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RESEARCH ARTICLE

A GLIMPSE OF PERIODONTAL REGENERATION!

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ABSTRACT

Periodontal disease is a chronic inflammatory disease which leads to destruction of the attachment apparatus and supporting structures of the teeth. The ultimate goal of periodontal therapy is to not only arrest the progression of periodontal disease but also to establish a functional dentition by regenerating the lost tissues. Conventional periodontal flap surgery provides access to the root surfaces for proper debridement of infected tissues and plaque and calculus from the subgingival root surfaces. However, these procedures bid partial potential for periodontal regeneration. Recently, newer procedures have been proposed for attempting complete periodontal regeneration. This article reviews all the materials available for regeneration in periodontal therapy.

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INTRODUCTION

Regeneration is defined as reproduction or reconstitution of a lost or injured part, whereas repair is defined as healing by a tissue that does not fully restore the architecture or function of the part. (American Academy of Periodontology, 2001) New attachment is defined as the union of connective tissue or epithelium with a root surface that has been deprived of its original attachment apparatus. On the other hand, Reattachment describes the union of epithelium or connective tissue with a root surface. (American Academy of Periodontology, 2001) Regeneration of periodontal tissues lost to periodontal disease is somewhat an intangible goal in periodontal therapy. It is said to be an impracticable goal due to the intricacy of biologic events, factors and cells underlying periodontal regeneration. (Periodontal Regeneration, 2005)

Bone Grafts

Bone grafts are the commonly used therapeutic strategies for periodontal regeneration. The use of bone grafts is based on the hypothesis that these materials regenerate alveolar bone and root cementum and create space required for the process of regeneration. They are categorized as materials containing bone forming cells (osteogenesis), growth factors (osteoconductivity) or materials serving as scaffold for bone regeneration (osteoconduction). Also, they are categorized as autologous (harvested from the same individual), allogenic (from different individuals of the same species), xenogenic grafts (harvested from different species) and all synthetic aand non organic materials are termed alloplasts.

Autogenous bone graft- It has osteoconductive as well as osteoinductive and is therefore considered the gold standard. (Rosenberg and Rose, 1998)

Intraoral autografts- harvested from maxillary tuberosity, edentulous alveolar areas, healing extraction sockets, mental and retromolar areas. (Nasr *et al*., 1999)

- Cortical bone chips: They are generally not used today as they are quite longer and have a possibility of sequestration. (Zaner and Yukna, 1984)

Osseous coagulum: Bone is harvested from intraoral sites with a round bur and mixed with blood. Advantages of osseous coagulum is that smaller particle size leads to more

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ostrogenesis than larger particles. Disadvantages are that the patient is not able to aspirate during the collection process, quality of the collected fragments is not known and the fluidity of the material. (Diem *et al*., 1972)

- Blend of cortical and cancellous bone: It is the combination of cortical and cancellous bone harvested with the help of burs, rongeurs or trephine. The harvested bone is then placed in a amalgam capsule and triturated to a slushy consistency. (Zaner and Yukna, 1984)

Extraoral autografts- They are obtained from iliac cancellous bone and marrow. These grafts are said to have a great osteogenic potential. Disadvantage of extraoral autografts is that additional surgery is required for the procurement of graft and the amount obtained is also not sufficient. Postoperative root resorption is another issue in these techniques. (Rosen *et al*., 2000)

