a dog model [123], a resorbable collagen barrier membrane was placed over the buccal dehiscences around hydroxyapatite-coated and grit-blasted implants and compared with non-membrane controls. The mean defect fill was 80.29% in the collagen membrane-treated group compared to 38.62% in the control group at 8 weeks. In humans, the combined use of ABM bone graft (Bio-Oss®) with a non-cross-linked resorbable collagen membrane (Bio-Gide®) on exposed implant surfaces and was compared with e-PTFE membrane (Gore-Tex®) alone. The results showed that changes in defect surface for both types of membranes were statistically significant, however, no statistical significance could be detected between the two membranes. The mean average percentage of bone fill was 92% for Bio-Gide® and 78% for Gore-Tex® sites. In the latter group, 44% wound dehiscences and/or premature membrane removal occurred. The resorbable membrane, Bio-Gide®, in combination with a bone graft, can be a useful alternative to the well-established e-PTFE membranes [93].

Disadvantages of Resorbable Membranes

Compared to (reinforced) non-resorbable barrier membranes, both collagen and synthetic polyester membranes lack space-making ability. These membranes are often used with tenting or supporting materials (different bone grafts or bone fillers) to prevent space collapse. When grafting materials are used with bioresorbable membranes, the results of GBR procedures are generally favorable and even comparable to the results achieved with non-resorbable barriers [124-127]. Grafting material alone seems to be less effective than the combination of a supporting material and a barrier [124].

When PGA or PLA resorbable membranes are used, degradation occurs mostly *via* hydrolysis. This creates an acid environment, which can have a negative effect on bone formation [59, 128, 129]. Only collagen membranes seem to be absorbed through catabolic processes resembling those involved in normal tissue turnover. One disadvantage of collagen membranes was shown in an animal study. The fast degradation of three types of collagen membranes (BioGide®, AlloDerm® porcine-derived, and AlloDerm® human-derived) puts in question the effectiveness of these types of resorbable membranes when they are used as physical barriers beyond one month [113].

Treatment Variations

There are two approaches of GBR in implant therapy: GBR at implant placement (simultaneous approach) and GBR before implant placement to increase the alveolar ridge or improve ridge morphology (staged approach). The size and type of each particular osseous defect influence the selection of the most suitable grafting procedure. Buser *et al.* [63, 130] stated that the simultaneous approach is indicated only when the osseous defect around the implant is not extensive and proper prosthetic placement and good primary stabilization can be achieved. However, if the bone around the implant is thin, complete bone regeneration on the implant surface may not be achieved even if GBR is used. In these cases, the treatment plan should be changed to the staged approach, in which the implant is placed after ridge augmentation.

For the choice of different materials, minor alveolar ridge defects suggest the use of an allograft material in a simultaneous approach, while moderate horizontal ridge defects require the use of more predictable grafting procedures such as autogenous grafts in a staged approach [88, 131, 132]. In cases of combined severe horizontal and vertical alveolar ridge defects, the use of reconstructive devices such as tenting screws, mesh and/or re-inforced membranes will be mandatory to ensure more predictable regenerative results [82, 133].

Blood Supply, Bone Marrow Penetration

Angiogenesis and ample blood supply are mandatory for bone development and maintenance. Formation of new blood vessels usually proceeds from existing blood vessels. For an intact dentate alveolar ridge, blood supply includes the complex of supraperiosteal arterioles, the subepithelial capillary network of the gingiva and the periodontal ligament, and the arterioles penetrating the interdental alveolar bone. However, when a tooth is lost, the blood supply from the periodontal ligament disappears, and the blood supply is only from the soft tissue and the supraperosteal blood vessels of the bone.

The cortical bone surface is usually perforated with a small round bur prior to placing a bone graft to open the marrow cavity and to stimulate bleeding into the defect area. This is called decortication or bone marrow penetration [28]. The rationale may include: (1) to enhance the healing process by promoting bleeding and blood clot formation; (2) to allow progenitor cells and blood vessels to reach the bone graft site [67, 134, 135] which facilitate angiogenesis; and (3) to improve the physical interlocking of grafted bone and a recipient site [136-138]. However, bone marrow penetration may also have some negative effects; additional blood loss, potentially greater postoperative pain, increased bone loss, and increased operative time [139].

Conflicting information has been reported with regard to the ability of bone marrow penetration to accelerate or increase bone regeneration in the experimental animal studies [140, 141]. Delloye *et al.* [142] found that perforating a cortical bone graft substantially improved the amount of new bone formation by the host compared to using a non-perforated cortical bone graft. In a controlled clinical trial using a rat model, tibial or femoral grafts were placed on

tibial bones with or without cortical perforation. It was noted that after 20 weeks of healing, there was migration of marrow components through the perforated area with an increased level of lamellar bone apposition compared to the non-decorticated grafts [137]. Decortications were also studied in a rat/rabbit spinal fusion model and found that decortications of vertebrae bone resulted in a statistically significant larger percentage of bone formation during spinal fusion and better graft integration after 9-10 weeks compared to sites that were not decorticated [143, 144]. Similar results were reported using a dog spinal fusion model for the first three months. However, no such benefits from decortications were identified at 6 months. Mixed results also exist with animal mandibular onlay bone grafting model. de Carvalho *et al.* [140] studied the healing of autogenous monocortical bone grafts placed on the mandible in six dogs and demonstrated a better healing with integrated bone at cortical perforation sites as opposed to non-perforated sites after 90 days. In contrast, other studies found decortication did not enhance the incorporation of onlay mandibular bone grafts [141]. There was no appreciable histological difference in healing with or without prior bone marrow penetration [145].

Similarly, conflicting results have also been reported about skeletal or extra-skeletal GBR (using barrier membranes) with or without decortications. Using a rabbit calvaria titanium dome model, there were more osteoblast-like cells at sites under the titanium dome that underwent decortications compared to controls after 2-3 months and the percentage of bone regeneration was significantly higher [146, 147]. A similar result was found using a calvaria rat model after 4 months [148]. However, several animal studies with negative results were also reported and claimed that cortical perforation did not enhance the amount of bone augmentation in rabbits [134, 149, 150]. Other studies showed GBR procedures could be performed successfully to different degrees without decortications [100, 151-154].

Regarding the effect of different sizes of cortical perforation, the data available is minimal. Nishimura *et al.* [155] found that initially (week 2-6), the larger cortical openings (3 x 15 mm) were associated with faster and more new bone formation compared to smaller perforation (1 x 15 mm). However, no significant difference was found regarding to the amount of bone regeneration after 12 weeks.

CONCLUSION

Guided bone regeneration can be achieved with using particulate autogenous bone grafts, allografts, xenografts, or alloplasts grafting materials and resorbable or non-resorbable barrier membranes techniques in 1-2 tooth defects that may allow for dental restoration.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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