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Review Article

Biomedical Applications of Calcium Phosphate Ceramics as Biomaterials

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ABSTRACT

The application of ceramics as bone substitutes is mainly due to their bioactivity property, presenting an ability to adhere to adjacent bone tissues. In the last decades the number of researches with bioactive ceramics in bone grafts has grown. The objective of the present study was to perform a literature review of the application of calcium phosphate ceramics in the biomedical fields. For this present study, 21 articles indexed indatabases, mainly through in PubMed and LILACS were selected and published between the years 2004 to 2019. Calcium phosphates are examples of bioceramics and are part of a group of combinations that constitute the natural structure of bones humans and teeth. The main reasons for calcium phosphate biomaterials standing out for bone replacement are their facility of use and biocompatibility. Current research indicates that the association of hydroxyapatite (HA) with tricalcium phosphate β (TCP-β) promotes better results regarding bone neoformation, showing promising results in the biomedical and biomaterials area, in the replacement of bone tissues. Synthetic bioactive ceramics have several applications and efficacy in the biomedical fields. HA and TCP-β have several properties scientifically demonstrated, the association of both being the result of the search for new materials and their improvement.

Key words: Biomaterials, Grafts, Calcium phosphate, Hydroxyapatite, Ceramics.

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INTRODUCTION

The search for replacing damaged bone tissues began in the old age, having its first report in the 17th century, when a way of implanting a gold plate to restore a cranial defect was being investigated. Since then, several materials have been used as bone tissue substitutes, where many currently demonstrate safe and satisfactory results.[1]

The graft technique considered "gold standard" is using autogenous bone, that is, it is when the individual's own bone tissue is used as a substitute, which promotes greater biocompatibility. Another type of graft is heterogenous, they use the bone tissue of a donor of the same species for bone reconstruction. Among the main properties of these grafts, osteogenesis, osteoinduction and osteoconduction can be mentioned.[2]

In the search for options where is not necessary a second surgical site, synthetic biomaterials have emerged. These do not have live cells, due to the purification process, but have osteoconductive or osteoinductive properties, in addition to promoting revascularizing activity.[3]

Biomaterials assist in tissue regeneration, having efficacy, a high rate of clinical success, being able to regenerate lost tissue, returning form and function. Among synthetic biomaterials, bioceramics stand out. Example of these materials are powder formulations, coatings or prostheses and are widely used for repair or replacement of biological tissues.[1,4]

The application of ceramics as bone substitutes is mainly due to their bioactivity property, presenting an ability to adhere to adjacent bone tissues. In the last decades the number of researches with bioactive ceramics in bone grafts has grown. The bioactive ceramic promotes the biomineralization of calcium phosphate, through an interaction with the blood plasma of the individual.[4]

The first bioceramic that stood out was dense alumina, being the same bioinert, biocompatible and with high mechanical resistance, thus being indicated for orthopedic purposes. Other important ceramics are zirconia, titanium dioxide, calcium phosphates and vitro-ceramics formed by silicate-based compositions. Currently, calcium phosphate-based bioceramics stand out due to the great chemical and crystallographic similarity with the human skeleton, being the most studied and used.[5,6]

Due to the importance of synthetic bone substitutes, the aim of the present study was to conduct a literature review about the use of calcium phosphate ceramics in the biomedical field.

MATERIALS AND METHODS

To this study, a literature review of articles published between 2004 and 2019 was carried out, mainly through the PUBMED and LILACS databases. Thus, articles from systematic reviews, clinical trials, *in vitro* and *in vivo* studies were selected in portuguese and english languages. We selected 21 articles related to the theme in question.

CALCIUM PHOSPHATE BIOCERAMICS

Bioceramics stand out for their biological and osteoinductive properties, in addition to their ability to self-adhere and excellent chemical and mechanical properties, such as excellent osteoconductivity, great resistance and biocompatibility. Calcium phosphates are examples of bioceramics and are part of a group of combinations that constitute the natural structure of human bones and teeth. Since 1980, research has shown the advantages of calcium phosphate bioceramics in the biomedical fields.[5,7]

The main reasons for calcium phosphate biomaterials standing out for bone replacement are the facility of handling and molding, without the need to have a shape prior to the implant, fully adapting to the shape of the bone cavity, ability to osseointegrate and for not heat up during the hardening process, avoiding tissue necrosis at the implantation site.[2]

Currently, in orthopedic bioengineering, research is directed towards biodegradable biomaterials, thus avoiding the need for procedures that require a second surgical site, with less invasive regeneration. The improvement and association of different biomaterials has been the object of study in the search for greater biological activity, greater cell viability, cell proliferation and printing capacity. Thus, in recent decades, many biomaterials have been improved or introduced in the biomedical area, seeking skeletal reconstruction and repair.[6]

For a long time, HA was the only ceramic used for bone grafting, however due to some limitations such as slow biodegradation, interest in other materials has increased, such as tricalcium phosphates (TCP). This presents a greater adsorption by the biological environment, when compared to HA, making this material a strong alternative for bone replacement.[8-10]

Current research indicates that the association of HA with TCP- Β promotes better results regarding bone neoformation. This association has shown promising results in the biomedical and biomaterials area, in the replacement of bone tissues. The use of the two biomaterials provides a better surface characteristic of grains and micropores, which causes better dissolution control. The adsorption of calcium and phosphorus ions in bone neoformation.[11]

