The use of tissue engineering in maxillary sinus augmentation: a review

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Abstract

Tissue engineering is an interdisciplinary field that applies the principles of engineering and the life sciences toward the development of biological substitutes that restore, maintain, or improve tissue function. The most studies are focused on the preparation of scaffolds, selection of the different cell sources and construction of engineered bone. The decrease in bone height in the sinus area after tooth loss is a major challenge in implantology, making the search for new materials a constant challenge. Faced with this, the aim of this review article is to discuss the tissue engineering techniques for maxillary sinus lifting in atrophic jaws.

Keywords: Maxillary sinus; Tissue engineering; Maxilla.

Introduction

Dental implants rehabilitation in the atrophic posterior maxilla continues to be a challenge in dentistry [1]. In those cases where the bone quality and volume are inadequate, maxillary sinus augmentation with placement of a dental implants, initially proposed by Boyne & James 1980 and Talum 1986 [2, 3], is a well-established technique for functional and aesthetic dental rehabilitation. The grafts materials used after the lifting of the sinus membrane are autologous, allogeneic or synthetic biomaterial.

Autologous bone graft is descrybed as the gold standard, but the site morbidity, limited amount of donor sites and graft resorption are factors that should be considered, different approa-

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ches have been investigated for an ideal substitute for autogenous bone [4, 5].

Tissue engineering is an interdisciplinary field that applies the principles of engineering and the life sciences toward the development of biological substitutes that restore, maintain, or improve tissue function [6]. It is based on knowledge of embryology, as well as tissue function, formation and regeneration, with the aim of growing new functional tissues. Three general aspects have been considered for producing a new tissue: cells or cell substitutes, the 3D scaffolds and tissue-stimulating compounds. The most studies are focused on the preparation of scaffolds, selection of the different cell sources and construction of engineered bone [7].

With respect of the association of maxillary sinus floor elevation and tissue engineering for oral rehabilitation, some studies have demonstrated encouraging results [8-10]. The aim of this paper is reviewing the employment of tissue engineering in maxillary sinus augmentation. In these review important aspects such as cell sources, types of scaffolds materials, construction of engineered bone as well as biological results will be discussed.

Results (Review)

This systematic literature review was performed evaluating published articles in the last 20 years in MEDLINE (PubMed) and Cochrane online databases using tissue engineering in maxillary sinus augmentation. Search keywords used for this systematic review were Maxillary Sinus, Sinus Lift, Bone Grafting, and Tissue Engineering.

From this, 48 studies were selected, but only 36 were included in this study due to inclusion´s criteria: 1. Studies performed in vivo. 2. Longitudinal studies. 3. Studies performed using sinus lift technique or similar procedures using biomaterials. Article was excluded if: 1. Study was performed using only in vitro techniques. 2. Clinical cases. 3. Lack of information related to surgical procedure or biomaterial´s charac-teristics.

Obtainig cells by tissue engineering cells

Tissue engineering requires the achievement of a number of criteria, which include easy, an extensive self-renewal or expansion capability of the source of cells, a capacity to differentiate readily into cell lineages, and a lack of or minimal immunogenic or tumorigenic ability of the source cells [11].

Cells can be separated into three distinct groups based on their differentiation capacity [7]: 1) Unrestricted cells are able to differrentiate into all, cell lineages (i.e., embryonic stem cells); 2) Multipotent progenitor cells that acquire specific phenotype depending on their maturation during differentiation (i.e., multipotent stem cells from bone marrow); 3) Determined cells or differentiated cells (i.e., osteoblasts). Depending on their source, stem cells are classified as embryonic, fetal or adult. Embryonic stem cells display high plasticity and are pluripotent, however, the ethical and legal concerns associated with embryonic stem cells and their tumorigenic potential make them less ideal for clinical application [12].

In all studies reviewed used adult stem cells from various sources for sinus augmentation procedures. Mesenchymal stem cells can be derived from various tissues including bone marrow, periosteum, trabecular bone, adipose tissue or skeletal muscle and do not express the hematopoietic antigens [13, 14]. The most common sources of cells used in the studies reviewed were iliac crest, periosteum, chin, lateral cortex of the mandibular body and maxillary tuberosity [15-18].

