APPLICATION OF BONE REPLACEMENTS IN THERAPY OF INFRABONY DEFECTS

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Background: Periodontal disease is one of the most common oral condition of human population, that is characterized by destructive processes of the tooth-attachment apparatus. If destructive processes are not remedied by conventional treatment, in patients can remain pockets that can be associated with infrabony defects. This defects require surgical therapy.
Objective: This paper presents the clinical treatment of infrabony and furcation defects using periodontal regenerative procedures and the most commonly used bone grafts and their alternatives.
Data sources: Available studies and literature reviews from Pub Med and Google Scholar corresponding to bone grafts, periodontal regeneration and infrabony defects as key words, were reviewed.
Study selection: Periodontal regeneration reviews and research articles that present bone grafts procedures were selected.
Data extractions: In the background information about infrabony and furcation defects and the possibility of therapy were blinded. Information about all types of bone grafts was customized to summarize the relevant facts.
Data synthesis: In recent years it has been intensively working on the formation of an optimal alloplastic material, which would achieve significant results for forming a new bone. Although we live in the age of modern medicine and dentistry, there is still no material available to fulfill all the requirements of an ideal bone substitute.
Keywords: bone grafts, periodontal desease, regeneration, infrabony defects.

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Review Article

1.Introduction

Periodontal disease is one of the most common oral condition of human population, that is characterized by irreversible destruction on tooth supporting tissues such as alveolar bone, periodontal ligaments and cement [1,2]. Overall, periodontal disease affects about 20-50% of the population around the globe [3]. Due to the enormous frequency of periodontal disease it is a serious medical, economic, and social problem.

Destructive processes of the tooth-attachment apparatus in periodontitis are the result of infection and inflammation caused by dental plaque biofilm. [4,5] By applying appropriate treatment, destructive processes can be stopped and, thus prevent tooth loss and preserve the functional integrity of periodontium. Successful treatment is evidenced clinically by a reduction of pocket depths and a decrease in bleeding scores (bleeding on probing). Even though conventional periodontal therapy, that consisting of non-surgical debridement such as scaling, gingival curettage – may lead to substantial clinical improvements, in patients with severe periodontitis residual periodontal pockets ≥ 6 mm can remain after initial therapy [6]. These pockets can be associated with intrabony defects or furcation involvement.

Based on clinical observations and observations on human skulls bony defects as a result to periodontal disease can be classified as:

- Suprabony or supracrestal: when the base of the pocket is located coronal or occlusal to the bone crest,
- Infrabony or subcrestal: when the apical end of the pocket is located below the bone crest. An infrabony defect may be subdivided to intrabony defect when the subcrestal component involves the root surface of only one tooth and crater when the defect affects the root surfaces of two adjacent teeth on an equal extent [7].

An intrabony defect therefore can be sub classified, with respect to the number of remaining bony walls, in three categories: the 1-wall, 2-wall and 3-wall defects [7].

On the other hand, there are more classification about fructation, but the most commonly used classification is the one that proposed by Hamp et al.:

- Class I: Horizontal bone loss not exceeding the one third of the tooth width
- Class II: Horizontal bone loss exceeding the one third of the width of the tooth but not involving the total width of the furcation area
- Class III: "Through-and-through" bone destruction [8].

Such pockets have a higher risk for future periodontal destruction, one of the clinically most important goals of periodontal therapy is the reduction or complete eradication of deep pockets ≥ 6 mm and elimination of furcation defects [6]. Earlier, in the treatment of advanced periodontitis was used conventional surgical therapy, that consists of gingivectomy and flap procedures of various types with or without bone recontouring, following non-surgical intervention [9].

Today, the clinical treatment of intrabony and furcation defects, can be implemented by a variety of reconstructive periodontal surgical methods and materials. Studies has shown that clinical parameters are improved when intrabony and Class II furcation defects are treated with bone fillers [7].

2.Bone replacement grafts

With the aim to stimulate osteogenesis, various materials and grafting procedures have been developed. Kandwal et al. have shown in their paper that the ideal material for the replacement of bone tissue should have the following characteristics: nontoxic, nonantigenic, resistant to infection, no root resorption or ankylosis, strong and resilient, easily adaptable, readily and sufficiently available, minimal surgical procedure, stimulates new attachment [10]. However, material that has all these properties has not yet been found, so the search for an ideal graft material continues to be a challenge.

The use of bone substitutes is based on the assumption that these materials facilitate the formation of new connective tissue attachment and bone regrowth. Based on their origin, bone grafts have been classically divided into autogenous, allogenic, xenogenic, and synthetic or alloplastic [11]. Furthermore, according to their characteristics all bone substituties are divided as materials containing bone-forming cells (osteoneogenesis), materials containing growth factors (osteoinduction) and materials serving as a scaffold for bone regeneration (osteoconduction) [12].

Autogenous bone is the highest quality bone substitute because the new bone is formed by processes of osteogenesis, osteoinduction and osteoconduction [13]. Hydroxyapatite and collagen play the role of osteoconductive matrix, stromal cells surrounding microspecies possess osteogenic potential, and growth factors within the bone matrix induce the production of new bone. These characteristics and absence of immunological reactions make autologous bone transplants considered a gold standard in bone surgery [14]. That the autogenous bone is the gold standard in bone surgery showed a study of Sakkas et al. They had the high graft success rate (95,6%) in preprosthetic dentoalveolar reconstruction [15]. Autografts used in periodontal regeneration may be of extraoral (iliac crest, calvaria) or intraoral (spina nasalis, the tuberosity and crista zygomatico-alveolaris from the maxilla, the ramus, retromolar region and the symphysis region in the mandible) origin [14]. Numerous studies have shown that intraoral transplants give better results than extraoral, since the actual creation of a new bone and a new attachment results [16,17]. Main disadvantages of autogenous grafts are donor site morbidity, and limited graft volume [14].

