APPLICATIONS OF HYDROXYAPATITE IN BONE REPAIR: ADVANCES, CHALLENGES AND PERSPECTIVES: AN INTEGRATIVE REVIEW

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ABSTRACT

Hydroxyapatite represents a natural bioceramic that acts in the repair of hard bone tissue in mammals. This work aims to review the literature on applications of hydroxyapatite in bone repair. An integrative review was carried out in the Scopus, Medline and SciELO databases, by crossing the terms Bone Regeneration AND Hydroxyapatite AND biopolymer. Initially, 201 documents were identified, including freely accessible articles available for full reading in english and Portuguese, works published between 2017 and 2023, and excluding duplicate studies and those with low reliability methodologies and works that did not fit the theme. proposed, 5 articles were selected to compose the sample. As a result, three main categories of alternative materials found application in the clinical context were highlighted, notably in procedures related to bone tissue. These categories include allografts (transplants between individuals of the same species), xenografts (transplants between different species) and alloplastic materials (synthetically produced, which demonstrate remarkable biocompatibility, efficacy in promoting osteoconduction, bone repair and microbiological control. In addition, the evaluation of This comparison highlights the importance of careful selection of biomaterials, considering not only their origin but also their specific properties. In conclusion, although these studies provide an optimistic outlook for the future of bone regeneration, it is imperative to conduct further clinical research to validate these findings, ensuring its broad applicability and long-term safety in patients.

Keywords: Bone Regeneration. Hydroxyapatite. Biopolymers.

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INTRODUCTION

Hydroxyapatite (HAp) represents a natural bioceramic present in the bone tissue of a variety of living things, including mammals, oviparous, and some marine animals [1]. Known as calcium hydroxyphosphate, this basic calcium phosphate has a minimum chemical formula of$Ca_5(PO_4)_3OH$ [2]. Although its crystalline unit cell is composed of two units with a molecular formula (Z = 2), the proper structural expression is $Ca_{10}(PO_4)_6(OH)_2$ [3], incorporating distinct coordination groups for calcium (Ca) atoms and tetrahedral clusters for phosphorus (P) atoms. Among the existing calcium phosphates, hydroxyapatite stands out as the most significant in this category, due to its biological importance. Its peculiarity lies in the need to follow a specific stoichiometry during the process of obtaining, where the molar ratio between Ca/P must be approximately 1.667 to reach the pure phase of these crystals [4].

HAp crystals can also be found in nature in the form of minerals, which can be called hydroxylapatite, which is similar to that found in the mineral bone [5]. However, it is also possible to find this mineral in different forms due to the substitution of the hydroxyl groups (OH^-) at the specific site designated as X in the general formula $Ca_{10}(PO_4)_6(X)_2$ by impurities or by modification with fluoride (F^-) ions, such as fluorapatite $Ca_{10}(PO_4)_6(F)_2$ in green, blue, pink, yellow, brown, violet and purple or carboxyapatite $Ca_{10}(PO_4)_6(CO_3)_2$ [6].

Synthetic (inorganic) and natural (bioceramic) HAp crystals have been synthesized, extracted and processed by different methods of synthesis and preparation, which can be subdivided into four types: wet [7], sol-gel [8], hydrothermal [9], solvothermic [10], microwave-assisted hydrothermal [11], microwave-assisted solvothermic [12], dry medium such as solid-state reaction, mechanochemical, high-temperature processing of the starting precursors and extraction from the bones of marine mammals such as (fish, shells, mussels, and snails) [13].

Regarding the electronic properties of hydroxyapatite, many investigations in the most diverse areas of knowledge have been reported in the literature [14], from applications such as luminescent materials [15], photocatalysis [16], bactericidal/fungicide [17], gas sensor [18], mechanical strength [19], and especially in repair of hard bone tissue of mammals, since this material is a bioceramic with high biochemical compatibility in the different types of living organisms of mammals. mammals, birds and some vertebrate marine animals as has been reported in several public surveys recently [20, 21, 22, 23, 24]. Thus, this study aims to review scientific articles on the use of hydroxyapatite in bone repair.

MATERIAL AND METHODS

The method adopted for this study was based on an integrative review, in which this type of review allows the knowledge and implementation of the applicability of significant studies in practice, where its objective is to present the component steps of an integrative review, and what are the aspects to be considered for the use of this resource [25].