The stem cells are usually isolated from bone marrow, which is described as a complex microenvironment, with two distinct cell population, hematopoietic and stromal cells. The stromal cell is composed of endothelial cells and multipotent stem cells, providing the potential for self-renewal and differentiation [19].

Stem cells are usually obtained from bone marrow aspirates harvested from the iliac crest with good results, however this procedure may be painful [4,17,20]. In this context cells derived from the periosteum are described as a cell source with great potential for bone tissue engineering.

Cells from periosteum can be expanded at least 7 passages [21,22]. A comparative study in the mouse model using mesenchymal stem cells, alveolar bone cells, and periosteal cells found periosteal cells were the superior choice for bone tissue formation [23]. Animals' studies, with critical size bone defects models, showed the great osteogenic potencial of cultured periosteal cells [24-26].

Scaffolds

Scaffolds for bone tissue engineering serves several purposes such as a) provide a delivery vehicle for osteoinductive molecules and/or osteogenic cells; b) must fill de gap in a bone defect and should facilitate healing; c) should act as the in vivo matrix and as a guide for angiogenesis to vascularize the new tissue formed [27].

Scaffolds should be 3D, porous with an interconnected pore network; biocompatible with a proper surface to allow cell adhesion, proliferation and differentiation, biodegradable with a controlled degradation rate; and should have adequate mechanical properties [6]. The two materials most studies as ideal scaffold in tissue engineering are the ceramics and polymers.

Properties of some ceramics such hydroxyapatite-based calcium phosphate compounds (CaP), are very similar to inorganic component of natural bone tissue, and bioactive glasses are considered to be potencial scaffolds [7]. On the other hand polymers such as poly (L-lactic acid, [PLLA]), poly(glycolic acid, [PGA]), poly(DL-lactic-co-glycolic acid, [PLGA]) has a high release efficiencies. Another possibility is to combine ceramics and polymers, thus we have a scaffold with a high osteoconductive and degradability such a CaP/PLGA [28].

Platelet-rich plasma (PRP) is also being used as autologous scaffolds in injectable tissue-engineered bone (BMSCs) with good results, however only one research group is using this method [29,30]. In relation to Collagen, your the fast resorption rate of the collagen may be not adequate to use as scaffold, this carrier do not adequately maintain a matrix for support of bone formation [31] and the collagen carrier may give some degree of collapse of the lateral wall of the sinus cavity after the implantation [32].

Biological uses results (literature review)

Zou et al. [33] explored the effects of maxillary sinus floor elevation and simultaneous dental implantation with a tissue-engineered bone complex of calcium phosphate cement (CPC) scaffolds combined with bone marrow stromal cells (BMSCs) in goats. After a healing period of 3 months, sequential triad-color fluorescence labeling, micro-CT, as well as histological and histomorphometric analyses indicated that the tissue-engineered BMSC/CPC complex could promote earlier bone formation and mineralization, and maximally maintain the volume and height of the augmented maxillary sinus.

By comparison, CPC-alone or autogenous bone achieved less bone formation and later mineralization. Besides, the average bone-implant contact value reflecting the osseo-integration was 35.63%–9.42% in the BMSCs/CPC group, significantly higher than 22.47%–4.28% in the CPC-alone group or 28.26%–8.03% in the autogenous bone group.

In conclusion, CPC serves as a potencial substrate for BMSCs for the maxillary sinus floor augmentation; the

tissue-engineered bone might enhance the stability of implants.

Wang et al. [18] studied effects of a tissue-engineered bone complex (osteoblasts / beta-TCP) for maxillary sinus augmentation in a canine model. The authors concluded that beta-TCP alone could barely maintain the height and volume of the elevated sinus floor, and that the transplantation of autogenous osteoblasts on beta-TCP could promote earlier bone formation and mineralization, maximally maintain height, volume and increase the compressive strength of augmented maxillary sinus.