Allogenous bone are obtained from other individuals of the same species but disparate genotype. They

include freeze-dried bone allografts (FDBA) and demineralized freeze-dried bone allograft (DFDBA) [18]. FDBA has been reported to be effective as a scaffold over which new bone may form. FDBA have osteoinductive potential due to the growth factors stored in the matrix [14]. DFBA is obtaind by demineralization of FDBA. DFDBA undergo resorption at a quick rate and often have osteoinductive potential due to the bone morphogenetic proteins (BMPs) and growth factors present in the graft matrix [14]. Both FDBA and DFDBA materials are widely used in periodontal therapy and there are no reports of disease transmission during the 30-year history of using freezedried bone allografts [18]. The advantage of allograft is the ability to take sufficient amounts of transplants for deep and multiple defects and which can be stored in the tissue bank until the time of use. Xenogenous bone is obtained from animals or from corals, which after processing have osteoconductive potential. Because of the high antigenic potential, the organic component is removed to eliminate the risk of immunological reactions and the transmission of various diseases. The commercially most commonly used material is the inorganic bone of bovine origin that is called Bio-Oss. The chemical composition of Bio-Oss is almost identical to the composition of human bone mineral with a total porosity of about 75% [8]. This type of bone graft is used for alveolar ridge augmentation and for infrabony defect filling [14]. As well as, in some studies it is shown that Bio-Oss is used for sinus lift, where dental implants placed in Bio-Oss grafts had survival rates at least similar if not better than autogenous grafts [19].

Different types of corals have a calcium carbonate skeleton whose geometry resembles structure of human spongy bone with interconnected macropores of size from 200-600μm. In the processing calcium carbonate is transformed into hydroxyapatite, and these grafts have shown potential for improved defect filling in periodontal regeneration applications and do not undergo fibrous encapsulatio [14]. In a study performed by Al-Fatlawi it is compared the effect of coralline calcium carbonate and open flap debriedment alone in the treatment of human periodontal infrabony pockets. He concluded that natural coralline porous calcium carbonate appears to be a clinically useful graft material and achieves essentially similar or slightly better responses in periodontal osseous defects as other bone replacement graft materials [20].

Allopastic bone grafts have been developed as alternatives of natural grafts due to enormous progress in the field of biomaterials science, the risk of infectious diseases transmission and finally, efforts to reduce morbidity and cost has [21]. These materials are inorganic, biocompatibile and/or bioactive and they may promote bone healing through osteoconduction. Alloplastic grafts are usually conductive with bone without any induction of bone and osteogenic capacity on their own and have been used frequently for periodontal regeneration. Among the most widely used alloplastic materials are hydroxyapatite (HA), tricalcium phosphate (TCP) and bioactive glass.

Hydroxyapatite (HA) is the primary mineral component of bone, therefore synthetic HA is most used as bone substitute, achieving a chemical bond with the bone at the site where it is applied. The most important feature of hydroxyapatite when compared with other inorganic materials is its unique biologic properties as it consists of only calcium and phosphate, which is found in the human organism and no toxicity or defence reaction is expected. The biocompatibility, tolerance, and biologically active property of hydroxyapatite make it an ideal bone substitutes [22]. There are three forms of synthetic HA: 1) Porous non-resorbable; 2) Solid non-resorbable; and 3) Resorbable (non-ceramic, porous) [23]. The porous HA is a pure uniquely resorbable HA implant material used for alloplastic augmentation and the repair of bone defects [22]. In controlled clinical studies, grafting of intrabony periodontal lesions with HA resulted in an attachment level gain of 1.1–3.3 mm which was greater as compared with non-grafted surgically debrided controls [21]. HA show slow resorption rate that allowed prolonged osteoconductive action [7]. The degradation rate of HA depends on the method of ceramic formation, the calcium to phosphate ratio, crystallographic structure and porosity. The ability of HA to resorb is also heavily dependent upon the processing temperature, therefore HA synthesized at high temperatures is very dense with very limited biodegradibility. These dense grafts are usually used as inert biocompatible fillers. At lower temperatures, the particulate HA is porous

and undergoes slow resorption [14]. Tricalcium phosphate (TCP) is a porous calcium phosphate compounds. TCP has two crystallographic forms: alpha (α-TCP) and beta (β-TCP). Both forms are produced similarly, although they display different resorption properties [18]. The most commonly used form of this material is β-TCP that is considered as the "gold standard" for synthetic bone [24]. It is a biocompatible and bioresorbable material with properties similar to the inorganic phase of bone. β-TCP is osteoconductive due to its composition and its porosity. β-TCP gradually resorbs, and although its resorption is unpredictable, β-TCP is meant to be completely resorbed by osteoclasts resorbs in approximately 13–20 weeks after implantation and is then completely replaced by remodeled bone [25]. In terms of bone regenerative potential, β-TCP grafts have been shown to be similar to autogenous bone, FDBA, DFDBA and collagen sponge [26]. In clinical study of Stavropoulos et al. TCP is used to repair periapical and marginal periodontal defects, as well as alveolar bony defects [27]. As well as, other authors used β-TCP for alveolar ridge augmentation in vertical and horizontal dimensions [28-30].

On the other hand, due to β-TCP can be resorbed unpredictably in biologic fluids and a variety of solvents, the development of a two-phased calcium phosphate or biphasic calcium phosphate (BCP) ceramic (HA and β-TCP) made it possible to control the resorbability of the material and at the same time maintain its osteoconductive property [31]. The resorption of β-TCP is faster than the resorption of HA but mechanical properties of HA are slightly better than βTCP's [32].

HA and β-TCP ceramics form a strong direct bond with the host bone. They can be found with different HA/β-TCP ratios and can be associated with bone marrow aspirate which then provides enhanced osteogenic properties to the material [25]. BCP with >99% crystalline structure consists of 60% HA and 40% β-TCP in particulate form [31]. Preclinical evidence suggests that the use of this ratio of HA and β-TCP allows better control of the bio-absorbable ability of the graft material resulting in accelerated new bone formation [33]. This form of BCP is biocompatible, nontoxic, resorbable, noninflammatory and bioactive. It causes no immunological, foreign-body, or irritating response, and has the excellent osteoconductive ability [31]. Bansal et al. in clinico-radiographic study evaluated the use of BCP composite graft in the treatment of intrabony periodontal defect. They concluded that BCP may elicit significant new bone formation due to combination of the available pore size and rigid space for maintaining the scaffold. Therefore, they found that BCP can be a very effective material in the treatment of intrabony three-wall periodontal defect [34].

