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Biologics Agents in Periodontal Regeneration:A Review

Dr Supra Ratan Karkera[1] ; Dr Manjushree Kadam[2] ; Dr Devishree CP[3] ; Dr Yashaswi Shetty[4] ; Dr Riolla Sanchia Dsouza[5]
[1]Post Graduate, Department of Periodontics, AJ Institute of Dental Sciences
[2]Professor, Department of Periodontics, AJ Institute of Dental Sciences
[3] Post Graduate, Department of Periodontics, AJ Institute of Dental Sciences
[4]Post Graduate, Department of Periodontics, AJ Institute of Dental Sciences
[5]Post Graduate, Department of Periodontics, AJ Institute of Dental Sciences

Abstract:- The field of periodontology and dental implantology has witnessed significant advancements in the use of molecular mediators and biologic agents over the past decade. Periodontal regeneration, which involves the complete restoration of cementum, bone, and connective tissue following removal of epithelial tissues, is considered superior to tissue repair. Recent research has focused on utilizing biologic materials as complementary therapies to enhance regeneration by accelerating wound healing. These biologic agents were investigated using the following search terms: tissue engineering, intercellular signaling molecules, and biological factors.

Enamel matrix derivative (EMD), platelet-derived growth factor (PDGF), platelet-rich plasma, bone morphogenetic proteins (BMPs), fibroblast growth factor (FGF), and parathyroid hormone (PTH) have demonstrated the capacity to stimulate both hard and soft tissue regeneration. However, no single biologic agent is universally effective, necessitating a case-by-case evaluation for optimal treatment selection. Currently, EMD and PDGF are the only biologic therapies approved by the FDA for periodontal regeneration, while BMP-2 is indicated for bone augmentation. Due to a lack of FDA approval for periodontal applications, the clinical use of FGF and PTH in this context is not recommended.

Keywords:- *Periodontal Regeneration, Enamel Matrix Derivative, Platelet Rich Fibrin, Platelet Derived Growth Factors, 3d Scaffolds, Biologics, Open Flap Debridement, Bone Morphogenic Proteins, Insulin Like Growth Factor, Fibroblast Growth Factors.*

I. INTRODUCTION

Subgingival dental biofilm induces an inflammatory and immunological response in a susceptible host, which ultimately results in the irreversible loss of the periodontal tissues (periodontial ligament and alveolar bone).Regenerative treatments represent a newer paradigm in periodontal care, with the goal of replacing damaged periodontal ligament, bone, cementum, and connective tissue. The use of various synthetic and natural materials for periodontal disease has long been researched.Resorbable and non-resorbable membranes, bone substitutes derived from human, animal, or synthetic sources, growth factors such as platelet-derived growth factor, bone morphogenic proteins, and fibroblast growth factor, hormones like teriparatide, platelet concentrates, and three-dimensional scaffolds are the primary materials employed in contemporary periodontal therapy[1]

Clinical investigations demonstrated that using barrier membranes and biomaterials was more effective than OFD alone in gaining clinical attachment (CAL) and reducing probing pocket-depth (PPD). Murphy, Gunsolley, and Needleman found that treating intrabony flaws with GTR resulted in a greater CAL gain, PPD decrease, and REC increase than OFD alone. Trombelli discovered that GTR resulted in better CAL and PPD changes as well as higher defect fill when compared to OFD alone.

Murray, Hurley, Boyne, Melcher, Nyman, and Karring contributed to the understanding of the physiologic principles underlying periodontal repair. Melcher postulated that the repopulation of cells on the root surface following periodontal surgery affected the type of attachment that would occur. Following surgery and biofilm removal, the root surface can be repopulated with epithelium, gingival connective tissue, bone, and periodontal ligament cells. Melcher proposed that the quickest cells, epithelial cells, colonize the periodontal defect area first. Nyman and Karring demonstrated the ability to repair missing periodontal tissues in a human patient. They placed a Millipore filter between the flap and the previously damaged root, performing the first case of periodontal guided tissue.[3]

Biological substances like PDGF, BMP, FGF, TGF-β, and enamel matrix derivatives can improve clinical outcomes in regenerating periodontal tissues lost due to disease. Over the last two decades, several biological mediators have been introduced, including rhPDGF, rhBMP FGF-enhanced substitution, and EMDs.

