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Review Article

Bio-materials and factors affecting periodontal regeneration: An overview

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ABSTRACT

The aim of periodontal regenerative therapy is to restore original architecture and function of lost periodontal tissues, as a result of trauma or following destructive periodontal diseases. This review includes the biological principles and efficacy and effectiveness of different biomaterials and factors affecting periodontal regeneration. Various human clinical trials showed a successful periodontal regeneration with different biomaterials. However, postoperative plaque control is one of the key factors influencing periodontal healing following regenerative periodontal therapy. A strong native regenerative potential of the periodontium can be conciliated by local and systemic factors.

1. Introduction

Periodontal regeneration is the reconstitution of the lost periodontium as a result of trauma or diseases to restore original architecture and function of the periodontium.[1] According to a position paper from AAP regenerative periodontal procedures includes soft tissue graft, guided tissue regeneration, bone replacement grafts, root bio-modification and combination thereof, for osseous, furcation and recession defects.[2] The objective of periodontal regenerative therapy is to augment the periodontal attachment and bone level of periodontally compromised tooth, decrease pocket depth along with limited/or minimal soft tissue recession. The outcomes of a regenerative periodontal treatment were evaluated clinically by means of periodontal probing, radiographs and re-entry re-evaluation. However, these methods are unfortunate for signifying true attachment gain. The efficacy of a periodontal regenerative therapy was assessed only by means of histology/histological method. From a biological point of view, periodontal treatment to be considered as regenerative procedures when controlled animal histological studies acknowledging new cementum, periodontal ligament and alveolar bone.[3] A strong native regenerative potential of the periodontium can be conciliated by local and systemic factors.

2. Different Biomaterials for Periodontal Regeneration

2.1. Guided tissue regeneration (GTR)

Basis for the development of the GTR principle was based on the understanding that the PDL has an essential significance to the regenerative processes of the tooth supporting structure. The guided tissue regeneration was the first technique to be used for periodontal regeneration that had a sound biological principle.

2.2. Biological principle for use of guided tissue regeneration

The rationale of the GTR concept was based on the use of a physical barrier membrane between the soft tissue flap and the root surface provide space by deflecting migration /proliferation of gingival epithelium and connective tissue cells from root surface during early healing phases and allows/favour the migration/proliferation of cells from the periodontal ligament and bone cells to repopulate root surface.

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2.3. Efficacy and effectiveness of GTR membrane

The periodontal ligament cells possibly forming a new connective tissue attachment only if the epithelium and gingival connective tissue were not permitted to occupy the wound area adjacent to the root surface.[4] Nyman et al.,[5] in a landmark proof of principle study, established that by using a Millipore filter, gingival epithelial and connective tissue cells were not permitted to repopulate the periodontal wound could resulting into periodontal regeneration. These treatment concepts were eventually named as guided tissue regeneration (GTR). The barrier membranes mainly contribute to a wound stability and space provision and to lesser extent in compartmentalization of tissue. Systematic reviews[6,7] and multicenter human clinical trials[8,9] support the efficacy and effectiveness of barrier membrane in reducing pocket depth and improving clinical attachment level and bone level gain in intrabony defect. A systematic review[6] and AAP position paper in 2005 found that there are no significant differences between non-resorable and bioabsorbable membrane.

2.4. Bone graft/ bone substitutes

Autogeneous bone, allogenic bone, xenogenic bone and alloplastic materials are collectively referred to as bone filler, all have been used with the aim of achieving periodontal regeneration.[10]

2.5. Biological principles for use of bone graft/ bone substitutes

The biological rationale behind the use of bone graft and or alloplastic materials for regenerative therapy is that these materials may have one of the following properties: 1. Osteogenesis- contains bone forming cells 2. Osteoconduction – scaffold for bone formation 3. Osteoinduction – the matrix of the bone graft contains bone inducing substances.

