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Guided Bone Regeneration: A Boon To Dentistry

Corresponding Author: Dr Shashikanth Hegde,Dr Swetha Jayan, Dr Rajesh K.S,Dr Arun Kumar M.S,Dr Vinita Boloor, Dr Priyanka Menon
(Department of Periodontology,Yenepoya Dental College,Yenepya (Deemed to be University),deralakatte ,Mangalore ,Karnataka

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I. Introduction

Periodontal disease is one of the most prevalent diseases worldwide. Bacterial plaque has been implicated as the major etiological agent in the initiation and progression of inflammatory periodontal disease. The hallmarks of periodontal disease are destruction of soft connective tissues, bone loss, and loss of connective tissue attachment to cementum; these alterations, if left untreated, lead to tooth loss.[1]

Periodontal therapy has almost always focused on the arrest of the disease progress and maintenance of the remaining periodontal support. Treatment to restore periodontal health and achieve re - institution of attachment apparatus has varied based on the aetiology and encompasses procedures such as root planing, soft tissue curettage and various types of flap procedures, often in combination with the placement of bone grafts or bone substitutes into the defects.

Regenerative procedures currently in use in periodontal therapy have not been able to achieve regeneration in the true sense. There have been reports of gaining new attachment by the formation of new cementum. However bone formation is largely insubstantial or delayed.[2]

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. Although many methods for bone reconstruction exist, they all have specific indications and limitations.

Guided bone regeneration provides space using barrier membrane that are to be subsequently filled with new bone.[3]

The term, guided bone regeneration, has been used in tissue engineering for some years and is actually a specialized sub-area of tissue engineering. The term states the aim of the work: the bony tissue regeneration and growth along the surface and the structure of the implanted scaffold.[4]

The technique of guided bone regeneration was first described by Hurley and colleagues in 1959 for experimental spinal fusion treatment. In 1964, Boyne PJ showed that the placement of cellulose acetate filters could improve the regeneration of alveolar bone defects in dogs. [5]

Dahlin et al [6] in 1989 applied the principle of GBR to bone formation and regeneration in bone loss areas in case of advanced periodontal disease and established the concept of 'osteopromotion'. In this technique, barrier membranes such as expanded polytetra-fluoroethylene (e-PTFE) membrane should be placed closely over bony defects, thereby creating an inductive space for osteogenic cells.

Lazzara et al in 1980's is credited with the first reported use of GBR techniques with implants in immediate extraction site.[7]

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.[4]

GBR has been demonstrated to be a new mechanism of filling the pocket with neo bone tissues by preventing the in growth of fibrous tissues and securing osteoconduction.[8]

GBR membanes also have an important function which encourages bone growth. It is utilized with dental implant or bone grafting materials.GBR membranes are available as non degradable and non degradable . Non degradable membranes include expanded poly tetra fluro ethylene and degradable poly lactic acid. [9]

GBR is a technique widely used for the augmentation of bony defects .It employs tissue engineering procedure to help achieve regeneration of tissues by acting as a barrier to impede migration of fast growing epithelium and connective tissue cells into bone graft space and allow slower migrating tissues to proliferate and differentiate.

GBR is reported as providing the best and the most predictable results when employed to fill peri implant bone defects with new bone. It improves the predictability of bone augmentation and provides long term stability to the new augmented site. [3] Vertical and horizontal alveolar ridge augmentation utilizing guided bone regeneration (GBR) has become a significant treatment option to provide optimal bone support for osseointegrated dental implants.[10]

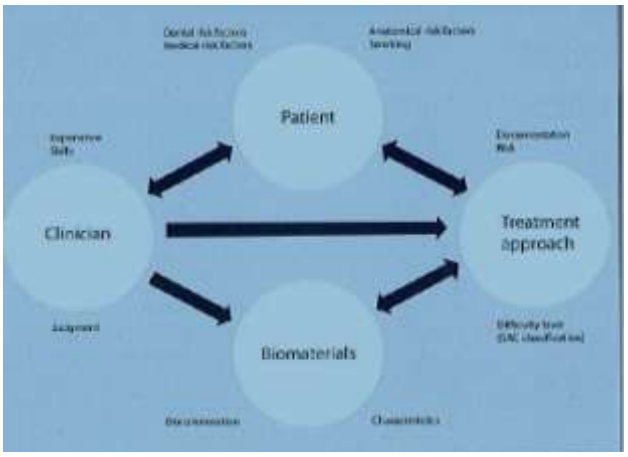
PRIMARY OBJECTIVES

1. Sucessful bone regeneration of the defect with high predictability to provide long - lasting function and esthetics
2.Low risk of complications