Bioactive glass compose from 45% silica (SiO2), 24.5% calcium oxide (CaO), 24.5% sodium oxide (Na2O), and 6% phosphorous pentoxide (P2O5) in weight percentage [25]. When subjected to an aqueous solution or body fluids, surface of bioglasses converts to a silica-CaO/P2O5-rich gel layer that subsequently mineralizes into hydroxycarbonate in a few hours. Bioactive glass is biocompatible, osteoconductive, and—depending on processing condition—offer a porous structure which promotes resorption of bioglass and bone ingrowth [35]. The use of bioactive glass does not induce an inflammatory response, and resorption is complete in 6months for silica-based bioglasses [36]. Literature data showed that bioactive glass was efficacious in the treatment of intrabony defects [37, 38]. Bioactive glass nanoparticles have been shown to induce cementoblasts to proliferate in an in vivo study [39]. Clinical reports of alveolar ridge grafting performed with bioactive glass reveal bone formation in close contact to the particles [14]. However, limited true periodontal regenerative outcomes based on human histological analysis has been demonstrated with the use of bioactive glass [40].

3.Guide tissue regeneration

Guided tissue regeneration (GTR), besides bone transplants and implants, belongs to the most commonly regenerative methods of treatment in periodontal disease. It implies procedures aimed at regenerating the lost periodontal tissue [7]. Regeneration of the coupling apparatus is a method of choice in clinical practice for the regeneration of infrabony and furcation defects.

GTR is a surgical method in parodontology that involves the separation of various tissues, surgical, by placing a physical barrier [14]. By placing the membrane as a barrier, the space for the formation of

formative cells of periodonium and bone is provided, as well as, it is enabled forming of a new cement root, new bones and functional fibers of the new periodontal membrane, and the creation of a new root surface. In addition to the stabilization function of the wound and avoiding the proliferation of the epithelium and connective tissue of the gingiva [7], the membrane placement, if used in combination with bone grafts, has the role of stabilizing and preserving the same [41]. They also reduce the possibility of graft resorption [42].

GTR can be made using membranes from resorbable and non-resorbable materials that are different in design, shape and composition. They must have the following requirements: appropriate institution approval, biocompatibility, good alveolar bone adaptability, ability to preserve the regeneration space, connective tissue should be able to grow into structures below the surface of the membrane, permeability to tissue fluids and growth factors, at least six weeks should be maintained in wound and easy handling [42- 45].

3.1.Non-resorbable membranes

Non-resorbable membranes have been studied for a long time and are clinically applied, so untill today they remain standard in GTR. They are biocompatible, have good structural durability, better preserve space from resorptive membranes that more often collapse into defects. However, they require another operation to remove the membrane, which presents a risk for newly developed bone tissue. In addition, they have a higher incidence of dehiscence, which increases the risk of secondary infection [46]. These disadvantages are the reason for the increasingly frequent use of resorbable membranes in periodontal surgery [47- 50].

Among the first commercial non-resorbable membranes, the membrane is of polytetrafluoroethylene (PTFE) and the so called titanium mesh. PTFE is divided into expanding (e-PTFE) and PTFE high density (d-PTFE). e-PTFE was developed in 1969. and until today it is the most abundant non-resorbable membrane. Given the longest clinical experience with these membranes, they are considered to be the standard in guided bone regeneration, which Trobos et al. proved in their study [51]. d-PTFE, an alternative to e-PTFE, was developed in 1993. The pore size of this membrane is 0.2 μm, which eliminates the possibility of bacterial contamination, so the possibility of infection is much lower than for e-PTFE [52]. Titanium has been widely used in periodontal and oral surgery due to its high strength and rigidity, low density and appropriate low weight and high resistance to high temperature and corrosion. Titanium mesh with its rigidity maintains space well and prevents membrane collapse, but it has sufficient elasticity to avoid mucosal compression. It adapts well to the defect, and the smooth surface reduces the adhesion of the bacteria [49]. PTFE membranes are also available in the form of e-PTFE and d-PTFE titanium-enhanced. The built-in titanium skeleton allows the membrane to adapt to different forms of defects and provides additional stability in large bone defects [47,52].

3.2.Resorbable membranes

Resorbable membranes can be divided into natural collagen (Bio-Gide®, BioMend®, Avitene®) from collagen, bovine or pig origin, and synthetic (Gore-Resolut®, Guidor®, Epi-Guide®) made from polyacidal and polyglycolic acid and their copolymers. The common property of resorptive membranes is that they are biodegradable, and no other operation is required for their removal [42, 53].

Polylactide is the main ingredient of numerous membranes due to sample handling, biocompatibility, good mechanical properties, and long absorption (about 4 years). Copolymers of lactide and ε-caprolactone, lactide and glycolide, glycolide and trimethylene carbonate were developed to shorten the absorption time [14]. However, the copolymers have their drawbacks: low stiffness, insufficient mechanical strength, pH changes caused by the decomposition products of the polymer that trigger the inflammatory reaction in the tissue [7,14]. Today, by adding calcium phosphate, it is trying to reduce this deficiency. Calcium phosphate should increase the rigidity of soft polymer and reduce pH. Kikuchi et al. [54] developed a membrane consisting of β-TCP and a mixture of polylactides and copolymers. Such a membrane during resorption regulates the local pH around 7. This membrane allowed the creation of new bone in large defects of mandible and dog tibia, while the pure blend allowed the soft tissue to enter defects [54].

Kinoshita et al. [55] developed a macroporous membrane built from copolymers of polylactides

and ε-caprolactone (75:25) and 30% of β-TCP that preserved the initial form until the completion of bone regeneration. The membrane is moderate stiffness, thermoplastic at 70ºC [55].Synthetic membranes are degraded by hydrolysis and are removed from the body through a citric acid cycle (Krebs cycle) in the form of water and carbon dioxide. The disadvantages of these materials are the possibility of causing an inflammatory reaction (around the membranes can be found fibrous incapsulates or infiltrates of the inflammatory cells). If exposure to the membrane of the oral cavity occurs, its resorption immediately begins. The excess resorption negatively influences the outcome of regeneration [56].