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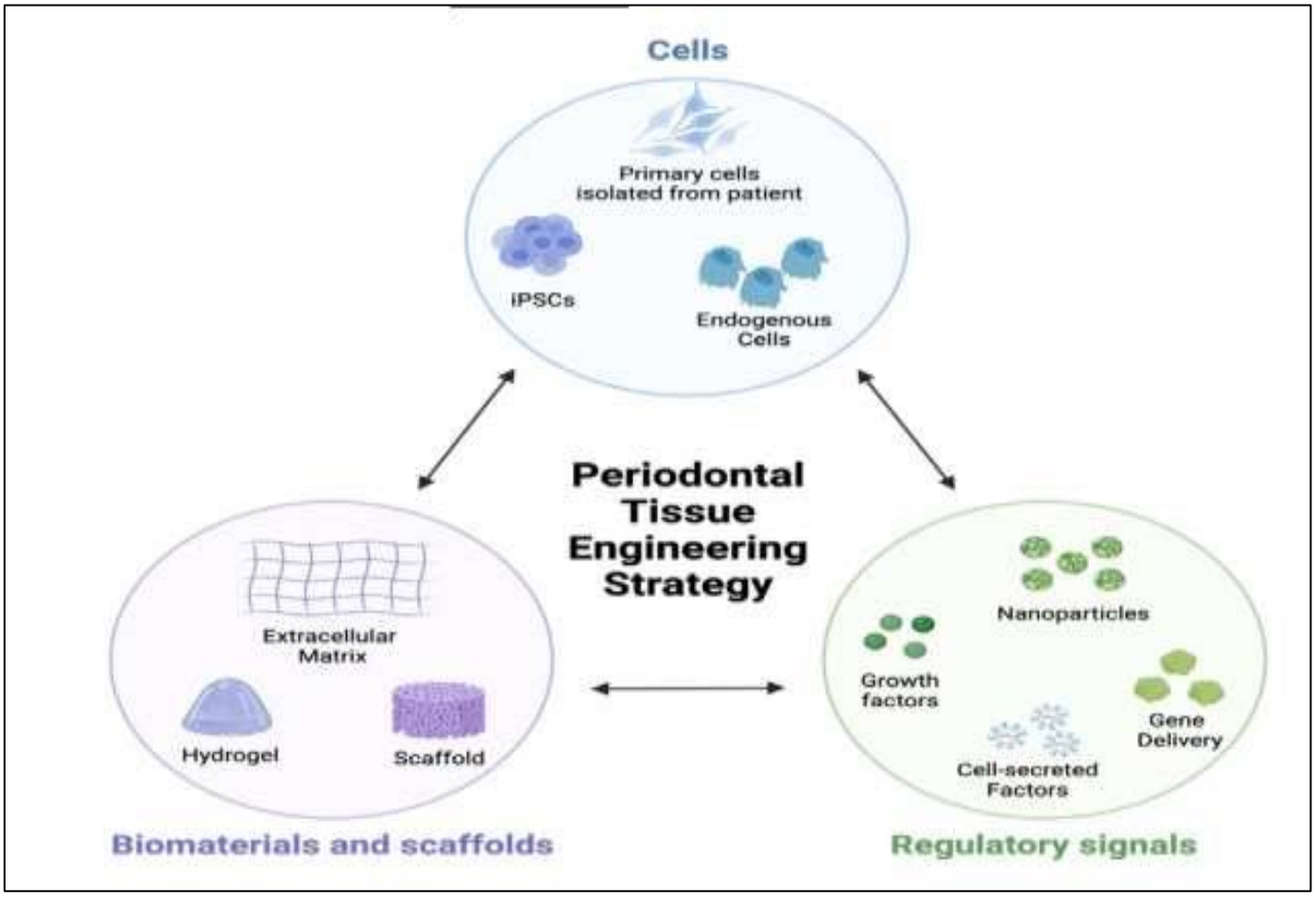

Fig 1 The Tissue Engineering Triad is a Fundamental Concept in the Field, Outlining the Three Essential Components Required for Successful Tissue Regeneration.

