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Review Article

Biological modifiers in bone graft for periodontal regeneration

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ABSTRACT

Periodontal diseases such as gingivitis and periodontitis leads to degradation of periodontal tissues, causing tooth movement, and eventually tooth loss. Regenerative periodontal therapies aim to promote the healing and regeneration of the damaged periodontal tissues. These therapies focus on restoring the lost periodontal structures, including the gum tissue, periodontal ligament, and bone, to a functional state. To promote periodontal regeneration and healing, the application of biologic modifiers such as growth factors has been investigated. Biologic modifiers-primarily growth factors are basically proteins that may act locally or systemically to affect the growth and function of cells in various ways.These agents act by anabolic bone formation, angiogenesis, cementogenesis, osteoblast differentiation mitosis, chemo taxis, and other processes that improve the healing environment.When deciding on which biologic modifier to use, it is important to consider the evidence supporting its effectiveness and safety, as well as the specific clinical scenario of the patient.

1. Introduction

Periodontitis is an inflammatory disease of the supporting tissues of the teeth caused by specific microorganism or group of specific microorganisms resulting in progressive destruction of the periodontal ligament and alveolar bone, with pocket formation, clinical attachment loss or both.[1] Severe periodontal disease are estimated to affect around 19% of global adult population representing more than 1 billion cases worldwide.[2] Newer approaches to periodontal therapy include regenerative procedures that aim to restore lost periodontal ligament, bone, cementum, and connective tissue which includes Guided tissue regeneration (GTR), root bio modification and bone grafts.This is up regulated by local production of growth factors, which have the capacity to stimulate cellular chemotaxis, proliferation, differentiation and formation of extra cellular matrix components.[3] Biomaterials, bioactive molecules (e.g., growth factors), and (stem) cells are the three critical factors behind the management of periodontal disease.[4]

Recent advances include: improved procurement and availability of bone graft material, improved methods for complete detoxification of diseased root surfaces, better understanding of the cell kinetics of wound healing, application of the principles of guided tissue regeneration and the use of growth factors to enhance healing.[5]

2. Bone Grafts and Substitutes

2.1. Autograft

Despite the development of numerous bone substitutes over recent years, autografts remain the gold standard for grafting materials because of its main properties: osteogenetic, osteoinductive and osteoconductive. In

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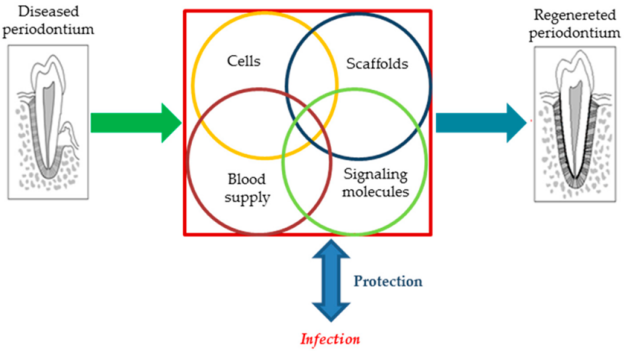

Fig. 1: Representation of the key parameters involved in the periodontal regeneration

contrast to osteoconductive cells, which lack the ability to induce or form bone but do provide an inert scaffold on which osseous tissue can regenerate bone, osteoinductive cells are stimulated to go through phenotypic conversion to osteoprogenitor cell types that can form bone.[6] Osteogenic cells, such as osteocytes or osteoblasts, are responsible for the formation of bone in autogenous bone grafts. The intraoral and extra oral sites are the two locations from which autogenous bone can be obtained. The mandibular ramus, maxillary tuberosity, and the mandibular symphysis are intraoral donor sites. The iliac crest, tibia, and skull are among the extraoral donor sites. Cancellous bone, which contains osteoblasts and progenitor cells with significant osteogenic potential, is most frequently used for autografts.[7]