Natural membranes are made from collagen type I or III and from their combinations, and are derived from the skin, tendons, bovine pericardium, pig and human origin. The benefits of using collagen as a membrane material are: haemostasis, chemotaxis of fibroblasts from the periodontal ligament and gingiva, poor immunogenicity, simple handling and adaptation, affect the formation of bones, the ability to increase tissue thickness [57]. It is degraded by macrophages and polymorphonuclear leukocytes to water and carbon dioxide.

Resorptive collagen membranes are often used to cover the wounds because they stimulate platelet aggregation, stabilize the clots, attract fibroblasts and thus promote healing. The application is also found in the enlargement of the ridge, the elevation of the sinus base, the formation of soft tissue and apicotomy. The choice of the membrane depends on the type of intervention, so that the GTR technique uses those more durable, with a longer resorption period (OsseoGuard, Collagen Matrix Inc., 6 - 9 weeks), while membranes with a short period of resorption (CollaTape, CollaPlug, CollaCote , Integra LifeSciences Corp., 10 - 14 days) are used to stop bleeding [50,57].

Zhou et al. proved that the combination of collagen, bioactive glass and chitosan is a multifunctional membrane that has the ability to induce the regeneration of the periodontal tissue of the dog, and at the same time showed a certain degree of antibacterial activity against Streptococcus mutans [58]. Chitosan is a polysaccharide consisting of a copolymer of glucosamine and N-acetylglucosamine [59]. It is biocompatible and non toxic [60]. In addition, it has bacteriostatic properties, ability to inhibit the growth of gram-negative and gram-positive bacteria, Actinobacillus actinomycetemcomitans and Streptococcus mutans, and is increasingly used in periodontal and oral surgery [61].

4.Active biomoleculs for therapy of intrabony defects

With the limitations of the previously described agents and grafting procedures in mind, more recent efforts in periodontal regeneration have been focused on the use of biological agents to assist in stimulating self-repair/regeneration mechanisms within the periodontium, that is referred as "endogenous regenerative therapy" [62]. Among these molecules there has been great interest in using growth/differentiation factors especially bone morphogenetic proteins (BMPs), matrix derivatives such as enamel matrix derivative (EMD), platelet rich plasma (PRP) and exploring mineralization strategies for in situ attachment of periodontal membranes [14].

4.1.Bone morphogenetic proteins (BMPs)

Bone morphogenetic proteins (BMPs) are osteoinductive growth factors, that belong to Transforming Growth Factor beta (TGFβ) superfamily [25]. BMPs play a crucial role in bone remodelling through their chemotactic properties, as well as they may function as mitogenic factors or induce the differentiation of mesenchymal progenitor cells into chondroblasts and osteoblasts [7]. The most commonly used are BMP-2 and BMP-7. BMP-2 may be more potent than BMP-7 as a bone forming agent due to its ability to induce both early and late osteogenic activity and matrix mineralization. BMP- 7 assists primarily in later stages of bone formation [14]. Genetic engineering allows to synthetize recombinant human BMP (rhBMP-2 and rhBMP-7), which are allowed by the Food and Drug Administration (FDA) as an alternative to autograft for sinus lift and alveolar ridge augmentation [25]. Yang et al. in their study on rats suggested that application of BMP-7 associated insulin-like growth factor-1 (IGF-1) could be a new potential method in gene therapy for periodontal reconstruction [63]. In a relatively new study, Kawai et al. successfully performed BMP-2/7 gene transfer, via in vivo electroporation, into the periodontal tissues of rats.

Exogenous BMP-2 and BMP-7 were detectable by immunohistochemistry analyses up to 3 days after gene transfer. Moreover, thay detected new alveolar bone formation 5 days after gene transfer. On this way these authors concludes that the combination of the BMP-2/7 non-viral vector and in vivo electroporation represents a promising candidate non-surgical strategy for alveolar bone regeneration therapy [64]. However, in order to get the right results with use of BMPs in therapy of infrabony defects, more clinical research needs to be carried out.

4.2.Enamel matrix derivative (EMD)

EMD is a purified, lyophilized product extracted from porcine enamel matrix from crowns of developing premolars and molars. A major component of EMD is amelogenin, and non-amelogenins consist of ameloblastin, enamelin, and amelotin [65]. Compared with growth factors, EMD emerged relatively late as a therapeutic option for periodontal regeneration.

The first studies that included histological results following the use of EMD in buccal dehiscences are conducted on animals and reported that there are up to 70% of new cementum and up to 65% bone gain eight weeks following the regenerative procedure [66]. The use of EMD in the treatment of Class II mandibular furcation defects was also tested and resulted in a higher rate of Class II to Class I conversion [67]. Other study reported that EMD with/ without the addition of a synthetic bone graft lead to clinical improvement in advanced intrabony defects [68].

EMD combined with β-tricalcium phosphate was shown to be efficacious in the regeneration of intrabony defects [69]. EMD is considered comparable to DFDB allograft and GTR and is considered better than open-flap debridement in the treatment of intrabony defects [68].

Meta-analysis showed that EMD produced additional clinical and radiographic benefits compared to open-flap debridement alone [70].

4.3.Platelet rich plasma (PRP)

PRP is an autogenous concentration of platelets, up to 338 %, in a small volume of plasma and is considered to be an extremely rich source of autogenous growth factors such as platelet-derived growth factor (PDGF), transforming growth factor-β1 and transforming growth factor-β2 (TGF-β1 and TGF-β2), and insulin-like growth factors 1 and 2 (IGF-1,2) [14, 71]. In clinical dental practice, the effective use of PRP has been described in sinus grafting procedures, alveolar socket preservation techniques, and also as an adjunctive procedure to support the regenerative process in periodontal infrabony and furcation defects [72-74]. In recent years, the Japanese group of authors emphasized the importance of combining PRP with mesenchymal stem cells in the treatment of infrabony defects [75].

As well as, other group of authors in their systematic review and meta-analysis about adjunctive PRP in infrabony regenerative treatment concluded that adjunctive use of PRP can be considered as an affordable technique to get a better clinical attachment gain and periodontal pocket depth reduction in the surgical treatment of periodontal infrabony defects [71].

They also concluded that regeneration/repair of infrabony defects would favour the use of adding PRP to a simple surgical repositioned flap technique, like in the open flap debridement with the use of bone grafts (xenografts, HA, or TCP). No better results would be achievable using combinations with biomodulators (Emdogain) or membranes, the PRP just would act as a biomodulator itself [71].

