DOI: 10.7860/JCDR/2021/47728.14714

Review Article

Dentistry Section

Guided Bone Regeneration- A Comprehensive Review

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ABSTRACT

Successful implant treatment requires prosthetically driven placement of an implant, primary stability at placement, and careful living bone management. The resorptive changes of alveolar bone are an inevitable process following tooth loss, periodontal disease or trauma which causes bone defects. This results in various aesthetic and functional complications such as soft tissue recession, infection and inflammation. Various methods have been tried and advocated for augmenting these bone deficiencies. Guided Bone Regeneration (GBR) is a successful modality for bone augmentation with a wide range of indications and helps restore the alveolar ridge dimensions. It utilises the principle of Guided Tissue Regeneration (GTR) for space maintenance within a bony defect. Different types of barrier membranes are being utilised along with various bone grafts in GBR. Thorough knowledge regarding the biology of bone is required before the initiation of any bone augmentation procedure. A combination of Collagen Membrane (CM) and graft material was found successful for GBR. Hence, this review focuses on presentation of best available evidence for various aspects of GBR.

Keywords: Barrier membrane, Bone grafts, Growth factors, Implants

INTRODUCTION

The practice of replacement of missing teeth using dental implants has become a routine procedure with predictable results. Prosthetically driven implant placement, in most cases, causes lateral or vertical bone defects [1]. This requires careful management of the living bone, which plays a considerable role in the implant's success. Incompletely covered implants may result in soft tissue recession, inflammation, infection, and implant loss. Hence, sufficient bone should cover the implant surface to prevent any complications. Various methods are available for bone augmentation, such as distraction osteogenesis, autogenous block grafts and GBR [2].

Guided Bone Regeneration (GBR) is a widely used technique with the most predictable results for the augmentation of bony defects [3]. It adopts the principle of GTR to help achieve tissue regeneration 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, thus providing sufficient bone at the augmented site [4,5]. Using GBR, vertical and horizontal alveolar ridge augmentation has become a popular treatment choice to provide adequate bone support for osseointegrated dental implants [6]. Besides, GBR can be used for regeneration in various other bone defects [Table/Fig-1] [7].

Periodontal/Peri-implant defects	Implant related defects	Extraction associated defects
Apical fenestrations	Sinus augmentation	Post extraction ridge preservation
Peri-implant defects (Peri-implantitis)	Crestal bone defects	Long standing extraction sites
Vertical bone defects and furcation defects	Early implant placement	Failed implant sites

[Table/Fig-1]: Indications for GBR [7].

Biological Principle of GBR

The fundamental requirement for the success of GBR is space maintenance within a bony defect. The growth of soft tissue is much faster than that of bone cells and blood vessels [8]. Hence, there is a necessity to place a barrier to prevent this unwanted migration of epithelial cells and connective tissue fibroblasts. This allows the growth of slower-growing bone cells. This can be achieved based on the principles of GTR for periodontal regeneration [8].

BARRIER MEMBRANE MATERIALS

The barrier membrane's basic requirement is to be biocompatible, well-tolerated by the patient, and cell occlusive. These are generally of two types: 1. Non-resorbable (ePTFE, Titanium reinforced PTFE); 2. Resorbable (Polylactides, Polyglycolides, CMs). Non-resorbable barrier membranes are first-generation membranes that are difficult to handle clinically. These are generally hydrophobic and do not adapt easily to the defects [9]. The major drawback of these membranes is the need for a second surgery for membrane removal [10]. Resorbable membranes generally include Polymeric and CMs. Biodegradation of these CMs is generally associated with multinucleated giant cells and an inflammatory reaction in soft tissue. This is frequently associated with polymeric membranes. To reduce the rate of biodegradation and to prolong their barrier function, some manufactures have cross-linked collagen [11]. Cross-linking with glutaraldehyde is the most widely used method, but there is a risk of residual cytotoxic residue in the membrane after the manufacturing process. These are less susceptible to complications. If early membrane exposure occurs, secondary soft tissue healing occurs within four weeks, and the bone regeneration outcome remains favourable. The non-resorbable membranes have little or no effect on the bone gain when used in combination with GBR [3].