Clinical studies on Autografts

Author and year	Objective of the study	Material and methods	Results
Froum *et al*. 1976	Autogenous bone (osseous coagulum) versus open flap debridement alone	75 sites in 28 patients were treated by two procedures.	Autogenous bone treatment resulted in significantly greater clinical attachment level gain (weighted mean difference: 0.72 mm, SD 1.82) and bone fill (weighted mean difference: 1.62 mm, SD 1.53)
Schallhorn *et al* 1970	Autogenous bone from iliac crest in the treatment of periodontal osseous lesions.	182 transplants were evaluated in 52 patients being treated for periodontitits	
Trombelli *et al*. (2002)	Comparing autogenous bone grafts to open flap debridement procedure	systematic review on autogenous bone grafts	There was greater clinical attachment level (CAL) gain for grafted group (CAL gain: 3.2 mm, SD 0.5) compared with controls (CAL gain: 2.0 mm, SD 0.8).
Reynolds *et al*. (2003)	Autogenous bone compared to open flap debridement.	systematic review on autogenous bone grafts	Autogenous bone treatment resulted in significantly greater clinical attachment level gain and bone fill
(Czuryszkiewicz-Cyrana and Banach 2006)	Autogenous bone graft plus PRP	Twenty-six healthy patients with chronic and advanced periodontitis (24 females and 2 males) were selected. 72 periodontal infrabony pockets were treated.	At 12 Month follow up there was improvement in pocket depth, CAL gain, Mobility,
Yilmaz *et al*. 2010	healing of deep intrabony defects treated with either a combination EMD+ autogenous bone or EMD alone	Forty patients with advanced chronic periodontitis, with one deep intrabony defect, were randomly treated with either EMD+ Autogenous (test) or EMD (control). Clinical assessments were performed at baseline and at 1 year after treatment.	The test treatment resulted in statistically higher PPD reductions, RAL gains and PBL gains compared with the control.
Rickert *et al* 2012	Bone substitutes and autogenous bone in sinus augmentation procedure	sinus floor elevations with autogenous bone (controls) were compared with autogenous bone combined with growth factors or bone substitutes, or solely with bone substitutes	Combination of autografts and bone substitutes is a reliable alternative for autogenous bone as a sole grafting material.
Clementini *et al* 2012	Autogenous bone used for ridge augmentation and subsequent implant placement.	Systematic review	Success rate of implants placed in onlay graft regenerated ridges range from 72.8% - 97% after follow up periods ranging from 6 months to 10 years.

Allogenic bone grafts- The allografts are obtained from other individuals of the same species but disparate genotype. They include freeze-dried bone allografts (FDBA) and demineralised freeze-dried bone allograft (DFDBA). (Reynolds *et al*., 2010)

FDBA: FDBA, which is not demineralised, works primarily through *osteoconduction*, a process in which the graft does not activate bone growth, but instead acts like a scaffold for the patient's own natural bone to grow onto and within. (Rosenberg and Rose, 1998)

Examples of commercially available products- Straumann® ***AlloGraft,*** LifeNet Health's OraGRAFT® Mineralized Cortical (***FDBA***), MinerOss® family by Biohorizons, Puros® (Zimmer Dental), SureOss (HansGBR Biomaterial)

•**DFDBA:** DFDBA has demineralised bone particles, which result in exposure of bone morphogenetic proteins within the bone matrix. These proteins induce a cascade of events resulting in cellular differentiation and induction of pluripotential cells to form osteoblasts. (Mellonig, 1992)

Examples of commercially available products- Straumann® AlloGraft, Puros, **DFDBA**, **DFDBA**, Osteohealth, NY, MinerOss Family of Allografts by Biohorizons

Author and year	Objective of the study	Material and methods	Results
Kassolis *et al*. 2000	FDBA + PRP	15 consecutively treated patients using autologous PRP in combination with freeze-dried bone allograft (FDBA) for sinus elevation and/or ridge augmentation.	89% were considered clinically successful demonstrating complete bone coverage of the implant, no mobility, and a normal radiographic appearance at the time of re-entry and 12 months post-implant exposure
Rosen and Reynolds 2001	FDBA + Barrier membrane	9 patients with 8 fenestration and 3 dehiscence defects on implants consecutively treated with GBR using bioabsorbable polymer barrier of poly(DL-lactide) in conjunction with a composite graft of freeze-dried bone allograft (FDBA)	90.9% achieved complete coverage of the osseous defects
Nevins *et al*. 2007	FDBA in treatment of periodontal defects	case series was to determine the clinical and radiographic regenerative potential of rhPDGF-BB-enhanced mineralized freeze-dried bone allograft (FDBA) for the treatment of severe periodontal intrabony defects	Clinical reentry and radiographs at up to 11 months showed complete bone fill in these challenging cases, indicating that rhPDGF combined with FDBA provides excellent clinical results.
Fagan *et al*. 2008	FDBA in alveolar ridge augmentation	37 defects were treated with FDBA, differing guided bone regeneration barrier membranes, and pediculated connective tissue graft.	Thirty-six implants osseointegrated and were stable and successful at the 6- and 12-month post-restoration evaluations.
Kolerman *et al*. 2008	FDBA in maxillary sinus augmentation	Mineralized freeze-dried bone allograft (FDBA) was used for sinus floor augmentation. After 9 months, 23 biopsies were taken from 19 patients	Histologic evaluation revealed a mean of 29.1% newly formed bone, 51.9% connective tissue, and 19% residual graft material. Graft particles were mainly in close contact with newly formed bone, primarily with features of mature bone with numerous osteocytes, and, to a lesser extent, with marrow spaces

