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Autogenous Materials in Periodontal Regeneration: A Narrative Review

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Abstract

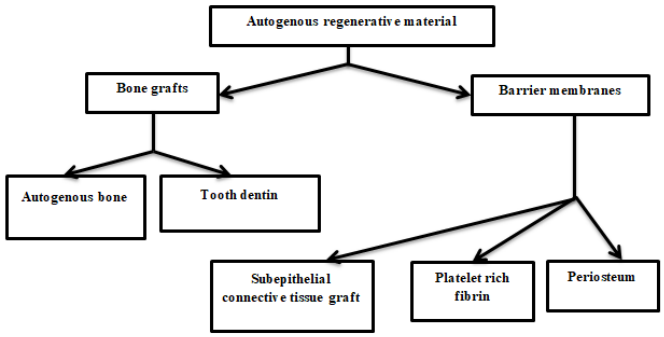
The regenerative potential of periodontal biomaterials has been established in various scientific evidences. The bone grafts and guided tissue regeneration (GTR) has increased the odds of defect fill substantially. However, the defect fill is actual histological bone is a matter of controversy. In terms of regenerative materials, bone grafts and GTR membranes are most prevalent. The synthetic materials do provide a scaffold for osteoconduction but lacks osteogenic and osteoinductive properties. Synthetic bone graft materials include alloplasts. The allografts and xenografts are believed to be osteoinductive but osteogenic potential is still lacking. Autogenous bone grafts can provide this oseteogenicity. Thus they are object of interest for various researchers. Autogenous bone grafts can be intra oral or extra oral bone and tooth dentin. Similarly GTR membranes are made up collagen and various polymers. The autogenous membranes comprise of multipotent osteoprogenitor cells which have superior properties as compared to commercially available products. This spiked use and research of such tissues which can act as barrier membranes. The periosteum, sub-epithelial connective tissue and platelet rich fibrin are such examples. The present review aimed to elaborate the same.

Keywords: Autogenous bone grafts, Deminelized Dentin Matrix, Periosteum, Platelet rich fibrin, Sub-epithelial connective tissue.

Introduction

Regeneration of lost periodontal structures can be tricky and deceptive. The osseous defects caused as a result of periodontal tissues needs to be corrected. The primary choice of such defects is regenerative surgeries. The wide prevalence of these defects has led to discovery and invention of numerous regenerative products ranging from allogenic, alloplastic to biomimetics. Autogenous materials are a boon to such as regenerative surgeries because of its many advantages. Autogenous grafts are considered to be gold standard due to following properties: a) retention of viable cells of the donor site which is a prerequisite in the recipient site b) no risk of any immunological response since they are own cells of the body c) they ensure a continuous supply of progenitor cells which is ideal environment for healing by regeneration d) these grafts fulfil all the requirements for tissue engineering, which are, scaffold, cells and signalling molecules as an additional benefit.[1]

The autogenous regenerative materials used in periodontal regeneration can be divided into two categories: bone grafts and barrier membranes. These autogenous products are derived from various tissues of the body. The tissues which can be employed for the same are bones, tooth, blood products and sub-epithelial connective tissues. The bone and tooth dentin can be used in the form of autogenous grafts, while prevalent autogenous membranes in the treatment are subepithelial connective tissue graft, platelet rich fibrin and periosteum.



Bone grafts

Auto grafts

The autogenous bone grafts/autografts were the first to be used in periodontal regenerative applications. They are procured from patient's body which behave as donor site. This tissue obtained is used in a recipient site. There are numerous autogenous periodontal bone grafts include cortical bone chips, osseous coagulum, bone blend, extraction socket bone and extraoral cancellous bone with marrow.[2] It is proposed that autografts probably maintain certain cell viability. These characteristics cell are the foundation of bone healing which is observed. The new bone formation is mainly through osteogenesis and/or osteoconduction. These grafts are gradually resorbed and replaced by new viable bone.[3] Preosteoblasts are the cells which are responsible to form the first deposits of new bone. The deposits formed by these osteoprogenitor cells (or preosteoblasts) proliferate, in presence of adequate vascularization, fills the gap between the graft and recipient bone leading to defect fill. The osteocytes which get transferred usually die in response to anoxia created in the procedure and the surgical injury. However, transplanted osteoclasts can survive transplantation and these may initiate the resorption of graft.[1] Once the graft is accepted at the recipient site, neovascularization and microanastomoses occurs. The circulation is restored and plays a vital role for survival and multiplication of osteoprogenitor cells and the formation of new products by the cells. The new