Table 1 Commonly used Biologics Agents used in Periodontal Therapy

Agent	Indications	Functions	FDA approval
EMD	Treating intra-bony defects In aesthetic zones, EMD is also utilised to optimise tissue height.	Promotes periodontal wound healing Promotes soft and hard tissue regeneration.	The therapy of intra-bony defects has been approved by the FDA by using EMD
PDGF-BB	Used in the socket augmentation Used in Guided bone regeneration.	Enhances wound healing soft and hard tissue regeneration promoted	Intra-bony defects, furcations, and gingival recession treatments by using PDGF-BB have been authorized by the FDA.
BMP-2	Used in the sinus augmentation Alveolar ridge augmentation is enhanced	Enhances mature bone formation Bone regeneration for implant related therapy is promoted	The FDA has approved use of BMP-2 in sinus augmentation and alveolar ridge augmentation procedures.
PRF	Used in sinus augmentation as graft material	Bone healing is enhanced Used in soft and hard tissue regeneration	Not regulated by the FDA
FGF-2	FGF-2 significantly improves defect fill	Promotes hard tissue regeneration	Currently seeking FDA approval

II. PERSPECTIVE ON PDL REGENERATION

The optimum clinical outcome after trauma or disease is regeneration of the periodontal support apparatus, which consists of alveolar bone, cementum, and PDL. New attachment requires regeneration of the PDL's major fibers and their reattachment to newly formed cementum on the root surface.

The periodontal ligament (PDL) houses a reservoir of self-renewing progenitor cells, termed PDL stem cells (PDL-SCs), primarily located within perivascular niches. These stem cells are instrumental in the PDL's adaptive and regenerative capacity over time.

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III. CURRENT PROGRESS IN PERIODONTAL REGENERATION

Periodontal regeneration aims to rebuild lost bone, cementum, and periodontal ligament (PDL) tissues. Clinical studies have shown that combining barrier membranes and biomaterials often yields better outcomes in terms of clinical attachment gain and pocket depth reduction compared to traditional flap surgery alone.

While limiting the use of other biomaterials, the advancement of regeneration procedures from huge flaps to increasingly minimally invasive ones opens up the option of using various biomaterials to repair periodontal tissues. Barrier membranes, grafting materials, biological agents, and more recently 3D scaffolds are the primary categories of biomaterials that have been employed in periodontal regeneration.

➢ *Barrier Membranes*

There were two main purposes for using barrier membranes. The first included applying the competition idea to build a wall separating the soft and hard tissues. Membranes that form barriers There were two main purposes for using barrier membranes. The second is the mechanical capacity of a membrane to enhance the stability of the underlying graft by separating the stresses applied to the soft tissues from the latter. To enhance the results of periodontal regenerative operations, membranes block out undesirable epithelial cells, make room for acceptable cells (such as PDL cells, bone cells, and/or cementoblasts), and strengthen blood clots. They also serve to stabilize and strengthen the underlying tissues, which enhances the clinical result of regenerative medicine procedures.

The most commonly used non resorbable and resorbable membranes.

- *Classification:*

Barrier membranes can be classified as non-resorbable or resorbable. Non-resorbable options include cellulose acetate, expanded polytetrafluoroethylene (e-PTFE) with or without titanium reinforcement, dense polytetrafluoroethylene (d-PTFE), and high-density polytetrafluoroethylene reinforced with titanium (Ti-d-PTFE). Resorbable membranes can be derived from natural or synthetic sources.

Historically, the first barrier membrane used in guided tissue regeneration (GTR) was a cellulose acetate-based bacterial filter. However, due to its limited clinical applicability, e-PTFE membranes were developed and became the foundation for early clinical research in periodontal regeneration

➢ *Grafting Biomaterials*

There are numerous bone grafting materials available today that have been employed for periodontal regeneration and alveolar ridge repairs.

There are four types of hard tissue replacement materials available for periodontal regeneration: autogenous bone, xenogeneic, alloplastic, and allogeneic bone substitutes, such as demineralized and freeze-dried bone allografts (DFDBA and FDBA). In the clinical situation, these materials are used to maintain the clot, encourage bone growth, and support the soft tissues so that they do not collapse into the defect.

