

REVIEW ARTICLE

The Role of Demineralized Dentin Material Membrane as Guided Bone Regeneration

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ABSTRACT

Guided Bone Regeneration (GBR) is a method treating a biomaterial that is located into the injured bone to prevent fibrous tissue from entering the injured bone area before the replacement bone grown completely, divided into polytetrafluoroethylene (e-PTFE), synthetic biodegradable polyester, and collagen membranes. The aim of this study is to present an evaluation of literature regarding the rule of novel Demineralized Dentin Material Membrane (DDMM) as GBR. Bone defect after surgical or trauma procedures can be corrected through several mechanisms, which depend on the level of restriction, the level of bone injury, and the physiological process. The use of guided bone regeneration aims to ensure perfect new bone growth, with the exact same shape as the original bone. The application procedure of DDMM as a GBR therapy for bone injury on craniomaxillofacial could be provide bone cells for bone regeneration and protects the bone regeneration process from non-osteogenic tissues.

Keywords: Guided bone regeneration, Bone healing, Human and health, Alveolar bone

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INTRODUCTION

Bone defects are problems that can be treated using various techniques. Bones defect can be caused by damage, carcinomas, contaminations, hereditary defects, and as a end result of surgical practices as well (1). Similarly, the bones in the oral cavity. Bone defects in the oral cavity can caused by surgical procedures when extracting teeth, periodontal disease, cysts, trauma, and infections (2). Post extraction, there is vertical alveolar bone defects about 1.5-2 mm and horizontal alveolar bone defects about 40-50% that can be heal within 6 months. without proper additional procedures, alveolar

bone will be defeated its size by 40% -60% in 3 years (3).

Bone has its own repair mechanism from damage. Post-traumatic bone repair includes the phases of inflammation, repair, and remodeling, which play an important role. Overall, these phases can run efficiently. However, 10% of bones that have experienced trauma will fail in the healing process (4,5).

Guided Bone Regeneration (GBR)

Guided Bone Regeneration (GBR) is a procedure to put a biomaterial that is placed into the injured bone to prevent fibrous tissue from entering the injured bone area before the replacement bone grown completely and protects the bone regeneration process from non-osteogenic tissues, mechanical disorders, and salivary

contamination to accelerate bone growth and prevent the growth of connective tissue from entering the bone defect area (3,6,7,33,37). The GBR membrane as a physical device for bioresorbable or non-resorbable as a barrier to create space around the defect to guiding the progression of bone restoration, preventing invasion of fibrous connective tissue into bone defects (8,9,39)

Some characteristics of the barrier membrane that need to be considered consist of biocompatibility, cell interaction, incorporation of host tissue, medical management, area composing ability, and acceptable physical and mechanical natures (10). Several in vitro studies that can be used to test barrier membranes include cytotoxicity tests, anti cellularity, degradability, antimicrobial properties, and physical-mechanical properties such as tensile strength, topography, micro-morphology, and microporosity (11,40).

Guided Bone Regeneration

Guided Bone Regeneration (GBR) is a clinical technique to produce enough bone volume to fill the defect. This technique is based on the phenomenon that the application of membrane barriers creates space to facilitate the multiplying of basal angiogenic and osteogenic cells into spaces where bone volume is needed without being affected by fibroblasts (12).

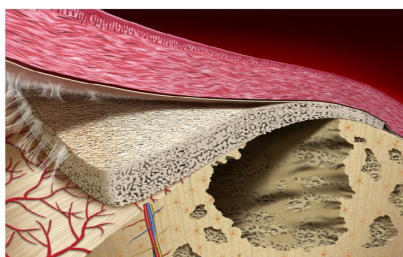


Figure 1. The illustration of GBR procedure using barrier membrane (10).

Traditionally, the theory of GBR has been operated in experimental reconstruction surgical procedure from the mid-1950s, for spinal and maxillofacial surgery. The development of connective tissue components such as fibroblasts is inhibited to enter the bone defect area (8). The medical use of dental material membranes in the mid-1980s, the GBR procedure has become a gold standard in dental surgery that requires the availability of space (7). GBR is the latest treatment to repair bone damage. Various materials, including bioresorbable and non-resorbable polymers have been developed into GBR materials. GBR bioresorbable materials have the benefit of avoiding secondary surgical procedures (9).

