The use of stem cells in bone regeneration in Implantology

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Introduction: Bone regeneration is one of the biggest challenges for Implantology. Finding a bone base with suitable volume and height for the installation of dental implants is not always possible, and various techniques have been improved to regenerate lost structure. The autogenous bone graft is considered the "gold standard" of regenerative therapies for having osteogenic properties that are not found in other techniques. Yet, the patient needs to perform two surgical procedures, resulting in increased surgical time, longer recovery, increased risk of infection, bleeding, fracture and post-operative pain. **Objectives:** The purpose of this article was to assess the bioengineering tissue and regenerative procedures performed in a less invasive way, with lower morbidity for the patient. **Results:** Checking the clinical applicability of stem cell therapy may be a routine for the implantologist. The results of this pattern of regeneration presented excellent maintenance of the formed bone, with low resorption rates, as well as vitality and adequate histologic quality of formed bone tissue, allowing the patient to perform larger restorations with more conservative and less invasive surgeries. **Conclusions:** It can be concluded that the use of bone substitutes optimized with mesenchymal stem cells have shown promising results in clinical application. **Keywords:** Dental implants. Bone regeneration. Stem cells.

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INTRODUCTION

Implantology is a reality in today's dentistry with high predictability of success on osseointegration, led to an increase in demand and trust for this kind of treatment by patients. Currently, focus on oral rehabilitation search function and aesthetics, drove the implant dentistry to new challenges to get prior to the implants installation an appropriate bone and gingival tissues, and there are situations where the ability to repair is limited by the size of the bone loss, often needing grafts.

The use of autogenous graft is the "gold standard", because it carries osteoprogenitor cells and growth factors with ability to form new bone, in addition to being completely biocompatible. Meanwhile, the removal of this graft presents a risk of morbidity, postoperative complications and is also less tolerated by the patient, because it is a more invasive procedure. The use of biomaterials is an alternative to the replacement of bone loss and in the maintenance of bone volume; however, it does not have the property of being osteogenics.[1]

Cell therapy comes with the aim of increasing the gap in the use of biomaterials, that is, bring the property of osteogenesis in your application, transforming a biomaterial primarily osseoinductor in a bone substitute with all properties and qualities of an autogenous bone graft, without the morbidity and the complications presented in these surgeries.[2]

The result of this pattern of regeneration has presented, in initial cases, excellent maintenance of this new bone, with low rates of reabsorption, as well as vitality and adequate histologic quality of this new bone tissue, providing to the patient the realization of larger restorations, with more conservative and less invasive surgeries.[3]

MATERIAL AND METHODS

The purpose of this article is to analyze the literature gathering information on the use of mesenchymal stem cells in bone regeneration and evaluate your clinical applicability in implant dentistry and clinical applicability in oral bone regeneration.

RESULTS

In 1968, osteogenic cells were removed from a small bone fragment of the bone marrow of femurs of rats and transplanted into their renal capsule and in the subcutaneous tissueTwo months after the procedure, the reabsorption of this tissue occurred, creating, after 14 months, a new bone fragment inside the renal capsule and in the subcutaneous tissue of these animals. Chromosome markers in histological examination demonstrated that this tissue was derived from bone marrow, proving that, beyond the capability of forming hematopoietic tissue, the bone marrow has the ability to induce osteogenesis, and the bone marrow cells are also osteogenic cells.[4]

In 1972, bone defects were made with a drill in the pelvis of mice. These defects where filled with a bone graft impregnated with bone marrow aspirate and, after 135 days, the animals were sacrificed and performed histological cuts, going on bone formation in 70% of the grafted sites, and in 20% there was a continuous mineralization. It was concluded that the cells present in the bone marrow promote better regeneration when associated with bone graft.[2]

In 1989, bone defects in rats femurs were created, being grafted a ceramic block enriched with bone marrow aspirate and, after 2 months histological sections demonstrating a bone formation or complete osseocondral in 68% of the blocks and in the remaining partial bone forma-

tion, indicating that repair with ceramic blocks associated with bone marrow aspirate presents clinical applicability and osteogenic potential in an osseoconductive material, due to some secretory factor present in the bone marrow, inducing a mesenchymal cell migration to the interior of the ceramic block leading to the differentiation of these cells in osteoblasts.[5]