SECONDARY OBJECTIVES

1. The least number of surgical interventions
2. Low morbidity for the patient
3. Reduced healing periods

FACTORS INFLUENCING THE TREATMENT OUTCOME OF GBR PROCEDURES.[5]



BIOLOGICAL BASIS OF BONE REGENERATION

Bone reveals a unique potential for regeneration. It is able to heal fractures or local defects with regeneration of tissues.GBR usually in combination with a grafting material is the most widely used to augment bone. [5]

Bone is a relatively slow growing tissue, both fibroblasts and epithelial cells have the opportunity to occupy available space more efficiently and to build up a soft connective tissue, much faster than bone is able to grow. Thus the biological mechanism behind GBR is the exclusion of undesirable cells from the wound environment to enable cells from the bone tissue to proliferate into the coagulum filled space under the barrier membranes. If the occlusive barrier function lasts long enough and if the barrier membrane is not exposed to the oral cavity ,optimal conditions exist for the stem cells and osteoprogenitor cells to differentiate to osteoblasts which deposit the bone matrix.[5]

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 or bone marrow.

○ **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. [11]

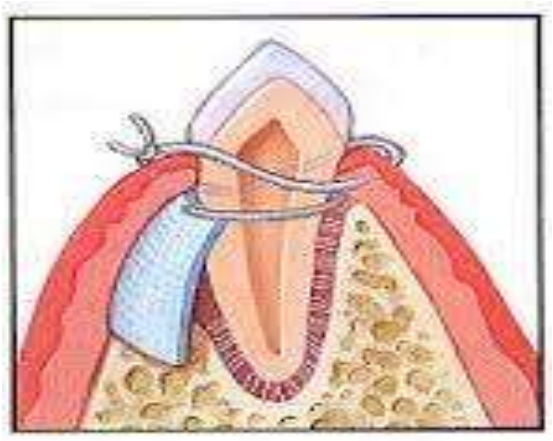


Figure - 1 - The membrane blocks unwanted tissues allowing ligament fibres and bone to grow.

BARRIER MEMBRANES

Guided bone regeneration is used to enhance bone growth of the alveolus for implant placement and around peri-implant defects.[7]

The first generation of barrier membranes developed in the 60s and 70s aimed to achieve a suitable combination of physical properties to match those of the replaced tissue with a minimal toxic response in the host. In the first GTR attempts, a bacterial filter produced from cellulose acetate (Millipore) was used as an occlusive membrane by Nyman et al.,[12] in 1982 Although this type of membrane served its purpose, it was not ideal for clinical application

A barrier membrane should satisfy the following conditions:

- Tissue adhesion without mobility,
- Block soft tissue in-growth,
- Easy to use, maintains a space, and biocompatibility.
- Appropriate integration with the surrounding tissue
- Clinical manageablity[13]

PROPERTIES OF BARRIER MEMBRANES

- Biocompatibility—the interaction between membranes and host tissue should not induce adverse effect;
- Space-making—the ability to maintain a space for cells from surrounding bone tissue to migrate for stable time duration;
- Cell-occlusiveness—prevention of fibrous tissue that delay bone formation from invading the defect site;
- Mechanical strength—proper physical properties to allow and protect the healing process, including protection of the underlying blood clot;
- Degradability- adequate degradation time matching the regeneration rate of bone tissues avoid a second surgical site for the membrane.[14]

Barrier membranes are of two types [14]