5.Conclusion

Most of the described bone substitutes, apart from autogenic bone, serve only to fill the bone defect and have minimal impact on the right periodontal regeneration. Only by introducing growth factors and biomembranes in therapy, and by combining them with bone substitutes, significant results are achieved in terms of the formation of new bone and a new epithelial attachment.

Although in recent years it has been intensively working on the formation of an optimal alloplastic material, there is still no material available to fulfill all the requirements of an ideal bone substitute.

The tendencies are directed towards the synthesis of materials that would have a double effect, i.e. the possibility of a local, prolonged and precisely dosed delivery of growth factors, which would also serve as scofolds and fillers for bone-generating. The challenge of controlling bone regeneration by strategies that imitate the natural bone formation cascades remains very current.

Author Contributions

All authors (MJ, RO, DS, MM) contributed in data collection and analysis, and manuscript writing. All authors agree to be accountable for the content of the work.

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References:

1. Nazir MA. Prevalence of periodontal disease, its association with systemic diseases and prevention. Int J Health Sci (Qassim). 2017;11(2):72–80. [Free PMC Article] [PubMed] Google Scholar(82)
2. Li S. Periodontal Regeneration: Promising and Challenging for Periodontal Complex Regeneration. J Bone Rep Recomm. 2017;3:1. DOI: 10.4172/2469-6684.100037 [Full text links]
3. Sanz M, D'Aiuto F, Deanfield J, et al. European workshop in periodontal health and cardiovascular disease-scientific evidence on the association between periodontal and cardiovascular diseases: A review of the literature. Eur Heart J Suppl. 2010;12(Suppl B):B3–12. DOI:10.1093/eurheartj/suq003 [Full text links] Google Scholar(68)
4. Tsuchida S, Mamoru S, Takiwaki M, et al. Critical Issues in Periodontal Regeneration - A Review. Int J Mol Sci. 2017;18(7):1476. DOI:10.3390/ijms18071476 [Full text links]
5. Pihlstrom BL, Michalowicz BS, Johnson NW. Periodontal diseases. Lancet. 2005;366:1809–1820. DOI:10.1016/S0140-6736(05)67728-8 [Full text links] [PubMed]Google Scholar(2813)
6. Koop R, Merheb J, Quirynen M. Periodontal Regeneration With Enamel Matrix Derivative in Reconstructive Periodontal Therapy: A Systematic Review. J Periodontol. 2012;83:707-720. DOI:10.1902/jop.2011.110266 [Full text links] Google Scholar (120)
7. Siaili M, Chatzopoulou D, Gillam DG. An overview of periodontal regenerative procedures for the general dental practitioner. Saudi Dent J. 2018;30(1):26–37. DOI:10.1016/j.sdentj.2017.11.001 [Full text links] [Free PMC Article] [PubMed] Google Scholar (2)
8. Hamp SE, Nyman S, Lindhe J. Periodontal treatment of multi rooted teeth. Results after 5 years. J. Clin. Periodontol. 1975;2:126–135. [Full text links] [PubMed] Google Scholar(661)
9. Seshima F, Aoki H, Takeuchi T, et al. Periodontal regenerative therapy with enamel matrix derivative in the treatment of intrabony defects: a prospective 2-year study. BMC Res Notes. 2017;10:256. DOI: 10.1186/s13104-017-2572-2 [Free PMC Article] [PubMed] Google Scholar(6)
10. Kandwal A, Bhardwaj J, Sunny, et al. Bone Grafts In Periodontal Surgery. A Review. J Dent Herald. 2014;1(3);30-32. [Full text links] Google Scholar(2)
11. Pilipchuk SP, Plonka AB, Monje A, et al. Tissue engineering for bone regeneration and osseointegration in the oral cavity. Dent Mater. 2015;31(4):317–338. DOI: 10.1016/j.dental.2015.01.006 [Full text links] [Free PMC Article] [PubMed] Google Scholar(79)
12. Hagi TT, Laugisch O, Ivanovic A, et al. Regenerative periodontal therapy. Quintessence Int. 2014;45(3):185-192. DOI:10.3290/j.qi.a31203 [Full text links] [PubMed] Google Scholar(20)
13. Galindo-Moreno P, Avila G, Fernández-Barbero JE, et al. Clinical and histologic comparison of two different composite grafts for sinus augmentation: a pilot clinical trial. Clin Oral Implants Res. 2008;19:755–759. DOI:10.1111/j.1600-0501.2008.01536.x [Full text links] [PubMed] Google Scholar(93)
14. Sheikh Z, Hamdan N, Ikeda Y, et al. Natural graft tissues and synthetic biomaterials for periodontal and alveolar bone reconstructive applications: a review. Biomaterials Research. 2017;21:9 DOI: 10.1186/s40824-017-0095-5 [Full text links] [Free PMC Article] [PubMed] Google Scholar(49)
15.Sakkas A, Wilde F, Heufelder M, et al. Autogenous bone grafts in oral implantology-is it still a "gold standard"? A consecutive review of 279 patients with 456 clinical procedures. Int J Implant Dent. 2017;3(1):23. DOI: 10.1186/s40729-017-0084-4 [Full text links] [Free PMC Article] [PubMed] Google Scholar(52)
16. Schwartz-Arad D, Dori S. Intraoral autogenous onlay block bone grafting for implant dentistry. Refuat Hapeh Vehashinayim. 2002;19:35–39. DOI:10.1902/jop.2005.76.4.636 [Full text links] [PubMed] Google Scholar(16)
17. Altiparmak N, Soydan SS, Uckan S. The effect of conventional surgery and piezoelectric surgery bone harvesting techniques on the donor site morbidity of the mandibular ramus and symphysis. Int J Oral Maxillofac Surg. 2015;44:1131–1137. DOI:10.1016/j.ijom.2015.04.009 [Full text links] [PubMed] Google Scholar(10)
18. Jangid MR, Rakhewar PS, Nayyar AS, et al. Bone Grafts and Bone Graft Substitutes in Periodontal Regeneration: A Review. Int J Curr Res Med Sci. 2016;2(8):1-7. [Full text links] Google Scholar(0)
19. Wallace SS, Froum SJ. Effect of maxillary sinus augmentation on the survival of endosseous dental implants. A systematic review. Ann Periodontol. 2003;8:328–343. DOI:10.1902/annals.2003.8.1.328 [Full text links] [PubMed] Google Scholar(1017)
20. Al-Fatlawi ZMH. Comparative Clinical Study of The Use of Coralline Calcium Carbonate as a Graft Material and Open Flap Debridement Alone for Treatment of Human Periodontal Infrabony Pockets. JUBPAS. 2013;21(5):1862-1872. [Full text links] Google Scholar(0)
21. Titsinides S, Agrogiannis G, Karatzas T. Bone grafting materials in dentoalveolar reconstruction: A comprehensive review. Jap Dent Sci Rev. 2018;55(1):26-32. DOI:10.1016/j.jdsr.2018.09.003 [Full text links] Google Scholar(0)
22. Gupta S, Vandana K L. Evaluation of hydroxyapatite (Periobone-G) as a bone graft material and calcium sulfate barrier (Capset) in treatment of interproximal vertical defects: A clinical and radiologic study. J Indian Soc Periodontol. 2013;17:96-103. DOI: 10.4103/0972-124X.107483 [Full text links] [Free PMC Article] [PubMed] Google Scholar(6)
23. Tevlin R, McArdle A, Atashroo D, et al. Biomaterials for craniofacial bone. J Dent Res. 2014;93:1187-1195. DOI: 10.1177/0022034514547271 [Full text links] [Free PMC Article] [PubMed] Google Scholar(89)
24. Galois L, Mainard D, Delagoutte JP. Beta-tricalcium phosphate ceramic as a bone substitute in orthopaedic surgery. Int Orthop. 2002;26:109–115. DOI: 10.1007/S00264-001-0329-X [Full text links] [Free PMC Article] [PubMed] Google Scholar(88)
25. Fernandez de Grado G, Keller L, Idoux-Gillet Y, et al. Bone substitutes: a review of their echaracteristics, clinical use, and perspectives for large bone defects management. J Tissu DOI: 10.1177/2041731418776819 [Full text links] [Free PMC Article] Google Scholar(10)
26. Nakajima Y, Fiorellini JP, Kim DM, et al. Regeneration of standardized mandibular bone defects using expanded polytetrafluoroethylene membrane and various bone fillers. Int J Periodontics Restorative Dent. 2007;27:151-159. [Full text links] [PubMed] Google Scholar(13)
27. Stavropoulos A, Windisch P, Szendröi-Kiss D, et al. Clinical and histologic evaluation of granular beta-tricalcium phosphate for the treatment of human intrabony periodontal defects: a report on five cases. J Periodontol. 2010;81:325–334. DOI:10.1902/jop.2009.090386 [Full text links] [PubMed] Google Scholar(58)
28. Shalash MA, Rahman HA, Azim AA, et al. Evaluation of horizontal ridge augmentation using beta tricalcium phosphate and demineralized bone matrix: a comparative study. J Clin Exp Dent. 2013;5:e253–259. DOI: 10.4317/jced.51244 [Free PMC Article] [PubMed] Google Scholar(22)
29. Wang S, Zhang Z, Zhao J, et al. Vertical alveolar ridge augmentation with beta-tricalcium phosphate and autologous osteoblasts in canine mandible. Biomaterials. 2009;30:2489–2498. DOI:10.1016/j.biomaterials.2008.12.067 [Full text links] [PubMed] Google Scholar(81)