bone which is formed is due to the surviving cells in graft initially. The graft later on induces bone formation by osteoinduction surrounding host bone cells. The area of new bone interdigitation and the quantity of donor bone that is resorbed are higher for cancellous bone grafts compared with cortical grafts.[4] It also eliminates potential problems of histocompatibility and disease transmission.

Hegedus , in 1923 used autografts. This was first scientific evidence for use of autografts. Hegedus used autogenous tibial grafts for the reconstruction of the deficient alveolar ridges as a result of "pyorrhea alveolaris."[5] Burwell, in his study concluded that a part of the material has to degenerate and the RNA released could induce the bone cells, they also reported that origins and conditions of osteoblastic differentiation.[6] Nabers, O'Leary and Robinson used bone chips, they suggested that they have to be resorbed completely before new bone formation could take place.[7] Schallhorn has reported use of autogenous cancellous bone with hematopoietic marrow from the iliac crest in the treatment of periodontal defects.[8]

Autogenous grafts can be harvested from intraoral or extraoral sites. The intraoral sites include mandibular symphysis and ramus, maxillary tuberosity, healing extraction sites, edentulous areas and tori. The extranoral site where the graft can be procured are crest, tibia, calvaria.[1] They can also be cortical bone or cancellous bone and marrow. The following are types of autografts used in periodontal regenerative surgeries:

Intraoral Grafts

Cortical Bone Graft: Autogenous cortical bone graft has osteogenic properties along with minimal osteoinductive. It acts as scaffold which provides an osteoconductive medium. It is optimal for structural defects for which immediate mechanical stability is required for healing. The dense cortical matrix causes a relatively slow revascularization and incorporation, thus, resorption must occur before the deposition of new bone. Limited perfusion and donor osteocytes make this option poorly osteogenic.[9]

Cancellous Bone Graft: Cancellous bone graft tabeculae are lined with functional osteoblasts, which makes it highly osteogenic. It offers an osteoinductive, osteoconductive, and osteogenic substrate. After implantation, a portion of the donor osteocytes survives, and these osteocytes, combined with graft porosity and local cytokines, promote angiogenesis and host mesenchymal stem cell recruitment.[10]

Osseous Coagulum: Robinson described a technique using a mixture of bone dust and blood that he termed osseous coagulum.[11] This osseous coagulum consists of small cortical bone particles. The small size of particle increases the surface area for the interaction of cellular and vascular elements. It can be obtained from various region such as lingual ridge on the mandible, edentulous ridges, bone distal to a terminal tooth, exostoses, bone removed by osteoplasty or ostectomy, as well as lingual surface of the mandible or maxilla at least 5 mm from the roots. Bone is extracted using a carbide bur #6 or #8 at speeds between 5000 and 30,000 rpm, placed in a sterile dappen dish or amalgam cloth.[12]

Bone Blend: The bone blend technique uses an autoclaved plastic capsule and pestle. Bone is removed from the designated site with appropriate means and later triturated in the capsule to form a workable, plastic-like mass, and packed into bony defects.[12]

Cancellous Bone Marrow Transplants: Cancellous bone can be obtained from the maxillary tuberosity, edentulous areas, and healing sockets. The maxillary tuberosity is a prime site which contains a good amount of cancellous bone, particularly if the third molars are

absent; also, foci of red marrow are occasionally observed. Edentulous ridges can be accosted with a flap reflection, and cancellous bone and marrow are removed with curettes, back-action chisels, or trephine. Sockets are then allowed to heal for 8 to 12 weeks, and the apical portion is used as donor material. The particles obtained are reduced to small pieces.[12]