2.2. *Allograft*

Allograft materials, which can be obtained from either a compatible living donor or from cadaveric bone sources, are the main substitute for an autograft. There are three main ways to prepare allograft materials: fresh, frozen, or freeze-dried.[8] Due to the higher danger of a host immunogenic response, the shorter shelf life, and the higher risk of disease transmission, fresh and frozen allograft materials are no longer often employed despite having superior osteoinductive qualities. Allografts have strong histocompatibility and come in a variety of shapes, including chips, wedges, pegs, powder, and Demineralized bone matrix (DBM).[9] Similar to cortical autografts, cortical allografts have high mechanical strength and are primarily used to create a mechanical scaffold for bone repair processes to take place after an initial inflammatory cascade. Allografts have been employed in dental applications to fill mandibular, maxillary, and periodontal abnormalities. In order to provide enough bone height for implant insertion, block allografts have frequently been used to address deficiency in alveolar ridge height or severe ridge atrophy. The usage of allograft materials has decreased recently due to worries about the scarcity of tissue supply and evidence of high failure rates after prolonged use.[10]

2.3. *Xenograft*

Grafting materials called xenografts come from species that are not genetically related to the host. Deproteinized bovine bone, marketed as BioOss, is the most prevalent source of xenograft materials in the dental sector.[11] Chitosan, a naturally occurring polymer generated from the exoskeletons of crustaceans and made of glucosamine and N-acetylglucosamine, is a promising xenograft material that is currently being investigated. Chitosan promotes osteoblastic activity, the development of mineralized bone matrix, and the differentiation of mesenchymal stromal cells into osteoblasts in a variety of in vitro environments, all of which are necessary for bone regeneration. There are several different ways to get chitosan, including beads, films, hydrogels, and more intricate structures like porous scaffolds.[12] There are further products made from bovine bone that are sold commercially, including OsteoGrafTM and CeraboneTM. The efficient application of chitosan-based materials as a membrane for guided bone regeneration (GBR), guided tissue regeneration, coating implant surfaces, periodontal regeneration, and restoring alveolar bone height.[13]

2.4. *Marine based bone graft*

Oceans are rich sources of a variety of substances that could be used in the healthcare industry, including as bioceramics, biopolymers, fatty acids, toxins and pigments, nanoparticles, and adhesive materials.[14] Marine skeletons, which are primarily made of aragonite (CaCO3), have shown to be a promising option for bone tissue creation, taking use of their porosity structure and mechanical robustness, in order to overcome the disadvantages associated with adhesive materials. After being cleaned, marine skeletons can be used to replace bone grafts, ideally after being hydrothermally converted into calcium phosphate scaffolds and maintaining the same porosity architecture. Depending on the hydrothermal treatment circumstances (temperature, duration, chemical environment), the transformation might be either partial or complete. Because only a portion of the calcium carbonate present in marine exoskeletons is converted into calcium phosphate (CaP), the resulting products are composite materials with an inner calcium carbonate core and an outer layer that closely resembles the mineral makeup of bone. This makes them suitable substitutes for bone in bone grafts.[15]

2.4.1. *Corals*

Corals are marine invertebrates typically living in compact colonies of many identical individual polyps. Each polyp is

a tiny, sac-like organism with a series of tentacles encircling its central mouth opening. They are only a few millimeters in diameter and a few centimeters long. Near the base, polyps take up components from the seawater, such as calcium ions and carbonic acid, and produce an aragonite-like calcium carbonate exoskeleton that develops over many generations. Corals contain oligoelements (0.5–1%), sodium (0.4–4.5%), magnesium (0.05–0.2%), amino acids (0.07%), and potassium (0.02-0.03%) in addition to calcium carbonate, which makes up 97–99% of their composition.[16] Among the most popular coral species used in medical applications are finger corals Porites, Goniopora, and Montipora digitate.[17]

2.4.2. *Cuttlefish bone*

Cuttle fish, a common demersal neritic species, is found primarily close to muddy and sandy bottoms up to 200 metres below the surface. About 9% of the cuttlefish is made up of cuttle fish bone, a hollow structure separated into lamellae.[18] The pore size and pore interconnectivity of cuttlefish bone, a widely accessible and reasonably priced substance with a special porous microstructure, have been shown to be advantageous for bone development and vascularization. It has been claimed that cuttlefish can be used as a bone graft alternative both in its natural state and as an aragonite source to create calcium phosphate materials while maintaining the same porosity structure.[19]