2.6. Efficacy of autograft

Some of human histological studies reported complete reconstruction of periodontal tissue i.e., the complete resolution of the defect,[11,12] whereas some reported healing by both long junctional epithelium and periodontal regeneration.[13] While Some studies noticed healing only by long junctional epithelium and osseous repair.[14]

2.7. Efficacy of allograft

Two studies reported almost complete periodontal reconstitution.[15,16] Some reported Combination of long junctional epithelium and periodontal regeneration/connective tissue attachment.[17] No studies to date have demonstrated complete defect resolution, but equally none has reported any significant inflammation.

2.8. Efficacy of xenograft

Partial periodontal regeneration was observed but none of the studies reported complete regeneration and no information on the degree of inflammation was provided.

2.9. Efficacy of alloplast

Healing was predominantly characterized by a long junctional epithelium and connective tissue encapsulation of the graft particles. Periodontal or cementum regeneration was usually limited to the apical parts of the defect. Partial periodontal regeneration was observed but none of the studies reported complete defect resolution and remarkably little inflammation was observed.

2.10. Efficacy and effectiveness of bone graft /bone substitute

Periodontal and bone regeneration supported by bone graft materials when used in combination with GTR is by space provision rather than the osteoconductive properties of the grafting material.[18] The ability of bone graft/bone substitute materials to restore lost connective tissue attachment is missing. A vital bone adjacent to biomaterial particles, especially in proximity to the resident alveolar bone, signifying a biocompability rather than a osteoconductive or osteoinductive properties. The native regenerative potential of the periodontium does not seem to improve by bone graft/bone substitute materials. With regard to periodontal regeneration, which includes the formation of new connective tissue attachment to the root surface, currently available data are not promising. Histological evidence of new connective tissue attachment is limited. No large scale multicenter human clinical trial on bone replacement grafts has ever been performed and hence the applicability of these results to clinical practice remains to be established. One systematic review[19] showed insufficient evidence to support bone graft whereas, another[20] showed that bone graft materials provide significant clinical improvement in periodontal osseous defect.

3. Enamel Matrix Derivative (EMD)

3.1. Biological principle of EMD

The EMD consists of a heterogeneous mixture of proteins containing amelogenins as a major component. These biologically active molecules capable of encouraging the development of an acellular cementum together with collageneous fibres that develops over newly formed bone.[21]

3.2. Efficacy and effectiveness of EMD

Human clinical trials, systematic reviews and Meta-analysis provide significant additional benefits of EMD in terms of

pocket depth reduction, clinical attachment level gain and radiographic bone level in intrabony defects. A large multi-centre human clinical trial[22] demonstrated both efficacy and effectiveness of EMD in intrabony defects.

4. Growth / Differentiation Factor

Growth/ differentiation factors represent a large family of polypeptidic molecules that modulate cell responses such as cell attachment/adhesion, cell survival, proliferation, chemotaxis and differentiation. Bone, PDL and cementum are highly differentiated tissues and different growth factors regulate the signalling events and their neoformation during wound healing. Different growth factors have specific functions on specific target cells in wound healing and their delicate balance is required for optimal tissue repair.

4.1. Biological principles of growth factors

Biological rationale for the use of several growth factors is that these biologically active molecules are able to regulate proliferation, accelerate activity and / or stimulate differentiation of key cells involved in the periodontal regenerative process, such as cementoblast, periodontal ligament fibroblast and osteoblast, encouraging successful regeneration of lost tissue.

4.2. Different types of growth factors

4.2.1. Platelet derived growth factor – BB (PDGF – BB

4.2.1.1. Efficacy and effectiveness of PDGF –BB. Two multi centre studies[22,23] on rh PDGF –BB in the treatment of intrabony defect have been conducted. Both the studies shows added benefits compared with controls in terms of bone gain, whereas one study[22] did not induce a significant difference in terms of CAL gain. Efficacy and effectiveness of human PDGF-BB have to be further explored before clinical application.

