Scientific Foundation SPIROSKI, Skopje, Republic of Macedonia
Open Access Macedonian Journal of Medical Sciences. 2020 Apr 20; 8(F):90-97.
https://doi.org/10.3889/oamjms.2020.4354
eISSN: 1857-9655
Category: *F - Review Articles*
Section: *Systematic Review Article*

Use of Biomaterials for Periodontal Regeneration: A Review

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Edited by: Filip Koneski
Citation: Reçica BF, Popovska M, Cana A, Bedxeti LZ, Tefiku U, Spasovski S, Spasovska-Gjorgovska A, Kutllovci T, Ahmedi JF. Use of Biomaterials for Periodontal Regeneration: A Review. Open Access Maced J Med Sci. 2020 Apr 20; 8(F):90-97. https://doi.org/10.3889/oamjms.2020.4354
Keywords: Periodontal disease; Biomaterials; Bio-Oss; Platelet-rich fibrin; 4MATRIX
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Received: 28-Jan-2020
Revised: 07-Mar-2020
Accepted: 19-Mar-2020

Funding: This research did not receive any financial support
Competing Interests: The authors have declared that no competing interest exists

Abstract

BACKGROUND: Management of bone periodontal defects, destruction, and loss of the alveolar bone is considered a challenge for modern periodontal regeneration and implant dentistry. Numerous of biomaterials are being used in periodontal regenerative treatment.

AIM: This study aims to know the characteristics of biomaterials and their efficiency in periodontal surgical treatment as regenerative therapy.

METHODS: A systematic review of the literature considering reviews, clinical studies, original papers, and articles from electronic data has been used.

RESULTS: Different biomaterials such as Straumann® *Emdogain*®, Geistlich *Bio-Oss*®, *MIS 4MATRIX – Bone* Graft, Platelet-rich fibrin (PRF), Mis Bone-4MATRIX, and PRF are being used for periodontal regeneration treatment, hence revealing more effective outcomes when combined. PRP together with conventional grafting procedures may be a beneficial treatment approach, guided tissue regeneration with bioabsorbable membranes in combination with Bio-Oss are stable on a long-term basis.

CONCLUSION: Biomaterials being used in periodontal surgical treatment have the different regenerative ability. The combined use of biomaterials might result in a better clinical outcome. There are also a number of other biomaterials used to treat periodontal regeneration, but generally all have the same ability and the same molecular structure as highlighted in this literature review.

Introduction

Periodontal disease is not new. Archeological investigations have revealed evidence of alveolar bone loss affecting human remains dating from around 700,000 years ago [1].

The main chronic infective disease of the gums that affects around 10–30% of the adult population is periodontitis.

Bacteria, present in the dental plaque, are capable of inducing an inflammatory response of the periodontal tissues. In susceptible individuals, this chronic inflammation will induce a breakdown of the periodontal ligament (PDL) and the surrounding alveolar bone resulting in the formation of periodontal pockets around the roots, thus causing periodontitis [2].

Periodontitis, the main cause of tooth loss in adults, is characterized by the bacterially induced inflammation, which frequently results in the formation of intrabony defects. It affects the supporting structures of the teeth, including the jawbone, PDL, and cementum. Apart of functional and esthetic problems in the oral cavity, periodontitis is being associated with systemic diseases, such as diabetes, preterm birth, cardiovascular disease, stroke, and pulmonary disease as well [3]. The ultimate involves the formation of new cementum on the tooth root, along with new periodontal attachment between newly formed bone and cementum [4].

Periodontitis is a disease characterized by pathological processes that involve all structures around the tooth (periodontium, cement, alveolar bone, and gingiva). During the development of the disease, complex and irreversible mechanisms induce bone destruction and resorption, which definitely leads to tooth loss [5]. It is commonly known that periodontal disease results in different types of alveolar bone defects. One of them is periodontal pockets which

represent the most important clinical sign of periodontal disease, thus are considered basic pathognomonic features of this very frequent disease present in the population [6], [7].

History

Descriptions of conditions that we would now refer to as periodontitis can be found in a number of ancient textbooks, papyruses, and manuscripts, such as Al-Tasrif, the medical encyclopedia written by Albucasis (936–1013) in Moorish Spain. In addition to the clinical features of periodontitis, some of these early authors also described treatment strategies for this condition.