Bone Swaging: Bone swaging is a technique where bone from the adjacent edentulous site is is pushed into contact with the root surface without fracturing the bone at its base. This technique is only possible if there is an edentulous area adjacent to the defect.[13]

Extraoral grafts

This material is obtained from either the anterior or the posterior iliac crest predictable bone growth ranging 3.53-4.36 mm and even complete eradication of furcation involvement and interdental craters have been reported by various authors.[14]

Autogenous tooth dentin bone graft/ Dentin demineralized matrix

The composition of a tooth is quite similar to that of bone (inorganic (55%) and organic (45%)). The physical and chemical properties of the dentin and bone also hold similarity to each other. The main ingredients of both of these mineralized tissues include collagenous (18%), non-collagenous proteins (2%), and mineralized content in the form of various calcium phosphates (70%) in weight volume. Demineralized matrices of both the tissues primarily compose type I collagen (95%), while the non-collagenous proteins include dentin sialophosphoprotien (DSPP), dentin matrix protein-1, bone sialoprotein, osteopontine, and osteonectin. Demineralized matrices constitute of bone morphogenetic proteins (BMPs) and fibroblast growth factors.[15] Human tooth is a rich source of stem cells, matrix, trace metal ions, and growth factors.[16]

The Dentin demineralized matrix (DDM) is composed of acid-resistant collagen. It is absorbable, micro-tubular in structure. DDM has blood coagulative properties. The presence of collagen I and III, DSPPs, BMPs, and TGF gives osteogenic and osteoinductive effects to dentinal bone graft proteins.[17] The inorganic component of dentinal bone graft material entails five different types of calcium phosphates. The presence of trace elements, such as zinc chloride, and iron is also seen. The calcium phosphates include hydroxyapatite, tri-calcium phosphate, amorphous calcium phosphate, dicalcium phosphate dehydrate, and octacalcium phosphate. The presence of these calcium phosphates imparts an osteoconductive property, thus it acts as a scaffold for new bone formation. Enamel offers more hydroxyapaptite content than that of dentin because of its better crystallinity; thus providing stability against dissolution.[18]

Bessho et al, in their discovery have shown successful extraction of BMPs from the dentine-derived matrix of human teeth. This BMP have shown to illustrate osteoconductive and osteoinductive potential, through BMP receptors and their downstream molecules Smad 1, 5, and 8; both in humans and in xenogenic models.[19] Wang et al depicted osteogenic potential of another protein (LIM-1) of human dentin.[20] These studies forms the basis of using human DDM as a bone graft as it not only supports new bone formation but also potentiates neo formation too. The various non-collagenous proteins found in the autogenous bone graft have a signaling role in new bone formation and remodeling. DSPP induces crystal formation in the hydroxyapatite, osteocalcin activates which helps in regulation bone mineralization, bone connexin binds minerals and collagen, osteopontin induces osteoblasts and osteoclasts thus helps in bone remodelling, and alkaline phosphatase has a

developmental role in the biomineralization of teeth and bones.[21]

Development: Kim et al in 1993, conducted studies for component analysis, using electron microscope, and production and autogenous bone graft material after incinerating human teeth at a high temperature of 135°C and then pulverizing to a particle size of 0.149 mm. The main component of tooth ash powder, which is formed after incineration and pulverization of teeth, has been identified to be hydroxyapatite and β-Tricalcium phosphate. They have been a prime component of alloplastic bone graft materials and thus can act as osteoconductive bone graft materials with excellent biocompatibility.[22]

Availability: Autogenous tooth bone graft materials are of two types as follows: block and powder types. The block type of graft material demonstrates osteoinduction capacity through blood wettability. It also shows osteoconduction capacity as it can maintain space through creeping substitution. The powder type is supplied based on various sizes of particles, porosity, blood wettability, osteoconduction, osteoinduction, and creeping substitution abilities. The use of these grafts can be in for extraction socket preservation, ridge augmentation, restoration of perforated sinus membrane, and augmentation of early stabilization of implant. Studies have shown its support in brilliant bone regeneration through osteoinduction and osteoconduction capability and minimizes foreign body reaction due to genetic homogeneity.[23]

The scientific literature has shown the potential of autogenous DDM as bone substitute and scaffold. The advantage is its low morbidity, easy to handle, bone-remodeling capabilities and absence of antigenicity. Autogenous DDM was also suggested to be an ideal scaffold for stem cells and bone growth factors.[24] Thus, use of autogenous DDM can be breakthrough in periodontal regeneration.