For better clinical outcomes using GBR, the membranes should possess the following qualities [12]:

1. **Cell exclusion:** The barrier membrane in GBR prevents fibroblasts, epithelial cells from attaining access to the wound site and developing fibrous connective tissue.
2. **Tenting:** In the process of tenting, the membrane is securely adapted to the defect so that there is a space formed between the defect and the soft tissue over it. The membrane must always extend 2-3 mm from the edges of the defect and should be trimmed accordingly, and the corners should be rounded to prevent soft tissue injury/perforation.
3. **Scaffolding:** The fibrin clot formed in the space created by the membrane acts as a scaffold and helps the progenitor cells to grow inward, forming bone.

4. **Stabilisation:** The membrane's principal role is to see that any mobility does not dislodge the clot from the flap during healing. This is achieved by immobilisation by sutures, mini bone screws and/or bone tacks. Care has to be taken to avoid flap tension [12].

Properties of Barrier Membranes

Biocompatibility: The interaction between the membrane and tissue should positively affect the surrounding tissue, leading to the healing of the defect. It is the most critical factor to be taken into consideration before choosing a membrane.

Space-making: A membrane must be durable enough and create space to promote bone formation.

Cell-occlusive: To limit the ingrowth of soft tissues into the regeneration site and allow oxygen, fluids, and bioactive substances for cell growth to reach the defect.

Mechanical strength: A membrane should not be too rigid because it hinders the integration with the tissues or creates soft tissue dehiscence, or too flexible, making it difficult to handle.

Degradability: If the membrane is resorbable, it should either degrade or integrate into the host tissues without causing harm to the surrounding tissues [13].

AUGMENTATION MATERIALS

Various biomaterials are available for hard tissue augmentation, such as autografts (osteogenesis, osteoconduction, osteoinduction), Allografts (osteoconductive, osteoinductive), Xenografts, Alloplasts (osteoconduction) [14]. Autografts generally resorb faster, while the osteoconductive potential is high for allografts and alloplasts, while xenografts are nearly non-resorbable. Autografts are generally termed as the gold standard of all bone grafts due to their high osteogenic potential. Autologous bone chips are used to accelerate the new bone formation and increase new bone formation. These chips are being harvested locally from the vicinity of the implant site. This reduces donor site morbidity, time efficiency, and lower treatment costs. These chips are generally used to cover the exposed portion of the implant surface [15]. Generally, a two-layer composite graft is used to cover the defect. The second layer generally comprises bone graft with a low substitution rate, which gives the graft stability for long periods. Deproteinised bovine bone material has been proven to have a low substitute rate when embedded in bone. This also supports the membrane overlying and thus prevents its collapse [16].

Non-resorbable membranes are termed as the gold standard among the available membranes. For years, it was thought that they had a more considerable number of complications than other membranes, which was contradicted in a recent meta-analysis by Thoma DS et al., [3]. The best results were shown when a CM was used in combination with a bone graft [3].

GBR is a reliable treatment modality for vertical bone augmentation compared with other available treatment modalities [17].

HEALING AFTER GUIDED BONE REGENERATION (GBR)

The fundamental principle for a successful GBR procedure is the achievement of primary closure as it creates an undisturbed environment that enhances wound healing. After GBR procedures, bone regeneration follows a specific sequence of events [18]. Within 24 hours, the defect space is filled with the blood clot, releasing growth factors and cytokines to attract neutrophils and macrophages. Later, the clot is absorbed and replaced with granulation tissue, rich in newly developed blood vessels and fibroblasts. Osteogenic stem cells, along with nutrients, are transported through the blood vessels and form osteoid.

Woven bone, formed from osteoid mineralisation, acts as a template for lamellar bone deposition. This matrix eventually organises as a compact and reticular bone within 12-16 weeks postsurgery [19,20].