2.4.3. *Marine shells*

2.4.3.1. Nacre. Nacre from the pearl oyster, Pinctada maxima, has the unique ability to stimulate osteogenesis and bone production from latent osteoprogenitors through an endochondral pathway that includes a phase of cartilage tissue as an intermediary. Nacre is mechanically tough, non-immunogenic, and quickly biodegradable due to its organic content and plate-like architecture; nonetheless, it does not cause negative physiological effects. These properties of nacre make it a special substrate for the delivery of functional (potentially osteopromotive) agents to locations of bone loss in amounts that promote quick bone repair and regeneration.[20]

2.4.4. *Marine sponges*

Collagenous marine sponge skeletons are extraordinarily strong, highly absorbent, elastic, and resistant to bacterial attack. marine sponge collagen fibers contain the polypeptides fibronectin, dermatopontin, and tenascin, which cross-react with antibodies made against their vertebrate analogues to emphasis their shared ancestry. An analogue of the type IV collagen present in the basement membranes of vertebrates can be discovered in some sponge species. Similar to the collagen type XIII that causes cells to attach to surfaces, collagen fibrils are organized in a specific way.[21] Because of these characteristics (fibronectin and cell adherent collagens), collagenous sea sponges have a great deal of potential to be used as bioactive tissue engineering scaffolds in the future.

2.5. *Synthetic*

2.5.1. *Hydroxyapatite*

The apatite's family of crystalline substances with crystalline hexagonal lattices includes hydroxyapatite (HA). Ca10 (PO4)6(OH)2 is the precise formula for HA, which is the main mineral in bones and teeth. HA is very biocompatible and doesn't trigger an inflammatory reaction. The material is typically kept in place for at least three years following implantation because HA resorption is extremely slow and permits slow bone ingrowth and cell colonization. Because HA has excellent mechanical qualities and can withstand compression up to 160 MPa, it is most likely to be used in minor bone defects under low loading conditions. Both natural and artificial versions of HA are available, and HA-TCP (tricalcium phosphate) ceramics are typically preferred to HA alone.[22]

2.5.2. β-*Tri-calcium phosphate*

Tri-calcium phosphate (Ca3(PO4)2), which has been widely utilised as a bone substitute for more than 25 years and is regarded as the "gold standard" for artificial bone, is mostly employed in orthopedics and dental applications. It is a biocompatible and bioresorbable substance that resembles the inorganic portion of bone in terms of its characteristics.[23] Due to its composition and porosity, which depend on the processing condition, TCP is osteoconductive. Its porous structure does, in fact, contribute to its osteoconductive properties. TCP is suitable for use as filler in bony defects and repair at morphological areas but not as a bone substitute. It is frequently used to treat marginal periodontal and periapical abnormalities as well as to fill up alveolar bone deficiencies with a partially resorbable material.[24]

2.5.3. *Bioactive glass*

Bioactive glasses (also known as bio glasses), which were first developed by Hench et al.[25] in the 1970s, are initially silicates that are combined with other minerals that are naturally present in the body (Ca, Na2O, H, and P). In terms of weight percentage, the original bioglass is composed of 45% silica (SiO2), 24.5% calcium oxide (CaO), 24.5% sodium oxide (Na2O), and 6% phosphorous pentoxide (P2O5).[26] The surface of bioglasses changes into a silica-CaO/P2O5-rich gel layer when exposed to an aqueous solution or bodily fluids, and in a matter of hours, this layer mineralizes into hydroxycarbonate. Bioglasses are biocompatible, osteoconductive, and, depending on how they were processed, they may have a porous structure that encourages bone ingrowth and resorption. Examples of commercially available BAG products with

particle sizes between 90 and 710 microm are PerioGlas® and UniGraft®. They have been successfully utilised in periodontal surgery to induce bone regeneration, and their benefits include being reasonably simple to handle and adapt to the problem site.[27]