It is known that a number of biologic substances can promote osteoinduction. it wasn't until the late 1980s and early 1990s that growth factors were first applied directly to periodontal regeneration.

Enamel matrix derivative (EMD) is a commonly used biologic agent introduced in the late 1990s. Derived from pig fetal enamel, EMD is believed to stimulate periodontal regeneration by inducing the formation of new bone, periodontal ligament, and cementum. This process is thought to mimic natural tooth development. Clinical and histological studies have shown EMD's potential to regenerate periodontal tissues in severe cases. However, not all clinical studies have demonstrated consistent therapeutic benefits.

IV. VARIOUS BIOLOGICAL AGENTS USED FOR PERIODONAL REGENERATION

➢ *Platelet Rich Fibrin*

Platelet Rich Fibrin (PRF), a patient-derived and autogenous live biomaterial, is rapidly being explored and used as an adjuvant autologous biomaterial to assist bone and soft tissue repair and regeneration. PRF promotes wound healing by enhancing chemotaxis, proliferation, differentiation, and angiogenesis.

Platelet alpha granules include growth factors such PDGF, VEGF, IGF, PDAF, and TGFβ, making them an effective biologic treatment for periodontal regeneration.[10]

Platelet-derived concentrates have been proven to improve tissue regeneration while indirectly aiding bone development.

Biological repercussions of PRF is made up of fibrin clots filled with platelets, leukocytes, immunological cytokines, and circulating stem cells. Although platelets and leukocytes are the principal cells responsible for PRF's biological activity, the fibrin matrix also plays an important part in the platelet concentrate's therapeutic action.

➢ *Growth Factors*

Growth factors (GFs) are recognized for their potential to expedite healing and enhance tissue regeneration in challenging clinical scenarios. To exert their biological effects, GFs are synthesized by specific cells, released, and transported to target cells. Upon reaching their destination, GFs bind to specific receptors, triggering intracellular signaling pathways that ultimately influence cellular behavio.[11,13]

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- *GF Applications for Oral and Periodontal Tissue Engineering*

The therapeutic application of growth factors (GFs) aims to replicate the body's natural healing processes by mimicking embryonic and postnatal development. The administration of a single recombinant GF can trigger multiple molecular and cellular pathways that contribute to tissue regeneration. Among the GFs extensively studied for periodontal regeneration are platelet-derived growth factor (PDGF), insulin-like growth factor (IGF), fibroblast growth factor-2 (FGF-2), transforming growth factor-beta (TGF-β), and bone morphogenetic proteins (BMPs).[13]

➢ *Platelet Derived Growth Factors(PDGF)*

PDGFs are dimeric proteins linked by disulfide bonds that activate two tyrosine kinase receptors, PDGF-α and PDGF-β. As a pioneer in preclinical research, PDGF was among the first growth factors studied for periodontal and peri-implant regeneration. In vitro studies have shown that PDGF stimulates proliferation, migration, and matrix synthesis in various periodontal cell types, including gingival and periodontal ligament fibroblasts, cementoblasts, and osteoblastic cells. Recombinant human PDGF (rh-PDGF) has been investigated for treating intrabony defects and gingival recession.

- *Preclinical Studies using PDGF for Periodontal and Peri-Implant Regeneration*

To assess the efficacy and safety of PDGF therapy, extensive preclinical studies were conducted. These investigations involved using PDGF alone or in combination with other growth factors, such as insulin-like growth factor (IGF), to treat periodontal and peri-implant conditions. The potential synergy between rhPDGF and tissue-specific scaffolds, composed of either allograft materials or synthetic bioresorbable ceramics, has been explored to identify optimal strategies for promoting periodontal or peri-implant regeneration.

➢ *Insulin Like GF (IGF)*

Insulin-like growth factors (IGFs) are single-chain proteins structurally similar to insulin. This family includes IGF-1 and IGF-2. IGF-1 plays a crucial role in growth and development, including bone formation and periodontal ligament (PDL) cell function. It is involved in bone remodeling, maintaining skeletal mass, and preventing age-related bone loss. IGF-1 also promotes cell survival, stimulates DNA and protein synthesis in PDL fibroblasts, and accelerates soft tissue wound healing.