Xin-quan Jiang et al. [34], evaluated the effects of maxillary sinus floor elevation by a tissue-engineered bone complex of β-tricalcium phosphate (β-TCP) and autologous osteoblasts in dogs by a sequential fluorescent labeling observation. The fluorescent and histological observation showed that the tissue-engineered bone complex had an earlier mineralization and more bone formation inside the scaffold than β-TCP along or even autologous bone. It had also maximally maintained the elevated sinus height than both control groups.

Riecke et al. [35] studied, mechanically, the effect of transplan-tation of precultured preosteoblasts derived from autogenic adult mesenchymal stem cells (aMSC) for experimental sinus floor augmentation on primary dental implant stability in comparison with conventional augment-tation procedures in rabbits, the carrier was bovine collagen. The evaluation of mechanical properties with percussion testing and resonance frequency analysis with Osstell revealed slightly higher primary stability of the stem cell group whereas the scanning laser Doppler vibrometer and measurement of pull-out forces showed no significant difference to the bone substitute group.

Transplantation of autogenous bone graft resulted in the highest primary implant stability. The experimental maxillary sinus floor augmentation with precultured osteo-blast precursor cells from autogenic stems cells clearly enhanced the primary stability of implants compared with the unaugmented sinus and lead to comparable primary mechanical properties to bone substitutes in rabbits. In comparison with the autogenous bone graft stability enhancement by stem cell transplantation declined.

Shayesteh et al. 2008 [20] in a clinical study assessed the clinical effectiveness of adult mesenchymal stem cells (MSCs) loaded to the biphasic scaffold (HA/TCP) on sinus augmenttation. Of 30 implants, 28 (93%) were considered clinically successful. Histologic evaluation of the biopsy specimens revealed numerous areas of osteoid and

bone formation HA/TCP, with no evidence of inflammatory cell infiltrate. Mean bone regenerate was 41.34%. Mean bone height was measured 3 and 12 months after sinus grafting (mean of SBH_1= 12.08 mm and mean of SBH_2= 10.08 mm). These clinical and histological findings suggest that sinus grafting with HA/TCP in combination with MSCs provide a viable therapeutic alternative for implant placement.

Zizelmann et al. [36] quantified the resorption rate of tissue-engineered bone grafts, sinus floor augmentation using autologous bone grafts from the iliac crest was compared with commercially produced transplants of human cells seeded on polyglycolid–polylactid (PLGA) scaffolds (Oral Bone), in the maxillary sinus using volume measurements. The total resorption rate for autologous transplants 3 months post operation was 29%, while the tissue-engineered bone showed a resorption rate of 90%. The autologous bone had a bone density of up to 266–551 Hounsfield units (HU), while sufficient mineralization of tissue-engineered bone was found in only one case (152 HU).

Nagata el al. [37] examined the treatment outcomes of 25 patients who underwent autogenous bone grafting (15 for alveolar ridge augmentation and 18 for maxillary sinus lift) with cultured autogenous periosteal cells (CAPCs) and PRP as a scaffold. Clinical outcomes were determined from high-resolution three-dimensional computed tomography (3D-CT) images and histological findings. The results suggested that CAPC grafting induced bone remodeling, thereby enhancing osseointegration and consequently reducing postoperative waiting time after dental implant placement.

Voss et al. [38] evaluated the success of augmentation and implants after lifting of the sinus floor using tissue-engineered polymer-based periosteal bone grafts compared with autologous bone. Lifting the sinus floor with autologous bone was more reliable than with tissue-engineered transplants. Although lamellar bone could be found in periosteum-derived, tissue-engineered transplants, the range of indications must be limited due to higher infection and resorption rates in larger augmentations.

Yamada et al. [29] used injectable tissue-engineered bone, with (BMDSCs) and platelet-rich plasma (PRP), to conduct maxillary sinus floor augmentation by the simultaneous placement of bone graft and dental implants and to examine the state of regenerated bone after functional loading in 16 sinus augmentations. All implants were clinically stable after second-stage surgery. The height of mineralized tissue at 2 years showed the

mean increases of 8.8 ± 1.6 mm compared to preoperative values, and no adverse effects and remarkable bone absorption were seen in the 2–6-year follow-up time.

