CURRENT KNOWLEDGE AND FUTURE PERSPECTIVES OF BONE REPLACEMENT GRAFTS

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Abstract

Bone and periodontal regenerative procedures represent a fundamental component of periodontal practice. While autologous bone graft has always been considered the ideal material for the repair and/or reconstruction of craniofacial defects, its limited availability and harvesting-associated complications and discomfort lead to a substantial interest in bone replacement grafts (BRG) throughout the years. With increasing technological advances and understanding, the spectrum of BRG has broadened and taking into consideration that not all BRM perform in the same way, the appropriate clinical choice needs to be performed among the large varieties of available biomaterials. Because an understanding of the properties of each BRG enables individualized clinical selection, the objective of this article is to provide a review on the different types of BRG intended for reconstructive therapy and provide an overview on the current innovations and future perspectives in this field.

Keywords: Bone replacement grafts – osteogenesis – osteoconduction – osteoinduction – periodontal - growth factors - tissue engineering.

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Résumé

Les procédures de régénération osseuse et parodontale représentent une composante fondamentale de la pratique parodontale. Bien que l'os autogène ait été toujours considéré comme le matériau idéal pour la réparation et/ou la reconstruction des défauts cranio-faciaux, sa disponibilité restreinte, les complications et la morbidité associés ont entraîné un intérêt considérable pour les matériaux de substitution osseuse (MSO) au cours des années. Avec l'évolution associées des moyens thérapeutiques cliniques, le spectre des MSO a été élargi. Etant donné que la connaissance des propriétés de chaque MSO permet un choix clinique individualisé, l'objectif de cet article est de faire le point sur les différents types de MSO destinés à la thérapie reconstructive et de donner un aperçu des innovations actuelles et les perspectives d'avenir dans ce domaine.

Mots-clés : matériaux de substitution osseuse - ostéogenèse - ostéoconduction -ostéoinduction - parodontale - facteurs de croissance - ingénierie tissulaire.

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Introduction

Following periodontal disease, trauma or tooth extraction, bony destruction occurs and leads not only to functional concerns but also to esthetic impairment. To regain lost bone and/or periodontal tissue, bone replacement grafts (BRG) played an important role in regenerative procedures for many years. Their use became an integral part of periodontal and implant therapy (infra-bony defects, furcation defects, ridge augmentation, socket preservation, peri-implant defects, and sinus augmentation) [1]. These rege can be categorized on the basis of their biological origin as autologous bone graft when obtained from the same individual receiving the graft; homologous bone graft, or allograft, when harvested from an individual other than the one receiving the graft; animal-derived heterologous bone graft, or xenograft, when deriving from a species other than human; and alloplastic graft, made of bone substitute of synthetic origin [2].

An ideal bone substitute should be biocompatible (absence of toxicity, teratogenity, carcinogenicity), non-allergenic, without a risk of disease transmission, space maintaining, resorbable, extensively researched and tested, easy to handle, cost-effective, and should possess optimal architecture for blood vessels ingrowth and adequate biological features: osteogenic (containing cellular elements) and/or osteoinductive (containing growth factors that allow an active recruitment of host mesenchymal stem cells from the surrounding tissue). Based on the above-mentioned properties and the therapeutic objectives, the clinician must select the most adequate available BRG in order to achieve desirable outcomes and maximal clinical effectiveness [3, 4].

On the basis of this knowledge along with the introduction of advanced new regenerative technologies, a big number of sophisticated BRG have been proposed for bone and/or tissue regeneration rendering the clinical selection very challenging. Thus, the aim of this article is to present an overview of the most commonly used bone substitutes in oral surgery according to their origin and disease-related indications in order to facilitate biomaterial-selection and to discuss the current innovations and future trends aiming at improving their properties.

Variety of bone substitute materials

Autogenous graft (Autografts)

Autogenous bone was the first bone replacement grafts to be reported for periodontal applications. It is thought of as the "gold standard" ensuring bone formation by the processes of osteogenesis, osteoinduction and osteoconduction. In fact, it is still considered the only bone graft, to date, that has osteogenic potential as it maintains viable cells after extraction from the donor site to the grafting area [5, 6].