If we spend a moment to imagine the likely oral health status of many of the people living in the Middle Ages, in the time of Albucasis, for example, we would probably conjure up images of abundant calculus deposits, inflamed gingival tissues, gingival bleeding, and halitosis. In the United States of America, Riggs (1810–1885) regarded calculus as the cause of periodontal disease, thus treated the condition by meticulous removal of calculus from pockets, "curettage" of the soft tissues and oral hygiene instruction. Furthermore, the etiological role of plaque in the development of gingival inflammation was confirmed in experimental studies on gingivitis conducted in the 1960s: Upon cessation of oral hygiene practices over periods of 3–4 weeks, plaque accumulation resulted in gingivitis, which was reversed following plaque removal and resumption of normal oral hygiene [8].

Studies on the natural history of periodontitis performed in Sri Lankan tea plantation workers between 1970 and 1985 provided basic information on oral conditions unaffected by any dental monitoring, prophylaxis or therapy and in the absence of any professionally recommended or supervised oral hygiene practices over a period of 15 years [9]. A subsequent examination of this distinct Cohort in 1990 confirmed the ongoing progression of periodontitis and the influence of tobacco consumption or betel nut chewing on attachment loss and periodontitis-related tooth loss over 20 years [10]. While clinical data from these studies generally suggested an overall increase in both prevalence and severity of the disease with advancing age, different disease progression rates within the subjects were recognized. Consequently, three subgroups of subjects were identified with various periodontal disease progression rates: (1) Rapid progression, in approximately 8% of the subjects, (2) moderate progression, in approximately 81% of the subjects, and (3) minimal progression, in approximately 11% of the subjects. Over a period of 15 years, the annual rates of clinical attachment loss in these three subgroups were up to 1.0 mm in the first group, 0.5 mm in the second group, and 0.1 mm in the third group [11].

Already some 4000 years ago, the ancient Egyptians and Chinese described periodontal diseases as inflammatory conditions, and Hippocrates (460-335B.C.) discussed the etiology and pathogenesis of different forms, including the situation when "the gums were bleeding or rotten" [12].

The early Hebrews Jews, the Romans, and later the Arabs of the middle ages contributed in various ways to the description and treatment of these diseases. However, it is probably fair to consider the 1746 publication of Pierre Fauchard [13] and Le Chirurgien Dentiste, as providing the first discussion of periodontal pathology and therapy with some modicum of intellectuality and usefulness. Fauchard recommended thorough scaling of the teeth with special instruments to remove calculus. He also prescribed mouthwashes, dentifrices, and the splinting of loose teeth.

The early English contribution to the understanding and management of periodontal diseases was made by John Hunter, a physiologist and surgeon of broad intellectual and scientific interests, widely known for his 1771 work on the natural history of the human teeth [14]. In another major work from 1802, a practical treatise on the diseases of the teeth, Hunter proposed a classification of the periodontal diseases that identified inflammatory processes in the gingiva as important factors in the resorption of the alveolar bone [15].

Etiology

The term "endotoxin" was first introduced to denote toxic substances within bacterial cells that were released upon the death of the bacteria. Today, the term is used synonymously with the term "lipopolysaccharide," which is a component of the outer cell wall of Gram-negative bacteria. It was hypothesized that this endotoxin would limit the effectiveness of periodontal therapy because even if plaque and calculus were removed from the root surface, the endotoxin still presents in the cementum would continue to irritate the tissues and thus compromise healing following treatment. This presumption led to the preeminence of the treatment concept known as "root planning," often combined as a treatment strategy with scaling, and abbreviated as "scaling and root planning."

Periodontal Regeneration and Biomaterials

Management of bone periodontal defects, destruction, and loss of the alveolar bone in the upper

or lower jaw is considered a challenge for modern periodontal regeneration and implant dentistry [16].

There are numerous of biomaterials that are being used in the regenerative therapy of periodontal disease such as Straumann® *Emdogain*®, Geistlich *Bio-Oss*® made from the mineral part of bovine *bone*, *MIS 4MATRIX – Bone* Graft, and Platelet-rich fibrin (PRF).

