Review Article

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Advances in Gingival Augmentation Techniques – A Literature Review

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ABSTRACT

Background: In the current practice of periodontics, clinicians are faced with the challenge of not only addressing biological and functional problems present in the periodontium but also providing therapy that results in acceptable aesthetics. The presence of mucogingival problems and gingival recession around anterior, highly visible teeth exemplifies a situation in which a treatment modality that addresses both biological and aesthetic demands is required from the therapist. A variety of soft tissue augmentation procedures directed at root coverage have been documented in the literature utilizing autogenous or allogenic soft tissue grafting or guided tissue regeneration (GTR). The purpose of this review was to assess the effectiveness of newer materials in gingival augmentation procedures.

Keywords: Gingival recession, Growth factors, guided tissue regeneration.

INTRODUCTION

Currently, one of the main objectives in dentistry and in particular, the field of periodontology is to achieve the best aesthetic results. The treatment of gingival recession is a clear example of the thorough search for a satisfactory and predictable method of aiming at maximal aesthetics. In the last few years, root coverage has become a predictable periodontal plastic surgical procedure. Traditionally, the coverage of denuded root surfaces has been performed with numerous surgical techniques[1]. The success of all these procedures varies considerably and is not always predictable. The type of gingival recession and the adaptation to the surgical principles seem to play key roles in the predictability. Although soft tissue grafts and in particular, the connective tissue graft provide excellent aesthetics and predictability, sometimes the quantity of donor material needed is limited when treating several gingival recessions at once. Likewise, soft tissue grafts will need another surgical area as a donor site. This area is usually the palate that eventually increases the morbidity of the patients. Also, some patients fear the surgical use of the palate as a donor site. Therefore, these complications have led to the search for other techniques for root coverage.

Acellular Dermal Matrix Allograft

Alloderm is donated human tissue chemically processed to remove all epidermal and dermal cells (antigenic cells) while preserving the remaining bioactive dermal matrix. The matrix consists of collagen, elastin, blood vessel channel and bioactive protiens that support natural revascularization, cell repopulation and tissue

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remodelling. Recently, an acellular dermal matrix (ADM) allograft was approved by FDA (Food and Drug Administration) as a substitute for autogenous grafts in mucogingival surgeries. The preparation of this dermal allograft involves cell component removal and preservation of the ultrastructural integrity, which if damaged would induce an inflammatory response. ADM was originally utilized for use in plastic surgery for the treatment of full thickness burns wound[2]. Over the last few years, several studies have evaluated the effect of ADM in mucogingival surgery with promising results[2,3].

Acellular dermal matrix has been used as a substitute to the palatal donor sites in increasing the width of keratinized tissue around tooth[2]. for the treatment of alveolar ridge deformities and also for root coverage procedures. Studies compared the results obtained with ADM (test group) and the SCTG (control group) for the treatment of gingival recessions[2]. None of them showed any significant differences in recession reduction between the procedures. However, Harris[2] showed that the SCTG produced a greater mean probing reduction and mean keratinized tissue increase than the ADM. In addition, Novaes et al[4] demonstrated that the SCTG group had a statistically significant increase in the area of keratinized tissue after 3 months compared to the ADM group.

Amnion Allograft

Amniotic membrane (AM) is the innermost lining of the fetal membrane that is in contact with the developing fetus. This lining serves as a natural barrier to protect the fetus from infections and trauma because of the lack of a fetal immune system. It has biologic properties that are able to reduce inflammation, diminish the occurrence of adhesions and scarring, modulate angiogenesis and promote wound healing[6,7]. It also promotes epithelialization, maintains a normal epithelial phenotype and has antimicrobial properties. Histologically, amniotic membrane is loosely connected to the chorion, the outermost portion of the fetal membrane and it consists of a simple cuboidal epithelium, basement membrane and an avascular stroma. A cryopreservation methodology was developed by Tseng[7] to preserve the biologic properties that this tissue exhibits in utero. Several factors contribute to the biologic actions of amniotic membrane, which are regulated through interleukin-1, -4 and -6, epidermal growth factors, basic fibroblast growth factor, transforming growth factor (TGF)-b, TGF-a, keratinocyte growth factor, neural growth factor, endostatins, anti-angiogenic factors and collagen I, II, III and IV, all of which were observed in a cryopreserved amniotic membrane[8].