3. Bone Modifiers

Biological modifiers are essentially proteins that have different effects on how cells develop and function, either locally or systemically. The local use of biologic modifiers, like growth factors, has been researched as a means of promoting periodontal regeneration and healing. The tissues of the gums have the ability to heal and regenerate and this procedure is governed through in-situ growth factor production, which can promote cellular chemotaxis, proliferation, differentiation, and the synthesis of extracellular matrix components. Various bone modifiers are bone morphogenic proteins (BMP) enamel matrix derivative (EMD), platelet-derived growth factor (PDGF), platelet-rich plasma (PRP), fibroblast growth factor (FGF), and parathyroid hormone (PTH), have all shown promise in enhancing regeneration.[3]

3.1. Bone morphoogenic proteins (BMP)

Probably the most well researched growth factors for treating skeletal abnormalities are bone morphogenetic proteins (BMPs), which are Transforming growth factor (TGF-β) superfamily members with exceptional osteoinductive capabilities.[10] Through the activation of osteoblastic development in human periodontal ligament cells, BMPs have an anabolic effect on periodontal tissue. In bone allografts, which are osteoinductive and can actively affect cell behavior in vivo, BMP-2, -4, and -7 are frequently preserved.[28] BMP-2 may be able to stimulate periodontal regeneration, according to some preliminary research, but it has also been linked to harmful healing outcomes such ankylosis and root resorption.[3] Because of their high production costs, synthetic BMPs can only be used in very small quantities in synthetic biomaterials. They stimulates alkaline phosphatase activity thereby promotes bone regeneration.[28]

3.2. Vascular endothelial growth factors (VEGF)

In the epiphyseal growth plate, hypertrophic chondrocytes release vascular endothelial growth factors (VEGF) to encourage blood vessel invasion of cartilage and blood flow, which aids in the development of new bone. The VEGF-containing group showed increased vascularization and improved bone quality, but there was no discernible difference in the amount of newly produced bone. Due to the risk of hemangiomas and tumor recurrence, the use of VEGF is restricted in patients who have undergone radiation.[10] Only osteoarthritic cartilage expresses the VEGF receptors, VEGFR-1, VEGFR-2 however VEGF is present in normal cartilage as well. In comparison to media from normal chondrocytes, the level of VEGF in the culture media from osteoarthritis chondrocytes was 3.3-fold higher. These findings imply that VEGF signaling via autocrine and/or paracrine mechanisms may contribute to the pathophysiology of osteoarthritis.[29]

3.3. Fibroblast growth factors (FGF)

FGFRs have been discovered and are secreted by mesenchymal stem cells, osteoblasts, and chondrocytes. FGF1, FGF2, and FGFR1-3 were discovered to be strongly associated with bone regenerations, with FGFR1 and FGFR2 having greater expressions in osteoprogenitors and osteoblasts and FGFR3 being more associated with chondrogenesis.[3] FGF2 was applied topically to experimentally created periodontal tissue defects in beagle dogs and non-human primates, and this resulted in a large amount of periodontal tissue regeneration with the production of new cementum and new alveolar bone.[30] A good local environment for tissue engineering is created when FGF-2 stimulates periodontal ligament cells to generate osteopontin, heparin sulphate, and hyaluronan.[31]

3.4. Enamel matrix derivatives (EMD)

The Hertwig's cells secrete proteins from the enamel matrix onto the root surface. These proteins include amelogenin, enamelin, and ameloblastin. An essential step in the formation of cementum, periodontal ligament, and alveolar bone is the deposition of these enamel matrix proteins onto the root surface. The cells that create cementum, known as cementoblasts, latch onto the deposited enamel matrix proteins to begin the production of cementum.[28] Similar to this, the presence of enamel matrix proteins affects the periodontal ligament fibroblasts and osteoblasts, which respectively contribute to the creation of periodontal ligament and alveolar bone and encourages the regeneration of both hard and soft tissues and speeds up the healing of wounds.[3]