The first step in the periodontal treatment procedures is the removal of supra and subgingival concernments deposits but in parallel with that an individual approach in educating and motivating patients to maintain oral hygiene, and then processing the hard and soft wall of the periodontal pocket, removal of granulation, ulceration and proliferation from the soft wall, polishing the root surface, and, where necessary, planning, and performing periodontal surgery. After the applied therapeutic procedures, it is possible to eliminate or reduce the depth of the periodontal pockets and to create a new junction epithelium [17]. The ultimate goal of any periodontal therapy is not only to prevent the progression of periodontal disease but also to regenerate the architecture and function of the periodontal complex, which involves the formation of a new cement of the root of the tooth, as well as a new epithelial attachment [4], and motivating patients to maintain proper oral hygiene.

Number of therapeutic modalities, nonsurgical, and surgical procedures, and aim to prevent progressive attachment loss, reduce probing pocket depths (PPD) and control both systemic and local risk factors associated with periodontal disease. In this literature review, we are going to highlight some of biomaterials and procedures which involve directly in periodontal.

One of the most important interventions recommended in this domain is guided tissue regeneration (GTR/guided bone regeneration). It is a surgical procedure that is aimed at restoring periodontal tissues. In general, the goal of periodontal therapy is the elimination of deep periodontal pockets. The treatment of periodontitis is cause-related, so it should be known the cause of periodontitis to treat and fight against that. The first step is to mechanically clean periodontal pockets from bacteria (debridement). The crucial role for the success of the therapy is the patient's home plaque control since pockets can be recolonized by bacteria in a few weeks. In the presence of deep pockets, surgery may also be indicated to get access to the deepest portions of the pockets to properly clean them and to reduce the depth of the pockets. The goal of this treatment approach is healing by repair without the formation of new periodontal attachment [18]. This can be done by different types of bone grafts, membranes, growth factors, etc. Using the grafts, we try to help the regeneration of lost periodontal tissue. There are many original papers which are talking about regenerative therapy in the treatment of periodontal intrabony defects. The main parameters that we check after regenerative therapy are plaque index, papillary bleeding index, and PPD. The ideal treatment would be to recover the periodontal tissues that have been lost (periodontal tissue regeneration). Several surgical techniques have been developed in the attempt to regenerate periodontal tissues, including GTR, bone grafting (BG), and the use of the enamel matrix derivative (EMD). All these treatments have been shown to have the potential to regenerate at least some periodontal attachment in humans [19]. Its seen that the effects of Enamel Matrix Derivative and Natural Bone Mineral with Platelet-Rich Plasma on the Healing of Intrabony Defects Treated was treated very good by Döri et al. where the use of PRP does not appear to improve the results obtained with EMD+NBM (Table 1) [20]. To compare mandibular bone regeneration by applying autologous bone, platelet-rich plasma and two biomaterials (synthetic calcium hydroxyapatite, and demineralized bone matrix), and thus establish the potential benefits of these biomaterials in the regeneration of post extraction alveolar bone the faster bone formation occurred in the groups where are used autologous bone and demineralized bone matrix, respectively (Table 1) [21].

Periodontal regeneration mediated by *EMD* is *based* on a *different concept*. The enamel matrix is composed of a number of proteins, 90% of which is amelogenin. The only commercially available product using EMD is called Emdogain and is produced by Biora (Malmö, Sweeden). One year after treatment of periodontal resorption by EMD showed statistically significant improvements in probing attachment levels (1.3 mm) and PPD reduction (1 mm) in comparison with flap surgery. However, the actual clinical advantages might be questioned since there is not yet evidence that more teeth can be saved using EMD. No evidence of major differences between EMD and GTR could be found with the expectation slightly more PPD reduction (0.6 mm) due to increased gingival recession (REC) 0.5 mm in GTR treated sites. On the other hand, EMD seems simpler to use, may not need antibiotic coverage and does not need a second surgical intervention (if compared with non-resorptive barriers). In addition, no post-operative infections or adverse events were observed with EMD versus two cases of infection (not statistically significant) in the GTR group.

