Journal of Advanced Medical and Dental Sciences Research

@Society of Scientific Research and Studies ***NLM ID:*** *101716117*

Journal home page: www.jamdsr.com doi: 10.21276/jamdsr Index Copernicus value = 85.10

(e) ISSN Online: 2321-9599; (p) ISSN Print: 2348-6805

Review Article

Directing the Growth of New Bone – A Narrative Review on Guided Bone Regeneration

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ABSTRACT:
At present, guided bone regeneration is predominantly applied in the oral cavity to support new hard tissue growth on an alveolar ridge to allow bone augmentation. By using a bioabsorbable or non-resorbable membrane that acts as a barrier to prevent soft-tissue invasion into the defect and forms a chamber to guide the bone regeneration process is used for bone reconstruction. It works on the principle of compartmentalization, allowing osteoblasts to populate the wound site before epithelial and connective tissue cells, thus regenerating bone. In situations with a bone defect at a site, where the primary stability cannot be achieved or when augmentation is not possible in ideal location for subsequent prosthetic therapy, guided bone regeneration prior to implantation represents the method of choice. After attaining primary closure, the wound site is left to heal for 4 to 6 months with non-resorbable barrier membranes along with tenting screws, promising outcomes have been achieved with the majority of bone replacement grafts.
Key words: Guided Bone Regeneration, Tissue Scaffolding, Bone Growth , Periodontology , Grafts.

Received: 02/05/2020 **Modified:** 20/06/2020 **Accepted:** 24/06/2020

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This article may be cited as: Vashisht S, Verma AT, Jindal V, Jindal V, Sharma P, Fanda K, Bawa SK, Chauhan P. Directing the Growth of New Bone – A Narrative Review on Guided Bone Regeneration. J Adv Med Dent Scie Res 2020;8(7):116-121.

INTRODUCTION

An adequate volume of bone plays an integral role in the maintenance of natural dentition and at the site of prosthesis to ensure favorable biomechanics and long term esthetic outcome.[1] A lack of horizontal and/or vertical bone may cause major clinical problems and needs to be corrected prior to any surgical procedure.[2] Large bone defects include segmental or large cortical defects created by trauma, infection, tumor resection, aseptic loosening around implants and skeletal abnormalities as Critical size defect (CSD) which is defined as the defect with the minimum length that cannot be spontaneously bridged leading to non-union. Such defects are generally accepted to be ≥ 1.5 to 2 times the diameter of the long bone diaphysis, but they vary according to the host and the bone.

Treatment of large bone defects represents a great challenge, as bone regeneration is required in large quantity and may be beyond the potential for self-healing, thus, a careful presurgical evaluation is essential to obtain the necessary information about the quality of the bone, the vertical bone height and the Orofacial bone width.[3] A main hindrance for successful bone healing and creation of new bone is the rapid

formation of soft connective tissue. Ingrowths of soft tissue may disturb or totally prevent osteogenesis in a defect or a wound area. Hence it is not surprising that newer methods are constantly being reviewed by the dental fraternity.[4] The possible solutions available to solve the problem include distraction osteogenesis and bone transport, or bone grafting GBR (membrane technology), in which a cell occlusive membrane is used to cover a defect against invasion by soft tissue, including autologous bone grafts, bone marrow aspirate, allografts, osteoconduction with bone or a bone substitutes or growth factors. Furthermore, the concept of an bone induced-membrane represents another strategy for bone regeneration in cases of large bone defects. Thus for the regeneration of bone defects utilizing barrier membranes, the term guided bone regeneration is preferred, since this term describes the purpose of the membrane application more precisely than does the term guided tissue regeneration.[3]

HISTORICAL BACKGROUND

Historically, the concept of GBR has been originally developed by Hurley et al (1959) for treatment of experimental spinal fusion and maxillofacial reconstruction.[4] In 1964, Boyne PJ showed that the placement of cellulose acetate filters led to improvement in the regeneration of alveolar bone defects in dogs.[5] In 1968, Boyne PJ again showed that the cellulose acetate filters could be used clinically, as a lining of implanted metallic cages, filled with autogenous marrow and bone for the restoration of jaw defects.[6] In 1979, **Kahnberg** studied the healing process in mandibular base defects in rabbits with subperiosteally implanted Teflon mantle leafs, and stated that the mantle leafs prevented ingrowth of fibrous scar tissue, allowing bone regeneration to occur.[7] Dahlin et al in 1983 placed implants in less desirable ridge areas using GBR techniques to gain bone on the exposed threads.[8] Lazzara et al in 1989 was credited with the first reported use of GBR techniques with implants in immediate extraction sites.[9] At the end of the eighties and during the beginning of the nineties, membrane technology for helping bone regeneration around implants (Guided Bone Regeneration) was successfully tested in animal experiments and clinically by Dahlin et al in 1988, 1990; Buser et al in 1993 and Zahedi et al in 1998.[10] The selective ingrowth of bone-forming cells into a bone defect region could be improved if the adjacent tissue is kept away with a membrane , which was confirmed in a study by Kosopoulos and Karring in 1994.[11]

BIOLOGY OF BONE REGENERATION

Regeneration is commonly understood as replacement of vanishing or lost components in the body by equally highly organized elements. Many tissues or organ systems undergo a physiologic regeneration i.e. continuous replacement of cells or tissue elements. Best known examples are the blood cells, epithelia, glands or the endometrium during the reproductive cycle.