Mangano et al. [39] evaluated the maxillary sinus augmentation responses to tissue-engineered bone graft obtained by a culture of autogenous osteoblasts seeded on polyglycolic–polylactic scaffolds and calcium phosphate. Sinus floor augmentation was performed bilaterally in five patients (mean age 58.4 years) with tissue-engineered bone (test site – Oral Bone®, BioTissue, Freiburg, Germany) or calcium phosphate (control site – Biocoral, Novaxa Spa, Milan, Italy).

The mean of vertical bone gain was 6.47± 1.39 mm and 9.14 ± 1.19 mm to test and control sites, respectively. The histological sections depicted mature bone with compact and cancellous areas. All biopsies contained varying percentages of newly formed bone and marrow spaces. The mean of bone tissue in the grafted area was 37.32 ± 19.59% and 54.65 ± 21.17% for tissue-engineered bone and calcium phosphate, respectively.

Rickert et al. [16] tested the differences occur in bone formation after maxillary sinus floor elevation surgery with bovine bone mineral (BioOsss) mixed with autogenous bone or autogenous stem cells. Significantly more bone formation was observed in the test group (17.7 ± 7.3%) when compared with the control group (12.0% ± 6.6). In both the test and control group, all implants could be placed with primary stability.

Sauerbier et al. [17], evaluated the potential of substituting autogenous bone (AB) by bone marrow aspirate concentrate (BMAC). Both AB and BMAC were tested in combination with a bovine bone mineral (BBM) for their ability of new bone formation (NBF) in a multicentric, randomized, controlled, clinical and histological noninferiority trial. NBF was 14.3%–1.8% for the control and nonsignificantly lower (12.6%–1.7%) for the test (90% confidence interval: - 4.6 to 1.2). Values for BBM (31.3% – 2.7%) were significantly higher for the test compared with control (19.3%–2.5%) ($p<0.0001$). Nonmineralized tissue was lower by 3.3% in the test compared with control (57.6%; $p = 0.137$). NBF after 3–4 months is equivalent in sinus, augmented with BMAC and BBM or a mixture of AB and BBM.

Trautvetter et al. [21] evaluated the long-term clinical repair effect of autologous periosteal bone grafts on atrophic maxillary bone using autologous tissue-engineered periosteal bone grafts based on bioresorbable polymer scaffolds and, in a 1-step procedure, simultaneous insertion of

dental implants. The clinical evaluation was performed by radiologic assessment of bone formation, with a follow-up of 5 years. Bone formation was further documented by measuring the bone height and by histologic examination. Excellent clinical and radiologic results were achieved as early as 4 months after transplantation of the periosteal bone grafts. The bone height remained significantly greater (median 14.2 mm) than the preoperative atrophic bone (median 6.9 mm) during the 5-year observation period. Histologically, the bone biopsy specimens of 2 patients obtained after 6 months showed trabecular bone with osteocytes and active osteoblasts. No signs of bone resorption, formation of connective tissue, or necrosis were seen.

Conclusions

The use of tissue engineering in maxillary sinus augmentation has demonstrated promising results and has traced a solid and impactful path in regenerative therapy in different fields of medicine and dentistry. Some of these initial results are (1) the development of cell membranes in laboratory; (2) transplantation of highly proliferative and non-immunogenic pluripotent cells from periodontal ligament, dental pulp, apical papilla, dental follicle, and gingiva into defects/cavities in order to potentiate the regenerative process; and (3) the development of carrier materials (scaffolds), such as collagen sponge and HA/β-TCP-based bone grafts. owever more research must be done in order to improve a) scaffolds - several scaffolds have been tested, with different biological, chemical, physical and mechanical properties.

Despite such research there is still no consensus on which scaffold must be used in these rehabilitations. b) cells – some questions like which cellular source, stage of differentiation and seeding should still be more enlightened. c) angiogenic growth factors or endothelial cells may be or not added to improve the oxygen and nutrient supplies?. Tissue engineering is a relatively new area of research andplenty studies are carried out with great discoveries every year, enabling this cellular regeneration therapy to benefit professionals and, above all, to be useful in the rehabilitation of patients in the daily clinic.

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