Some clinical study recommends the use of Bio-Oss deproteinized bovine bone mineral alone or in combination with Emdogain for surgical regenerative procedure in human periodontal intrabony defects. In the study by Koop *et al*. [22], the use of Bio-Oss combined with EMD-Emdogain as a biologic factor in consistence with the regenerative surgical procedure is recommended for the periodontal healing. The conclusion of this study was that in the treatment of intrabony defects, the use of EMD is superior to control treatments but as effective as resorbable membranes. The additional use of EMD with a coronally advanced flap for REC coverage will give superior results compared with control but is as effective as a connective tissue graft. The use of EMD in furcations will give more

Table 1: Studies of different biomaterials used for periodontal regeneration

Authors	Application of	Year publication	Follow-up	Main results	Reference
Koop *et al.*	Enamel Matrix Derivative	2012	12 months	Effective in reduction of horizontal furcation	[22]
Najeeb *et al.*	PRF with open flap debridement	2017	12 months	Very god outcomes in regenerative therapy	[23]
Hou *et al.*	PRP in treatment of intrabony defects	2016	6 months	PRP together with conventional grafting procedures may be a beneficial treatment approach	[24]
Stavropoulos and Karring	GTR with bioabsorbable membranes+DBB (Bio-Oss)	2005	5 years	GTR with bioabsorbable membranes in combination with Bio-Oss is basically stable on a long-term basis	[25]
Agarwal *et al.*	PRF+DFDBA	2016	12 months	PRF+DFDBA more effective than DFDB with saline	[26]
Pradeep *et al.*	Platelet Rich Fibrin with 1% Metformin	2015	9 months	PRF +1% MF group showed better results in clinical parameters and radiograph defect depth reduction compare to MF, PRF, or OFD alone	[27]
Shah *et al.*	PRF+DFDBA	2012	12 months	PRF shows comparable results to DFDBA in terms of clinical parameters	[28]
Lekovic *et al.*	PRF and BPBM	2012	6 months	Both PRF and PRF-BPBM groups showed significant pocket depth reduction at 6 months compared with baseline	[29]
Panda *et al.*	Autologous platelet concentrates (APCs)	2016	9 months	APCs in surgical treatment of intrabony defects have been increasing in recent years	[30]
Esposito *et al.*	Emdogain	2009		Very good regenerative effect on bone healing	[2]
Galgut	Biodegradable oxidized cellulose and hydroxyapatite	1990	8 weeks	Guided tissue regeneration techniques have been shown to enhance new attachment formation with minimal post-operative recession	[31]
Kökdere *et al.*	PRF and PRF-mixed particulate autogenous bone graft	2015	2 months	PRF increase new bone formation and has a positive effect on early bone healing	[32]
Albanese *et al.*	PRP from the wound healing to bone regeneration	2013	12 months	Positively influence bone regeneration	[33]
Célio-Mariano *et al.*	Autologous platelet rich plasma after impacted third molar mandible surgery	2012	6 months	Autologous PRP was found to accelerate alveolar bone regeneration, and men presented better repair after tooth extraction	[34]
Dohan *et al.*	Platelet-rich fibrin (PRF	2006	6 months	The biologic activity of the fibrin molecule is enough in itself to account for the significant cicatricle capacity of the PRF	[35]
Arenaz-Búa *et al.*	Platelet-rich plasma, hydroxyapatite, demineralized bone matrix, and autologous bone	2009	10 days	The faster bone formation occurred in the groups where we used autologous bone and demineralized bone matrix, respectively	[21]
Kobayashi *et al.*	Comparative release of growth factors from PRP, PRF, and advanced-PRF	2016	10 days	PRP can be recommended for fast delivery of growth factors whereas A-PRF is better-suited for long-term release.	[36]
Needleman *et al.*	Guided tissue regeneration for periodontal infra-bony defects	2012	12 months	GTR has a greater effect on probing measures of periodontal treatment than open flap debridement	[37]
Sebben *et al.*	Platelet-rich plasma alone and in combination on with alpha-tricalcium phosphate cement	2012	8 weeks	The data from this study suggest that treatment with α-TCP cement combined with PRP does not show any significant difference in comparison with PRP alone	[38]
Ozdemir and Okte	Beta-tricalcium phosphate alone and in combination with platelet-rich plasma	2011	6 months	After 6 months, both treatment modalities showed statistically significant clinical and radiographically improvements	[39]
Döri *et al.*	Platele-trich plasma enamel matrix derivative and natural bone mineral	2013	5 years	(1) The clinical outcomes obtained with both treatments can be maintained up to a period of 5 years and (2) the use of PRP does not appear to improve the results obtained with EMD+NBM	[20]

reduction in horizontal furcation defect depth compared with resorbable membranes.