DISCUSSION

GBR and Implants

Prosthetically driven implant placement can result in peri-implant bone defects. Regeneration of bone around the implant ensures that the implant body is entirely covered by hard tissue. GBR ensures clinicians place implants into deficient alveolar bone successfully. The decision to place implants simultaneously or use a staged approach generally depends on the type of defect. Two and three wall defects are generally treated with a simultaneous approach, where one wall defects are treated with a staged approach [21]. The decision of a staged or simultaneous approach is solely dependent on the primary stability. The flapless extraction technique is preferred to minimise trauma and bone loss. Another important aspect of GBR is the decortication of the bone. This accentuates the blood supply to the augmentation area, thus increasing the mobility of the osteoprogenitor cells to the GBR treated area [22]. Bone conditioned media is the best-documented evidence regarding the use of bone grafts around the implants [23]. A tension-free flap closure is also a crucial step in GBR. If tension exists in the flap, it may compromise the area's blood supply, causing necrosis [24].

Recent Advancements/Future Directions in GBR

1. **Stromal-cell Derived Factor-1a (SDF-1a) in PCL/gelatin electro-spun membranes for Guided Bone Regeneration (GBR):**

Ji W et al., assessed the significance of membrane functionalisation with a chemotactic factor on cell recruitment and bone formation. GBR membranes were developed by electrospinning poly (ε-caprolactone) with type B-gelatin and activated with Stromal-cell Derived Factor-1a (SDF-1a) via physical adsorption. The outcomes revealed that SDF-1a loaded membranes have significantly enhanced bone formation after eight-weeks of implantation. Sites with SDF-1a loaded membranes showed a higher amount (six times) of total bone formation than those implanted with bare membranes [25].

2. **Alveolar Ridge Augmentation with Titanium Mesh**

Titanium mesh (Ti-mesh) has better mechanical properties which allows for the stabilisation of bone grafts under the membrane. Also, it is sufficiently rigid to provide significant space maintenance and thereby prevents contour collapse; its elasticity prevents mucosal compression; its stability prevents graft displacement. Ti-mesh's drawback is that it has increased exposure due to their stiffness and a more complex secondary surgery to remove them [26].

Poli PP et al., selected 13 patients for alveolar ridge reconstruction treatment before implant placement. Every subject underwent bone augmentation through a Ti-mesh filled with a mixture of intraoral autogenous bone and deproteinised anorganic bovine bone in a 1:1 ratio. Implant placement was done six months after healing. The study resulted in superior results at a mean follow-up of 88 months. This technique's clinical advantages offer the possibility of correcting severe vertical atrophies and the lack of significant complications if soft-tissue dehiscence and mesh exposures do occur [27].

3. **Influence of Piezosurgery on Bone Healing**

Sirolli M et al., conducted a histological study to evaluate the influence of two different techniques for implant site preparation on bone healing around titanium implants. Conventional drilling technique (control–DRILL group) or with a piezoelectric device (PIEZO group). A higher bone area within the threads was observed in the PIEZO group. The piezosurgery also showed a higher proportion of mineralised tissue. However, the DRILL group presented better results for bone-implant contact. In conclusion, it was deemed that the piezo group had better results in terms of the parameters mentioned above compared to the conventional drilling technique [28].

4. Amniotic membrane for Guided Bone Regeneration (GBR)

Ríos LK et al., compared bone density of bone defects treated with the Lyophilised Amniotic Membrane (LAM) and CM. Lyophilised amniotic membrane/CM was used to cover one defect while the other was left uncovered (NC). The results showed a high bone density and defect repair by new bone in the LAM group. At three weeks, the bone density of the defects treated with LAM was higher than NC and equivalent to the density obtained with CM ($p<0.05$). This tomographic study showed that the lyophilised amniotic membrane provides equal or greater bone density than the CM used in GBR procedures [29].

