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Guided Tissue Regeneration – Principles Revisited

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Abstract
Periodontitis is a disease characterized by inflammation of the gingiva that results in the periodontal pocket formation with loss of the supporting periodontal ligament and alveolar bone around teeth. For this reason, traditional non-surgical therapeutic modalities have aimed at eliminating the gingival inflammatory process and preventing the progression of periodontal disease, whereas surgical procedures have been directed towards the elimination and / or regeneration of the defects caused by the disease. During the last two decades, significant research and clinical advances in the area of periodontal therapy have led the therapist closer to achieving the predictable regeneration of the periodontium via the principle of Guided Tissue Regeneration.

Key Words
Periodontitis, Periodontal Regeneration, Barriers, Epithelial Attachment

Introduction

Periodontitis is one of the most prevalent diseases of the dental tissues and is defined as "inflammation involving and destroying the supporting alveolar bone and periodontal ligament." The lesion of periodontitis, is characterized by severe inflammation, subgingival plaque and calculus and results in the breakdown of tooth's supporting apparatus and leads to apical positioning of the pocket and junctional epithelium often with subsequent tooth loss[8].

The treatment of periodontitis thus involves not only the control of further breakdown by eliminating periodontal infection, but also regeneration of previously lost support. Main step in periodontal therapy involves the elimination of bacterial plaque. Following this, clinical signs of gingival inflammation, i.e. redness and bleeding, disappear. However increased probing depth, loss of clinical attachment and radiographically observed bone loss remains[6].

Conventional periodontal surgical techniques including gingivectomy, open flap debridement, modified Widman flap and osseous surgery have been used to eliminate such defects and have shown probing depth reductions and clinical attachment gain[5]. Until the mid -1970s, this gain of clinical attachment was interpreted to indicate that a true regeneration of the periodontium has occurred. However results from the controlled animal studies and human block sections have shown that conventional periodontal surgery resulted in repair by long junctional epithelium rather than regeneration and the defects persisted[11].

Histological studies showed that minimal or no attachment was achieved and that the rest of the marginal seal was established by long junctional epithelium[16].

Since then, a number of techniques have been proposed to delay the downgrowth of epithelium during healing and to provide an opportunity for regeneration to occur on previously diseased root surfaces.

There are two primary approaches to eliminate these defects.

i) **Resective Surgery:**
Seeks to eliminate periodontal defects by removal of the gingival and bony walls.

ii) **Regenerative Surgery:**
Seeks to eliminate periodontal defects by creating new bone and periodontal ligament and coronally displacing the gingival attachment and margin[7].

The importance of periodontal ligament in these regenerative procedures was shown by Loe and Waerhaug[12]. Later Melcher had hypothesized that selected cell populations residing in periodontal ligament could produce new cementum, alveolar bone and periodontal ligament, provided they occupy the periodontal wound[13]. This led to the development of concept of Guided Tissue Regeneration and the first human histological evidence of periodontal regeneration in response to guided tissue regeneration was given by Nyman et al[14].

The 1996 World Workshop in Periodontics defined Guided Tissue Regeneration as "procedures attempting to regenerate lost periodontal structures through differential tissue responses. Barriers are employed in the hope of excluding epithelium and gingival corium from the root surface in the belief that they interfere with regeneration".

Since then, Guided Tissue Regeneration is an evolving, multifaceted surgical technique that has tremendously improved the predictability of periodontal regeneration[18].

Rationale

Studies showed that the absence of new attachment is due to epithelial migration along the root surface and suggested that total exclusion of the epithelium was necessary for complete regeneration of attachment apparatus to occur[4]. Furthermore, Melcher hypothesized that periodontal ligament regeneration can only occur from cells of periodontal ligament and this could be attained by excluding connective tissue and junctional epithelium from the healing wound. Endosteum of bone was considered to be the source of undifferentiated cells[13].