Reparative regeneration takes place when tissues are lost because of injury or disease.[4] Articular cartilage is practically unable to regenerate, and full-thickness defects are filled by fibrous tissue or are replaced by less differentiated fibrocartilage.[12]

To achieve predictable results with Guided Bone Regeneration procedure, following steps are necessary:

- Blood supply - Cortical perforations
- Stabilization - Fixation screws, membrane tacks
- Osteoblasts - Autogenous bone graft
- Confined space - Barrier membrane
- Space maintenance -Tenting screws, bone graft materials
- Wound coverage - Flap management, tension-free suturing [4]

ACTIVATION OF BONE REGENERATION

Among the highly organized tissues, bone has the unique potential to rebuild its original structure after a defect or fracture. The pattern of bone healing closely resembles development and growth. Any bone lesion (fracture, defect, insertion of implants, interruption of blood supply) activates local bone regeneration by the release of growth factors (GF) and inductors. Bone is in fact, one of the richest sources for growth factors. Among the growth factors detected in bone, some are produced by bone cells (insulin like growth factor (IGF), transforming growth factor (TGF), fibroblast growth factor (FGF), and platelet-derived growth factor (PDGF) whereas others are synthesized by bone-related tissues (interleukin-1 [IL-1], tumor necrosis factor α).[2] In addition, some bone inducing factors are of great interest, such as Lacroix'sosteogenin and the bone morphogenic protein (BMP) of Urist et al, which has now been fractioned into at least seven different proteins (BMP family).[13]

PRINCIPLE OF GBR

The principle of Guided Bone Regeneration is based on the creation of a cavity with the help of a barrier in the form of a membrane or foil, thus preventing the growth of gingival tissue into the bone defect. With the placement of a barrier membrane, preference is given to bone forming cells that originate from adjacent bone to populate and regenerate these defects with bone, since competing soft tissue cells from the mucosa are excluded from these defects.[14]

To achieve better clinical outcomes, the GBR barrier should possess the following properties:

Cell exclusion
In GBR, the barrier membrane is used to prevent gingival fibroblasts and/or epithelial cells from gaining access to the wound site and forming fibrous connective tissue.

Tenting
The membrane is carefully fitted and applied in such a manner that a space is created beneath the membrane, completely isolating the defect to be regenerated from the overlying soft tissue. It is important that the membrane be trimmed so that it extends 2 to 3 mm beyond the margins of the defect in all directions. The corners of the membrane should be also rounded to prevent inadvertent flap perforation.

Scaffolding
This tented space initially becomes occupied by a fibrin clot, which serves as a scaffold for the in-growth of progenitor cells. In GBR, the cells will come from adjacent bone.

Stabilization
The membrane must also protect the clot from being disturbed by movement of the overlying flap during healing. It is therefore often, but not always, fixed into position with sutures, mini bone screws, or bone tacks. Sometimes, the edges of the membrane are simply tucked beneath the margins of the flaps at the time of closure, providing stabilization.

Framework
Where necessary, as in non-space maintaining defects such as dehiscences or fenestrations, the membrane must be supported to prevent collapse. Bone-replacement grafts are often used for this purpose. They serve as a sort of internal framework to provide a measure of support to the graft. Stiffer membranes such as titanium reinforced membranes have also been used for this purpose.[15]
Wang and Boyapati proposed the PASS principles for predictable bone regeneration in 2006. To attain horizontal and/or vertical bone augmentation beyond the envelope of skeletal bone, four principles are needed to be met: primary wound closure, angiogenesis to provide blood and nutrient supply, space maintenance and stability of wound to include the blood clot formation.[16]

INDICATIONS
- Augmentation around implants placed in immediate extraction sockets.
- Augmentation around implants placed in delayed extraction sockets.
- In fenestration and dehiscence defects around implants.
- Localized ridge augmentation.
- Alveolar ridge reconstruction.
- Filling of bone defects after root resection, cystectomy and removal of retained teeth. [17]

GRAFTING MATERIAL
Dental bone grafting plays an important role where structural or functional support is necessary. Grafts are used to provide a scaffold for bone regeneration, augment bony defects resulting from trauma or surgery, restore bone loss resulting from dental disease, to fill extraction sites to preserve the height and width of the alveolar ridge, and augment and reconstruct the alveolar ridge.[16] Bone grafting material is generally classified as autografts, allografts, xenografts or alloplasts.