The advantages of using autogenous bone are numerous [3, 6] and their source can be divided into two categories: extra-oral (i.e. calvaria, iliac rest, tibia) and intraoral sites (i.e. chin, ramus, maxillary tuberosity, zygoma, nasal spine, canine fossa) [2, 3, 7]. While extra-oral donor regions allows harvesting of large amounts of bone tissue for extensive repair of defects, the choice of intraoral sites as donor sites for bone grafts has shown clear advantages (easier surgical access, contiguity between donor and recipient sites sharing the same intramembranous embryologic origin, less scars and discomfort) [5]. Their origin can also be divided into two categories with different healing pattern (creeping substitution and reversed creeping substitution): cortical and spongy bone [8].

While autogenous bone is the "gold standard", multiple clinical considerations have limited their exclusive use: the relatively limited amount of conveniently available autogenous bone, the harvest time involved in obtaining these grafts (greater clinician chair time), dysesthesia, unpredictable resorption rate, morbidity and discomfort associated with the donor site [3, 7, 9] .

These drawbacks have led clinicians to utilize other BRG. Oftentimes whatever amount of autogenous bone that can be obtained is used in combination with other BRG and it has become the standard treatment in bone augmentation procedures [2, 6].

Allogenic graft (allografts)

Allografts are tissues taken from human donors processed by freezing or demineralizing and then sterilized and supplied by licensed tissue banks as bone particles or blocks [6, 9]. It is the most frequently used alternative to autogenous bone for bone grafting procedures [7].

There are three main divisions: (1) frozen, (2) freeze-dried and (3) freeze-dried demineralized. They can also be classified as cortical, cancellous or mixed based on the location of the donor site. It is believed that cancellous bone shows better bone incorporation and more rapid revascularization compared to cortical bone, however faster resorption is expected [10, 11].

Frozen iliac cancellous bone and marrow (FFB)

FFB maintains its healing capabilities, that is, its osteoinductive and osteoconductive properties similar to autologous bone, because of the presence of a mineral constituent expressing bone morphogenic proteins (BMPs) [12, 13]. It is not considered an osteogenic biomaterial, even if some scientific evidence suggests that the cryoprotective substance 'dimethylsulfoxide', used for the bone graft during freezing, allows osteoblasts, osteoclasts, osteocytes and periosteal cells to survive; thus accelerating the biologic integration phases [14, 15].

Clinically, as well as histologically, FFB seems to be a successful bioma-

terial. Several studies have shown perfect integration of the biomaterial in preexisting bone, without any distinction from newly formed bone, lined by osteoblasts for socket preservation and maxillary sinus augmentation [16, 17]. However, their use was discussed for years because of the possibility of disease transfer, antigenicity and the need for extensive cross matching. These shortcomings hindered their use today in modern periodontics [2] despite the rare risk of viral diseases transmission reported when a careful selection of the donors is performed (less than 1 in 1,000,000) [2, 18].

Mineralized freeze-dried bone allografts (FDBA)

FDBA is generally extracted from live healthy donors undergoing orthopedic surgery of the hip. Freeze-drying process markedly reduces the health risks associated with fresh frozen bone [19].

Favorable results reported in field trials with FDBA have led to its extensive use in the treatment of periodontal osseous defects. However, only the osteoconductive effect has been recognized [2, 5].

Demineralized freeze-dried bone allografts (DFDBA)

Demineralization of allografts was performed because the bone mineral was thought to block the effect of the factors stimulating bone growth sequestered in bone matrix including BMPs. They are thought to stimulate bone formation through osteoinduction by inducing pluripotential stem cells to differentiate into osteoblasts [20, 21]. It is obtained from deceased donors within 24 hours after death then processed [22].

DFDBA have shown osteoconductive, as well as osteoinductive properties due to the release of BMPs during the demineralization process [9]. However, research has shown controversies in the osteoinductive properties of DFDBA [6]. Schwartz et al. have found that while DFDBA samples from some tissue banks showed osteoinductive potential, others did not. It appears that the osteoinductive properties of the material is related to the providing tissue bank and the donor's age (decreased amounts of BMPs are more evident after the age of 50 years) rather than the material itself [23, 24].