1. Non-Resorbable
2. Resorbable membranes - Synthetic and Natural Biodegradable

NON RESORBABLE MEMBRANES

1. Expanded Poly Tetra Fluoro ethylene (e PTFE)
2. High Density Poly tetra Fluoro ethylene (d- PTFE)
3. Titanium mesh

RESORBABLE MEMBRANES

SYNTHETIC

1. Polyesters
- Polyglycolic acid (PGA),
- Polylactic acid (PLA),
- Polyε-caprolactone (PCL) and their co-polymers

2. Collagen

COMPARISON OF NON-RESORBABLE MEMBRANE AND BIORESORBABLE MEMBRANES IN GTR

Jen-Chang Yang, Nai-Chia Teng et al (2008)[15] conducted a study to examine the historical changes of implanted three commercial GTR (Guided Tissue Regeneration) membranes for confirming the clinical feasibility in vitro and vivo. Among the resorbable GTR membranes, the collagen membrane is collagen base, and the PLA-PGA membrane is synthesized membrane, while the e-PTFE (Expanded polytetrafluoroethylene) is synthesized but nonresorbable.. In contrast, cementum height of 2.31 mm was observed in e-PTFE group. The collagen membrane and the PLA-PGA membrane seemed to be efficient in treatment of Guided Tissue Regeneration.

MEMBRANES BASED ON NATURAL MATERIALS

Membranes based on natural materials are typically derived from human skin, bovine tendon or porcine skin, and can be characterized by their excellent cell affinity and biocompatibility.

The main drawbacks of these membranes are the potential of losing space maintenance ability in physiological condition, high cost and possible danger of transmitting disease to humans when applying animal-derived collagen.[14]

CURRENT TRENDS IN THE DEVELOPMENT OF MEMBRANES

Chi-Fang Cheng A,B , Kai-Ming Wu C (2015) [16] compared bacterial adhesion onto various GTR membranes incorporated with antibiotics. Methods: Three barrier membranes, including expanded polytetrafluoroethylene (ePTFE) membrane, collagen membrane, and glycolide fiber membrane, were loaded with tetracycline or amoxicillin. The adhesion of Streptococcus mutans and Aggregatibacter actinomycetemcomitans onto the GTR membranes with or without antibiotics was analyzed using the scanning electron microscopy (SEM) analysis. The SEM analysis showed no apparent alteration in the physical structure of the membranes loaded with antibiotics. Both S. mutans and A. actinomycetemcomitans attached best on the collagen membranes, followed by the ePTFE membranes, and then the glycolide fiber membranes without antibiotics. Moreover, higher numbers of bacteria were observed on the fibril areas than on the laminar areas of the ePTFE membranes. The amounts of attached bacteria on the GTR membranes increased after longer incubation. Incorporation of tetracycline or amoxicillin greatly reduced the adhesion of S. mutans and A. actinomycetemcomitans onto all of the GTR membranes examined.

COMBINATION OF MEMBRANES WITH GROWTH FACTORS

Much advancement has been made since the original e-PTFE membranes, and surgical procedures are no longer necessary as they partially obstruct wound healing and increase patient discomfort. Synthesis and natural biomaterials have now been utilized in dentistry with great clinical success for over 20 years, and improvements are continuously being made regarding their mechanical properties and degradation rates. Furthermore, osteoconductive calcium phosphates and bioactive growth factors are now being incorporated to allow better bone formation, while antimicrobial substances aim to minimize the influence of bacterial contamination. The next generation of membranes are expected to combine more functional biomolecules projected to increase the success of GBR therapy.[14]

FOCUS ON PLASMA RICH PROTEINS AS GROWTH FACTOR MEMBRANES.

Platelet rich plasma isolated from platelets are a source of autologous growth factors. Choukroun platelet-rich fibrin (PRF) is a second generation of platelet derivatives after platelet rich plasma (PRP). It can be prepared by a single step and does not require any additives.[17]

When fibrin is used with the autogenous bone graft, however, it can increase bone formation, and act as a scaffold for the restoration of bony defects.

Fernandez-Barbero JE, Galindo-Moreno P et al (2006)[18] conducted a study in which twenty PRP gel samples from healthy volunteers were collected. These PRP gel specimens were prepared for transmission (TEM) and scanning electron microscopy (SEM) examination of their morphological ultrastructure. Flow cytometry with CD41-PE monoclonal antibody was used to detect platelet cells, as this antibody recognizes human-platelet-specific antigen CD41. Both SEM and TEM showed that PRP gel contains two components: a fibrillar material with striated band similar to fibrin filaments, and a cellular component that contains human platelet cells. Both techniques indicated that no morphological elements were bound between the cellular

component and the fibrillar material. The cells were confirmed as platelet cells by flow cytometric study after incubation with specific monoclonal antibody CD41-PE. PRP gel contains a fibrillar and a cellular (largely human platelet cell) component. This unique structure may be capable of acting as a vehicle for carrying cells that are essential for soft/hard tissue regeneration

BONE GRAFTS AND BONE SUBSTITUTES

Bone replacement grafts are widely used to promote bone formation and periodontal regeneration. Bone grafting materials function, in part, as structural scaffolds and matrices for attachment and proliferation of anchorage-dependent osteoblasts.