1. **Autografts**
   Autograft transplants are those taken from one region and placed in another region in the same individual. Autograft bone is very compatible with the patient's body, but it requires a second surgical procedure to harvest the graft material (e.g., chin, hip, ribs). Autografts are known as the "gold standard" because of the lack of antigenicity of the graft material.
2. **Allografts**
   Allografts are transplanted from one individual to a genetically non-identical individual of the same species. An allograft requires no additional surgical procedure for bone harvesting, thus decreasing the risk of infection or additional discomfort for the patient. The success of these grafts is well documented.
3. **Xenografts**
   Transplants from one species to another are known as xenografts. Animal bone, most commonly bovine, is specially processed to make it biocompatible and sterile. The graft material acts as filler, which, in time, the body replaces with host bone.
4. **Alloplastic**
   Alloplast transplants are synthetic, chemically derived bone substitute. For an alloplastic bone replacement, a manufactured material that mimics natural bone is used. Alloplastic bone graft material acts as filler of the bone defect and not a true regenerative material.[18]

PROPERTIES OF BONE GRAFT MATERIAL
To qualify as a bone graft material, a substance must possess at least one of the following properties:
Osteogenic property
Osteoconductive property
Osteoinductive property

1. Osteogenic property

Osteogenesis is the formation of new bone from bone-forming cells (osteoblasts) that are transplanted as viable cellular component in autogenous bone grafts. Cells with osteogenic potential include osteoblasts and undifferentiated osteoblastic pluripotent stem cell. Osteoblastic stem cells are present in bone, stromal cells, in bone marrow, periosteum and in muscle.

Transplantation of osteogenic cells is required for a material to be called a bone graft. Materials which are osteogenic in nature contain growth factors e.g. transforming growth factor-β, insulin-like growth factor I and II, platelet-derived growth factor etc., which regulate cell proliferation of undifferentiated tissues.

2. Osteoinduction activity

Osteoinductive materials are those which contain morphogens e.g. bone morphogenetic proteins/substances which initiate the development of tissues and organ systems by stimulating undifferentiated cells to convert phenotypically (e.g. mesencymal stem cells – chondroprogenitor and osteoprogenitor cells) (Kenley et al 1993, Urist 1994).

3. **Osteoconductive activity**

Those materials are osteoconductive, which provide simply a framework or scaffold effect for the host bone-forming cells to infiltrate, proliferate and form new bone.[19]

MEMBRANES FOR GUIDED BONE REGENERATION

As the use of an occlusive or semi-occlusive membrane to provide a protected, blood clot-filled space adjacent to a bony surface results in predictable bone tissue formation, there is an increasing demand for membranes in regenerative therapy. Therefore to select the best-suited material for guided bone regeneration, it is necessary to understand the functional requirements of membrane materials.

The GBR procedure performed in the alveolar process pose specific challenges that must be addressed in membrane design if the membrane is to function at the optimal level in clinical use. However, a membrane that is utilized for alveolar ridge GBR must meet a number of requirements in addition to acting as a passive physical barrier.[20]

Therefore the uses of membranes are outlined as follows:

1. Lack of soft tissue closure
    i. Prevents bacterial contamination
    ii. Prevents saliva contamination
2. Control cell invasion
    i. Epithelial cells
    ii. Connective tissue cells

Various membrane materials have been used by many clinicians for effective bone regeneration with varying results. The selection of the membrane is determined by the clinician's objective of the procedure and the qualities of the barrier material.

Thus the membranes may be also classified by its origin as

Autograft – Subepithelial or connective tissue graft

Allograft – Fascia lata, freezed-dried skin, acellular human dermis

Xenograft – Absorbable collagen from porcine-derived or bovine-derived grafts

Alloplastic – Expanded e-PTFE, Vicryl mesh, polylactic acid, calcium sulfate, polyglycolic acid and others. [21]

In large, non-contained, non-space making osseous defects, there is insufficient support to prevent collapse of the barrier membrane into the defect, thus occluding the space. In these instances bone augmentation materials have been used to support the barrier membrane and to provide either a lattice network for osteoconduction or bone inductive proteins for osteoinduction. Fixation screws or pins are used or without grafting materials, to tent the membrane.[22]

Therefore, the physical barrier membrane which are used for GBR should satisfy the five basic criteria, i.e. **Biocompatibility**, **Cell occlusivity**, **Tissue integration**, **Space making** and **Clinical manageability.**