Compared to FDBA, DFDBA tends to be more rapidly resorbed and thus less space-maintaining than FDBA. Therefore, DFDBA might be best indicated for periodontal regeneration (potential presence of BMPs), whereas FDBA might be more suitable for augmentation procedures [25].

At this time, DFDBA remains the only bone replacement graft proven to result in periodontal regeneration in a controlled human histological study and is recognized in the consensus report by the 1996 World Workshop in Periodontics to fulfill all criteria considered for promotion of periodontal regeneration [26, 27].

Xenogenic grafts (xenografts)

Xenografts are obtained through different processing techniques (chemical or low heat) providing deproteinized products that are biocompatible and structurally similar to human bone and thus permitting only osteoconductive properties. With their organic phase removal, the concern about immunological reactions becomes minimal. The remaining inorganic structure provides a natural architectural matrix as well as an excellent source of calcium.

There are four sources of xenografts: bovine, natural coral, equine and porcine. While the porcine and equine sources are gaining popularity in recent years, the two remaining sources (bovine and coral) remain the most reported bone replacement grafts in the literature [2, 6, 7].

Bovine-derived bone

Anorganic bovine bone graft (ABM) is a naturally derived porous and deproteinized bovine bone mineral. It is the most researched and documented bone substitute in the literature and the most commonly used xenogeneic grafts. It is well tolerated by the body with no reports of disease transmission [28].

Even though the process of removing the entire organic component is crucial, it modifies the mineral structure of bone hydroxyapatite (HA) reducing substantially its resorption potential. In fact, it has been reported that the granules of biomaterial undergo slow or poor resorption and therefore tend to be surrounded by newly formed bone tissue rather than being reabsorbed and replaced entirely by new bone [29]. In a recent clinical study, unchanged bovine bone particles integrated with the regenerated bone were identified 11 years after sinus floor augmentation [9]. To overcome this limitation, recent studies showed that a biologic deantigenation by a proteolytic process through digestive enzymes could leave unaltered the ability of the biomaterial to be reabsorbed in vivo [30]. Despite the advantages of such proteolytic process, more studies are required until it becomes routinely applied.

Significant gains in clinical attachment level and hard tissue fill in human intrabony defects were reported using ABM [31]. Histological sections showed good integration of particles with newly formed bone filling in the inter-particle space and in direct contact [5].

Coralline calcium carbonate

The calcium carbonate exoskeleton of coral species, such as Porites, can be obtained and used as a mineral bone graft substitute. The porosity and pore size distribution of HA, which is dependent primarily on coral species, provides an osteoconductive scaffold that enhances bone formation and undergoes dissolution and resorption with bone remodeling [32, 33].

Coralline calcium carbonate produces comparable results to other BRG with significant gain in clinical attach-

ment, reduction of probing depth and defect fill [34, 35].

Alloplastic grafts (alloplasts)

Alloplastic grafts are completely synthetic materials produced using a process allowing a good control of the inter-particle spaces and consistency in an attempt to make them resemble to natural bone [3]. Based on the inherent advantages of the material (no donor site, no limitation in amount and no risk of disease transmission), the focus began to shift to alloplastic grafts in the 1970's. Clinical success has been reported in terms of defect bone fill, but with little evidence of periodontal regeneration [2]. The composition, morphology, and surface topography provide an osteoconductive platform for promoting bone formation along the surface of the grafting material [36]. In fact, the 1996 World Workshop in Periodontics reported that "synthetic graft materials function primarily as defect fillers. If regeneration is the desired treatment outcome, other materials are recommended"[26].

At present, alloplasts fall into three broad classes: ceramics, polymers and bioactive glasses [7].

Polymers (HTR: *hard tissue replacement polymer*)

Polymers can be classified based on their source: natural or synthetic. Natural polymers that have been used in the fabrication of bone grafting materials include polysaccharides (i.e. agarose, alginate, hyaluronic acid, chitosan) and polypeptides (i.e. collagen, gelatin); however, their weak mechanical strength and variable rates of degradation have limited their use as standalone bone grafting materials. Therefore, they may serve an important role in composite grafts or in the orthopedic field [5].