Membranes that are widely used are mainly divided into three types based on the main material expanded polytetrafluoroethylene (e-PTFE), synthetic biodegradable polyester, and collagen membranes.

The three membranes have proven to be clinically effective with several considerations such as surgical removal requirements, inflammatory response, and undesirable mechanical properties and infections in the application of each membrane (12). Bone graft material must have at least one of the following properties, such as osteoinductive, or osteoconductive and osteogenic. In addition, the graft material must be biocompatible, bioresorbable and accessible and low cost (13). The GBR theory uses a bioresorbable or non-resorbable membrane used for bone reconstruction as a barrier to prevent soft tissue invasion into the defect. (8).

Bioresorbable Barrier Membrane

In tissue regeneration, the membrane barrier is one of the scaffolds that needs special attention. The type of membrane affects the healing time. Bone regeneration is primarily aimed at the regeneration of bones that support mechanical loads such as cranial, oral, and maxillofacial bones. (8).

biomaterials for bone repair must have sufficient bioactivity to allow rapid tissue growth, be absorbable, and have sufficient mechanical strength. (14). As a dental implant material, the barrier membrane must have biocompatible properties, do not cause side effects, and be able to maintain space in the bone defect from soft tissue invasion. This membrane must be able to block fibrous tissue to influence the location of bone damage, have a mechanical strength to protect the clot, and be degraded by the host so that it does not require secondary surgery (7,10,41).

Synthetic materials for resorbable membranes consist of polyester, copolymers, poly-lactic acid, poly-glycolic acid, and poly-caprolactone. Each membrane has a different resorption mechanism. Collagen membranes are generally absorbed by the reaction enzymatic activity of infiltrating macrophages and polymorphonuclear leukocytes. Polymer materials are generally degraded through hydrolysis, and metabolized through the citric acid cycle. Natural membranes are generally obtained from various parts of the human body, cow or pig. These natural materials have excellent cell affinity and biocompatibility properties. The disadvantages of this membrane are the possibility of loss of defect space due to physiological processes, high operational costs, and the possibility of transmitting disease to humans when using collagen of animal origin. (7,34).

Overcoming this problem, various bioresorbable materials, such as polylactide and poly glycololid acid or collagen have been used as barrier membranes. Membrane material derived from collagen types I and III from pigs or bovine shows its usefulness in the procedure. However, some problems such as premature membrane degradation, epithelial development, and premature material loss. (15). Collagen membranes

originate from various bovine and pig tissues eg tendons, dermis, and gut. The difference in degradation depends on the animal material used. Various physical/chemical crosslinking methods have been developed to improve the mechanical properties of collagen membranes and slow down the membrane degradation time. The methods used were ultraviolet (UV) radiation, genipin (Gp), glutaraldehyde, and 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride. (EDC). Although chemical crosslinks increase the stability of collagen, residues of chemicals such as amide or aldehyde can induce severe inflammation at the implantation site (10).

Surgical methods with the use of bioresorbable membranes require only a single surgical procedure, so there is no need for secondary surgery, reducing the risk of morbidity and extensive tissue damage. Disadvantages of operating methods with bioresorbable membranes include the resorption time cannot be predicted, degradation cannot be controlled, thus affecting the shape of new bone. The ideal membrane must be degraded or reabsorbed at the same time and rate of degradation (7). The use of non-resorbable membranes as mechanical barriers results in complete healing of bone defects in vivo, and collagen membranes prevent apical epithelial migration and support new connective tissue attachment and tissue regeneration (8).

Demineralized Dentin Material Membrane

Mineralized tissues like bone and dentin have similar supporting chemical composition, They are made up of body fluids, collagen, non-collagen protein, and hydroxyapatite. Type I collagen constitutes 90% of the organic matter in dentin. Other organic components are non-collagenous proteins, phosphorylated and unphosphorylated proteins. The dentin matrix is a storage site for growth factors, such as platelet-derived growth factor (PDGF), basic fibroblast growth factor (bFGF), transforming growth factor-- β (TGF- β), and bone morphogenetic protein (BMP). Some non collagen proteins like osteopontin and osteocalcin are abundant in both bone and dentin. Non collagen protein is a phosphoprotein that exclusively found in dentine (13,16).