I. BIOCOMPATIBILITY

a. Patient safety

Patient safety is the foremost concern in the selection of a biomaterial as a potential GBR membrane. Safe and effective degradable GBR membranes are currently available and the breakdown products of these material needs to be better understood in terms of local and systemic effects.

b. Immunologic response

The immunologic response of primary concern for patient safety involves direct or indirect hypersensitivity to the implanted material. As a result, potential antigenic responses must be considered in the selection of materials for an implantable device.

c. Osteogenesis potential

The general function of a membrane used for GBR therapy is to create an environment that will allow normal healing processes to form bone in a defined region. Therefore, the host-biomaterial interactions should not interfere with bone formation and maintenance to a clinically significant degree.

d. Tissue integration and biocompatibility

Membranes used in GBR therapy need to achieve an adequate degree of tissue integration between the

connective tissue and the membrane. The basic goal of material design is to provide an acceptable chemical composition and an appropriate material structure that will allow connective tissue ingrowth or attachment to the membrane during healing.

II. CELL OCCLUSION:

a. Membrane structure

Boyne PJ hypothesized that the use of microporous membrane create a suitable environment for osteogenesis by excluding connective tissue cellular elements from the bone healing region.

b. Nutrient transfer

Membranes used for bone regeneration should have porous properties that allow for the transfer of nutrient fluids and gases.

III. TISSUE INTEGRATION:

a. Clinical benefits

Tissue integration appears to be necessary for optimal performance of a GBR membrane, chemical and structural properties that encourage tissue integration must be balanced with the overall functional requirements of alveolar ridge regeneration.

b. Wound stability

Directbone healing (bone healing without a cartilage precursor) is dependent of establishing, at least initially, a mechanically stable environment Integration of a membrane material with the surrounding tissue helps to provide the stability necessary for both osseous and soft tissue healing. Thus the membrane should provide wound stability and should incorporate structural features that allow and encourage tissue integration.

IV. SPACE MAKING

The term "bone regeneration" implies that, during treatment, a specific volume of space, preferably in a specific geometry, is filled with viable bone tissue to restore function or esthetics. This space and geometry must be created and maintained for an adequate period of time during healing for acceptable therapeutic results.

a. Membrane characteristics and space making

The resistance to collapse of a GBR membrane is determined largely by the material stiffness. However, the space making function (stiffness) of a membrane must be balanced with the capacity to adapt the membrane to the contours of the adjacent bone and to minimize the tendency for the material to perforate the delicate soft tissues of the oral cavity.

b. Membrane characteristics and space making duration

Space maintenance throughout the necessary healing period is dependent on maintenance of the mechanical and physical integrity of the membrane. An inert material (nondegradable) with sufficient strength to maintain mechanical and structural integrity in the face of normal mechanical challenge, will maintain full spacemaking capabilities throughout the necessary healing period.

V. CLINICAL MANAGEABILITY

Clinical manageability of a GBR membrane is determined largely by the ease of surgical manipulation and postoperative management. Optimal membrane design requires minimal difficulty in operative healing to allow the clinician to achieve proper membrane placement.

a. Membrane characteristics and clinical handling

Membranes used for GBR must undergo a series of physical manipulations. They are cut, shaped, and sometimes fixed in place with sutures or screws. Therefore the GBR membranes should be easily trimmed and manipulated without fraying or fragmenting.

b. Membrane structure and postoperative management

In addition to the biologic need for a GBR membrane to maintain structural integrity during healing, the membrane must also maintain its structure in the event it must be removed. In case of second-stage surgery or any postoperative complication which indicates removal, the structural and mechanical integrity should ensure complete removal without fragmentation.[23]

CONCLUSION

The dental profession has entered into a new era with respect to bone preservation and reconstruction. However, the technique and materials of the future are still on the "drawing board". The future will be determined by a joint effort of all disciplines. The communication among clinicians and researchers must be maintained to provide the best possible care to patients. Hence it can be quoted that **"failure does not indicate that something was done wrong." Rather, failure must be a learning process to be shared among those in the profession.** Presently available data demonstrates GBR therapy to be a predictable and successful procedure to augment bone in a horizontal direction at sites exhibiting insufficient bone volume for implant placement under standard conditions. Among the techniques introduced for vertical ridge augmentation, GBR is a successful technique, although distraction osteogenesis allows for more vertical bone augmentation than other techniques. For horizontal ridge augmentation, resorbable membranes have

successful and predictable results as nonresorbable membranes. The predictability of this procedure have been proved and established through various experimental and clinical studies. Diagnosis, treatment planning, careful execution of the surgical treatment, post-operative follow-up and appropriate implant loading are all important factors in achieving success.[24]

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