Synthetic polymers (i.e. polyglycolic acid, polylactic acid, polyorthoester, polyanhydride) provide a platform for controlling the biomechanical properties of scaffolds as well as targeting drug delivery in tissue engineering. Their resorption rate depends on their composition (i.e. resorption of polyglycolide is faster than of polylactide) [37]. It is possible to control this phenomenon by acting on the density, molecular weight, percentage of polymer present, thus obtaining materials with theoretical times of degradation that may vary from 5 to 7 weeks to a maximum of 2 to 3 years [5].

Today, polymers are mostly used as barrier materials in guided tissue regeneration (GTR) procedures for the treatment of periodontal defects and manufacturing of surgical sutures rather than fabrication of BRG [7].

Bioceramics

Bioceramic alloplasts have been used since 1970's in dentistry and since the 1980's in orthopedics (4). They are comprised primarily of calcium phosphate, with the proportion of calcium and phosphate similar to bone. The two most widely used forms are tri-calcium phosphate (TCP) and hydroxyapatite (HA) (2).

TCP is a porous form of calcium phosphate, with similar proportions of calcium and phosphate to cancellous bone. The most commonly used form of which is β-tricalcium phosphate. It serves as a biological filler which is partially resorbable and allows bone replacement [38, 39]. It has gained clinical acceptance as a bone substitute, but the results are not always predictable. While, good results are reported with maxillary sinus augmentation, histologic evidence reveals periodontal repair through the formation of a long junctional epithelial attachment, with limited new connective tissue attachment when used in periodontal intra-bony defects. TCP particles are generally encapsulated by fibrous connective tissue and do not stimulate bone growth [40, 41]. When compared to allogeneic cancellous grafts, the allogeneic grafts appear to outperform TCP [42].

Synthetic HA have been marketed in a variety of forms: a dense/solid non-resorbable, porous non-resorbable and a resorbable (non-ceramic, porous) form. Processing of the basic calcium phosphate mixture dictates which of the listed properties it will possess.

When prepared at high temperature (sintered), HA is non-resorbable, dense, and has a larger crystal size [43]. Dense HA grafts are osteoconductive and act primarily as inert biocompatible fillers. They have produced greater clinical defect fill than flap debridement alone in the treatment of intrabony defects. Histologically, new attachment is not achieved [44, 45].

Porous hydroxyapatite (Interpore 200®, Irvine, CA) is obtained by the hydrothermal conversion of the calcium carbonate exoskeleton of the natural coral genus Porites into a calcium phosphate HA. Unlike coralline calcium carbonate, the heat conversion make this biomaterial non-resorbable. Clinical defect fill, probing depth reduction and attachment gain have been reported. However, regeneration is limited to the apical aspect of the defect. Thus, it should be considered as a biocompatible filling material [46, 47].

Because these two materials do not resorb or remodel, implant placement through a grafted site is virtually impossible, thus limiting its value in implant therapy [6].

The third form of synthetic hydroxyapatite is a resorbable, particulate material processed at a low temperature (OsteoGen®, Impladent, Holliswood, NY; OsteoGraf LD, CeraMed Dental, LLC, Lakewood, CO). Its reported advantage is the slow resorption rate, allowing it to act as a mineral reservoir at the same time acting as a scaffold for bone replacement [48].

Combinations of the two primary forms of calcium phosphate have been studied to take advantage of the rapid resorption of β-tricalcium phosphate and the inert scaffold of dense HA. Therefore, a biphasic calcium phosphate has been released, (e.g.,

Straumann Bone Ceramic®, Institut Straumann AG, Basel, Switzerland). It is a homogenous 60⁄40 mixture of HA and β -TCP. The rapid dissolution of the β-TCP provides calcium and phosphate as well as space for bone formation, while the slower resorbing HA maintains the scaffold. Jensen et al. varied the proportion of HA and β-TCP showing alteration of the substitution rate and bone formation, making the material in a 20⁄80 formulation comparable to an autograft [49, 50].

Bioactive glasses

Bioactive glasses are composed of CaO, NaO, SiO, P2O5 and bond to bone through the development of a surface layer of carbonated hydroxyapatite [51]. There are two forms of bioactive glass available: PerioGlas® (Block Drug Co., Jersey City, NJ) and BiogranTM® (Orthovita, Malvern, PA):

*PerioGlas® has a particle size ranging from 90 to 710µm, which facilitates manageability and packing into osseous defects. Compared to TCP, HA and non-grafted controls, Fetner et al. showed that PerioGlas® produced significantly greater bone and cementum repair [52].