Demineralized dentin matrix (DDM) has matrix type I collagen such as BMP and osteocalcin, osteonectin, and phosphoproteins. These proteins are involved in bone mineralization. (13).

BMP in dentin and bone is the main stimulant with osteoconductive properties (16). DDM can increase alkaline phosphatase (ALP) activity, mineralized nodules and induce odontoblastic differentiation in vitro (6). BMP is a protein found in the bone matrix, around the osteosarcoma tissue, and in the dentin matrix. Research on DDM focuses on the particle size of the material, the methods used in the production of biomaterials, and a

more perfect bone healing process. (17)

DDM has a higher osteoinductive efficiency and simultaneously induces bone growth. DDM can be considered as a type I collagen complex (COL-I) and growth factor that has lost bound mineral crystals, which are released from the matrix; this has a significant biological osteoinductive and osteoconductive effect. Autologous and xenogenous DDM have been used to treat bone injury and bone defects (6, 42). DDM containing collagen-based ingredients has lower antigenicity and this material is able to release bone morphogenic protein growth factors (BMPs). this material is used clinically as a bone filling material in the maxillary region. The DDM production method involves crushing and demineralizing dentin and cementum, as well as removing enamel. The application of DDM has been investigated by Urist and others with the result that bone transplantation using demineralized dentin promotes bone formation. (17).

Pang et al (18) conducted a study of autogenous human DDM (Korea Tooth Bank, Seoul, Korea) versus bovine inorganic bone using a randomized controlled clinical trial for tooth extraction socket augmentation. The results of this study show that the vertical dimension of augmentation is as effective as augmentation using bovine inorganic bone. Both study groups showed good wound healing, good implant stability, and good histology of new bone formation. The results of this study indicate that autogenous bone graft material is a good choice for alveolar bone augmentation after tooth extraction (13, 43). In vivo studies have shown that DDM can be used for bone strengthening more effectively compare to calcified dentin matrix (CDM), because CDM particles affect the bone healing process. This is influenced by the suppression of apatite crystals against BMP (16).

DISCUSSION

Protection of vital organs, hematopoiesis as well as regulation and storage of minerals protected by bone, facilitator of activators, and others. Bone is a very dynamic network that experiences a constant remodeling process that lasts forever. This is to accommodate mechanical pressure changes, and developing fractures. Bone remodeling is an effort to maintain bone strength, maintain bone mineral homeostasis, and repair bones from damage caused by a lesion. Apart from this remodeling process, bones have tremendous regeneration potential. When bones are injured, Bone regeneration is influenced by several things including trauma and infection. (19,20,44).

Bone has its own repair mechanism in the face of damage. Post-traumatic bone repair includes the phases of inflammation, repair, and remodeling, all of which

play an important role. Overall, these improvement phases can run efficiently. However, Bone union often fails or has an extended healing time in 10% of all cases of bone regeneration. (4,5).

Bone defect after surgical or trauma procedures can be corrected through several mechanisms, which depend on the level of immobilization, area of surgical treatment, and natural processes. This affects the process of intramembranous bone formation in fractured bone regeneration. We can see two patterns of bone healing. First, primary repair, influenced by osteoclasts and osteoblasts. It can be found in defects after minor trauma, and fixation of mandibular ramus fractures. Second, endoperiosteal layer mediated the secondary repair. Callus formation occurs in fracture healing treated with mandibulomaxillary immobilization without surgical intervention. After fracture, the mandibular bone cells form new bone through the process of endochondral ossification, although most of the facial bones are formed by intramembranous ossification. (21,22,23,45) A type of bone ossification in which bone tissue is formed directly over mesenchymal tissue, not through cartilage formation as in endochondral ossification is intramembranous ossification. This generally occurs in bone healing and early cranial bone formation. This process also occurs in the formation of the jaw and collarbone (24,25,26).

The process of intramembranous ossification begins with mesenchymal stem cells (MSCs) in the mesenchyme or medullary cavity of the bone fracture. A small group of MSCs replicates and forms a group of cells. Once formed, the MSCs in it stops replicating. osteoprogenitor cells are formed from MSCs resulting in changes in the shape of the cell body. There is an increase in the endoplasmic reticulum and the Golgi apparatus. The osteoprogenitor cells then differentiate into columnar osteoblasts. The extracellular matrix is composed of osteoblasts containing Type-I collagen (osteoids). Osteocytes are formed from several osteoblasts fused with osteoid. then bone mineralization occurs. trabeculae are formed from spicules joined to each other. The growth of the trabeculae causes woven bone to form. (35,36,44)

The term primary spongiosa occurs in the early trabecular tissue. Then the periosteum forms around the trabeculae. Osteogenic cells of the periosteum cause apposition and bone formation. Finally woven bone substituted with lamellar bone(25,26).