In 1991, stem cells from mesodermal layer of embryos were able to differentiate themselves into different lineages and form various tissues, among them, including bone and cartilage. This demonstrated that progenitor cells can differentiate into bone or cartilaginous tissue - when exposed to different chemical factors, such as the presence or absence of oxygen and the location in which they are - and possible repositories of bone cells are bone marrow and periosteum.[6]

In 2004, analyzing the osseointegration of dental implants was observed using mesenchymal cells in defects created in the lower jaw of dogs and, after 2 months, the site was reopened and dental implants were installed in these regions. After 2 months osseointegration, a histological evaluation was performed and the amount of bone-implant contact (BIC) and bone density were increased by 10% where used mesenchymal stem cells were used, when compared to the autogenous bone.[7]

In 2004, in maxillary sinus lift in humans with a synthetic bone incremented with mesenchymal stem cells cultured from periosteum, it was observed, in 3 months, that in 60% of these sinuses occurred the formation of a bone with excellent quality - radiological, histological and clinically - for implants instalation.[8]

In 2008, in a clinical trial in patients to increase alveolar bone (about 5 mm in height) for installation of implants, the bone marrow was removed from the iliac and stem cells were cultivated and added to the platelet rich plasma. They were evaluated radiologically and visually. In 100% of the patients, there was bone formation and it was observed good implant stability, even after 2 and 5 years after the procedure and without symptoms of implant failure.[3]

Again in 2008, in culture of mesenchymal cells of bone marrow of mice, they differed in bone progenitor cells, and with 2 weeks occurred the presence of markers of bone proteins as alkaline phosphatase and osteocalcin, which demonstrate the ability of tissue mineralization. Ceramic blocks of hydroxyapatite were impregnated with these cells and transplanted into the subcutaneous tissue, where after 6 weeks through CT scans and histological analysis, it was verified that bone neoformation occurred in composites, showing that medullary and periosteum mesenchymal cells may be an indication to promote bone regeneration.[9]

In 2008, stem cells from the pulp of deciduous teeth were used as a promising source for tissue regeneration, having easily access for collection and low morbidity, possessing extensive differentiation capability, being capable of differentiation into multipotent osteoblasts and endoteliocells, good interactivity with biomaterials, can be cryopreserved and having a long shelf life, being able to form a bone with Haver's channels and appropriate vascularization.[10]

In 2010, in a study in rabbit skulls to growth in bone height, mesenchymal cells were implanted in various concentrations and, after 1 month, it was observed that there were bone growth and the height and bone density formed was higher in the group with the greatest amount of mesenchymal cells and tomographically and histologically contact titanium-bone were also directly proportional to the amount of mesenchymal cells used, concluding that the vertical bone

augmentation is dose-dependent from mesenchymal cells derived from fat tissue.[11]

In 2009, a study was carried out in an experimental model with human stem cells from primary teeth to regenerate defects created in the skull cap of rats. . After the experiment, samples of bone tissue were extracted to perform histological analysis. A molecular study confirmed the presence of human cells in neoformed bone without rejection during the studied period, and that the use of human stem cells from deciduous teeth associated with collagen membrane represents an important strategy for the reconstruction of bone tissue and may be considered an option for repair of large skull bone defects.[12]

In 2012, in third molars extracted from human donors, the dental pulp was used and placed under culture for which stem cells were developed, being grown in 3 different culture types, developing osteoblastic and endothelial cells, liver lineage cells and neural cells, indicating that the tissue originated form the pulp of third molars are pluripotent, able to differentiate into cells of 3 germ layers, opening a new possibility in regenerative medicine.[13]

In 2013, patients had their sockets filled: with autologous bone marrow and only with blood clot; block grafting technique without the use of bone marrow; and others with blocks impregnated with autologous bone marrow. After 6 months, a trephine bur was used to prepare these sites, and histological revealed a higher bone volume in the group treated with bone marrow, with no difference in the quality of the bone formed. Tomographic measurements, in cases of grafting on block showed that with the use of bone marrow there was a greater bone volume gain and histologically showed that there was a more mineralized bone tissue, showing that bone marrow can optimize grafting results.[14]

In 2014, an experiment in rabbits associating cell therapies with xenograft in bilateral bone defects showed that some types of graft-associated cell therapy improve the regenerative results, showing the lowest rates of reabsorption, similar to what is observed in the natural bone and that the use of the mononuclear fraction enhances the use of tissue engineering improving the processing cell under culture, enabling the clinical use of tissue engineering.[15]