Author and year	Objective of the study	Material and methods	Results
Bowers *et al*. (1989a, 1989b)	To compare the healing of intrabony defects with and without the placement of decalcified freeze-dried bone allograft (DFDBA) in a nonsubmerged environment in humans	Free gingival grafts were placed over grafted and nongrafted defects to retard epithelial migration. Biopsies were obtained at 6 months and regeneration was evaluated histometrically. Data from 12 patients with 32 grafted and 25 nongrafted defects were submitted for statistical analysis.	There was a greater chance for regeneration of a new attachment apparatus and component tissues in grafted defects than in nongrafted defects.
Nevins *et al* 2007	To compare the effectiveness of two-ridge preservation treatments.	Forty subjects with extraction sockets exhibiting substantial buccal dehiscences were enrolled and randomized across 10 standardized centres. Treatments were demineralised allograft plus reconstituted and cross-linked collagen membrane (DFDBA + RECXC) or deproteinized bovine bone mineral with collagen plus native, bilayer collagen membrane (DBBMC + NBCM).	DBBMC + NBCM provided better soft tissue healing and ridge preservation for implant placement.
Piemontese *et al*. (2008)	to compare PRP combined with a DFDBA to DFDBA mixed with a normal saline solution in the treatment of human intrabony defects	Twenty interproximal intrabony osseous defects in twenty non-smoking, healthy subjects diagnosed with chronic periodontitis were treated in this study. Ten subjects each were randomly assigned to the test group (PRP + DFDBA) or the control group (DFDBA + saline)	Treatment with a combination of PRP and DFDBA led to a statistically significantly greater improvement in plaque index at 3 months, probing depth at 6 months and radiographic defect fill at 6 months in intrabony periodontal defects as compared to DFDBA with normal saline.
Kothiwale *et al*. 2009	to clinically and radiographically evaluate and compare the efficacy of demineralized freeze dried bone allograft (DFDBA) and bovine derived xenogenic bone graft (BDX) [Bio-Oss] with amniotic membrane (AM) as guided tissue regeneration (GTR) in the treatment of human periodontal Grade II buccal furcation defects.	Ten patients suffering from chronic periodontitis, displaying bilateral Grade II buccal furcation defect, were randomly treated using DFDBA with AM (Experimental site A) or using bovine derived xenograft (BDX) with AM (Experimental site B).	1) at 9 months after surgery both therapies resulted in significant PD reductions and CAL gains and (2) significant improvement was seen in bone fill and percentage gain with both the material, however, there was no significant difference between both.
Aspriello *et al*. 2010	To compare the use of enamel matrix derivative (EMD) and demineralised freeze-dried bone allografts (DFDBA) with DFDBA alone for the treatment of human periodontal intrabony defects at 12 months post-surgery.	Fifty-six intrabony osseous defects in 56 periodontis patients were randomly assigned to the test group (DFDBA + EMD) or the control group (DFDBA) for periodontal treatment.	Compared to baseline, the 12-month results indicated that both treatment modalities resulted in significant changes in all clinical parameters.