The chosen articles underwent a preliminary analysis of the titles, abstracts, and keywords to assess their adherence to the central research question. Next, each selected study was submitted to a detailed critical evaluation, covering the methodologies employed and the results achieved. The relevant information from each study was condensed into a summary table that encompasses information such as title, authors, year, journal, type of study, methodological approaches used, and most relevant conclusions. To conduct the research, the following databases were consulted: Scientific Electronic Library Online (Scielo), MEDLINE and SCOPUS.

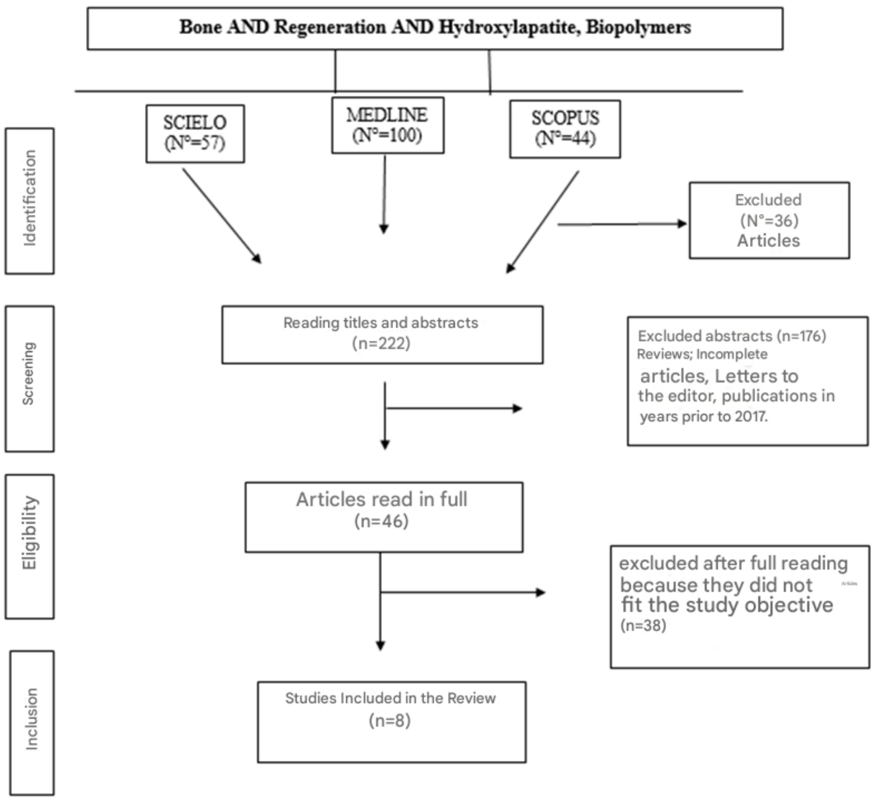
The search was carried out using specific keywords following the Health Descriptors (DeCS). The descriptors used were: Bone, Regeneration, Hydroxylapatite, Biopolymers and their counterparts in Portuguese: Bone, Regeneration, Hydroxyapatite and Biopolymer, combined by the Boolean operator AND and OR. The integrative review methodology was guided by specific inclusion and exclusion criteria, in addition to following rigorous steps for the identification, selection, and analysis of relevant studies. This ensured the coherence and reliability of the process, resulting in a reasoned review regarding the use of biopolymers in bone regeneration.

For the inclusion of articles, the following criteria were established: articles with free access and available for full reading in English and Portuguese, delimited to the focus of the research works published between 2017 and 2023 on the indicated platforms. The exclusion criteria were for duplicate studies with low reliability methodologies and studies that did not fit the proposed theme, as well as studies outside the determined period and incomplete.

RESULTS AND DISCUSSION

Through the combinations of descriptors, 201 articles were identified and 36 articles were excluded because they were repeated in more than one database. After this stage, based on the inclusion and exclusion criteria, 176 were eliminated because they did not correspond to the proposed theme. Thus, 46 articles were selected for reading. Then, the readings were carried out and 5 articles were chosen to compose the review base. The process of searching and selecting articles is represented by flowchart 1.

Flowchart 01: Flowchart of the selection of studies.



Source: authors (2023).

Chart 1 shows the distribution of publications in terms of authors, year, sample, type of study, objective, and results. The publications are arranged in chronological order.

Table 01: Summary of the articles included in the review. Teresina, Piauí, Brazil, 2023.