*Biogran® (Biomet 3i; Palm Beach Gardens, USA) are amorphous materials, based on acid axodes (e.g. phosphorus pentoxide), silica (also alumina oxide) and the alkalines (e.g. calcium oxide, magnesium oxide and zinc oxide). It is available both in compact and porous forms. It has a narrower range of particle sizes of 300 to 355 µm size range which has been reported to be advantageous for guiding blood vessels formation [4, 53].

It is argued that the more uniform sized BiogranT® would have a clinical advantage over the PerioGlas® preparation, which has multiple particle sizes. Clinically, no comparison has been made between the products [2].

Good results are reported with their use in maxillary sinus [54] and extraction socket [7]. However, despite the increase of clinical attachment level and hard tissue fill in intrabony defects [55], histologic analysis revealed a healing by connective tissue encapsulation of the graft material and epithelial down-growth, with minimal evidence of new cementum or connective tissue attachment limited to the most apical part of the defect [56].

Disease-related indications

Periodontal defects

Intrabony defects and Class II furcation defects are the main indications for bone grafting in periodontal defects. Compared to allografts, limited evidence is available to support the superiority of the use of xenografts or alloplasts in the treatment of periodontal defects [57, 58].

Therefore, to date, autologous bone grafts and allografts are recommended because of the favorable results reported in the literature [1].

Peri-implant defects

Regarding defect morphology of peri-implant lesions, guided bone regeneration (GBR) is indicated in 2-wall or 3-wall intrabony defects and circumferential defects.

In human models, various bone replacement grafts have been applied to manage peri-implant bone loss with positive outcomes. They include autologous, allogeneic, xenogenic and synthetic bone substitutes. However experimental designs are very heterogeneous and to date, limited evidence is available to make a conclusion to suggest any specific type of bone replacement materials to use as a gold standard to treat peri-implant defects. Additional research is expected to address the regenerative procedures in peri-implant lesions [1].

Socket preservation

The use of autologous bone failed in most of the studies to substantially reduce ridge resorption despite its osteogenic properties. This is maybe due to its fast resorption when compared to other biomaterials. When to the use of allografts, more favorable results are reported in the literature. Whereas the extraction sockets grafted with xenografts exhibited a delayed healing pattern [59, 60]. In addition, the percentage of vital bone fill after the healing were significantly inferior when using xenograft (26%) compared to allograft (61%) [61].

Fibrous encapsulation surrounding the residual bone particles has been observed when xenografts and alloplasts were used leading to less bone-to-implant contact after implant placement [61].

It can be concluded that allografts and xenografts are effective for socket augmentation. Allografts may be preferred if a future implant placement is intended for a faster and a greater percentage of vital bone fill and thus a superior bone to implant contact. When to xenografts and alloplasts, their slow resorption rate may be advantageous in a socket that will not be used for a future implant placement but rather for improving esthetics by preserving the bone and soft tissue architecture under prosthetic pontics.

Ridge augmentation

Usually, a combination of various bone grafts is preferred and reported in the literature. The mostly used combinations include:

- Layers of cancellous and cortical allografts [62].
- Mixture of autogenous grafts and deproteinized bovine bone mineral [63].

These combinations of BRG are advantageous because of the capacity of space maintenance with low-turnover rate bone grafts (cortical allografts and deproteinized bovine bone mineral) and the property of osteogenesis and/or osteoinduction and/or osteoconduction of autografts/cancellous allografts [1].

Sinus augmentation

From previous studies, comparable clinical outcomes and a similar histologic appearance have been suggested regarding the efficacy of different types

of BRG used for sinus augmentation [64].

It can be assumed that to date, no association has been found between the best type of grafts used in sinus augmentation and surgical outcomes in terms of implant survival rates and occurrence of complications [65]. Therefore, it can be concluded that all types of BRG are suitable for sinus augmentation procedures [1] with a slight preference towards bone grafts with slow resorption rates to assure space-maintenance [66].