Ideal characteristics of a bone graft are: (Rosenberg and Rose, 1998; Nasr et al., 1999)[19]

- It should be nontoxic.
- It should be nonantigenic.
- It should be resistant to infection.
- Should not cause any root resorption or ankylosis.
- Strong and resilient.
- Easily adaptable and available.
- Should require minimal surgical intervention.
- Should stimulate new attachment and be able to trigger osteogenesis, cementogenesis and formation of a functional periodontal ligament.[19]

SURGICAL PROTOCOL FOR GUIDED BONE GENERATION

The following is the steps in GBR technique utilizing resorbable membranes (RMB) for successful bone augmentation.[20]

Step 1 - FLAP DESIGN

The incisions are designed in accordance with the following five goals:

A. Access to the bone defect

B. Maintenance of the blood supply of the elevated flap and the neighboring tissues

C. Preserving the interdental/implant papillae

D. Providing sufficient advancement of the flap

E. Allowing for tension-free primary closure

A full-thickness midcrestal (or slightly facial to the midcrest) incision is made between the teeth bordering the defect. Two full-thickness vertical incisions (preserving the bordering papillae) are then made down to the bone, starting in the area of the base of the vestibule and continuing coronally in one continuous cut to meet the crestal incision. In an edentulous area the incision design is a rectangular shape, whereas in a dentulous area the vertical incisions extend apical to the root apices. These incisions extend past the mucogingival junction into the mucosa and are designed to preserve the mesial and distal papillae while maintaining the blood supply of the neighboring tissue.

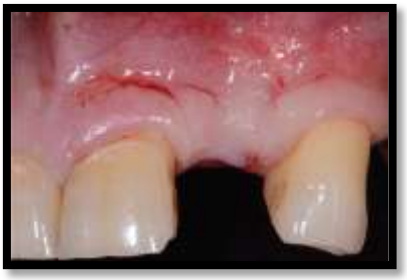


Fig.2 - Incision design: Mesial and distal vertical incision connected to midcrestal incision, preserving the mesial and distal papillae

STEP 2 - RECIPIENT SITE PREPARATION

The bony defect is debrided of granulation tissue and tissue tags, using curettes and back- action chisels. Cortical perforations (decortications) are then made with a #1 or #2 round bur using high speed with copious irrigation to create bleeding at the surgical site .(figure 3)

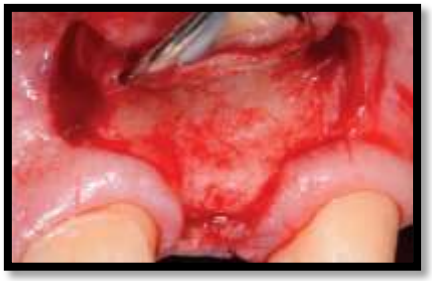


Fig.3- Flap is elevated, allowing for acces to the buccal bone

STEP 3 - RELEASING INCISIONS

Periosteal releasing incisions are made with a sharp 15 C blade on the inner apical portion of the flap creating a 2-3 mm split-thickness dissection [Figures 4]. These releasing incisions allow for better flap release and subsequent advancement of flap closure.

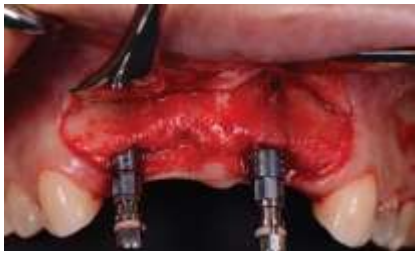


Fig.4 - Implant placement

STEP 4 - GRAFT MATERIALS AND MEMBRANE PLACEMENT

An autoclaved tinfoil is used as a template, fitted and trimmed to the ideal shape . A resorbable collagen membrane is then cut to the same shape as the template and placed over the surgical site. Once the membrane is in the correct position, it is then adjusted to extend 2-3 mm beyond the augmented area. The demineralized allograft bone (porous bone graft) is placed and condensed to fill the bone defect, ensure proper space maintenance and bone contact, and support the membrane.