Insulin-like growth factors (IGFs) are a family of hormones with diverse biological functions, including cell movement, growth, specialization, and transformation. They play a critical role in development, stimulating organ formation and growth during early embryonic life and regulating specific tissue and organ functions later on.[19]

➢ *Transforming Growth Factor (TGF)*

It belongs to the cytokine family known as epidermal growth factor (EGF). It is a mitogenic polypeptide and secreted protein that is expressed by monocytes, keratinocytes, and different tumor cells.

Transforming growth factor beta (TGF-β) belongs to a family of structurally related proteins with diverse functions. Primarily, TGF-β regulates cell growth, stimulates extracellular matrix production, and modulates immune responses. As a key regulator of cellular processes, TGF-β can either promote or inhibit cell proliferation. While it influences osteoblast activity, its effect is considered moderate.

➢ *Bone Morphogentic Proteins(BMP's)*

Urist created the term "BMP" in 1965. BMPs are regulatory glycoproteins belonging to the TGF-β superfamily.They promote the angiogenesis, migration, proliferation, and differentiation of mesenchymal stem cells into cartilage and bone-forming cells. More than 20 BMP-related proteins have been found, including some that promote bone formation.Much of the research on periodontal regeneration has centered on BMP-2 and BMP-3 (osteogenin).

- *Classification of BMPs*

Twenty different human BMPs have been found and categorized into subfamilies, but the BMP family contains almost 30 members, including activin, inhibin, and growth differentiation factors (GDFs). BMPs are categorized into four subfamilies based on their sequence similarity and functions. a. The first group consists of BMP2 and BMP4, which are extremely similar molecules with 80% homology. They differ mostly in the amino terminal region, with BMP2 containing a heparin-binding domain. b. Second group: BMP3, BMP3B (GDF10), also known as osteogenin. c. Third group-BMP5, BMP6, BMP7, BMP8a, and BMP8b - (78% homology) d. The fourth group includes GDF5, GDF6, and GDF7 (cartilage-derived morphogenetic protein).

Bone morphogenetic proteins (BMPs) possess remarkable regenerative capabilities. A pioneering study by Bowers et al. demonstrated the successful application of BMPs for periodontal regeneration. BMPs influence various cellular processes essential for tissue repair, including DNA synthesis, cell migration, differentiation, and matrix formation. Numerous studies have reported enhanced regeneration of alveolar bone, periodontal ligament, and cementum in various clinical settings, such as bone defects, fracture healing, dental implant osseointegration, oral and maxillofacial reconstruction, and endodontic treatments. Research has shown that dental implants treated with bovine BMP and recombinant human BMP-2 exhibit increased bone formation and improved implant integration over time..[18]

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➢ *Fibroblast Growth Factor*

Fibroblast growth factors (FGFs) constitute a large family of proteins with similar structural features. These versatile molecules influence a wide range of cellular processes, including growth, differentiation, and blood vessel formation, making them crucial for embryonic development and wound healing. Basic fibroblast growth factor (bFGF, or FGF-2) is the most well-known member of this family. It promotes blood vessel growth, cell proliferation, and the production of non-collagenous proteins, all of which contribute to tissue repair. While predominantly produced by periodontal ligament fibroblasts and endothelial cells, bFGF levels are often decreased in chronic periodontitis.

➢ *Functions*

Fibroblast growth factor-2 (FGF-2) is particularly effective in stimulating angiogenesis, promoting all phases of new blood vessel formation both in laboratory and living organisms. FGF-1 also contributes to endothelial cell growth. Additionally, FGF-2 plays a crucial role in periodontal ligament (PDL) tissue repair by enhancing the production of collagen and laminin.

Fibroblast growth factors (FGFs) accelerate wound healing by stimulating the growth and movement of various cell types involved in the process, including endothelial, epithelial, and connective tissue cells. FGF-2 is particularly effective, promoting the formation of new blood vessels, and increasing the production of proteins essential for tissue repair, such as fibronectin, proteoglycans, and collagen. Additionally, FGF-2 enhances wound strength and scar quality.

Fibroblast growth factors (FGFs) play a dual role in hematopoiesis: influencing the development of specific blood cell types and contributing to the formation of bone marrow support tissue. FGFs possess a unique ability to bind to heparin and heparan sulfate, protecting them from degradation and preserving their biological activity.