The attachment of epithelial cells to the tooth surface and their migration in an apical direction were very rapid as compared with the formation of the new cementum and periodontal ligament[4]. The resultant long junctional epithelium could be established as early as 7 to 10 days after instrumentation. Although, this could be associated with acceptable clinical results, but re-establishment of connective tissue attachment was preferred for following reasons:

1) A connective tissue attachment on the root surface generally favours more regeneration of bone.
2) A connective tissue attachment consists of reservoirs of cells with the potential to form new bone, cementum, and periodontal ligament.
3) A connective tissue attachment can also mean a normal junctional epithelium, suggesting a shallower pocket depth and thus easier maintenance[2].

Wikesjo hypothesized that:

1. Apical migration of epithelium in periodontal wounds is not spontaneous but result from breakdown of the root surface fibrin clot interface.
2. Connective tissue attachment following periodontal regenerative surgery is directly related to maintenance of the root surface-adhering fibrin clot during early wound healing events[19].

Research was directed to make attempts either to slow down rate of epithelial attachment or to expedite the rate of formation of connective tissue attachment[1]. This resulted in the use of barriers during surgical intervention. It was observed that Barrier membranes, in addition to effectively eliminating gingival epithelium and gingival connective tissue from the healing wound **(Fig.3)**, also seem to protect the healing clot by eliminating the effect of the flap margin on the healing site. When a membrane is placed, it acts as an artificial flap, which protects the healing wound. Thus the flap margin interfaces with membrane and not with the healing wound itself. Thus, unwanted trauma or movement at the flap margin doesn't cause rupture of the fibrin clot-root surface interface.

Principles Of GTR

A number of materials were since employed and observed that not all materials could achieve desired objective. The design criteria's for guided tissue regeneration devices have been composed by Scantlebury[15], Gottlow[9] and Hardwick et al[10]. These criteria may be used to predict the effectiveness of different membrane materials used for guided tissue regeneration and to design specific membranes for individual guided tissue regeneration applications.

The design criteria's are :-

1) Tissue Integration:

In 1982, George Winter, had proposed that specific porosities ingrew with connective tissue and stopped or slowed the migration of epithelial tissues. He called this phenomenon "contact inhibition". To test this theorem, he placed small silicone buttons made with skirts of porous ePoly Tetra Floro Eethylene(ePTFE) material in the gingiva of dogs. The result of his experiments led to the evolution of the first design criteria :

"Membranes need an organised open microstructure to encourage tissue integration, which should result in stabilization of wound and inhibition of epithelial migration".

This stabilization of wound during early healing and inhibition of epithelial migration will result in increased connective tissue attachment.

2) Cell Separation:

In 1982, Dr. John Prichard indicated that ePTFE membranes limited the migration of epithelium, stabilized the wound and kept epithelium out of the healing periodontal defect.

Around the same time, Dr. Sture Nyman and co workers using paper filters, were able to regenerate periodontal ligament attachment to teeth. These landmark studies led to the second design criteria:

"Membranes should separate cell types so that the desired cells originating from periodontal ligament and bone could repopulate the defect area".

Cell exclusion requires incorporation of structural elements within the barrier that support isolation of the overlying gingival flap from the maturing fibrin clot in the wound. The overall shape of the barrier and how it adapts to the defect site, will also affect its ability to isolate regenerating tissues.

3) Clinically Manageable:

In June 1985, investigators in Europe and US began testing porous ePTFE clinically. The first membranes were difficult to cut, sutures sometimes pulled out or left large holes in the membranes and the removal of membranes was difficult because their porous structures were so well incorporated in the tissues.

All these findings led to the third design criteria:

"Materials should be cut and shaped easily. They should hold sutures and, in case of complications, should be removed easily".

With these criteria in mind, W.L. Gore and associates, Inc. in 1985 introduced two-part material:

a) **An open microstructure collar:** which could be implanted subgingivally, ingrows with the connective tissue and limits epithelial migration.
b) **An occlusive portion:** That would stabilize the wound area, separate cell types for guided tissue regeneration, give a strong structure to retain sutures, be easy to cut and shape with no sharp edges to perforate tissues and, in the event of complication, allow the membranes to be easily removed.