Barrier membranes

Periosteum

Periosteum is an external highly vascular connective tissue layer covering the outer surface of all the bones. It is absent at sites of articulation and muscle attachment. The structure of periosteum is divided into two layers, an inner cellular or cambium layer, and an outer fibrous layer.[25] The outer layer comprised of collagens, which are aligned in the longitudinal axis and elastin. The components include dense collagen fibers, fibroblasts, and their progenitor cells; osteogenic progenitor cells. This layer serves structural role.[26] The inner layer shows the presence of abundant osteoblasts and osteoprogenitor cells. Osteogenic progenitor cells of the periosteal cambium layer induce the cell differentiation process of bone repair by initiating and driving the osteoblastic cell differentiation. This results in development of fracture callus, woven bone and remodelling. The periosteum is the tissue lining the bone which maintains itself. In case of trauma, tumors and/or lymphocyte mitogens, it is capable of being activated to proliferate. Periosteum is divided in to three zones. Zone 1 has an average thickness of 10–20μm comprising principally of osteoblasts representing 90% of cell population, while collagen fibrils form 15% of the volume. Zone 2 is filled with fibroblasts and endothelial cells being most of the rest. Zone 3 has the highest volume of collagen fibrils and fibroblasts amongst the three. Fibroblasts take up more than 90% of the cells in zone 3.[27]

Regenerative capacity of periosteum can made it possible to be used in periodontal intraosseous defects. It has been seen that in case of surgical injury, periosteum shows both appositional and resorptive properties. It

shows following changes favouring the regeneration: (1) the progenitor cells of periosteum differentiate into osteogenic and fibrogenic cell lineages, (2) the cells are capapble of producing protein-polysaccharide complexes which froms the matrices of connective tissue, bone and blood vessels, (3) they also result in neovascularization, endothelial proliferation and formation of lymphatic vessels, (4) periosteum provides regenerative tissues centripetally in to the wound area in both partial and full thickness flap (5) periosteum's vasculature responds rheologically and by dilatation and permeability to provide hydration and nutritive materials to adjacent tissues and itself in the healing process.[28]

Periosteum and regeneration: In 1742, Duhame was the pioneer for the osteogenic potential of periosteum. He published his findings in the article "Sur le Development et la Crueded Os des Animaux".[29] In the next century, Ollier, another French surgeon, discovered the potential of transplanted periosteum in de novo bone formation. Urist and McLean conducted experimental studies to demonstrate about the osteogenicity of periosteal membrane. They reported that periosteum can produced bone when transplanted to the anterior chamber of the eye of the rat.[30] Ever since then few techniques have been proposed and carried out using periosteum as a regenerative tool.

Gaggl et al. devised a periosteum eversion technique or perioplasty to cover the denuded roots. It was used successfully on patients with severe gingival recessions. The technique involved the reflecting of periosteum then its eversionand its subsequent coronal repositioning over the exposed roots. They speculated that tissue regeneration in this technique is similar to that of connective tissue graft.[31] Steiner et al. introduced an inverted periosteal graft (IPG) technique. As the name suggests, the technique involves inversion or reversal of normal anatomy of the periosteum i.e. cambium layer which consists of osteoblasts, osteoblast progenitor cells and multipotent stem cells cover the fibrous layer comprising of fibroblasts, fibroblast progenitor cells; is placed immediately adjacent to the root surface. This result in apposition of fibroblasts, fibroblast progenitor cells, which produce cementum and periodontal ligament, put to the root surface. The osteoblasts, osteoblast progenitor cells and multipotent stem cells lie immediately outside and produce the osseous counterpart. Thus, IPG seats the appropriate cells in the correct site for the periodontal regeneration.[28]