The clinical application of amniotic membrane for guided tissue regeneration while fulfilling the current mechanical concept of GTR, amends it with the modern concept of biological GTR. Biomechanical GTR proposed herein using amniotic membrane, not only maintains the structural and anatomical configuration of regenerated tissues, but also contribute to the enhancement of healing through reduction of post-operative scarring and subsequent loss of function and providing a rich source of stem cells. Amnion layer possesses several types of laminins, with laminin-5 being the most prevalent which plays a role in the cellular adhesion of gingival cells. It also contains growth factors that may aid in the formation of granulation tissue by stimulating fibroblast growth and neovascularization[9]. The use of processed dehydrated allograft amnion provided good results in terms of root coverage, increased tissue thickness and increased attached gingival tissue. There were no adverse reactions reported during the course of treatment and patient reported with relatively little post-operative discomfort. The ability of processed dehydrated allograft amnion to self-adhere eliminates the need for sutures, making the procedure less technically demanding and significantly decreasing surgical time[25]. This ability to self adhere makes processed dehydrated allograft amnion an attractive option for multi-teeth procedures and recession defects in particularly hard to reach areas such as the molar region.

Enamel Matrix Derivatives

Periodontal regeneration mediated by EMD is based on a different concept. It is believed that EMD used in periodontal lesions mimics the development of the tooth supporting apparatus during tooth formation (Hammarström 1997)[10]. The enamel matrix is composed of a number of proteins, 90% of which are amelogenins. Such proteins are thought to induce the formation of the periodontal attachment during tooth formation. The only commercially available product using EMD is called Emdogain® and is produced by Biora

(Malmö, Sweden). The involvement of enamel proteins in root formation was first proposed by Slavkin and Boyd. They suggested that the basement membrane contains chemotactic proteins deposited by the Hertwig's epithelial root sheath (HERS) cells, which serve to direct the migration of pre-cementoblast cells or induce cementoblast differentiation from the dental follicle cells. Recession type defects treated with Emdogain® plus connective tissue grafts resulted in the histologic evidence of 1.87 mm of new bone and PDL over the previously diseased root surface.[11,12] In a recent study, Emdogain® plus a coronally positioned flap (CPF) compared to a connective tissue graft demonstrated similar clinical outcomes of 95.1% and 93.8% root coverage respectively. As the results were clinically similar, Emdogain® plus coronally positioned flaps (CPF) eliminated the need for a donor site that is required for the connective tissue grafts[13].

Platelet Rich Plasma

Platelet-rich plasma was introduced in oral and maxillofacial surgery by Whitman et al 1997 and Marx et al 1998[14]. PRP is an autologous concentration of platelets, containing a number of important growth factors such as platelet derived growth factor (PDGF), transforming growth factor-α,β, insulin-like growth factor (IGF), epidermal growth factor (EGF) and vascular endothelial growth factor (VEGF). Additionally PRP also contains proteins (i.e fibrin, fibronectin, vitronectin) known to act as cell adhesion molecules for osteoconduction and as a matrix for bone, connective tissue and epithelial migration. The use of PRP is based on the premise that the large number of platelets in PRP release significant qualities of growth factors that promote chemotaxis of precursor cells, cell mitosis, collagen production, initiating vascular in-growth and inducing cell differentiation (Freymiller and Aghaloo 2004).