Author and year	Objective of the study	Material and methods	Results
Movin *et al*. 1982	Allografts in the Treatment of Periodontal Osseous Defects	Probing and X-rays	3.2 mm gain attachment in grafted site and 2.0 mm gain attachment in non grafted site.
J. M. Rummelhart 1989	FDBA versus DFDBA	Twenty–two defects (11 intrapatient pairs) in 9 patients were grafted with either DFDBA or FDBA.	These findings reveal no significant differences between the two materials in primarily intraosseous defects when evaluated at a minimum 6 months postsurgery.
Feuille, Frank *et al* 2003	To evaluate the use of FDBA in conjunction with a titanium-reinforced (TR e-PTFE) barrier in the treatment of localized alveolar ridge deficiencies	Twelve patients (aged 23 to 65 years) requiring tooth replacement with ridge augmentation were recruited to participate in this study.	The clinical and histologic findings of this study demonstrate that sites grafted with FDBA in conjunction with an e-PTFE barrier can provide a predictable way to augment deficient alveolar ridges prior to implant placement.
Prakash *et al*. 2010	To evaluate the efficacy of Polylactic Acid/Polygycolic Acid (PLA/PGA - Fisiograft®) with Open Flap Debridement (OFD) and OFD alone in the treatment of intrabony defects over a period of 9 months.	Twenty Nine systemically healthy subjects with total of 30 defects were included in the present, randomized, controlled and two arm parallel study. Tests were treated with OFD along with Fisiograft® and controls with OFD alone.	Synthetic bone replacement graft materials are commonly used for periodontal regeneration. The present study was conducted by using PLA/PGA reveals no additional benefit over OFD alone in treatment of intrabony defects.

Alloplasts- An alloplast is a biocompatible, inorganic synthetic bone grafting material. At present, alloplasts marketed for periodontal regeneration fall into two broad classes: ceramics and polymers. (Reynolds *et al*., 2010)

Examples of commercially available products-Calcitite (20–40 Mesh (420– 840 mm) and 40–60 Mesh (250–420 mm)) (Calcitek, Inc., Carlbad, CA), OsteoGraf/D300 (particle size 250–420 mm) or OsteoGraf/D700 (particle size 420– 1,000 mm) (CeraMed Corp., Lakewood, CO), Interpore 200 (Interpore International, Irvine, CA) and Pro-Osteon 500R (Interpore Cross International, Irvine, CA, USA), Osteogen R (Impladent, NY, USA),

Xenogenic bone grafts- Currently, there are two available sources of xenografts used as bone replacement grafts in periodontics: bovine bone and natural coral. Both sources, through different processing techniques, provide products which are biocompatible and structurally similar to human bone. Recently, porcine bine xenografts have also been described. They are osteoconductive in nature. (Nasr *et al*., 1999)

Examples of commercially available products- Bio-OssR (Osteohealth Co., Shirley, NY), Bio-Oss CollagenR (Osteohealth Co., Shirley, NY), OsteoGraf/NR (CeraMed Dental, LLC, Lakewood, CO) and PepGen P-15R (Dentsply Friadent, Mannheim, Germany).

Author and year	Objective of the study	Material and methods	Results
Sculean *et al*. 2004	to compare clinically the treatment of deep intrabony defects with a combination of a bovine-derived xenograft (BDX) and a bioresorbable collagen membrane to access flap surgery.	wenty-eight patients suffering from chronic periodontitis, and each of whom displayed one intrabony defect, were randomly treated with BDX + collagen membrane (test) or with access flap surgery (control).	(i) at 1 year after surgery both therapies resulted in significant PD reductions and CAL gains, and (ii) treatment with BDX+collagen membrane resulted in significantly higher CAL gains than treatment with access flap surgery.
Mellonig *et al* 2000	To histologically evaluate a bovine-derived bone xenograft (Bio-Oss) in the treatment of human periodontal osseous defects.	Four patients with at least one tooth that had been recommended for extraction because of interproximal advanced periodontal disease volunteered to participate.	This study indicates that periodontal regeneration is possible following grafting with a bovine-derived xenograft.
Myron Nevins *et al* 2011	to investigate the potential of xenograft (cancellous bovine bone) granules to form vital bone in non-natural bone-forming areas of maxillary sinuses.	Fourteen sinus augmentations were performed in 14 patients.Clinical reentry at 6 months revealed bone formation at the osteotomy site.	Vital bone formation using the xenograft granules was supported by both clinical and histologic evidence.
Antonio Barone *et al* 2013	To evaluate and compare the histologic and histomorphometric aspects of extraction sockets grafted with two commercially available bovine bone xenografts: Endobon (test group) and Bio-Oss (control group).	Thirty-eight patients contributed 62 augmented extraction sites to the study.	This investigation provides support for the efficacy of bovine bone xenograft for socket preservation when subsequent implant placement is planned.
Deepthi Palachur *et al* 2014	To compare the efficacy of bovine-derived xenograft (Bio-Oss Collagen) and Type I collagen membrane (Bio-Gide) with bovine-derived xenograft (Bio-Oss Collagen) and fibrin fibronectin sealing system (TISSEEL) in the treatment of periodontal infrabony defects.	Fourteen healthy patients in the age range of 20 to 60 years, showing bilateral or contralateral infrabony defects were selected.	Both groups showed potential for enhancing the periodontal regeneration with no statistically significant between the two groups.