For the period of human development, mainly human skeletons are formed through endochondral ossification. Intramembranous ossification formed most craniofacial bones. However, the formation of endochondral bone is known to be present in the growth of the mandibular column, base of the cranium, and temporal bone. Although endochondral ossification at craniofacial framework is regulated to the area stated previously,

endochondral ossification is the original pathway in the growth of the human face and skull. In addition, restorative trauma to the craniofacial bone is comparable to a long skeleton. Based on mechanical environment, fracture type and location, endochondral ossification can be originate in healing sites of craniofacial fractures. Endochondral ossification is a natural mechanism of ossification, following to the intramembrane pathway, which can be originate in the craniofacial region in the growth and restorative of bone fractures. This creates the endochondral ossification route a viable selection for bone regenerative approaches for maxillofacial treatments (22,24,38,44)

According to Runyan & Gabrick (27), in studies with models of rabbit mandibular fractures showed Without the application of mandibular rigid fixation, histologically fracture healing was similar to that of long bone fractures. There was callus formation which was replaced by trabecular bone over the next 2 weeks, supported by new neovascular and Haversian systems. The observations of Paccione et al (28) on a rat mandibular fracture model showed simultaneous islet formation originating from an imperfect cartilage matrix, blood vessel growth, activation of osteoblasts, mineralization and formation of lamellar bone, simultaneously be similar to secondary bone healing endochondral pathway.

The first stage in the remodeling process is hematoma formation followed by acute inflammation. After the bone defect, vascular damage will occur so that the blood comes out of the vascular and meets the defect Hematomas are formed due to activation of the plasma and platelet coagulation cascades due to extravascular protein expression. Macrophages activated during the inflammatory phase secrete the proteins TNF- α , TFG- β , BMP, IL-1 β , IL-6, IL-17F, and IL-23. Chemotaxis occurs from osteoprogenitor cells and migratory mitogenic and osteogenic molecules (20,29,30,34).

If the defect is too large, then a material is needed to stimulate bone regeneration to be faster and better, in this study used a barrier membrane in the form of DDMM. The suggested morphology of the membrane is in the form of concave where it can increase the speed of cell migration, secretion of pro-inflammatory cytokines such as TNF- α , IL-6, IL-12/23, IL-10, and increase ALP activity. This affects the inflammatory phase or during hematoma formation (20,29,30).

The next phase is the formation phase of the soft callus where cell proliferation occurs and the hematoma is replaced by granulation tissue. There is neovascular growth on the site of the cartilage defect and bone. Osteoprogenitor cells proliferate and migrate to the callus site and are stimulated to differentiate into osteoblasts. A good membrane has a porosity standard of 100-500 μm , and is optimal for porosity > 300 μm .

If the standard porosity is met, it will increase cell proliferation & aggregation to the site of the defect, in addition to suitable penetrability, angiogenesis and nutrient vehicle (13,31). This has an effect on the soft callus formation phase (20,30).

The next phase is the formation of hard callus, chondrocytes in hypertrophy of soft callus apoptosis eventually leaving the cartilage bone extracellular matrix. Vascular growth is associated with differentiation of osteoprogenitor cells into osteoblasts and by accumulation of woven bone. Woven bone is formed through intramembranous and endochondral ossification (20).

The remodeling phase begins with coordinated osteoblast and osteoclast activity over a range of several months to several years. lamellar bone replaces woven bone through surface erosion and osteonal remodeling. this step continues until the bones actually return to their original morphology (32).

CONCLUSION

The use of DDMM as a GBR therapy for bone defect on craniomaxillofacial could be provide bone cells for bone regeneration and protects the bone regeneration process from non-osteogenic tissues, mechanical disorders, and salivary contamination to encourage bone differentiation which is develops slower than fibrous tissue. This procedures could be used as gold standard for therapy of craniofacial bone defect.

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