Sound biologic rationale and a multitude of basic science research support the use of PRP to promote soft tissue healing, although evidence of its role in enhancing periodontal applications, especially root coverage, is limited. Current scientific research has yet to elucidate all of the mechanisms by which PRP can affect soft tissue healing and assess its capacity to stimulate regeneration. Furthermore, clinical evidence on the use of PRP in root-coverage procedures is extremely limited, with only two randomized controlled trials published till now[15]. A pertinent review of medical and dental literature relating to PRP and its role in wound healing and enhancement of root-coverage procedures was performed. Preliminary reports in this area suggested that the potential benefits of PRP in root-coverage procedures may be improved aesthetics, decreased patient morbidity and accelerated wound healing[15].

Platelet Rich Fibrin

Choukroun's platelet rich fibrin (PRF) is a fibrin matrix in which platelet cytokines and cells are trapped which are released after a certain time and that can serve as a resorbable membrane[16]. More recently, Gassling et al have shown that PRF is a suitable scaffold for breeding human periosteal cells in vitro, which may be suitable for bone tissue engineering applications. Autologous platelet rich fibrin (PRF), considered to be a healing biomaterial, was initially used in oral implantology by its promotors and presently studies have shown its application in various disciplines of dentistry. Developed in France by Choukroun et al[16], PRF production protocol attempts to accumulate platelets and released cytokines in a fibrin clot. Granules present in platelets contain many proteins, which may be platelet specific (eg. beta-thromboglobulins) or non-platelet specific (fibronectin, thrombospondin, fibrinogen and other coagulation growth promoters, fibrinolysis inhibitors, immunoglobulins etc), calcium and serotonin etc. PRF is in the form of a platelet gel and can be used in conjunction with bone grafts, which offers several advantages including promoting wound healing, bone growth and maturation, graft stabilization, wound sealing and hemostasis as well as improving the handling properties of graft materials.

PRF in gingival recession

PRF can also be used as a membrane. Aroca S et al (2009)[22] stated that the addition of a PRF membrane positioned under the coronally advanced flap provided inferior root coverage but an additional gain in ginigval thickness. Aleksić Z et al (2010)[23] stated that the utilization of the PRF resulted in a decreased postoperative discomfort and advanced tissue healing. Jankovic S et al

(2012)[24] found no difference between PRF and CTG procedures in gingival recession therapy, except for a greater gain in keratinized tissue width obtained in the CTG group and enhanced wound healing associated with the PRF group.

LIVE CELL BASED THERAPIES FOR MUCOGINGIVAL SURGERIES

Human Fibroblast-Derived Dermal Substitute[18]

The tissue-engineered human dermal replacement graft used in this study was manufactured through a three-dimensional cultivation of human diploid fibroblast cells on a polymer scaffold[18]. The scaffold is a bioabsorbable polyglactin mesh (Vicryl, Ethicon), which degrades by hydrolysis and is lost after transplantation, leaving the cellular and extracellular matrix components. The human fibroblast cell strains used to produce this material come from newborn foreskins and are cultured by standard methods. The fibroblasts secrete a mixture of growth factors and matrix proteins to create a living dermal structure that, following cryopreservation, remains metabolically active after being implanted on the graft bed.

The proposed mechanism of action of the HF-DDS material involved multiple components acting in concert, including colonization of the wound bed by cells, angiogenesis and promotion of re-epitheliallzation. The biologic activity was designed to work simultaneously along two fronts. The dermal tissue would fill the bed, producing a substrate that encouraged keratinocyte migration of epithelium over the graft. The collagen and fibronectin provided by the HF-DDS were required for optimal keratinocyte attachment and migration. Living fibroblasts were included to produce a variety of growth factors[18].

Living, Bilayered Skin Substitue[19]