FGFs stimulate bone cell proliferation; however, under specific conditions, they can inhibit the production of bone matrix. Systemic administration of FGFs has been shown to accelerate bone fracture healing, induce new bone formation, and increase bone density, suggesting potential therapeutic applications for conditions like osteopenia.

FGFs significantly influence periodontal wound healing and regeneration. Their ability to stimulate new blood vessel formation, attract and stimulate the growth of key cells like fibroblasts and osteoblasts, positions them as crucial players in periodontal tissue repair.[17]

FGF-2 is found in virtually all periodontal tissues, including gingiva, periodontal ligament, and bone. FGF-2 has been shown to promote periodontal ligament and endothelial cell migration.

➢ *The Enamel Matrix Derivative (EMD)*

Extract enamel matrix derived from pig teeth is EMD, which contains many proteins, 90% of which are amelogenins, that cause periodontal attachment during tooth formation. Nonamelogenins, including as ameloblastin, tuftelin, enamelin, and amelotin, are also found in EMD. In 1996, the United States Food and Drug Administration approved it for the treatment of periodontal disorders and soft tissue recession. EMD has been widely studied in dental clinics and proved as a practical and safe method of periodontal regeneration.[3] Emdogain® (Straumann, Basel, Switzerland), a porcine-derived dental enamel matrix product, has been available for over 15 years.

- *Recent Developments in Applications of EMD*

EMD has shown clinical benefits, such as root coverage and stimulation of the soft and hard structures surrounding the tooth during regeneration. EMD is a popular choice for orthodontic applications because it has been used successfully for over two decades. EMD has been used to promote the regeneration of alveolar bone, periodontal ligament, and new cementum. Another remarkable feature of EMD is its suppressive effect on pathogenic dental plaques.

EMD may enhance early wound healing by reducing gingival fibroblast-induced inflammation. Deep intrabony periodontal defects treated with EMD promote periodontal regeneration. When EMD alone was compared to EMD with various types of bone graft/bone substitute, soft and hard tissue metrics were found to improve.

➢ *3D-Printed Scaffolds*

3D-printed scaffolds currently stand out as a particularly promising avenue in periodontal tissue regeneration**.** Their primary advantage lies in the precise control offered during the manufacturing process, enabling the creation of structures that closely mimic the extracellular matrix found in natural tissue. By utilizing specialized software, it's possible to meticulously design and produce these scaffolds to support optimal tissue growth.

3D printing offers significant advantages in scaffold production, reducing time, cost, and enhancing consistency. Human periodontal ligament cells, harvested from molar and premolar teeth, were seeded onto polycaprolactone 3D printed scaffolds. These constructs were then implanted into rats to evaluate their regenerative potential and ability to induce new mineralized tissue formation. In vivo studies revealed that periodontal ligament cells cultured on the implanted scaffolds successfully produced type I collagen fibers and established proper alignment of bone-ligament structures, replicating the complex three-dimensional architecture of native periodontal tissues.

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The scaffolds were designed with three distinct regions: a 100-micrometer microchannel layer for the cementum-dentin interface, a 600-micrometer microchannel layer for the periodontal ligament, and a 300-micrometer microchannel layer for the alveolar bone. These tri-phase 3D-printed scaffolds were further enhanced by incorporating amelogenin to stimulate cementum and bone regeneration, connective tissue growth factor to promote periodontal ligament regeneration, and bone morphogenetic protein 2 to induce alveolar bone formation.[7].

- *3D Printed Scaffolds in Periodontal Defects*

Monophasic scaffolds are distinguished by the presence of a single compartment that acts as a barrier membrane, maintaining and stabilizing the bone defect under regeneration; ensuring bone proliferation without epithelial interference in the bone defect; and controlling the healing process in time and space. Furthermore, these scaffolds can be loaded with growth factors or cells to promote bone neoformation. causing alveolar bone tissue to heal.[12]

V. DEVELOPMENT OF NEXT GENERATION REGENERATIVE THERAPEUTICS A LITERATURE REVIEW

➢ *The Optimum Regenerative Therapy will Meet the Following Regenerative Criteria:*

- Cementoblastogenesis at the tooth root surface.
- Oblique insertion of PDL fibers into the cementum and alveolar bone.
- A important supporting bone.