Current innovations and future trends

The presence of three fundamental elements is necessary to obtain bone regeneration: (1) a source of cells that are able to differentiate and secrete a mineralized matrix; (2) growth factors to guide the regenerative process and (3) a scaffold (i.e. bone replacement grafts) for assuring a mechanical support and a substrate for the new forming tissues [67]. The understanding and application of these elements can help converting BRG from a simple filling substance to an innovative biomaterial in the sense of a scaffold, which will play an important role in bone tissue engineering applications [4].

Growth factors

Growth factors (GF) are the signaling molecules that regulate cell growth and development. They modulate cell proliferation, migration, extracellular matrix formation and other cellular functions. Key growth factors are platelet-derived growth factor (PDGF), transforming growth factor-β (TGF-β), fibroblast growth factor (FGF), insulin-like growth factor (IGF), vascular endothelial growth factor, parathyroid hormone (PTH) [6].

The first attempts to deliver GF with BRG used semi-purified natural materials such as platelet-rich plasma (PRP) and enamel matrix proteins:

- Platelet-rich plasma is derived from centrifuged autologous blood by drawing off the platelet-rich buffy zone. This source of highly concentrated platelets produce GF that are beneficial for healing. It can be placed in the periodontal or bony defect, or added to a graft material. When mixed with a bone graft, PRP facilitates graft placement and containment [3, 68]. Despite the attractive rationale and the in-vitro, in vivo pre-clinical [69] and clinical [70] observed beneficial effects of PRP and other platelet concentrates (platelet-rich fibrin and platelet lysate), the results are promising but still not consistent [71].
- Developed originally by Biora in Sweden, enamel matrix proteins are extracted from the tooth buds of piglets, suspended in a polyglycol gel and marketed as Emdogain (EMD) (Institut Straumann AG, Basel, Switzerland). EMD contains over 95% amelogenin with small amounts of enamelin and other proteins. Initial studies showed histological evidence of regeneration in monkeys [72]. Subsequent clinical studies showed the material to be of benefit in infrabony and angular periodontal defects [73] and reported that EMD promotes angiogenesis and stimulates the production of other GF, such as BMPs [74]. EMD can be added separately to a graft material in order to grant it some osteoinductive properties or present within the grafting material itself (eg. Emdogain Plus: a mixture of EMD and Straumann Bone Ceramic).

More recent attempts have used recombinant human proteins: synthetically produced proteins by DNA technology (replicas of natural proteins). Manufacturing GF removes the issues of varying concentration and small amounts available in naturally derived materials and allows for the use of a single protein at any concentration desired. BMP-2 and BMP-7 have been developed as recombinant human proteins for use primarily in orthopaedics, but also periodontics and implant dentistry [75]. An example of available rhBMP-2 on the market is Infuse® (Medtronic, USA, rhBMP2 combined with collagen fleece) [4]. Mokbel et al. in 2013 studied the effect of different bone substitutes soaked in rhBMP-2 on the healing of critical size defects rats. They showed that the addition of rhBMP-2 to bone substitutes was efficacious in regenerating bone [76].

In 2005, FDA approved a new dental bone filling device, GEM 21S® (Osteohealth/Luitpold Pharmaceuticals, Inc, Shirley, NY, USA) which combines rhPDGF-BB and β-TCP for the treatment of periodontal-related defects. It contains over 100 times the concentration of platelet-derived growth factor obtainable in current PRP preparations. It promotes angiogenesis as well as enhances cell recruitment and proliferation of bone and periodontal ligament cells [77]. The efficacy and safety of GEM 21S for the treatment of intrabony defects has been established in a large scale multicenter, randomized controlled clinical trial [78]. In a further clinical study, Nevins et al. in 2007 evaluated the use of FDBA with rhPDGF-BB in intrabony defects. The radiographical and re-entry results have proven full defects fill proving the efficacy of such treatment [79].

Despite the attractive rationale for their use, current researches are focusing on the best scaffold for GF and the effect of different concentrations for optimizing the results. In fact, most GF used in tissue engineering have a very short half-life. Thus, they may not be present at the right time or in the correct amount when needed. More long term studies are needed before their routine use in periodontal practice.