STEP 5- STABILIZATION OF GRAFT MATERIAL AND BARRIER MEMBRANE

Stabilization of the membrane and the underlying graft material is achieved by using horizontal mattress sutures extending from the apical portion of the facial periosteum to the palatal aspect of the flap.

Fig.5 - Membrane is brought to the surgical site

STEP 6 - SUTURING TO ADVANCE THE FLAP CORONALLY

To coronally advance the flap, a horizontal mattress suture is used to connect the inner middle portion of the buccal flap to the inner aspect of the palatal flap. On the facial aspect, the suture is placed to the depth of the tissue while not completely perforating through the flap.

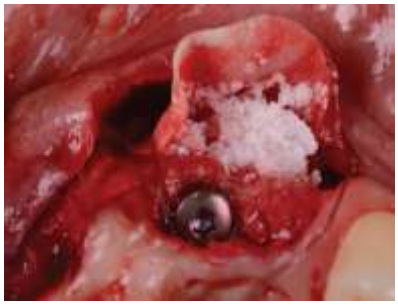
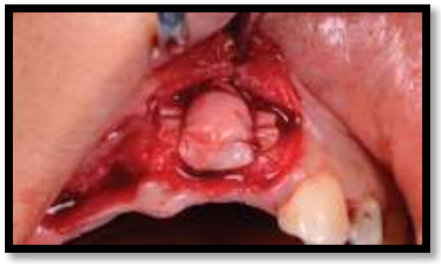


Fig.6 - Bone graft material is placed under the membrane and condensed

STEP - 7 : SUTURING TO ENSURE PRIMARY CLOSURE

Final tissue adaptation is achieved by means of multiple interrupted 4-0 chromic gut sutures, regularly spaced to close the incisions .



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Membrane is secured, tightened, and the knot is positioned inside the flap with membrane stabilizing sutures

Fig.8 - Final closure of flap after horizontal mattress suture is placed

HEALING AFTER GUIDED BONE REGENERATION

- **Primary wound closure is a fundamental surgical principle for GBR because it creates an environment that is undisturbed/unaltered by outside bacterial or mechanical insult**
- After GBR procedures, bone regeneration follows a specific sequence of events.

○ Within the first 24 hours after 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.

○ Mineralization of osteoid forms woven bone which later serves as a template for the apposition of lamellar bone. 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.[8]

CLINICAL APPLICATIONS OF GUIDED BONE REGENERATION

- Resorbable membranes have been developed to avoid the need for surgical removal. In situations where the bone defect margins are well maintained by the membranes, favorable results have been reported . [21]

Overall, their advantages are:

- single step procedure;
- patient's lower stress and morbidity;

- low risk of complications;
- better cost-benefit ratio;
- Allow to raise a split thickness flap at 2-stage implant surgery.

Peri-implant defects can be grouped into:[22]
• Fenestrations
• Dehiscence
• Horizontal defects
• Vertical defects

FENESTRATION

Implant fenestrations are the clinical conditions that occur when the middle or apical (buccal or lingual) surface of the implant is exposed. It is a typical consequence of implant placement corresponding to an alveolar ridges concavity at the most apical portion, or to residual defects after granulomas or cysts extraction or in cases where, for prosthetic reasons, the position of the implant follows a different angle from that of the ridge. In these defects only a small implant portion (< 2 mm) is shown in vestibular/lingual plate.[22]

DEHISCENCE

Implant dehiscences are clinical conditions that occur when a part of the implant (also including the coronal portion) remains exposed from the bony ridge. They are frequently observed in cases of tiny alveolar ridges, or in the case of post-extraction implants with no buccal or lingual cortical bone. In the case of intra-alveolar defects and peri implant dehiscences, in which the volume stability of the region to be augmented is provided by the adjacent bone walls, a bioresorbable membrane, in combination with a particulate bone substitute, represents the treatment of choice.[22]

Fig.9 - Clinical evaluation showing concavity at crest and facial aspect of missing tooth and loss of clinical attachment in tooth

Fig.10 - Revealed dehiscence during implantation with 5 to 6 visible threads.