4) Space Making:

By 1988, barrier membranes had been clinically tested in Class – II furcations and 2 - and 3 - wall intrabony defects. It appeared that the space defined and protected by the membrane determined the volume of bone that could be regenerated. This led to the development of the fourth design criteria:

"The barrier should provide adequate space for the regenerating alveolar bone, periodontal ligament and cementum".

This criteria of space making becomes more critical in case of bone defects and it is seen that the healing bone follows the contours of the membrane like the contours of a mold. This criteria requires mechanical properties and structural features allowing barrier to withstand forces exerted by the overlying flaps or those transmitted through the flaps and prevent collapse of soft tissue and reduction of wound space[1],[2],[5].

Keeping this criteria in mind materials were redesigned with centre portion stiffened,(to support membrane and resist collapse from the pressure of overlying tissue), and the periphery was left soft and more porous (to provide for tissue in growth and wound stabilization).

5) Biocompatibility:

Biocompatibility is the ability of a material to perform with an appropriate host response in a specific situation, which means that neither the material adversely affects the body nor the physiological tissue environment adversely and significantly affects the material.

ePTFE is one of the most inert materials known and body can not react with it chemically, hence tissues accept it, while exhibiting a healthy tissue reaction.

However, resorbable and degradable materials are not inert. If they were inert they would not resorb or degrade. In such cases, a localized chronic inflammatory response may be acceptable, but a systemic immune response in which a patient's body actually becomes allergic to its own collagen presents more serious issues.

With any new material, in vitro and in vivo tests for biocompatibility are conducted which include heavy metals analysis, pyrogen and hemolysis testing, Cell culture cytotoxicity, animal experiments and short and long term histological tissue reaction.

With these design criteria establishing a general framework for barrier devices, quite diverse barriers have been introduced. These design criteria may expand to include other principles as more research and better understanding about biological demands of Guided Tissue Regeneration is carried out. In future, specific membranes may be designed to satisfy the requirements of individual applications.

Guided Bone Regeneration

Developing artificial replacement for missing teeth had been an elusive goal for more than 1500 years. Branemark in a landmark study initiated the replacement of missing teeth using an implant in 1952 and the first patient was treated with implants in 1965. Branemark presented his research for the first time in 1982 at a conference held in Toronto. His finding have since then opened a new era in the field of dental prosthesis and oral rehabilitation[3]. Since then, the principles of Guided Tissue Regeneration have been successfully applied to increase the volume of the host bone at sites chosen for implant placement. The concept of bone regeneration employs same principles of specific tissue exclusion and space provision, but is not associated with the teeth. Hence the term Guided Bone Regeneration (GBR) is used for this technique. Guided Bone Regeneration allows space maintained by barrier membranes to be filled with new bone.

Conclusion

During the last two decades, significant research and clinical advances in the area of periodontal therapy have led the therapist closer to achieving the predictable regeneration of the periodontium via the principle of Guided Tissue Regeneration.

Guided Tissue Regeneration is based on scientific evidence indicating that the type of healing resulting after periodontal surgery is determined by the tissues that first repopulate the root surface. This evidence indicates that periodontal regeneration occurs when cells originating from the periodontal ligament and / or the alveolar bone are selectively allowed to repopulate the root surface and the adjacent alveolar wound area. This is clinically obtained by placing a physical barrier between the gingival flap and the instrumented root surface during surgery. Placement of this barrier excludes the gingival epithelium and connective tissue from the root surface and creates an area into which progenitor cells from the periodontal ligament and / or the alveolar bone can migrate.

Guided Tissue Regeneration has now become a well- documented and accepted therapeutic modality to facilitate periodontal regeneration, and the use of non-resorbable and resorbable barriers should be a part of armamentarium for treating periodontitis.

Research is further being carried out to introduce device that maintain biocompatibility while exhibiting improved efficacy. Several modifications are currently being explored125 such as alteration of surface properties, incorporation of adhesion molecules, antimicrobial agents and growth factors.

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