4.2.2. Fibroblast growth factor -2

4.2.2.1. Efficacy and effectiveness of FGF- 2. Two multicenter studies[24,25] on FGF-2 in the treatment of intrabony defect have been conducted. Both the studies shows added benefits compared with controls in terms of bone gain, whereas no study demonstrated a significant difference in terms of CAL gain. Both efficacy and effectiveness of FGF- 2 have to be further explored before clinical application.

4.2.3. Bone morphogenic protein – 2

4.2.3.1. Efficacy and effectiveness of BMP-2 . Long term follow up with BMP-2 in some human trials supported its use in hard tissue augmentation. No human studies are available regarding its use in true periodontal regeneration. Some reports showed that BMP- 2 stimulates root resorption and ankylossis. FDA approved BMP -2 for sinus augmentation and alveolar ridge augmentation associated with extraction socket defects. A randomized controlled trial[26] provides evidence that rh GDF-5 / β TCP may substantially support periodontal wound healing/ regeneration. Further studies with larger sample size will have to be conducted to verify these findings.

4.3. Factors affecting outcomes of periodontal regenerative therapy

4.3.1. Patient-related factors

4.3.1.1. Oral hygiene. Postoperative plaque control is one of the key factors influencing periodontal healing following regenerative periodontal therapy.[27,28] The self-performed plaque control has a greater influence on the outcome of periodontal regeneration. Patients with high levels of plaque control has get more advantageous effect in term of better CAL gain than in patients with low level of plaque control.[27,28] The long term stability of the periodontal regeneration were mainly depend on optimum levels of plaque control.[28]

4.3.1.2. Smoking. Smoking is considered as a potential negative predicator as it impaired periodontal wound healing and increases risk of post-surgical infection, resulting into less favourable regeneration.30 Regenerative outcomes significantly impaired in smokers compared to non-smokers.[29]

4.3.2. Defect/tooth -associated factor

Innate characteristics of the defects assured optimal conditions for periodontal wound healing/ regeneration. Defect morphology plays a major role in healing following periodontal regenerative treatment of intrabony defects.

4.3.2.1. Depth of defect component. Depth of the intrabony component of the defect has a significant influenced on the amount of clinical attachment and bone gained at 1 year. Superior amount of clinical improvement were remarkably observed in deeper defect.[30,31] However, in a multicenter controlled study, it was established that regenerative potential of both deep and shallow defects were equivalent.[32]

4.3.2.2. Width of defect component. Another important morphological characteristic of the defect is the width of the intrabony component. Remarkably reduced amounts of CAL and bone gain at 1 year for wider defects when compared to narrower defects. Cortellini&Tonetti[33] established that defects with a radiographic defect angle of $\leq$25 showed significantly more attachment gain than did defects with a radiographic defect angle $\geq$37. Analysis showed an unfavourable association between the radiographic angles of the intrabony defect.[34]

4.3.2.3. Numbers of residual bony wall. The number of residual bony wall is correlated with the outcomes of various regenerative approaches.[35] The number of residual walls have more detrimental effects when non-supportive biomaterials were used. Study established an influence of the numbers of residual bony walls and the defect width were reduced with EMD under MIST.[36]

4.3.2.4. Endodontic status. Significance of the tooth vitality has been considered as a pertinent factor in periodontal regenerative therapy. Successfully root canal treated teeth has no detrimental effects on the healing response following periodontal regenerative therapy and the stability of the attachment level gain following regenerative therapy showed no significant differences between vital and root canal treated teeth.[37]

4.3.2.5. Tooth mobility. Tooth mobility has been determinately affects the outcomes of periodontal regeneration.[38] Increased tooth mobility significantly resulting in less favourable clinical outcomes of regeneration.[39]

4.3.3. Surgery associated factors

A series of preclinical studies by Wikesjo et al.,[40] established that the healing of periodontal tissue under optimal circumstances no apical migration of the gingival epithelium should occur. Primary closure and wound stability has a significant impact on outcomes of periodontal regeneration.[3,41]

4.3.3.1. Space maintenance. During early healing phase space maintenance is considered as one of the significant factor to allows periodontal ligament and bone cells to repopulate root surface and to prevent apical migration of cells from gingival epithelial and connective tissue. A long junctional epithelium is probably considered as consequences of wound failure rather than a cause.