3.5. Platelet derived growth factors (PDGF)

Five different isoforms of the versatile peptide PDGF exist: PDGF-AA, PDGF-AB, PDGF-BB, PDGF-CC, and PDGF-DD.[31] PDGF promote the ability of bone, cementum, and periodontal ligament, to regenerate after injury. By stimulating hyaluronate synthesis by gingival fibroblasts and fibroblast proliferation, PDGF enhances collagen synthesis. It also has a chemotactic impact that can promote collagen synthesis. They have osteoinductive qualities that speed up bone repair in bony deformities. With increase in stem cells, platelet-derived growth factor enhances wound repair and bone regeneration.[32]

3.6. Insulin like growth factors (IGF)

They belong to a group of proteins called mitogenics that regulate the differentiation, growth, and upkeep of many different tissues. Six IGF binding proteins and three ligands (insulin, IGF-1, and IGF-2) are members of this family. IGF-1 is a protein made up of amino acids that has effects on the endocrine, paracrine, and autocrine systems.[33] It is an effective fibroblast chemo attractant that promotes the growth of mesenchymal tissues, such as cementum and collagen bone, which in turn promotes periodontal regeneration. Compared to IGF-1, IGF-2 has less strength. Uncertainty still exists regarding IGF-2's impact on gingival fibroblast metabolism.[34]

3.7. Transforming growth factors (TGF)

Platelets, epithelial cells, macrophages, and fibroblasts are the cells that are involved in their synthesis.TGF stimulate cell chemo taxis in gingival and periodontal ligament fibroblasts with great potency. They may have an impact on ECM molecule synthesis and differentiation.TGF could promote gum tissue renewal. The synthesis of extracellular matrix is strongly influenced by TGF.[35] additionally; it promotes the production of plasminogen activator inhibitors and tissue inhibitors of mellaloproteinases, which reduces the degradation of connective tissue.[3]

3.8. Parathyroid hormone (PTH)

PTH is an endogenous hormone that can have both catabolic and anabolic effects on bone, depending on concentration and dosage. Keratinocytes, activated lymphocytes, osteoblasts, and mammary glands all make them stimulate the production and resorption of bone. Its capacity to encourage bone development in the mouth cavity for both periodontal and implant applications is supported by animal research.[36]

3.9. Epidermal growth factor (EGF)

The submandibular gland creates Epidermal growth factors. EGF suppresses collagen production while encouraging keratinocyte growth. EGF is able to increase extracellular matrix mineralization, which helps dental pulp stem cells (DPSCs) differentiate into osteoblasts.[3] EGF just needs to be present at low concentrations (10 ng/ml) to cause morphological and phenotypic alterations. A successful stem cell-based therapy for bone tissue engineering applications in periodontics and dental implantology may be possible when DPSCs and EGF are combined.[37]

3.10. Keratinocyte growth factors (KGF)

Keratinocyte Growth Factor (KGF), sometimes referred to as FGF7, is a potent mitogen for numerous epithelial cell types that controls their migration and differentiation as well as defends them from various injuries under stressful circumstances. They are expressed by several different kinds of epithelial cells, such as hepatocytes, intestinal epithelial cells, and epidermal keratinocytes. KGF helps wounds heal.[38]

3.11. Platelet rich fibrin (PRF)

Uncoagulated blood is centrifuged using a commercially available technology to make PRF, which is then placed inside a fibrin scaffold and has a layer with higher platelet and leukocyte concentrations. PRF improves wound healing by increased chemotaxis, proliferation, differentiation, and angiogenesis.[10] Since thrombocytes are a naturally occurring source of growth factors that are crucial for tissue repair, they are crucial for the healing of periodontal wounds. There are numerous types of platelet-rich plasma (PRP), pure-PRP, leukocyte-PRP, PRF, and leukocyte-PRF), as well as TPRF, which are created using various centrifugation techniques.[39]

Table 1:

Growth factors	Source	Functions
BMP	Bone	Stimulates bone formation.[28]
VEGF	Platelets, chondrocytes in callus Vascular endothelial cells	Increases angiogenesis and vascular Development.[10]
FGF	Macrophage, mesenchymal cells, chondrocytes, osteoblasts	Mitogenic for mesenchyme stem cells, chondrocytes, and osteoblasts.[3]
EMD		Accelerates healing, promotes hard and soft tissue regeneration.[3]
PDGF	Platelets, macrophages	Protein synthesis.[32]
IGF	Bone,liver,blood	Proliferation, differentiation and synthesis of DNA.[33]
TGF	Bone,platelet,epithelial cells	Stimulates epithelium, immunosuppressive.[35]
PTH	Keratinocytes, lymphocytes, osteoblasts, mammary gland	Stimulates bone resorption and Formation.[36]
EGF	Submandibular glands	keratinocyte proliferation, inhibits collagen synthesis.[3]
KGF	Epithelial cells	Promote wound healing.[38]
PRF	blood	Accelerates healing, promotes hard and soft tissue regeneration.[10]

4. Bioinorganic Ions

It is still possible to think of bioinorganic ions like silicon, magnesium, strontium, zinc, and copper as crucial cofactors of enzymes, coenzymes, or prosthetic groups. They actively participate in ion channels or secondary signalling, either in response to direct stimulation or an analogue. When compared to growth factors, the incorporation of these ions offers cheap cost, a longer shelf life, and maybe lesser risk. Thus, the inclusion of bioinorganic ions—a natural but safer method—has been emphasised.[10]

4.1. Magnesium

In osteogenesis, angiogenesis, and neuronal stimulation, magnesium plays a part. The bulk of the magnesium that builds up in bone tissue is focused on the hydrated surface layers of apatite crystals rather than being integrated into the lattice structure of bone crystals.[10] Magnesium has been discovered to be a cofactor for a number of enzymatic activities involved in energy metabolism, protein and nucleic acid synthesis, functional maintenance of parathyroid glands, and vitamin D metabolism that are specifically connected to bone health.[40,41]

4.2. Strontium

The skeleton contains 98% of the element strontium, which is attracted to bones. While reducing the activity of bone-resorbing osteoclasts, strontium stimulates the activity of bone-forming osteoblastic cells. It activates downstream signalling cascades and calcium detecting receptors. It boosts OPG production while lowering RANKL expression. This triggers osteoclast death, which reduces bone resorption, and enhances osteoblast proliferation, differentiation, and viability.[42]

4.3. Silicon

By up regulating nitric oxide synthase and increasing VEGF synthesis at low concentrations when cultivated with human dermal fibroblasts, silicon has been demonstrated to promote angiogenesis.[43] It has been demonstrated that silicon plays a crucial role in mineralization at greater concentrations. As a vital component of glycosaminoglycan and associated protein complexes, silicon is abundant in bone and connective tissue, which may therefore affect bone development and maintenance.[44]

4.4. Copper

According to reports, copper acts as a substance that mimics hypoxia and triggers angiogenesis. Copper may indirectly cause a robust osteogenic differentiation of bone morphogenic stem cells by inducing an immunological microenvironment.[45] Increased extracellular matrix (ECM) synthesis and rapid and improved vascularization in copper-doped porous scaffolds demonstrate that collagen creation stimulates the development of additional blood vessels in vivo.[46]

4.5. Lithium

Lithium (Li)'s function in osteogenesis has garnered interest. Lithium use lowered the likelihood of fracture. Lithium is thought to inhibit glycogen synthase kinase 3 (GSK3), a protein that acts as a brake on the Wnt signalling pathway, which is thought to be the mechanism behind osteogenesis. Li has also been demonstrated to promote catenin signalling during bone and cartilage fracture repair by influencing osteoblast proliferation, differentiation, and maturation.[47]

4.6. Cobalt

When bone marrow stem cells were treated with a 100 mMCoCl2 enriched growth media, VEGF expression was noticeably increased. These CoCl2-treated cells then enhanced vascularization and osteogenesis when implanted in vivo on collagen scaffolds.[10]

5. Conclusion

The use of biologic modifiers in regenerative therapies holds considerable potential because they have a major impact on cell behavior. In the past ten years, significant progress has been made in the regeneration of complicated periodontal and alveolar bone abnormalities. Lack of osteoinductivity is one of the factors contributing to inferior bone repair when synthetic alternatives are utilised. Human growth factors can be added to bone allograft and other replacements, and the results have been thought to be widespread.

6. Source of Funding

None.

7. Conflict of Interest

None.

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