Bilayered Cell Therapy (BCT, Apligraf, Organogenesis) can be used as gingival autografts for their ability to generate attached gingiva around teeth that do not require root coverage. This BCT device was compared to palatal tissue for the purpose of enhancing keratinized tissue and wound healing around teeth that did not require root coverage. Bilayered cell therapy was the first biomedical device containing viable human cells to be approved by the US Food and Drug Administration[19]. It is a living, bilayered, tissue-engineered skin substitute composed of a dermal layer of human fibroblasts and an overlying cornified epidermal layer of living human keratinocytes on a bovine type I collagen lattice. The dermal layer is formed in vitro by the combination of fibroblasts with collagen, serum, and tissue culture media in a special mold that limits lateral contraction. The collagen assembles into a gel in which human fibroblasts are interspersed, and these fibroblasts contract the network of collagen fibers. A suspension of keratinocytes was added to the surface of the collagen fibroblast layer and, after several days of growth, it was submersed in tissue culture media. At this time, the surface of the BCT was exposed to the air to promote epidermal differentiation. After 7 to 10 days of incubation under those conditions, a matured, cornified epidermis developed at the air–liquid interface. BCT is morphologically, biochemically, and metabolically similar to human skin. However, the dermo–epidermal junction is flatter in BCT than in normal human skin, but the cell proliferation rate is similar to that of human skin. Mitotic activity occurs in the basal keratinocytes of the epidermis and in the fibroblasts within the matrix. The device is supplied as a circular disk; 7.5 cm in diameter and 0.075cm thick on a clear plastic tray of gelled support medium (agarose) stored at room temperature. Study has revealed that Compared to the control group (FGG), the BCT group had significantly better color and texture matching with surrounding tissue at 6 months ($p < 0.001$)[19]. Research has also revealed that the product is dynamic, with a cytokine profile that changes in response to injury[19]. To date, preliminary periodontal results appear encouraging. If these positive results are confirmed, larger multicenter trials involving a variety of applications are anticipated. Many advances have been made over the past decade in the reconstruction of complex periodontal and alveolar bone wounds. Developments in polymeric and ceramic scaffolding systems for cell, protein and gene delivery have undergone significant growth. The targeting of signaling molecules or growth factors of the periodontium has led to significant new knowledge and generation using bioactive molecules that promote cell proliferation, differentiation, matrix biosynthesis, and angiogenesis. Further advancements in the field will

continue to rely heavily on multidisciplinary approaches combining engineering, dentistry, medicine and infectious disease specialists in repairing the complex periodontal wound environment.

Platelet-Derived Growth Factor-Bb Tricalcium Phosphate (E.G-Gem 21)[20]

A new and superior wound healing and bone regeneration technology termed growth-factor-enhanced matrix (GEM 21S®) has recently become available for clinical use. This graft material consists of a concentrated solution of pure recombinant human platelet-derived growth factor (rhPDGF-BB), the synthetic form of the body's key natural wound-healing stimulator PDGF-BB and an osteoconductive (bone scaffold) matrix which is beta-tricalcium phosphate (β-TCP). This is the first available purified, recombinant (synthetic) growth factor product and is the result of over a decade of extensive research. Clinical and animal study results with this graft material demonstrate that it is capable of simultaneously promoting wound healing, regeneration of bone and acceleration of gingival attachment gain in challenging periodontal and peri-implant defects. Preetinder Singh and DK Suresh carried out a study to evaluate and compare the clinical efficacy of GEM 21S® (rhPDGF-BB and beta-tricalcium phosphate) along with a collagen membrane (Healiguide) to the use of only a collagen membrane for the treatment of recession defects using a coronally advanced flap in both the cases based on various clinical parameters[20]. On observing the clinical parameters, the present study showed better results in both the groups of GEM 21S® and collagen (Healiguide) and only collagen-treated sites. On comparison, there was a statistically non-significant ($p>0.05$) increase in the mean difference of the width of keratinized tissue scores from baseline, 1, 3, and 6 months with the *P* value of 1.000, 0.731, 0.061, and 0.061, respectively, suggestive of the fact that both GEM 21S® along with collagen and only collagen (Healiguide) can be used effectively in root coverage procedures[20].