30. Nyan M, Miyahara T, Noritake K, et al. Feasibility of alpha tricalcium phosphate for vertical bone augmentation. J Investig Clin Dent. 2014;5:109–116. DOI:10.1111/JICD.12022 Google Scholar(5)
31. Jain G, Dhruvakumar D, Wadhawan A. Comparative evaluation of efficacy of hydroxyapatite and ß-tricalcium phosphate (Biograft-HT®) with or without type 1 collagen membrane (Cologide™) in the treatment of intrabony defects in molars: A clinico-radiographic study. Int J Oral Health Sci. 2018;8:26-34. DOI: 10.4103/2231-6027.232171 [Full text links]
32. Saikia KC, Bhattacharya TD, Bhuyan SK, et al. Calcium phosphate ceramics as bone graft substitutes in filling bone tumor defects. Indian J Orthop. 2008;42(2):169–172. DOI: 10.4103/0019-5413.39588 [Free PMC Article] Google Scholar(55)
33. Sculean A, Windisch P, Szendröi-Kiss D, et al. Clinical and histologic evaluation of an enamel matrix derivative combined with a biphasic calcium phosphate for the treatment of human intrabony periodontal defects. J Periodontol. 2008;79:1991-1999. DOI:10.1902/jop.2008.080009 [Full text links] [PubMed] Google Scholar(71)
34. Bansal R, Patil S, Chaubey KK, et al. Clinical evaluation of hydroxyapatite and β-tricalcium phosphate composite graft in the treatment of intrabony periodontal defect: a clinico-radiographic study. J Indian Soc Periodontol. 2014;18(5):610–617. DOI: 10.4103/0972-124X.142455 [Full text links] [Free PMC Article] [PubMed] Google Scholar(9)
35. De Aza PN, Luklinska ZB, Santos C, et al. Mechanism of bone-like formation on a bioactive implant in vivo. Biomaterials. 2003;24:1437–1445. DOI:10.1016/S0142-9612(02)00530-6 [Full text links] [PubMed] Google Scholar(96)
36. Moimas L, Biasotto M, Di LR, et al. Rabbit pilot study on the resorbability of three-dimensional bioactive glass fibre scaffolds. Acta Biomater. 2006;2:191–199. DOI: 10.1016/j.actbio.2005.09.006 [Full text links] [PubMed] Google Scholar(56)
37. Mengel R, Schreiber D, Flores-de-Jacoby L. Bioabsorbable membrane and bioactive glass in the treatment of intrabony defects in patients with generalized aggressive periodontitis: results of a 5-year clinical and radiological study. J Periodontol. 2006;77:1781–1787. DOI:10.1902/jop.2006.060029 Google Scholar(61)
38. Sohrabi K, Saraiya V, Laage TA, et al. An evaluation of bioactive glass in the treatment of periodontal defects: a meta-analusis of randomized controlled clinical trials. J Periodontol. 2012;83:453–464. DOI:10.1902/jop.2011.110347 [Full text links] [PubMed] Google Scholar(22)
39. Carvalho SM, Oliveira AA, Jardim CA, et al. Characterization and induction of cementoblast cell proliferation by bioactive glass nanoparticles. J Tissue Eng Regen Med. 2012;6:813–821. DOI:10.1002/term.488 [Full text links] [PubMed] Google Scholar(22)
40. Nevins ML, Camelo M, Nevins M, et al. Human histologic evaluation of bioactive ceramic in the treatment of periodontal osseous defects. Int J Periodontics Restorative Dent. 2000;20:458–467. [PubMed] Google Scholar(115)
41. Sheikh Z, Abdallah MN, Hamdan N. et al. Barrier membranes for tissue regeneration and bone augmentation techniques in dentistry. In: Matilinna KP, editor. Handbook of oral biomaterials. First ed. New York: Pan Stanford Publishing; 2014.
Khan AS, Roohpour N et al. Protein adsorption capability on polyurethane and modified-polyurethane membrane for periodontal guided tissue regeneration applications. Mater Sci Eng C. 2016;68:267–725. DOI: 10.1016/j.msec.2016.05.026 [Full text links] [PubMed] Google Scholar (23)
42. Scantlebury TV. 1982-1992: a decade of technology development for guided tissue regeneration. J Periodontol. 1993;64(11 Suppl):1129-1137. DOI:10.1902/jop.1993.64.11s.1129 [Full text links] [PubMed] Google Scholar (279)
43. Hardwick R, Dahlin C. Healing pattern of bone regeneration in membraneprotecte defects: a histologic study in the canine mandible. Int J Ora Maxillofac Implants. 1994;9:13–29. [PubMed] Google Scholar (620)
44. Dahlin C, Linde A, Gottlow J et al. Healing of bone defects by guided tissue regeneration. Plast Reconstr Surg. 1988;81:672–676. [PubMed] Google Scholar (1228)