Another use of periosteal membrane was demonstrated by Gamal and Mailhot. They used marginal periosteal pedicle (MPP) graft as barrier membrane to treat deep angular 2- and 3- wall infrabony defects. The results showed signicant in clinical and radiographic parameters. This periosteal pedicle graft is composed of partial-thickness facial side and a full thickness lingual side. It results in creation of a facial marginal periosteal strip adjacent to the defect. Periosteum is then separated laterally on the facial aspect, keeping it attached to its base to be used as a pedicled biologic barrier membrane.[32] A numerous studies and case report have shown successful use of periosteal pedicle graft in intrabony defects.[33,34]

Periosteum also offers a resource of periodontal tissue engineering as it can offers multipotent cells to differentiate into osteoblasts, fibroblasts, chondroblasts, adipocytes and skeletal myocytes. The other advantage of periosteum is easily accessible and can be procured from many sites, such as adjacent to surgery; making it an ideal option for periodontal regeneration.

Subepithelial connective tissue graft

Connective tissue graft or subepithelial connective tissue graft (SCTG) refers to the autogenous soft tissue

procured from the palatal masticatory mucosa. The SCTG is devoid of overlying epithelium but the underneath connective tissue. It is widely used in periodontal plastic but recently some studies have shown use of it as guided tissue regeneration.[35] It was first introduced by Langer and Calagna in 1980. Langer & Langer (1985) introduced a palatal flap approach that allowed for harvesting of SCTG.

A subepithelial connective tissue graft (SCTG) have shown the capability of being used as a barrier membrane for various infrabony defects such as furcation and two or three walled defects. Previous studies have shown success of SCTG as an autogenous membrane.[36] SCTG have shown the presence of mesenchymal cells which are osteogenic in nature.[37] It was proposed that the gingival connective tissue contains mesenchymal cells. These cells are osteogenic, chondrogenic, osteoblastic, and have immunomodulatory capacity.[38] In addition to this, the easy availability, cost-effectiveness, and versatility of the SCTG membrane were also appealing.[35] Literature had suggested that the membrane harvested as the palatal connective tissue do not proliferate into the defect. Thus, it is suitable to act as biologic membrane and can be well tolerated in the body. Being autogenous also negates the risk of disease transmission and its exposure into the oral cavity will not compromise the treatment outcome.[39]

Numerous techniques have been devised to harvesting the connective tissue grafts. Edel in 1974 introduced a trap door approach for procuring SCTG. He advocated use of oral mucosa rich in subepithelial tissue such as from palatal mucosa, maxillary tuberosity or edentulous area. Raetzke (1985) used two converging horizontal incisions. Harris (1992) used a specialized knife with two blade marking two horizontal incisions. Hurzeler et al., 1999; Lorenzana et al., 2000 used an envelope technique. Del Pizzo et al. 2002 advised a single incision technique. Ribeiro et al. used a split CTG technique. Kumar et al. used a Modified Hurzeler and Weng single incision technique.[40]

Since it is harvested from an area of complex anatomy, a thorough knowledge of the area is absolute must. The anatomy of palatal tissue comprises of its extension superiorly from the CEJ of maxillary posteriors (approximately 2 to 3 mm) and soft tissue near the median palatal raphe. This tissue is composed of very dense lamina propria, and is directly bound to periosteum. This masticatory mucosa is the most common site for extracting connective tissue grafts. The donor tissue consists of connective tissue and loosely organized glandular and adipose tissue.[41] This tissue contains two parts: pars corporis adipose which shows the presence of adipose tissue and is present in the area of premolars while whereas the pars corporis glandulosum comprises of glandular tissue and is found posteriorly to the soft palate.[42] The two are separated from each other by thin mucosa over the palatal root of the first molar.[43] If the connective tissue decreases, the thickness of the donor tissue must be increased as it become loosely organized. This tissue will then be too thin to manipulate and can tear while suturing to the graft. The best site to obtain connective tissue is closest to teeth and not midline of the palate. However, a minimum distance of 2 mm is to be maintained otherwise it increases the risk 0f postoperative gingival recession. Vice versa, if the donor tissue is obtained in vicinity of the epithelial layer, the retained flap will not have an adequate blood supply and the palatal flap will slough. This will result in similar type wound as an epithelialized donor graft wound.[44]

SCTG is used for regeneration of both soft and hard tissue such as root coverage, ridge augmentation,

mucogingival surgeries around implants and barrier membrane. However, there is disadvantage of second surgery.