Guided Tissue Regeneration (GTR)

GTR is a technique where an occlusive membrane is placed which guides the progenitor cells from periodontal ligament to repopulate the osseous defects in order to lead to periodontal regeneration. The biologic principle of GTR is that periodontal regeneration occurs when cells from epithelium and connective tissue are excluded from colonizing the root surfaces and periodontal defects. Cells from periodontal ligament and alveolar bone will then populate the root surface. Studies have shown that GTR (both resorbable and non resorbable membranes) showed positive outcomes when used for the treatment of two and three walled intrabony defects. (Gottlow *et al*., 1986)

Author and year	Objective of the study	Material and methods	Results
Pini Prato G *et al* 1996	To evaluate the results of GTR membrane versus a two step mucogingival procedure-a 4 year study.	25 patients	The average reduction in the recession was similar in the two groups while probing depth reduction and clinical attachment level were greater in the GTR group.
Murphy KG *et al* 2003	to assess the efficacy of guided tissue regeneration (GTR) procedures in patients with periodontal osseous defects compared with surgical controls	A systematic review.	Overall, GTR is consistently more effective than OFD in the gain of clinical attachment and probing depth reduction in the treatment of intrabony and furcation defects.
Young-Mi Chung *et al* 2014	To assess and compare the clinical and radiographic outcomes of guided tissue regeneration therapy for human periodontal intrabony defects using two different collagen membranes: a porous nonchemical cross-linking collagen membrane (NC) and a bilayer collagen membrane (BC).	3 groups: a test group (NC+BM), in which a NC was used with xenograft bone mineral (BM), a positive control group (BC+BM), in which a BC was used with xenograft BM, and a negative control group (BM), in which only xenograft BM was used.	The results suggest that both NC and BC were comparable in terms of clinical and radiographic outcomes for the treatment of periodontal intrabony defects in human subjects.

Emdogain (EMD)

An important advancement in periodontal regeneration is Enamel Matrix proteins (EMPs), that are produced by Hertwig's epithelial root sheath. These proteins play an important role in cementogenesis and development of periodontal attachment apparatus. This observation led to the development of Enamel matrix derivative (EMD, Emdogain; Straumann AG, Basel, Switzerland). (Hammarström L. Enamel matrix, 1997) Emdogain is extactedd from porcine tooth buds. EMD stimulates the proliferation of pre-osteoblasts and differentiation of osteoblast like cells as well as proliferation and differentiation of normal osteoblasts. Clinical and histological studies have shown that periodontal defects treated with EMD resulted in periodontal regeneration. (Sculean *et al*., 2008a) EMD is composed of different enamel related proteins, mainly amelogenin (90%). Other proteins include enamelin, tuftelin, ameloblastin, amelotin, apin, proteinases etc. It is said that during the embryological development of root, enamel matrix proteins are secreted from the Hertwig's epithelial root sheath with their primary role being cementogenesis. It was demonstrated that EMD has a significant influence on the cell