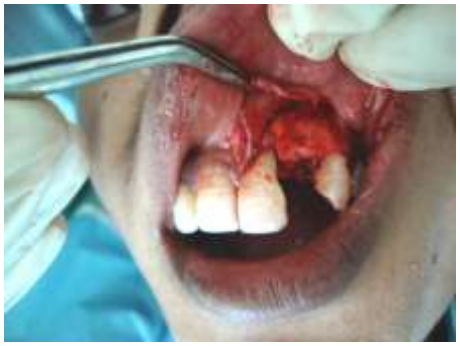


Fig.11 - Photograph of Guided Bone Regeneration (GBR) procedure with Bio-Oss and BioMesh (Resorbable Barrier Membrane

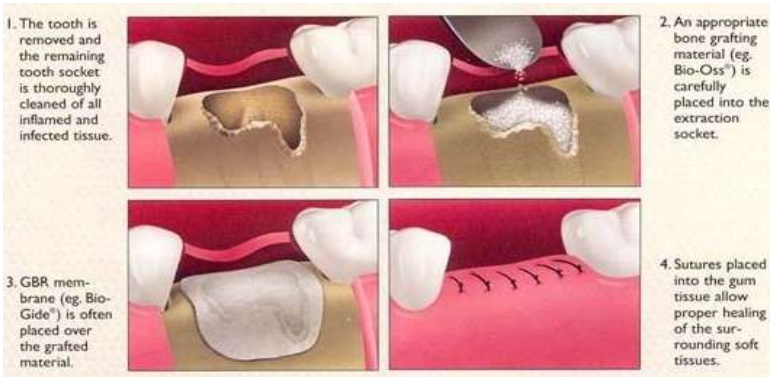
RIDGE PRESERVATION

The alveolar ridge undergoes a significant remodeling process following tooth removal. When implant placement is planned at a time point after the tooth extraction, it may be advisable to perform a ridge preservation procedure to counteract the subsequent reduction of the ridge dimension .[23]

CLASSIFICATION OF BONE DEFECTS

BONE DEFECT	DESCRIPTION
CLASS 0	Site with a ridge contour deficit and sufficient bone volume for standard implant placement
CLASS 1	Intra-alveolar defect between the implant surface and intact bone walls
CLASS 2	Peri-implant dehiscence, in which the volume stability of the area to be augmented is provided by the adjacent bone wall.
CLASS 3	Peri-implant dehiscence, in which the volume stability of the area to be augmented is not provided by the adjacent bone walls
CLASS 4	Horizontal ridge defect requiring bone augmentation before implant placement
CLASS 5	Vertical ridge defect requiring bone augmentation before implant placement

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.

SOCKET GRAFTING

In 1993, Misch and Dietsh suggested different graft materials and techniques based on the number of bony walls that remained after the tooth is removed. A thick five bony wall defect will grow bone with almost any resorbable graft material (RGM); for example an alloplast, allograft, or autograft. When a wall of bone is less than 1.5 mm or a labial plate is missing (four bony wall defect), an autograft or an alloplast or freeze-dried bone (FDB) with BM and GBR increased the predictability of restoring the original bony contour.

ALVEOLAR RIDGE AUGMENTATION BEFORE IMPLANT PLACEMENT

GBR has been experimentally applied for regeneration of alveolar ridge defects before implant placement. **Seibert & Nyman (1990)** [24] 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. **Smukler et al. (1995)**[25] reported that the application of barrier membranes in Class III ridge defects led to a mean augmentation by 3.31 mm. **Buser et al (1995)**[26] reported a mean gain of 1.5–5.5 mm in new bone formation 6–10 months following GBR application.

SINUS AUGMENTATION

Augmentation of maxillary sinus is way of attaining sufficient bony height for placement of posterior maxillary implant

II. Conclusion

Guided bone regeneration is a surgical procedure of choice for localized hard tissue augmentation. A predictable result can be achieved if the prescribed surgical protocol is followed. The available evidence clearly shows the predictability of GBR procedure in regeneration of bone in deficient alveolar ridge both in height and width. 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. Much advancement has been made since the original e-PTFE membranes, and surgical procedures are no longer necessary as they partially obstruct wound healing and increase patient discomfort. The next generation of membranes is expected to combine more functional biomolecules projected to increase the success of GBR therapy . 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.

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