Platelet rich fibrin

Platelet concentrates have gained popularity in recent years. The development of platelet concentrates started with platelet-rich plasma (PRP) and plasma rich in growth factors (PRGF).[45] They have been studied and used extensively. The second generation concentrates were PRF (Platelet rich fibrin) and its derivatives. PRF was first used by Choukroun et al in 2001 for oral and maxillofacial surgery.[46] It is considered as second generation of platelet concentrate. PRF consists of matrix of autologous fibrin and has several advantages over PRP which includes easy preparation and no chemical manipulation of the blood.[47] This autologous platelet concentrates is used regularly in dentistry due to fact that it contains fibrin fibres and growth factors, which make it ideal for regeneration. This obtained fibrin mesh is characterized by a three-dimensional matrix, where platelets, glycanic chains and cytokines structural glicoprotein are entrapped.[48] This PRF mesh, therefore, provides an optimium scaffold for cellular growth and a osteoconducive medium.

The polymerisation of blood clot activates the growth factors in it which in turn increase the reparative mechanism in the wound healing processes. The various growth factors released are platelet-derived growth factor (PDGF), transforming growth factor beta (TGF-β), insulin-like growth factor (IGF), epidermal growth factor (EGF), fibroblast growth factor (FGF) and bone morphogenetic protein (BMP). The effects exerted by the growth factors are: PDGF causes cell proliferation and collagen synthesis in fibroblasts. TGF-beta simulates collagen synthesis by fibroblasts and osteoblasts in an early stage of development and also induces the expression of extracellular matrix proteins; IGF causes differentiation and osteoblasts proliferation and regulation of differentiated functions such as type I collagen expression.[49]

PRF has also been used for guided bone regeneration (GBR) as a resorbable membrane.[50] It has the property of prevention of migration of undesirable cells into bone defect. Thus, it provides a space which allows the immigration of osteogenic and angiogenic cells and permits the underlying blood clot to mineralize.[51] It is observed that PRF membrane has a degradability of around 1-2 weeks, thus it increase this it can be reinforced by cross-linking of fibers. This can provide resistance against enzymatic degradation and more stablility during the healing time.[52]

Simonpieri et al[53] mentioned the concept of “natural bone Regeneration” (NBR). In this they stated that regeneration using PRF membranes can cause increase in both, the bone volume and gingival tissue. They have also shown successful use of PRF membranes in achieving adequate mechanical and aesthetic properties around peri-implant bone as well as restoration of gingival volume and reshaping the whole alveolar bone. PRF membrane has shown good clinical results in successful treatment of periodontal infrabony defects.[50] It has been used as a sheath for protection of open wounds in oral environment when the suture cannot bind the mucosal margins[50,53], and accelerating hard and soft tissue healing.[53] Some clinical studies used PRF membrane as a sole grafting material to achieve maxillary sinus floor augmentation, presenting promising results.[54]

Ever since PRF came to light it has become preferred material for regeneration. It has several advantages like no second surgical site, ease of preparation and availability, autologous hence avoid rick of cross

contamination. The numerous advantages have worked in its favour.

Conclusion

The materials used for regeneration has been changed and updated from time to time as per requirements and usage. Any material which guarantees induction of progenitor cells as well as serves as scaffold to those cells to proliferate is considered superior. Autogenous regenerative materials fulfil the aforementioned. Autografts and demineralized dentin matrix are reservoirs for the desired cell thus promising the new bone formation. SCTG, PRF and periosteal membranes also provides the required stem cell and growth factors which aids in healing with regeneration and not just repair. The quest for ideal circumstance of regeneration is perpetual. The histologic evaluation of healing is relatively difficult and avoidable. Thus such a material which may increase the odds of regeneration, however minute, is preferred.

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