The results of the study of Gojkov-Vukelic *et al.* [40] using Maxresorb (Botiss dental) as regenerative grafts in periodontal pockets showed a significant reduction in probing depth for both groups of patients (treated by open flap surgery and treated by open flap surgery in addition with Maxresorb), 1 and 6 months after the performed surgical therapy. By comparing the results between the groups, they did not get significantly better results for Group 2, where Maxresorb was used as bone replacement. This research is the opposite with findings of the study by Gokhale [41], whose results showed significant improvement for clinical parameters at sites treated with Bio-Oss compared to control sites.

In the research by Shivjot Chhina comparing of treatment results using standard flap surgery and flap surgery with the addition of free gingival graft revealed better treatment outcomes in the group with free gingival graft [42]. The conclusion was that the treatment of supracrestal defects with a combination of open flap debridement (OFD) and SECTG led to significantly better clinical results compared to OFD alone.

Results from meta-analysis indicated that the treatment of periodontal bone defects with intraoral BGs in periodontal regeneration is not always predictable [43]. The literature review of GTR in a lot of case studies has shown that this procedure is more effective than OFD, with an additional gain in clinical attachment level of 1.2 mm [37].

Platelet-rich plasma (PRP) is autologous plasma which has been enriched with platelets and leukocytes in addition to jellifying agents, growth factors, cytokines, bovine thrombin, and anticoagulants [44], [45]. One of the drawbacks of PRP is the fact that it has liquid nature and therefore required its combination with other biomaterials, including bone grafts derived from human cadavers (allografts) or animal products (xenografts). Data points out to the quick “burst” release of growth factors from PRP [46].

In many reviews, we noticed that PRP has been used as a regenerative substituent to promote wound healing and tissue regeneration [47]. Comparing with PRF, PRP has some limitations because the growth factors are released for a very short period of time, also the bovine clotting factors may react with human clotting factors to give rise to bleeding. There

is a reason that PRF as a second-generation platelet derivative, called PRF has been used in regenerative medicine and dentistry [35], [48], [49]. One of the main differences between PRF and previously utilized PRP is the incorporation of leukocytes in PRF. Several studies have shown their key importance during anti-infectious pathogen resistance, as well as their implications in immune regulation [50], [51], [52]. The platelet-rich fibrin when combined with open-flap debridement produces better outcomes compared to the open flap debridement alone. The regenerative potential of platelet-rich fibrin results in better augmentation and regeneration of periodontal bone defects (Table 1) [23]. The adjunctive use of PRP together with conventional grafting procedures may be a beneficial treatment approach. However, when combined with the use of a regenerative technique, such as GTR, the beneficial effect of PRP on the treatment of intrabony defects is negligible (Table 1) [24].

By used of GTR with bio absorbable membranes in combination with Bio–oss are basically stable on a long term basis and the clinical and radiographical data from baseline and from the 1- and 5-year control wich are presented on this article treatment resulted in statistically significant clinical improvements (i.e., PPD reduction, PAL gain) 1 year after surgery, which were preserved during the following 4- year observation period. PPD had increased to a minor extend (0.4 mm) from the 1- to the 5-year control visit, but the average amount of residual PPD was not significantly different between the two observation periods (Table 1) [25].

In usage of demineralized freeze-dried bone allograft (DFDBA) alone with saline and PRF with DFDBA the 12-month results indicated that both treatment modalities resulted in significant changes in all clinical and radiographic parameters. However, the PRP/DFDBA group exhibited statistically significantly greater changes compared with the DFDBA/saline group in PD, CAL, REC,bone fill and defect resolution table (Table1) [26].

Treatment of furcation defects with RSV 1.2mg in situ gel combined with autologous PRF and porus-HA bone graft, results in significant improvements of clinical and radiographic parameters when compared with OFD alone. Combining RSV with PRF and HA, implies their synergestic effects explaining their role as a regenerative material in the treatment of furcation defects (Table1) [27].

PRF shows comparable results to DFDBA in terms of clinical parameters (Table 1) [28].