4.3.3.2. Wound stabilization. During early healing phase of wound stabilization of blood clot is an important as it provides a scaffold for cell migration and or proliferation. However, compromised wound stability may lead to impaired adhesion of fibrin clot to the root surface, this lead to formation of the long junctional epithelium and compromised outcomes of regenerative theraapy.[42,43] The maintenance of wound stability seems to be critical during first post-operative weeks.[44] Compromise wound stability as result of wound dehiscence inhibit the cascade of biologic events leading to periodontal regeneration.[45]

4.3.3.3. Primary closure. For periodontal regeneration primary passive closure of wound is prerequisite to avoid exposure of biomaterials and to avoid bacterial contamination of wound area. Furthermore, partial or complete exfoliations of the graft materials, contamination of the membrane or premature clearance of biologic agent are the consequences following post-operative loss of primary closure. During the early healing phases of wound, the surgical management of the supracrestal soft-tissue including flap design and suturing technique is of vital significance in achieving primary passive wound closure.[46] Optimal wound closure showed superior clinical outcomes (greater CAL gain and minimal soft tissue recession) when compared with defect showed incomplete wound closure.[47]

4.3.4. Bio-materials associated factors

4.3.4.1. Barrier membrane. Delayed wound healing and poor regenerative outcomes are the consequences of membrane exposure, bacterial contamination and infection. Bio-Resorable membrane do not posses necessary structural rigidity, resulting into membrane collapse onto root surface as result of pressure from overlying flap leads to space loss which in turn compromised outcomes of regenerative therapy.[42] Machetei et al.[48] in his meta analysis concluded that, membrane exposure following GTR and GBR have a remarkably deleterious effects on bone formation.

4.3.4.2. Bone graft/bone substitute. In allograft preparations limiting factors includes donor age,[49] variability in techniques for commercial preparations[50] and particle size.[51] Bone graft particles have a sufficient porous structure that allows in growth of regenerating tissues and should be bio-compatible so it will resorb without impairing healing of maturating tissue whilst maintaining structural integrity.

4.3.4.3. Enamel matrix derivative (EMD). One of the possible drawbacks associated with enamel matrix derivative preparation is its gel-like consistency after reconstitution. When used in intrabony defects it may limit the space provision potential of the preparation.[52] Application of EMD is a technique sensitive procedures and contamination of the material jeopardizing the regenerative potential.

4.3.4.4. Growth/differentiation factor. They lack structural integrity and rigidity to help in the provision of space and blood-clot stabilization. Probably because of proteolytic breakdown receptor-mediated endocytosis and solubility of the delivery vehicle, growth factors undergo unsteadiness and rapid dilution from the target sites.[53] so, their half lives are remarkably reduced and the period of exposure should not be enough to act on osteoblast, cementoblast or periodontal ligament cells. Therefore, growth factor delivery by different methods needs to be considered.[54]

5. Conclusion

Guided tissue regeneration has a sound biological principle for periodontal regeneration. However, various human clinical studies support the use of other biomaterials

like bone graft/bone substitute materials, enamel matrix derivative and several growth/ differentiation factors for periodontal regeneration. Finally, it should be kept in mind that structural complexity of periodontium is probably one of the reasons to make periodontal regenerative therapy difficult. Postoperative plaque control is one of the key factors influencing periodontal healing following regenerative periodontal therapy. The periodontium has a strong innate regenerative potential that can be compromised by local and systemic factors.

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None.

7. Conflict of Interest

The authors declare no conflict of interest.

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