GUIDED BONE REGENERATION (GBR)

INTRODUCTION

Guided bone regeneration (GBR), a therapeutic modality, aiming to achieve bone regeneration (Dahlin et al. 1988). GBR, a surgical procedure that uses barrier membranes with or without bone grafts or/and bone substitutes.[1] Major function of barrier membrane includes: provides stability to the bone graft, prevents soft tissue from collapsing into the defect, prevents competing non-osteogenic cell migration into the site, and accumulates growth factors.

Although the concept was initially proposed for the regeneration of tissues associated with the periodontium, the proof of principle was soon applied to regenerate edentulous alveolar ridges.

Osseous regeneration by GBR be governed by the migration of pluripotent 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).[2]

HISTORICAL BACKGROUND

In 1947, Berg hypothesized that osteosynthesis in the spine was more surely and rapidly achieved if the paraspinal muscles were elevated from decorticated laminae by bone grafts, creating a space in which bone-forming granulation tissue could grow. Shortly, Hellstadius put Berg's theory to test by using stainless-steel cups and rings to elevate muscles from the roughened cortes of a rabbit's femur. He concluded that bone would not form in granulation tissue if the soft parts were held away.

In 1959, Hurley et al first described the principle of placing membrane between a bone defect and the surrounding soft tissues, (later termed as Guided bone regeneration).[3]

Barrier membranes was first evaluated in 1950s and 1960s by Bassett, et al and Boyne, et al. for osseous facial reconstruction by Nyman., et al.[4]

GTR was first developed in the early 1980s by Nyman et al.[5]

Murray first described the procedure of placing barrier membranes for regeneration of lost bone in reduced alveolar width. The term guided bone regeneration (GBR) was introduced in the 1980s as an upshot of GTR by Nyman and Gottlow, who applied occlusive barriers in periodontal healing studies to stop the cell migration from gingival connective tissue and epithelium to the periodontal defect, which can interfere with tissue regeneration.[6]

Dahlin and colleagues headed early research on GBR in an attempt to solve the confounding problem of reconstructing large osseous defects in the jaws and for the treatment of the atrophic maxilla or mandible.[7]

PRINCIPLES OF GUIDED BONE REGENERATION

Basic Principle

The principle of GTR is to impede apical migration of epithelium by placing a membrane between the flap and root surface (preventing contact of the connective tissue with the root surface); cells derived from the periodontal membrane are induced on the root surface selectively and periodontal tissue is regenerated. The concept of guided tissue regeneration was first developed by Melcher in 1970.[8]

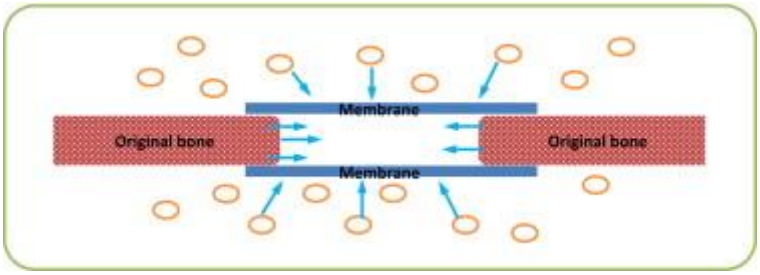

Image source: Rakhmatia et al. Principle of Guided Bone Regeneration. 2013. 57.10.1016/j.jpor.2012.12.001.

Biological Principle

Wang et al. in 2006 described 4 major biologic principles (i.e., PASS) necessary for predictable bone regeneration:

a) *Primary Closure*

   True healing by primary intention is often difficult to achieve. However, 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.

b) *Angiogenesis*

   The addition of bone grafting materials and membranes, in accordance with the principles of GBR, serves to create space and mediate osteogenesis via potential release of bone morphogenetic proteins. The first 24 hours are characterized by formation of a blood clot, the initial blood clot is removed by neutrophils and macrophages, and initial formation of granulation tissue begins within the next days and weeks. There is an intimate relationship between newly formed blood vessels and de novo bone formation.[9] The granulation tissue is rich in blood vessels, and it is these vessels that are key to osteoid formation and subsequent mineralization to woven bone.[10] Melcher and Dryer also emphasized the importance of the blood clot in healing of bony defects.[11]

c) *Space Creation/Maintenance*

   Providing adequate space for bone regeneration is a fundamental principle of GBR. Space is needed to ensure the proliferation of bone forming cells while excluding unwanted epithelial and connective tissue cells. Reinforced membranes allow space maintenance by preventing membrane collapse that may occur from pressure of overlying tissues.

d) Stability

The role of a barrier membrane is double, it not only excludes unwanted cells but also acts to stabilize the blood clot.[12] The importance of initial clot adhesion and wound stabilization is critical in wound healing. The initial blood clot is a rich source of cytokines (e.g., interleukin-1, interleukin-8, tumor necrosis factor), growth factors (e.g., platelet derived growth factor, insulin-like growth factor, fibroblast growth factor), and signaling molecules that recruit clearing cells to the wound site. Platelet derived growth factor in particular is a potent mitogen and chemoattractant for neutrophils and monocytes.[13]