The results of this study indicate that PRF can improve clinical parameters associated with human intrabony periodontal defects, and BPBM has the ability to augment the effects of PRF in reducing pocket depth, improving clinical attachment levels and promoting defect fill (Table 1) [29].

Based on the results obtained from the systematic review by Panda et al.can be concluded that the evidence on the beneficial additive effect of APCs in surgical treatment of intrabony defects has been increasing in recent years (Table 1) [30].

By using Biodegradable oxidized cellulose and hydroxyapatite Guided tissue regeneration techniques have been shown to enhance new attachment formation with minimal post- operative recession (Table 1) [31].

PRF alone or PRF-mixed particulate autogenous bone increase new bone formation and has a positive (Table 1) [32]. The use of PRP in the alveolar socket after tooth extractions is certainly able to improve soft tissue healing and positively influence bone regeneration but this latter effect seems to decrease a few days after extraction (Table 1) [33].

Analysis of radiographic bone density by periods 1, 2, and 3 months after extraction of impacted mandibular third molars bilaterally where in one side was used PRP and in other side just blood clot there were favorable significant differences for the PRP group. At 7 days and at 6 months, there were no statistical differences; however, higher means of radiographic bone density were observed in the PRP group (Table 1) [34].

To compare mandibular bone regeneration by applying autologous bone, platelet-rich plasma and two biomaterials (synthetic calcium hydroxyapatite, and demineralized bone matrix), and thus establish the potential benefits of these biomaterials in the regeneration of post extraction alveolar bone the faster bone formation occurred in the groups where are used autologous bone and demineralized bone matrix, respectively (Table 1) [21].

PRP, PRF, and A-PRF were able to release growth factors over time from their respective platelet formulations. Interestingly, PRP demonstrated the ability to release significantly higher levels of growth factors at very early time points whereas PRF and A-PRF had a more gradual release of growth factors up to a 10-day period (Table 1) [36].

By compare the effect of alpha-tricalcium phosphate (α-TCP) cement combined with platelet-rich plasma (PRP) on osteogenesis, and to compare the results with use of PRP alone was seen that treatment with α-TCP cement combined with PRP does not show any significant difference in comparison with PRP alone (Table 1) [38].

Beta-tricalcium phosphate alone and in combination with platelet-rich plasma as modalities for treatman of intrabony defects showed significant clinical radiographically improvements (Table 1) [39].

Unlike PRP, PRF contains a fibrin matrix instead of jellifying agents and bovine clotting factors [53]. It is important to note that PRF contains a number of cells, including platelets, leukocytes, macrophages, granulocytes, and neutrophils. Furthermore, PRF exhibits a slow and sustained release of growth factors, such as transforming growth factor-b1, platelet-derived growth factor, and vascular endothelial growth factor which all have been proven to promote the wound healing and tissue regeneration [54].

The PRF when combined with open-flap debridement and combined by GTR produces better outcomes and better regenerative power compared to the OFD alone. The regenerative potential of PRF results in better augmentation and regeneration of periodontal bone defects. In addition, PRF may augment the regenerative potential of bone grafts. However, more long term and well-designed clinical trials are needed to ascertain the clinical efficacy of PRF and PRF containing bone grafts.

MIS 4MATRIX bone grafts is a new synthetic bone replacement product that helps in bone dental replacement procedures. The 4MATRIX composition is pure 66.6% biphasic calcium sulfate (BCS) and 33.3% hydroxyapatite (HA) and is characterized by predetermined setting time and resorption rate. 4MATRIX is the preferred augmenting-replacement product for a wide variety of dental bone replacement procedures.

Considering the bone regeneration, resorption rate and stabilization 4MATRIX have its advantages. During the administration procedure, the 4MATRIX BCS component remains intact in the presence of blood and saliva and stimulates bone growth when placed in contact with the bone or periosteum. 4MATRIX consists of two different components. BCS has a complete resorption rate in close connection with bone formation rate (4–10 weeks), while HA acts as a long-term spatial maintainer. A component such as HA contributes to the maintenance of longer-term space and provides higher mechanical strength and stabilization of new regenerated bone grafts.

Conclusion

Biomaterials being used in periodontal surgical treatment have the different regenerative ability. The combined use of biomaterials might result in a better clinical outcome.

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