Bovine Pericardium Based Non-Cross Linked Collagen Matrix for Successful Root Coverage[21]

Recently a matrix derived from bovine pericardium was used in order to cover teeth of Miller's class I and II recession[21]. The matrix was well tolerated by all of patients with no allergic reaction or other complications observed within the study period. The data of this study was able to prove that obviously, the application of the Copios® matrix leads to a marked increase in the clinical attachment level after the observation time point of 6 months. In this study a matrix derived from bovine pericardium, Copios® (Zimmer, Freiburg, Germany) was employed. This matrix was processed according to the Tutoplast manufacturing methodologies. The Tutoplast® process is a chemical method, originally developed more than 30 years ago for sterilization and preservation of tissue intended for implantation. The Tutoplast®process combines osmotic, oxidative and alkaline treatment of the tissues in order to break down cell walls, inactivate pathogens, and remove bacteria. The pericardium is delipidizated in an ultrasonic bath with acetone. Alternating washing in NaCl, H_2O_2 and acetone breaks down the cellular walls, removes fat and proteins, dehydrates, inactivates and eliminates viruses and prions. The product is sterilized with a low-dose gamma irradiation (17.8 kGy). Prior to usage, the material needs to be rehydrated with sterile saline solution. By means of this procedure, the original cross linking and the 3-D structure of this type I collagen stays unchanged.

The harmlessness of the use of Tutoplast, which is the basis of Copios® has been previously described for application in dental surgery as well as for closing ventricular septal defects in cardiovascular surgery and dura replacement in neurosurgery. Approximately 60% of the original membrane thickness remained. The results underline that obviously, non-cross linked collagen based matrices such the above mentioned material, show similar integrative capacities for soft tissue augmentation as observed for the CTG and other porcine derived matrices. However, further investigations with this material and with patients own connective tissue is necessary to critically assess the potential of this new membrane for a long-term clinical use[21].

CONCLUSION

In the recent years, with changing concepts and advancements in periodontal surgical procedures, clinicians have started focusing on

esthetics of the patient. Thus mucogingival surgery has evolved into a more accurate terminology – Periodontal plastic surgery. New techniques are constantly being developed and are slowly being incorporated into periodontal practice. Each procedure has clear advantages and disadvantages that need to be evaluated according to the patient's needs. In addition, all procedures are limited by the amount of avascular root surface, the height of the interproximal papillae, and the alveolar bone. The practitioner should be aware that, at times, new methods are published without adequate clinical research. In order to ensure the predictability of the results further clinical trials should be undertaken which on a long run benefits the patient.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

REFERENCES

1. Sullivan HC, Atkins JH. Free autogenous gingival grafts: Utilization of grafts in the treatment of gingival recession. Periodontics 1968; 6(4): 152-60.

2. Harris RJ. A comparative study of root coverage obtained with an acellular dermal matrix versus a connective tissue graft. The results of 107 recession defects in 50 consecutively treated patients. Int J Periodont Restor Dent 2000; 20: 51-9.

3. Harris RJ. Gingival augmentation with an accelular dermal matrix: human histologic evaluation of a case—placement of the graft on periosteum. Int J Periodont Restor Dent 2004; 24: 378–85.

4. Novaes AB Jr, Grisi DC, Molina GO et al. Comparative 6-months clinical study of a subepithelial connective tissue graft and acellular dermal matrix graft for the treatment of gingival recession. J Periodontol 2001; 72: 1477–4.

5. Wennstrom, J.L. and Zucchelli G. Increased gingival dimensions. A significant factor for successful outcome of root coverage procedure? A two year prospective clinical study. J Clin Periodontol 1996; 23: 770- 7.

6. Solomon A, Wajngarten M, Alviano F et al. Suppression of inflammatory and fibrotic responses in allergic inflammation by the amniotic membrane stromal matrix. Clin Exp Allergy 2005; 35: 941-8.

7. Tseng SC, Li DQ, Ma X. Suppression of transforming growth factor-beta isoforms, TGF-beta receptor type II, and myofibroblast differentiation in cultured human corneal and limbal fibroblasts by amniotic membrane matrix. J Cell Physiol 1999; 179: 325-35.

8. Shimazaki J, Shinozaki N, Tsubota K. Transplantation of amniotic membrane and limbal autograft for patients with recurrent pterygium associated with symblepharon. Br J Ophthalmol 1998; 82: 235-40.