45. Tatakis DN, Promsudthi A, Wikesjö UM. Devices for periodontal regeneration. Periodontol 2000. 1999;19:59–73. [Full text links] [PubMed] Google Scholar (129)
46. Liu J, Kerns DG. Mechanisms of guided bone regeneration: a review. Open Dent J. 2014;8(Suppl 1-M3):56–65. DOI: 10.2174/1874210601408010056. [PubMed] [Free PMC Article] Google Scholar (131)
47. Shin SY, Rios HF, Giannobile WV, et al. Periodontal regeneration: current therapies: Current Therapies. In: Vishwakarma J,Sharpe P, Songtao S, Ramalingam M, editors. Stem cell biology and tissue engineering in dental sciences. London: Elsevier Inc; 2015.
Rakhmatia YD, Ayukawa Y, Furuhashi A et al. Current barrier membranes: titanium mesh and other membranes for guided bone regeneration in dental applications. J Prosthodont Res. 2013;57(1):3–14. DOI: 10.1016/j.jpor.2012.12.001. [Full text links] [PubMed] Google Scholar (219)
48. Almazrooa SA, Noonan V, Woo SB. Resorbable collagen membranes: histopathologic features. Oral Surg Oral Med Oral Pathol Oral Radiol. 2014;118(2):236–240. DOI: 10.1016/j.oooo.2014.04.006. [Full text links] [PubMed] Google Scholar (18)
49. Trobos M, Juhlin A, Shah F et al. In vitro evaluation of barrier function against oral bacteria of dense and expanded polytetrafluoroethylene (PTFE) membranes for guided bone regeneration. Clin Implant Dent Relat Res. 2018;20(5):738-748. DOI: 10.1111/cid.12629. [Full text links] [PubMed] Google Scholar (2)
50. Ghensi P, Stablum W, Bettio E et al. Management of the exposure of a dense PTFE (d-PTFE) membrane in guided bone regeneration (GBR): a case report. Oral Implantol (Rome). 2017;10(3):335-342. DOI: 10.11138/orl/2017.10.3.335. [PubMed] [Free PMC Article] Google Scholar (3)
51. Requicha J, Viegas C, Hede S et al. Design and characterization of a biodegradable double-layer scaffold aimed at periodontal tissue-engineering applications. J Tissue Eng Regen Med. 2016;10(5):392-403. DOI: 10.1002/term.1816. [Full text links] [PubMed] Google Scholar (12)
52. Kikuchi M, Koyama Y, Yamada T et al. Development of guided bone regeneration membrane composed of beta-tricalcium phosphate and poly (L-lactide-co-glycolide-co-epsilon-caprolactone) composites. Biomaterials. 2004;25(28):5979-5986. DOI:10.1016/j.biomaterials.2004.02.001 [Full text links] Google Scholar (186)
53. Kinoshita Y, Matsuo M, Todoki K et al. Alveolar bone regeneration using absorbable poly(L-lactideco-e-caprolactone)/b-tricalcium phosphate membrane and gelatin sponge incorporating basic fibroblast growth factor. Int J Oral Maxillofac Surg. 2008;37(3):275–281. DOI: 10.1016/j.ijom.2007.11.010. [Full text links] [PubMed] Google Scholar (47)
54. Eickholz P, Kim TS, Holle R. Regenerative periodontal surgery with non-resorbable and biodegradable barriers: results after 24 months. J Clin Periodontol. 1998;25(8):666-676. [Full text links] [PubMed] Google Scholar (63)
55. Sheikh Z, Qureshi J, Alshahrani A et al. Collagen based barrier membranes for periodontal guided bone regeneration applications. Odontology. 2017;105(1):1-12. DOI: 10.1007/s10266-016-0267-0. [Full text links] [PubMed] Google Scholar (36)
56. Zhou T, Liu X, Sui B et al. Development of fish collagen/bioactive glass/chitosan composite nanofibers as a GTR/GBR membrane for inducing periodontal tissue regeneration. Biomed Mater. 2017;12(5):055004. DOI: 10.1088/1748-605X/aa7b55. [Full text links] [PubMed] Google Scholar (8)
57. Kweon D-K, Song S-B, Park Y-Y. Preparation of water-soluble chitosan/ heparin complex and its application as wound healing accelerator. Biomaterials. 2003;24:1595–1601. [Full text links] [PubMed] Google Scholar (239)
58. Kumar MNR. A review of chitin and chitosan applications. React Funct Polym. 2000;46:1–27. DOI: 10.1016/S1381-5148(00)00038-9 [Full text links] Google Scholar (5433)
59. Xu C, Lei C, Meng L, Wang C et al. Chitosan as a barrier membrane material in periodontal tissue regeneration. J Biomed Mater Res B App Biomater. 2012;100:1435–1443. DOI: 10.1002/jbm.b.32662 [Full text links] Google Scholar (81)
60. Bartold PM. Group C Initiator Paper Periodontal regeneration - fact or fiction? Journal of the International Academy of Periodontology. 2015;17(1 Suppl):37–49. [PubMed] Google Scholar(6)