HYDROXYAPATITE

HA is an important inorganic compound in bone tissue, being a dense or porous polycrystalline complex, whose composition varies with age, diet and pathologies associated with the individual. It is mainly composed of minerals such calcium, phosphorus and calcium hydroxide.[12]

This material has osteoconductive properties and allows a connection to the connective tissue that surrounds it, thus facilitating osseointegration. Another reason for the widespread use of this material in the biomedical field is the similarity with the mechanical, chemical and physical aspect of bone tissue.[11]

Studies indicate that unlike other calcium phosphate ceramics, HA does not break, remaining thermodynamically stable and doing strong chemical bonds with the surrounding tissue, under physiological conditions. These properties have been reported and used in several areas, especially surgery, traumatology and for filling cavities after resection of bone tumors.[7,13]

Despite the excellent physical-mechanical properties, they are not sufficient for load resistance applications, as in orthopedic cases. Thus, in these cases it is used as a cover for materials such as titanium and titanium alloys, supporting the weight and contributing to greater and better osseointegration.[11]

TRICALCIUM PHOSPHATE

One of the variations of calcium phosphate materials is tricalcium phosphate (TCP), being one of the biomaterials with greater application in bone substitution, also having a chemical composition similar to bone tissue, bioactivity and biocompatibility. TCP is a resorbable biomaterial found in the form of powder or blocks that acts as a raw material for the growth and maintenance of a new tissue that will facilitate the osteoconduction process, thus allowing this ceramic to have great application as a functional substitute.[11,14]

Among the types of TCP, the ones with the most studied properties in biomedical fields are TCP-α and TCP-β. The chemical and crystallographic similarity of TCP with the bone matrix of hard tissues arouses research and, consequently, its improvement.[10]

Studies that compared the bone neoformation of TCP-β with other biomaterials, such as the BMP-2 morphogenetic proteins and the autogenous bone, identified similar results.[15] When compared histologically to xenogenous graft and blood derivatives in guinea pigs, TCP-β presents less bone gap formation and greater healthy bone neoformation.[16]

DISCUSSION

In order to reduce the limitations and disadvantages of some biomaterials and improve their biological activity and bone neoformation, scientists are constantly looking for an association between them. The result of this was the development of a two-phase ceramic formed by the HA / TCP-β composition, in order to improve the control of ion dissolution in the biological processes of bone neoformation.[10]

When assessing the effect of the association between HA / TCP-β as a bone substitute in guinea pigs with induced osteopenia, it was found that the animals treated with this association showed better results in repairing bone defects, in addition to a more organized neoformation than the group control.[17]

Another study compared the histological aspects to the biocompatibility of HA, TCP-β and the association of the two (HA / TCP-β) in the form of particles implanted in subcutaneous tissue of guinea pigs. It was observed that the group treated with TCP-β particles showed a large amount of fibroblasts and blood vessels, in addition to an exacerbated inflammatory response, with presence of macrophages and multinucleated giant cells in the first 60 days. The HA group demonstrated greater biocompatibility and after 10 days, the spaces between the particles were filled with connective tissue, with small number of inflammatory cells and several fibroblasts and collagen fibers. In the group treated with the HA / TCP-β association after 14 days, the TCP-β was practically not present, promoting greater space between the particles, thus realizing that the association of the HA / TCP-β reduced the undesirable responses of each ceramic individually, decreasing the inflammatory process of TCP-β and favoring a greater space between particles for tissue neoformation, due to the rapid reabsorption of TCP.[18]

When comparing the effect of the HA / TCP-β association with other materials such as calcium phosphate and calcium pyrophosphate as bone substitutes for guinea pig femurs, the group of the two biomaterials showed greater bone neoformation in evaluations made 30 and 60 days after surgery.[19,20] Compared the intrinsic osteoinduction of HA with HA / TCP-β in the left fibula of guinea pigs, keeping the right as a control group. Bone neoformation was studied by histology, histomorphometry and immunostaining, where the group with the fracture was the one with the most bone neoformation and the fastest.

One study developed a composition with 23% HA / 77% TCP-β to be used as a low-cost alternative to orbital implants. The *in vitro* evaluation in guinea pig orbits demonstrated excellent stability and biocompatibility, in addition to a good result in the orbital implant, allowing vascularization and osteoconduction.[7]

Through specialized 3D technology, a study created structures of 15% HA / 85% TCP-β to promote bone repair. Through analysis by computed microtomography (microCT) significant neoformation and bone remodeling was observed, being identified as soon as this combination is effective in promoting bone regeneration in bone defects.21 Thus, associating two biomaterials can be an important strategy to enhance or decrease the effect of each one and studies are needed to improve the evidence about the association of HA / TCP-β reported in few studies.

CONCLUSION

It is noticeable the wide applicability of synthetic bioactive ceramics in the biomedical area. There is an increasing number of researches that seek through technology and innovation to improve these materials, improving their biological properties and decreasing their limitations. HA and TCP-β have several properties demonstrated by numerous studies *in vivo* and *in vitro*. The association of both materials is the result of this search for new materials and better properties.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ABBREVIATIONS

HA: Hydroxyapatite; **microCT:** Microtomography; **TCP-β:** Tricalcium phosphate.

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