➢ *Next-Generation Growth Factors for Periodontal Regeneration*

Next-generation growth factor. Therapeutics must take into account the periodontium's intricacy and will benefit from a better understanding of its physiological evolution.

BMP-6 shares a similar structure with BMPs 5 and 7 and plays a crucial role in osteoblast differentiation. A study by Huang et al. (2005) demonstrated the effectiveness of BMP-6 in treating periodontal fenestration defects in rats. When delivered via a collagen sponge carrier, BMP-6 led to complete bone regeneration within four weeks.

In a pilot study, GDF-7/BMP-12 was shown to stimulate PDL formation in a supra-alveolar periodontal lesion model. This study found that GDF-7 has a high potential for promoting PDL regeneration (Wikesjo et al., 2004).

Growth differentiation factor-5 (GDF-5), also known as BMP-14, is a member of the transforming growth factor-beta (TGF-β) family that promotes periodontal regeneration. Expressed in developing periodontal tissues and early cartilage, GDF-5 interacts with specific receptors, including BMPR1B, BMPR2, and Activin Type II. Clinical studies in humans have confirmed its effectiveness in treating periodontal regeneration, intrabony defects, and sinus augmentation.

➢ *Next-Generation Biomaterial Design for Periodontal Regeneration*

Scaffold design plays a critical role in guiding tissue regeneration through physical cues such as texture and porosity. Nanofibrous structures enhance cell attachment and provide increased surface area for protein adsorption, while porosity facilitates tissue integration and nutrient exchange. To mimic the complex structure of the periodontium, multiphasic scaffolds with varying architectural and biochemical properties can be employed. Studies have shown that biphasic scaffolds with distinct regions for connective and calcified tissues outperform random-porous designs in promoting organized tissue formation. Triphasic scaffolds, incorporating specific growth factors, hold promise for achieving complete periodontal regeneration.

VI. FUTURES BIOLOGICS

Future potential biologics comprise a variety of growth factors with specialized roles that are currently undergoing randomized clinical studies in humans and dogs. Protein 15 (P-15), osteogenic protein 1 (OP-1), parathormone (PTH), and antisclerostin antibodies (SOST) are under investigation. Several growth factors have already been examined, however they are always used in conjunction with a scaffold or bone filler.

Recent research indicates promising advancements in periodontal and bone regeneration. Micrografts, as explored by Mummolo et al., show potential as an alternative to traditional treatments like guided tissue regeneration and bone substitutes. Additionally, 3D printing technology is emerging as a valuable tool, allowing for customized scaffolds to address specific bone lesions. A study by Rasperini et al. successfully utilized a 3D printed resorbable scaffold to treat a large bone defect. Furthermore, the connective tissue graft wall approach, combining connective tissue grafts with enamel matrix derivatives, demonstrates potential for preventing gingival recession and even soft tissue restoration.

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VII. CONCLUSION

Periodontal tissues have the ability to regenerate; however, present therapies do not achieve predictable and consistent regeneration. Cell and molecular biology research in periodontal regeneration holds enormous promise in offering an improved understanding of this complicated phenomenon and directing us towards novel possibilities for future clinical applications. Over the last 40 years, a wide range of biomaterials, biologics, and membranes have been used to regeneratively cure periodontal infrabony abnormalities. Biologic drugs have gradually acquired acceptance among physicians and are now commonly utilized for periodontal regeneration. Many of these biologic modifiers have considerable effects on cells, which aligns with the goals of the American Academy of Periodontology's (AAP) Best Evidence Consensus (BEC) on the use of biologic mediators in modern clinical practice.

As previously noted, more research is needed at both the molecular and clinical levels to increase the predictability of regenerative therapies. Establishing the necessary environment for periodontal tissue regeneration should be possible with active investigations aimed at understanding the biology of the healing site, including identifying appropriate cells to target, as well as designing delivery systems that can control the release of agents at the local site. Even though biologics have been shown to improve clinical outcomes, proper patient and case selection, bone augmentation type, and basic surgical principles remain crucial.

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