9. Mahgoub MA, Ammar A, Fayez M, et al. Neovascularization of the amniotic membrane as a biological immune barrier. Transplant Proc 2004;36:1194-8.

10. Hammarström L. Enamel matrix, cementum development and regeneration. J Clin Periodontol 1997; 24: 658-68.

11. Rasperini G, Silvestri M, Schenk RK, Nevins ML. Clinical and histologic evaluation of human gingival recession treated with a subepithelial connective tissue graft and enamel matrix derivative (Emdogain): a case report. Int J Periodontics Restorative Dent 2000; 20(3):269-75.

12. McGuire MK, Cochran DL. Evaluation of human recession defects treated with coronally advanced flaps and either enamel matrix derivative or connective tissue. Part 2: Histological evaluation. J Periodontol 2003; 74(8):1126-35.

13. McGuire MK, Nunn M. Evaluation of human recession defects treated with coronally advanced flaps and either enamel matrix derivative or connective tissue. Part 1: Comparison of clinical parameters. J Periodontol 2003; 74(8):1110-25.

14. Eppley BL, Pietrzak WS, Blanton M. Platelet-rich plasma: a review of biology and

applications in plastic surgery. Plast Reconstr Surg 2006; 4: 115-25.

15. Bashutski JD, Wang HL.Role of platelet-rich plasma in soft tissue root-coverage procedures: a review. Quintessence Int 2008; 39(6):473-83.

16. Choukroun J, Diss A, Simonpieri A, Girard MO, Schoeffler C, Dohan SL et al. Platelet-rich fibrin (PRF): A second generation platelet concentrate: Part I: Technological concepts and evolution. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2006; 101: 37-44.

17. Myron nevis, Mycelio camero. Periodontal regeneration in humans using recombinant human platelet derived growth factor-BB. J Periodontol 2003; 74: 1282-2.

18. McGuire MK, Nunn ME. Evaluation of the Safety and Efficacy of Periodontal Applications of a Living Tissue-Engineered Human Fibroblast-Derived Dermal Substitute. I. Comparison to the Gingival Autograft: A Randomized Controlled Pilot Study. J Periodontol 2005; 76(6): 867-80.

19. McGuire MK, Scheyer ET, Nunn ME, Lavin PT. A pilot study to evaluate a tissue-engineered bilayered cell therapy as an alternative to tissue from the palate. J Periodontol 2008; 79(10) : 1847-6.

20. Preetinder Singh, DK Suresh. Clinical evaluation of GEM 21S® and a collagen membrane with a coronally advanced flap as a root coverage procedure in the treatment of gingival recession defects: A comparative study. J Indian Soc Periodontol 2012; 16(4): 54-7.

21. Marcus Schlee, Shahram Ghanaati, Ines Willershausen. Bovine pericardium based non-cross linked collagen matrix for successful root coverage, a clinical study in human. Head Face Med 2012; 8: 6.

22. Aroca S, Keglevich T, Barbieri B, Gera I and Etienne D. Clinical evaluation of a modified coronally advanced flap alone or in combination with a platelet-rich fibrin membrane for the treatment of adjacent multiple gingival recessions: a 6-month study. J Periodontol 2009; 80: 244-52.

23. Aleksic Z, Jankovic S, Dimitrijevic B, Divnic-Resnik T, Milinkovic I and Lekovic V. [The use of platelet-rich fibrin membrane in gingival recession treatment]. Srpski arhiv za celokupno lekarstvo 2010; 138: 11-8.

24. Jankovic S, Aleksic Z, Milinkovic I and Dimitrijevic B. The coronally advanced flap in combination with platelet-rich fibrin (PRF) and enamel matrix derivative in the treatment of gingival recession: a comparative study. The European journal of esthetic dentistry 2010; 5: 260-73.

25. Brian Gurinsky. A novel dehydrated amnion allograft for use in the treatment of gingival recession: An observational case series. The Journal of Implant & Advanced Clinical Dentistry 2009; 1: 11- 6.