Author and year	Objective of the study	Material and methods	Results
Heijl L *et al* 1997	to compare the long-term effect of EMDOGAIN treatment as an adjunct to modified widman flap (MWF) surgery with the effect of MWF and placebo treatment.	33 subjects with 34 paired test and control sites	topical application of EMDOGAIN onto diseased root surfaces associated with intrabony defects during MWF periodontal surgery will promote an increased gain of radiographic bone and clinical attachment compared to control
M.S Tonetti 2002	EMD versus open flap debridement	172 patients with advanced chronic periodontitis were recruited in 12 centers in 7 countries.	EMD provides beneficial effect in terms of CAL gain and probing depths reduction when compared to open flap debridement alone
A. T. Castellanos 2006	to clinically evaluate the use of EMD in association with CPF to cover localized gingival recessions compared to CPF alone.	Twenty-two patients with Miller Class I or II gingival recessions >2 mm were included. One recession from each patient was treated in the study. Two treatments were randomly assigned: coronally positioned flap with EMD (test) and coronally positioned flap alone (control).	The addition of EMD significantly improves the amount of root coverage.
Bosshardt 2008	To analyse all available biological data of EMPs at the cellular and molecular levels that are relevant in the context of periodontal wound healing and tissue formation.	Systematic review	Application of EMD on the diseased root surfaces enhances the formation of a new connective tissue attachment (i.e. new cementum with inserting collagen fibers) and of new alveolar bone
Esposito M *et al* 2009	To test whether EMD is effective, and to compare EMD versus GTR, and various BG procedures for the treatment of intrabony defects.	A Cochrane systematic review	One year after its application, EMD significantly improved PAL levels (1.1 mm) and reduced PPD (0.9 mm) when compared to a placebo or control, however, the high degree of heterogeneity observed among trials suggests that the results have to be interpreted with great caution.
Lucas A. Queiroz 2017	To identify the changes in periodontal microbiome following treatment with EMD using a deep-sequencing approach.	39 patients having mandibular class II buccal furcation defects were randomized to beta-tricalcium-phosphate/hydroxyapatite graft (BONE group), EMD+BONE or EMD alone.	EMD treatment predictably alters a dysbiotic subgingival microbiome, decreasing pathogen richness and increasing commensal abundance

behaviour of many cell types by mediating cell attachment, spreading, proliferation, and survival, as well as expression of transcription factors, growth factors, cytokines, extracellular matrix constituents, and other molecules involved in the regulation of bone remodelling.

Growth factors/Matrix proteins

The wound healing events involved in repair and regeneration are controlled by polypeptide growth factors. Therefore it is rational to consider them important in periodontal regeneration. (Giannobile *et al*., 2011) They have regulatory effects on proliferation and differentiation of cells from bone and connective tissues. Studies have shown that the use of growth factors in periodontal regeneration produces favorable results. Some growth factors have been made commercially available for use in clinical practice, however, there are still some issues that still hamper the progress and need to resolved. These issues include the complexity of periodontium, limited knowledge regarding the gamut of periodontal cells, identification of the target cell to be modified by the growth factor, the stability of the tissues that are to be formed under the influence of these factors, dosages of growth factors, ideal carrier has still not been found, high cost required for the production of these factors. (Giannobile *et al*., 2011)

Growth factors used for periodontal regeneration-

- Platelet derived growth factor
- Bone morphogenetic proteins
- Transforming growth factor beta
- Insulin- like growth factor
- Fibroblast growth factor