Gene therapy or delivery

The transduction of cells with genes for particular GF is a novel interesting method. Using an adenovirus, Giannobile et al. has successfully transferred PDGF and BMP-7 genes into cementoblasts, fibroblasts and other periodontal cell types [80]. When the cells containing the gene were placed in periodontal defects in rats, they stimulated bone and cementum regeneration. Using this approach, it may be possible to manipulate the periodontal healing response in order

to obtain a favorable regeneration. However, the safety and efficacy of this technique need to be further evaluated [3].

Cell-based materials

Cell sheets

This approach consists of culturing cells, such as fibroblasts, in the laboratory to create cell sheets or scaffolds full of cells that could be used in regeneration [81]. Hasegawa et al. created periodontal ligament cell sheets in vitro and transplanted them into a dehiscence defect model in immunodeficient rats. Four weeks post-surgery they were able to show regenerated ligament tissues anchored to the previously root-planed dentine surface [82]. This approach has also been used to seed cells onto a membrane or mesh in the treatment of gingival recession with similar good and promising results [74].

Stem cells

Stem cells have two characteristics: the ability for indefinite self-renewal to give rise to more stem cells and the ability to differentiate into a number of specialized daughter cells. Their use is of interest because mesenchymal cells usually migrate toward the bone substitute conveyed by the bloodstream and by the newly formed vessels and differentiate into osteoblasts. When added to bone substitute, it is thought to promote bone formation [5]. Seo et al. were the first to report the presence of mesenchymal stem cells in the periodontal ligament that can be isolated and used for regeneration. More recently, immortalized dental follicle cells were shown to be able to generate periodontal ligament-like tissue after implantation [83].

Even though this therapy represents a great step forward in a more predictable biologically based therapy, however, the best stem cell source for regeneration of the periodontal ligament remains to be determined [3]. This novel option will surely find its place in the near future in reconstructive surgery.

To this date, there is no reliable evidence suggesting which cell source and/or scaffold and/or growth factors are the most effective when combined together for apredictable bone regeneration.

Customized scaffold

Computer-based applications are some of the most recent developments in tissue engineering: by scanning the three-dimensional anatomic geometry of a defect using computed tomography or magnetic resonance imaging, a template for a scaffold on an anatomic level can be fabricated. Since it is produced from the three dimensional model, this three-dimensional printed scaffold can precisely fills the defect space and assure a mechanical support as well as a substrate for the new forming tissues [84].

Autogenous teeth (AutoBT)

Researchers and development of biomaterials using human teeth have started since 1993. Since then, many case reports have been published on the use of this novel technique. Autogenous teeth can be obtained as granules or block form [85, 86].

The inorganic components of teeth (mainly HA, small amounts of β-TCP, amorphous calcium phosphate, dicalcium phosphate dehydrate and octacalcium phosphate) are similar to those of alveolar bone. Interacting together, these calcium phosphates are capable of remodeling the existing bone when grafted [86].

The organic component can be preserved ensuring a rapid alveolar bone remodeling. In the organic parts, dentin and cementum include type I collagen and various growth factors such as BMPs that can promote the healing. However, when teeth from unrelated individuals or animals are intended to be used, the organic phase must be removed to abolish infection risk factors and possible unfavorable immunological response [85].

Most of the AutoBT resorb within 6 months and the new bone form a direct union with the remaining particles. The healing process is promoted by osteoconduction and osteoinduction. [87]. In clinical studies, AutoBT has been grafted in sinus bone graft, guided bone regeneration, ridge augmentation, ridge splitting and socket preservation; good results have been reported [88, 89].

Conclusion

There is no ideal BRG suitable for all the regenerative procedures. Selection of a bone graft should be based on the inherent properties of the material, the clinical situation and the desired outcome.

With the advent of technology, autologous bone grafts remain the best choice in most situations but are no longer the only option in modern dentistry. Various BRG from other sources are available, and tissue engineering holds a great promise.

Maybe in the near future, the dental surgeon will be able to scan any defect by computed tomography and choose the adequate stem cell or gene delivery system in association with specific GF in order to obtain complete and reliable regeneration. Only through extensive further research and development in this field that tissue engineering can continue to advance in order to be used in clinical practice.

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