61. Yang L, Zhang Y, Dong R, et al. Effects of adenoviral-mediated coexpression of bone morphogenetic protein-7 and insulin-like growth factor-1 on human periodontal ligament cells. J Periodontal Res. 2010;45:532–540. DOI: 10.1111/j.1600-0765.2009.01268.x [Full text links] Google Scholar(37)
62. Kawai M, Kataoka YH, Sonobe J, et al. Non-Surgical Model for Alveolar Bone Regeneration by Bone Morphogenetic Protein-2/7 Gene Therapy. J Periodontol. 2018;89(1):85-92. DOI:10.1902/jop.2017.170328 [Full text links] Google Scholar(2)
63. Lyngstadaas SP, Wohlfahrt JC, Brookes SJ, et al. Enamel matrix proteins; old molecules for new applications. Orthodontics & Craniofacial Research. 2009;12:243-253. DOI:10.1111/j.1601-6343.2009.01459.x [Full text links] [Free PMC Article] [PubMed] Google Scholar(113)
64. Hammarstrɛm L. Enamel matrix, cementum development and regeneration. J Clin Periodontol. 1997; 24:658–668. DOI: 10.1111/j.1600-051X.1997.tb00247.x [Full text links] [PubMed] Google Scholar(938)
65. Casarin RC, Del Peloso Ribeiro E, Nociti Jr FH, et al. A doubleblind randomized clinical evaluation of enamel matrix derivative proteins for the treatment of proximal class-II furcation involvements. J Clin Periodontol. 2008;35:429–437. DOI: 10.1111/j.1600-051X.2008.01202.x [Full text links] Google Scholar (42)
66. Hoffmann T, Al-Machot E, Meyle J, et al. Three-year results following regenerative periodontal surgery of advanced intrabony defects with enamel matrix derivative alone or combined with a synthetic bone graft. Clin Oral Investig. 2016;20:357–364. DOI:1007/s00784-015-1522-4 [Full text links] Google Scholar (17)
67. DiGiovanni CW, Lin SS, Baumhauer JF, et al. Recombinant human platelet-derived growth factor-BB and beta-tricalcium phosphate (rhPDGF-BB/beta-TCP): An alternative to autogenous bone graft. J Bone Joint Surg Am. 2013;95(13):1184-1192. DOI:10.2106/JBJS.K.01422 [Full text links] [PubMed] Google Scholar(53)
68. Graziani F, Gennai S, Cei S, et al. Does enamel matrix derivative application provide additional clinical benefits in residual periodontal pockets associated with suprabony defects? A systematic review and meta-analysis of randomized clinical trials. Journal of Clinical Periodontology. 2014;41:377-386. DOI:10.1111/jcpe.12218 [Full text links] [PubMed] Google Scholar(13)
69. Saleem M, Pisani F, Zahid FM, et al. Adjunctive Platelet-Rich Plasma (PRP) in Infrabony Regenerative Treatment: A Systematic Review and RCT's Meta-Analysis. Stem Cells Int. 2018;2018:9594235. DOI: 10.1155/2018/9594235 [Full text links] [PubMed] [Free PMC Article] Google Scholar(3)
70. Arora NS, Ramanayake T, Ren YF, et al. Platelet-rich plasma in sinus augmentation procedures: a systematic literature review: Part II Implant Dentistry. 2010;19(2):145–157. DOI:10.1097/ID.0b013e3181cd706d [Full text links] [PubMed] Google Scholar (59)
71. Simon D, Manuel S, Geetha V, et al. Potential for osseous regeneration of platelet-rich plasma--a comparative study in mandibular third molar sockets. Indian Journal of Dental Research. 2004;15(4):133–136. [PubMed] Google Scholar(67)
72. Pradeep AR, Shetty SK, Garg G, et al. Clinical effectiveness of autologous platelet-rich plasma and peptide-enhanced bone graft in the treatment of intrabony defects. Journal of Periodontology. 2009;80(1):62–71. DOI:10.1902/jop.2009.080214 [Full text links] [PubMed] Google Scholar(66)
73. Yamada Y, Ueda M, Hibi H, et al. Translational research for injectable tissue-engineered bone regeneration using mesenchymal stem cells and platelet-rich plasma: from basic researchto clinical case study. Cell Transplant. 2004;13(4):343-355. [Full text links] [PubMed] Google Scholar(155)

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Questions

1. Intraoral transplants give:

❑a. Worse results than extraoral;
❑b. Better results than extraoral;
❑c. Do not lead to the creation of a new bone;
❑d. Do not create a new attachment.

2. Hydroxyapatite show:

❑a. Rapid resorption rate that allowed shortened osteoconductive action;
❑b. Rapid resorption rate that allowed prolonged osteoconductive action;
❑c. Slow resorption rate that allowed prolonged osteoconductive action;
❑d. Slow resorption rate that allowed shortened osteoconductive action.

3. What require non-resorbable membranes:

❑a. Require another operation to remove the membrane;
❑b. More often collapse than resorptive membranes;
❑c. Do not require another operation;
❑d. They are not used in GTR

4. The enamel matrix derivative origin is:

❑a. Porcine enamel matrix from crowns of developing premolars and molars;
❑b. Porcine enamel matrix from bovine of developing premolars and molars;
❑c. Porcine enamel matrix from root of developing incisors;
❑d. Porcine enamel matrix from root of developing premolars and molars.