Author and year	Objective of the study	Material and methods	Results
Matteo Piemontese 2008	to compare platelet-rich plasma (PRP) combined with a demineralized freeze-dried bone allograft (DFDBA) to DFDBA mixed with a saline solution in the treatment of human intrabony defects.	Sixty interproximal intrabony osseous defects in 60 healthy, non-smoking subjects diagnosed with chronic periodontitis were treated in this study.	Treatment with a combination of PRP and DFDBA led to a significantly greater clinical improvement in intrabony periodontal defects compared to DFDBA with saline.
Sofia Aroca *et al* 2009	To determine whether the addition of an autologous platelet-rich fibrin clot (PRF) to a modified coronally advanced flap (MCAF) (test group) would improve the clinical outcome compared to an MCAF alone (control group) for the treatment of multiple gingival recessions.	Twenty subjects, presenting three adjacent Miller Class I or II multiple gingival recessions of similar extent on both sides of the mouth.	The addition of a PRF membrane positioned under the MCAF provided inferior root coverage but an additional gain in GTH at 6 months compared to conventional therapy.
Ma José Martínez-Zapata 2009	to evaluate the efficacy and safety of PRP in tissue regeneration.	a systematic review	PRP improves the gingival recession but not the clinical attachment level in chronic periodontitis
A.R. Pradeep 2012	To explore the clinical and radiographic effectiveness of autologous platelet-rich fibrin (PRF) and platelet-rich plasma (PRP) in the treatment of intrabony defects in patients with chronic periodontitis.	Ninety intrabony defects were treated with either autologous PRF with open-flap debridement or autologous PRP with open-flap debridement or open-flap debridement alone.	There was similar PD reduction, CAL gain, and bone fill at sites treated with PRF or PRP with conventional open-flap debridement.
Roselló-Camps À *et al* 2015	Use of PRP in intrabony defects.	Meta-analysis	PRP might offer some beneficial effects on clinical and radiographic outcomes for regeneration of periodontal intrabony defects.

The rhBMP-2 (INFUSE®, Medtronic) and the rhPDGF (GEM21S®, BioMinetic Therapeutics) have been approved by the FDA for dentistry.

Platelet concentrates

Platelets, which are derived from megakaryocytes, are small irregular anucleated cells with a diameter of 2 to 4 micrometers. Average life span is 8-12 days and normal platelet count ranges from 1.5 to 4 lacs/ microlitre. Platelets play an essential role in haemostasis and are an important source of growth factors in periodontal wound healing. Depending on the processing technique, different types of platelets concentrates have been described including but not limited to Platelet-Rich Plasma (PRP), Pure Platelet-Rich Plasma (P-PRP), Leukocyte- and Platelet-Rich Plasma (L-PRP), Platelet-Rich Fibrin (PRF), and Leukocyte and Platelet-Rich Fibrin (L-PRF). The potential of these substances as a biologic agent in periodontology relies on the growth factors stored within platel*et al*pha granules containing platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), insulin-like growth factor (IGF), platelet-derived angiogenic factor, and transforming growth factor-beta (TGF-β). (Fernando Suárez-López del Amo *et al*., 2015)

PRP

Platelet-rich plasma (PRP) is defined as an 'autologous concentration of platelets in a small volume of plasma'. (Robert E. Marx. Platelet-Rich Plasma, 2004) Platelets contain more than 300 biologically active molecules which are released upon activation and subsequently influence the tissue regeneration process.PRP is an autologous preparation of blood enriched in growth factors such as transforming growth factor beta (TGF-β), vascular endothelial growth factor (VEGF), and platelet-derived growth factor (PDGF).

PRF

PRF (platelet rich fibrin) was first developed in France for use in the field of oral and maxillofacial surgery. PRF is classified as a second generation platelet concentrate as it is prepared as a natural concentrate without the addition of any anticoagulants. PRF has a dense fibrin network with leukocytes, cytokines, structural glycoproteins and also growth factors. Its advantages over platelet-rich plasma include ease of preparation, ease of application, minimal expense, and lack of biochemical modification (no bovine thrombin or anticoagulant is required). (Chandran Preeja *et al*., 2014)