The barrier membrane placement should result in:

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: A procedure in which 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. 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 dehiscence or fenestrations, the membrane must be supported to prevent collapse.[14]

INDICATIONS FOR GBR

1. Local alveolar ridge deficiencies (horizontal or vertical).
2. Osseous fill around immediate implant
3. Dehiscence and fenestration associated with implants.
4. Bone defects associated with falling implants.
5. Residual bone lesions
6. To aid in repair of sinus membrane perforations

GRAFTING MATERIALS

GBR is a surgical procedure that uses barrier membranes with or without particulate bone grafts or/and bone substitutes.

Classification of Barrier Membranes:

Membranes used for periodontal regeneration are mainly classified on the basis of their property of getting resorbed:

1. Nonresorbable expanded Poly Tetrafluoroethylene (e-PTFE) Gore-Tex High density poly tetrafluoroethylene (d-PTFE) Titanium mesh Titanium reinforced PTFE

2. Resorbable Polymeric (vicryl, atrisor, Epiguide) & collagen derived.[15]

Membranes for guided bone regeneration:[16]

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.

The second generation of barrier membranes was designed to be resorbable to avoid the need for surgical removal. There are two broad categories of bioresorbable membranes: the natural and the synthetic membranes.

Natural bone graft and substitute materials.			
Material Type	Forms Available	Material Source	Examples of clinically used bone grafts
Cortical Allograft	Fresh, frozen, freeze-dried Whole bone segments, block, pieces	Mineralized cortical allograft	MinerOss Cortical™
Cancellous Allograft	Fresh, frozen, freeze-dried Chips, wedges, pegs, powder	Mineralized cancellous allograft	MinerOss Cancellous™
Demineralised Bone Matrix	Putty, moldable pastes, blocks, particulates, powder	Human DBM	Dynagraft D Putty™ Opteform™ Grafton DBM™
Deproteinised bovine bone	Block, granules, particulates	Bovine	BioOss™ OsteoGraf™ Cerabone™
Algae-based	Granules	Red algae	Algipore™
Coral-based	Block, Granules	Marine coral	ProOsteon™ BioCoral™ InterPore™
Synthetic bone grafting materials.			

Material Type	Forms Available	Examples of clinically used bone grafts
Hydroxyapatite	Blocks, wedges and granules	Ostim™ Endobon™
Tricalcium phosphate ceramics	Blocks, cylinders, wedges, granules	Cerasorb™ OSferion™ Orthograft™
Biphasic calcium phosphate ceramics	Moldable putty, granules	MASTERGRAFT™
Bioglasses	Particulates	Perioglas™ Biogran™
Calcium phosphate cements	Injectable paste, moldable putty	Norian™ ChronOS inject™ Hydroset™ BoneSource™
Calcium sulfates	Various sizes pellets	OsteoSet™
Polymers	Particulates, granules, ready to use in syringe	Bioplant HTR Synthetic Bone™
Metals	Mesh/membrane available in lateral and papilla design forms	OSS Builder™
Composites	Putty, granulate, block, ready to use “QD”	NanoBone™ (nanocrystalline HA/silicon dioxide)
	Paste	Fortoss Vital™ (_-TCP/calcium sulphate)
	Blocks, microchips, plate, granules, wedge, cylinder, rod	SmartBone™ (DBM/polymer/collagen)

Table1: Table Source Zhao R. Bone Grafts and Substitutes in Dentistry. 2021. doi: 10.3390/molecules26103007.

SURGICAL PROCEDURE

Step 1: The flap is designed in accordance with the following five principles.

a. Access to the bone defect

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

c. Preserving the interdental papilla

d. Providing the sufficient advancement of the flap

e. Allowing for tension-free primary closure

A full-thickness midcrestal incision is made between the teeth preserving the interdental papilla. Two full-thickness vertical incisions are made down to the bone on either side, starting in the area of the base of the vestibule and continuing coronally in one continuous cut to meet the crestal incision.

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. The decortications are designed to increase the blood supply and osteogenic progenitor cell migration from the bone marrow to the site of augmentation.[17]

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.

Step 4: Graft materials and membrane placement

Step 5: Stabilization of graft material and barrier membrane

Step 6: Suturing to advance the flap coronally

Step 7: Suturing to ensure primary closure

Final tissue adaptation is achieved by means of multiple interrupted regularly spaced to close the incisions.