In 2014, it was proved that age doesn't interfere in stem cells derived from dental pulp of third molars extracted from young adults (19-30 years old) and older adults (44-70 years old) and have the same quality, quantity and capacity of differentiation, being a great hope for tissue regeneration to the older age groups, Since the population tends to become more senile over the years.[16]

In 2015, circular defects on skullcap of rats were treated with 3D artificial parts with biodegradable polymers manufactured identical to defect, which formed a bone substitute with adequate porosity, in which the stem cells from the dental pulp colonized the created surface, occurring an extensive formation of quality bone tissue, organized and with collagen matrix in its new structure.[17]

DISCUSSION

The autogenic bone graft is considered the "gold standard" in grafting by biocompatibility, physical-chemical characteristics and its osteogenic osteoconductives and osteoinductives properties.[12,14,15] Morbidity in the donor area can include pain, transitory or permanent paresthesia, bruises, bleedings, fractures, intra or extrabucal suture dehiscence, being the bone substitutes a good option but do not have osteogenic properties.[1,3,8,9,12,14,15]

The bone tissue bioengineering aims to add a progenitor cells into a bone replacement primarily osseoinductive and osseoconductive and turn it into a material similar to autologous, with the advantage of being less invasive and with less morbility.[2,5,8,9,11,14,15,17]

The stem cells are derived from the embryo and are considered pluripotent, with high power to differentiate into all the cells of the human body and tissues of the three germ layers, the ectoderm, the mesoderm and the endoderm. When adults, cells are considered multipotent cells and able to differentiate in the tissues of your germ layer, the mesodermal layer, responsible for the formation of tissues of conjunctive origin, among them the bone tissue.[13,15]

Mesenchymal cells can be obtained from periosteum,[9,15] adipose tissue, dental pulp[10,12,13,16,17] and from bone marrow[4,5,14] and the latter can be easily collected, through puncture aspiration and used in fresh form, in concentrated form, in the mononuclear fraction and in cell culture.[2,3,6,7,8,11,15]

The fatty tissue can be collected by liposuction or lipectomy in subcutaneous tissue and in humans can still be collected by intraoral access in removing Bichat's fat ball of being used through cell culture.[15]

Stem cells derived from pulp can be obtained from deciduous teeth, human dental pulp or third molars, where in third molars opens a new possibility, because it is very present in older people, and exhibit pluripotency similar to embryonic cells, besides the possibility of research into embryonic cells without ethical or legal problems interfering during the process. Mesenchymal cells, with the age, decrease in quality and in quantity, However in pulp cells there is no such relationship, remaining preserved in quantity and quality, regardless of age's patient.[10,13,15,16,17]

A bone regeneration is required the presence of osteogenic cells, growth factors and substrate that can be, ceramic blocks based on calcium phosphate, inorganic bovine bone, platelet rich plasma and synthetic polymers.[1,5,10,14] The growth factors are the platelet rich plasma and the human recombinant growth factor derived from platelets associated with the mesenchymal cells from different origins.[2,3,4,11,15,16]

In studies of this type of therapy associated with dental implants occurred a good bone-implant interface, without implant failures,[3,7,8,11,12] and the use of stem cells optimizes the regenerative results, being that the amount of bone formed can be dependent on the amount of mesenchymal stem cells used,[11] and the use of membranes proved to be even more important to prevent invasion of cells in the place being regenerated, hindering the formation of expected bone tissue.[15]

The advent of three-dimensional bioimpressoras helped develop prototypes of bone substitutes for use in the receptor site increased with stem cells and are currently the focus of several studies, being the bone tissue one of the most difficult to be regenerated, because it requires layers that allow the exchange of nutrients and a correct vascularization where to improve the interconnectivity of the pores is the greatest challenge, However, when the bone substitute is used without stem cells often occurs no bone tissue formation.[17]

CONCLUSION

The use of mesenchymal stem cells in bone regeneration has been increasingly developed and well known in the bone regenerative therapies. Aiming to repair bone tissue, the association of mesenchymal stem cells with various biomaterials have shown promising clinical results in the newly bone tissue formed, in addition to excellent structural and biological quality. However, to be considered a viable therapy and routine clinical application in Implantology, it must be made more researches for which protocols and technologies are simplified.

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