Author and year	Objective of the study	Material and methods	Results
Sandro Bittencourt 2007	to evaluate the outcome of gingival recession therapy using the semilunar coronally repositioned flap (SCRF) with or without EDTA application for root surface biomodification.	Fifteen patients with bilateral Miller Class I buccal gingival recessions (≤4.0 mm) were selected. Thirty teeth with recessions were assigned randomly to receive the semilunar coronally repositioned flap with (SCRF-E group) or without (SCRF group) the application of an EDTA gel	The use of EDTA gel as a root surface biomodifier agent negatively affected the outcome of root coverage with the SCRF.
Alparslan Dilsiz 2010	to evaluate and compare the outcome of gingival recession therapy using the subepithelial connective tissue graft (SCTG) with or without Er:YAG laser application for root surface biomodification.	Twenty-four teeth in 12 patients with Miller class I and II recession were treated with SCTG with (test group) or without (control group) the application of an Er:YAG laser (2 Hz, 60 mJ/pulse, 40 s, with air spray).	The present study showed that root surface conditioning with an Er:YAG laser does not enhance the results achieved when SCTG was performed alone.
Harpreet Singh Grover *et al* 2011	To compare the efficacy of citric acid, ethylenediaminetetraacetic acid (EDTA), and tetracycline hydrochloride as root biomodification agents. (In Vitro SEM Study)	Fifteen freshly extracted teeth were root planed and specimens obtained from the cervical twothirds of the root.	All three agents are equally effective root biomodification agents. In clinical practice, EDTA might be more useful owing to its neutral pH.
Guilherme H.C. Oliveira *et al* 2012	To evaluate the efficacy of RSB in root coverage and its impact on the outcomes.	A Systematic Review	RSB provided no additional benefit in terms of the evaluated clinical parameters.

Root surface biomodification

The hypothesis behind root surface modification is that the periodontally involved root surface is modified for enhanced new connective tissue attachment. Several histological studies have shown evidence of periodontal regeneration following the application of citric acid, controlled clinical trials have failed to show any improvements in clinical parameters when compared to control sites. (Initiator Paper Periodontal regeneration, 2015)

Agents used

1. Root conditioners- Citric Acid, Tetracycline HCL, EDTA, Fibronectin, Laminin, Doxycycline, Minocycline, Polyacrylic Acid, Phosphoric Acid, Formalin, Chlorhexidine, Hydrogen Peroxide, Cetyl Pyridinium Chloride & Sodium-N-Lauryl Sarcosine, Bile Salts And Plasma Fractions
2. Enamel matrix proteins
3. Platelet rich plasma
4. Growth factors
5. Lasers

Need for root surface biomodification (Roxanne A. Lowenguth *et al*., 2000)

1. Reduced collagen fiber insertion
2. Alterations in mineral density & surface composition
3. Root surface contamination by bacteria & endotoxins
4. Progenitor cell populations- destroyed by the disease process or lack the capacity to form the structures of periodontium
5. The pathologically exposed root surface may lack the necessary chemotactic stimuli for migration of cells capable of producing periodontal regeneration.
6. The apical migration of JE along the root surface precludes regeneration by acting as a physical barrier between gingival connective tissue & root surface.

Combination therapy

- Bone grafts + GTR – Bone grafting along with GTR has been used with the hypothesis that placement of bone graft beneath the membrane preserves space for progenitor cell population. Combined use of bone grafts and GTR has resulted in similar or more bone gain when compared to GTR alone.
- Bone grafts + EMD – EMD has a property of semi-fluid consistency and lack of space making effect. Therefore if EMD is combined with bone grafts, the problem of flap collapse and space maintenance can be overcome. While bone grafts intended to promote bone formation, their combination with EMD would designate a biological effect on the cascade of events leading to periodontal regeneration. Some studies indicate that the clinical outcomes of EMD may be improved when used in combination with bone grafts with respect to EMD alone. (Sculean *et al*., 2011)
- Bone grafts + growth factors- The addition of growth factors to bone grafts enhances the maturation process of bone regeneration and increase graft-to-bone contact in humans.

Future technologies for periodontal regeneration

The field of periodontal regeneration is evolving rapidly these days. These advancements are largely based on tissue engineering, which is the science of reconstructing the periodontal tissues with the use of polymer scaffolds that are implanted into the host. Another field involved in the future of periodontal regeneration is nanotechnology, which is a science of bioengineering at the molecular level. Tissue engineering along with nanotechnology will pave the future of periodontal regeneration. Gene therapy is a method whereby genes for regeneration promoting growth factors using plasmid and adenovirus gene delivery methods are used. (Christoph A. Ramseier *et al*., 2012)

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