Complications associated with GBR

Postoperative complications occurring after periodontal surgery can be categorized as following

A. General Complications arising after periodontal surgery:

- Bleeding
- Swelling
- Postoperative pain
- Root hypersensitivity
- Increased tooth mobility
- Delayed wound healing
- Trismus

- Postoperative bacteremia
- Taste changes
- Bruising

B. Complications arising due to the surgical procedure employed

- Local anaesthesia related
- Flap related
- Graft related
- GTR related
- Suture related
- Periodontal pack related[18]

Complications that are specifically related to GBR are mentioned below:

Complication classification associated with non-resorbable membrane.

Complications can be classified as either healing (Class I to IV) or surgical (A to C).

Healing complications:

Class I: Small membrane exposure (≤ 3 mm) without purulent exudate

Class II: Large membrane exposure (> 3 mm) without purulent exudate

Class III: Membrane exposure with purulent exudate

Class IV: Abscess formation without membrane exposure

Surgical complications:

- A: Flap damage

- B: Neurologic complications
- C: Vascular complications

CONCLUSION

It can be concluded that GBR can predictably lead to regeneration of critical size maxillofacial defects and to de novo bone formation via a synchronised progression of events recapitulating intramembranous ossification. 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. Preclinical and clinical trials investigating the physiology and pathophysiology of the healing process following GBR application at the molecular level are warranted, with a view to develop and implement novel therapeutic strategies, e.g. tissue engineering, drug delivery and/ or gene therapy aiming to promote the bone formation and regeneration potential following GBR treatment.

REFERENCES

1. Dahlin C, Linde A, Gottlow J, Nyman S. Healing of bone defects by guided tissue regeneration. Plast Reconstr Surg 1988; 81(5): 672-6.
2. Healing of bone defects by guided tissue regeneration. Dahlin C, Linde A, Gottlow J, Nyman S Plast Reconstr Surg. 1988 May; 81(5):672-6.
3. Hurley, La, Stinchfield, F. E., Bassett,A. L., Lyon,W. H.The role of soft tissues in osteogenesis. An experimental study of canine spine fusions. J. Bone joint surg. Am. 1959. 41, 1243-1254
4. Bassett CAL, Creighton DK and Stinchfield FE (1961). Contributions of endosteum, cortex and soft tissues to osteogenesis. Surg Gynecol Obstet 112: 145.

5. Nyman S, Karring T, Lindhe J, Planten S. Healing following implantation of periodontitis-affected roots into gingival connective tissue. J Clin Periodontol 1980; 7(5): 394-401
6. Dahlin C, Gottlow J, Linde A, Nyman S. Healing of maxillary and mandibular bone defects using a membrane technique. An experimental An experimental study in monkeys. Scand J Plast Reconstr Surg Hand Surg 1990; 24(1): 13-9.
7. Dahlin, C., Sennerby, L., Lekholm, U., Linde, A. et al., Generation of new bone around titanium implants using a membrane technique: an experimental study in rabbits. Int. J. Oral Maxillofac. Implants 1989, 4, 19-25.
8. Caffesse G, Becker W. Principles and techniques of guided tissue regeneration. Dent clin of N Am1991;35(3):479-93.
9. Schmid J, Wallkamm B, Hämmerle CH, Gogolewski S, Lang NP. The significance of angiogenesis in guided bone regeneration. A case report of a rabbit experiment. Clin Oral Implants Res. 1997 Jun;8(3):244-8. doi: 10.1034/j.1600-0501.1997.080311.x.
10. Melcher AH, Dryer CJ. Protection of the blood clot in healing of circumscribed bone defects. J Bone Joint Surg. 1962;44B:424-429.
11. Kostopoulos L, Karring T, Uraguchi R. Formation of jawbone tuberosities by guided tissue regeneration. An experimental study in the rat. Clin Oral Implants Res. 1994;5:245-253.
12. Weng D, Hurzeler MB, Quinones CR, et al. Contribution of the periosteum to bone formation in guided bone regeneration. A study in monkeys. Clin Oral Implants Res. 2000;11:546-554
13. Schenk RK, Buser D, Hardwick WR , et al. Healing pattern of bone regeneration in membrane-protected defects: a histologic study in the canine mandible. Int J Oral Maxillofac Impl. 1994;9:13–29.

14. Winet H. The role of microvasculature in normal and perturbed bone healing as revealed by intravital microscopy. Bone. 1996;19:39S-57S.
15. Bartold M, Gronthos S, Haynes D, Ivanovski S. Mesenchymal stem cells and biologic factors leading to bone formation. J Clin Periodontol. 2019 Jun;46 Suppl 21:12-32.
16. Wang HL, MacNeil RL. Guided tissue regeneration. Absorbable barriers. Dent Clin North Am. 1998;42(3):505–22.
17. Stuart J. Froum, Sang-Choon Cho, Leon Pariente. A surgical protocol for guided bone regeneration procedures using absorbable membranes to minimize and treat complications. Dental Learning 2012;6:3-13.
18. Zerr KJ, Furnary AP, Grunkemeir GL, et al: Glucose control lowers the risk of wound infections in diabetics after open heart operations. Ann Thorac Surg 1997;63:356–361.