5. Effect of Platelet Rich Fibrin (PRF) on Guided Bone Regeneration (GBR):

Data regarding the clinical application of PRF in bone regeneration is scanty. Knapen M et al., conducted a study on the calvaria of 18 rabbits and found that the early phase of bone regeneration (one week) had a higher proportion of connective tissue colonised the regeneration chamber. In the model chosen for the study, the L-PRF did not provide any additional effect on the kinetics, quantity, and quality of bone when used for GBR [30]. Another human retrospective study also found a significant bone gain when PRF was used to treat peri-implant defects. However, PRF had limited bone gain compared with that of the CM in terms of bone gain. Besides, future studies with proper study designs are required to prove the efficacy of LPRF [31].

6. Effect of Collagen Scaffolds, Growth Factors and Periodontal Ligament Stem Cells (PDLSC) on Guided Bone Regeneration (GBR):

Kämmerer PW et al., evaluated different approaches for GBR of peri-implant defects in minipigs. Fifteen peri-implant defects around calcium phosphate-coated implants were created and randomly filled with collagen/hydroxyl apatite/β-tricalcium phosphate scaffold (CHT), jellyfish collagen matrix, CHT+ Growth Factor Cocktail (GFC), jellyfish collagen matrix + GFC, collagen powder, and collagen powder + Periodontal Ligament Stem Cells (PDLSC) and control group (blank). In all groups, histological examination was conducted evaluating Bone to Implant Contact (BIC), New Bone Height (NBH), and vertical bone apposition to estimate new bone formation after four months. No statistically significant differences were detected among the groups except for BIC and NBH, significant with the collagen powder group compared to the collagen matrix and collagen matrix + GFC groups. This study concluded that GBR procedures, combined with implants coated with CaP, will lead to enhanced peri-implant bone growth. No additional significant enhancement of osseous regeneration was observed using GFC or PDLSC [32].

7. Effect of Spatiotemporal Delivery of IL-8 and BMP-2 on Guided Bone Regeneration (GBR):

Lin D et al., thoroughly investigated the synergistic effect of IL-8 and BMP-2 on bone healing, and underlying mechanisms were thoroughly investigated. Regeneration of large bone defects requires endochondral ossification, which is initiated by endogenous repair mechanisms. Exogenous chemokine IL-8 and BMP-2 were linked with a mesoporous bioactive glass based spatiotemporal delivery system to achieve rapid initiation and stimulation IL-8 followed by sustained long term release of BMP-2. IL-8 served as a reservoir for endochondral ossification by upregulating the chondrogenic genes, inducing the formation of extensive cartilage tissues, promoting accelerated bone transformation by BMP-2. Sequential signal stimuli of IL-8, rapid initiation induced by BMP, osteo chondrogenic balance at the first stage of endochondral ossification, osteoconductivity promoted by scaffolds with high expression of BMP receptors, together resulting in initial bone mineralisation and regeneration of the large bone defect. However, future human studies are required to prove this hypothesis created by the invitro studies [33].

CONCLUSION(S)

GBR is a surgical procedure of choice for augmenting hard tissue around teeth and implants. A predictable result can be achieved if one has a thorough knowledge regarding the biomaterials involved and the above prescribed surgical protocol is followed, particularly around implants. The choice of selection of bone grafts and the membranes is up to the clinician skills and availability of the materials. Despite its predictability, GBR, like any other surgical procedure, has shortcomings due to its dependency on biomaterials. The available preclinical and clinical evidence suggests that GBR constitutes a successful therapeutic approach for treating peri-implant bone defects and preserving the alveolar socket's dimensions and configuration following tooth extraction. Further, the research scope is immense in GBR procedures, as new biomaterials are being introduced to provide better bone gain, thus increasing the reliability of the procedure.

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PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Nov 12, 2020
- Manual Googling: Feb 10, 2020
- iThenticate Software: Mar 09, 2021 (20%)

ETYMOLOGY: Author Origin

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was informed consent obtained from the subjects involved in the study? NA
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **Nov 11, 2020**
Date of Peer Review: **Jan 12, 2021**
Date of Acceptance: **Feb 11, 2021**
Date of Publishing: **Apr 01, 2021**