AUTHOR/YEAR	TYPES OF STUDIES	OBJECTIVE	RESULTS
Beladi, Samandari, Samandari, 2017	Experimental study	Development and characterization of a new 3D nanocomposite made of cellulose (Cel) and polyacrylamide and nanocomposites hydroxyapatite-based for use in bone repair applications	The results of the cell culture experiments showed that the scaffolds extracts do not present cytotoxicity at any concentration. The results suggest that the introduced scaffolds are comparable to bone trabeculae from a compositional, structural and mechanical point of view and

			have great potential as a bone substitute.
Palma *et al.*, 2017	Prospective experimental study	Perform histomorphometric evaluation of the association of the antibiotic rifamycin with synthetic hydroxyapatite in repair Bone in tibia of rabbits	The association tested demonstrated superiority in local microbiological control, in the rate of formation and in the total final amount of bone matrix deposition.
Kattimani *et al.*, 2019	Randomized controlled clinical study	To evaluate and compare the efficacy of nano-hydroxyapatite for improving bone regeneration after surgical removal of bilateral impacted mandibular third molars	Eggshell-derived nanohydroxyapatite showed improvement in bone regeneration compared to the control group. Grafting maintained bone height and avoided the appearance of periodontal problems. Eggshell-derived nanohydroxyapatite is a safe substitute for synthetic grafting because it is derived from eggshell with no risk of disease transfer, unlike allografts

Moreno *et al.*, 2019	Randomized clinical trial	To analyze a modified biphasic phychogenic biomaterial compared to inorganic bovine bone in maxillary sinus floor elevation in humans	Both combinations of materials show bone formation after 6 months of healing in the maxillary sinus cavity. However, the combination with biphasic phycogenic biomaterial induces greater vertical radiographic resorption and graft collapse compared to the combination with inorganic bovine bone.
Hofmann *et al.*, 2020	Multicenter, prospective, randomized, controlled, open-label, clinical, non-inferiority clinical trial	Investigate differences in quality of life, pain, and outcomes Radiographic in the treatment of bone defects associated with tibial plateau fracture with autologous bone grafts or bioabsorbable hydroxyapatite and calcium sulfate cement	Age, gender, fixation methods, and fracture pattern were comparable in both groups. There was a significant reduction in blood loss ($p = 0.007$) and pain levels ($p = 0.008$) on the 1st postoperative day. in the hydroxyapatite group. The rates of fracture healing, defect remodeling, and joint subsidence were not significantly different ($p > 0.05$) in both groups.

Source: authors (2023).

Three main categories of alternative materials find application in the clinical field, notably in procedures related to bone tissues. These categories include allografts (transplants between individuals of the same species), xenografts (transplants between different species), and alloplastic materials (synthetically produced).

Alloplastic materials, predominantly composed of hydroxyapatite crystals or other calcium phosphate minerals, resemble those naturally present in bone tissue. These materials favor the osteoconduction process, providing a favorable framework in which osteoblasts can gradually deposit new osteoid tissue [4]. In addition, the structural similarity between synthetic and organic hydroxyapatite has been demonstrated, ensuring excellent biocompatibility [26,27].

The chemical bonds formed when these materials are grafted onto bone defects have also been confirmed. These options offer versatility in orthopedic surgical and bone reconstruction procedures, meeting diverse clinical needs with favorable properties for bone regeneration [28].

Among the studies reviewed, it is interesting to note that all of them aim to evaluate the advances in the use of hydroxyapatite and its possible combinations in bone repair in both animal and human species. Using or not associating hydroxyapatite with other substances.

In this review, it was observed in two of the articles, *scaffolds* of Cellulose and Polyacrylamide 3D Nanocomposite vs. association of Rifamycin to Synthetic Hydroxyapatite: Both studies show promising results in terms of biocompatibility and efficacy in bone repair. While the first study focuses on the composition of the nanocomposite and development of a 3D nanocomposite support model made of cellulose (Cel) and polyacrylamide and hydroxyapatite nanocomposite. The results of the cell culture experiment showed that the scaffolds did not show cytotoxicity at any concentration.

Cel is a promising material for biomedical applications, including drug delivery and tissue engineering, due to its biocompatibility, non-toxicity, reactive surfaces for protein binding, biodegradability, easily modified properties, and mechanical strength and resistance to degradation *in vivo* [29].

Polyacrylamide is a synthetic polymer used in biomedical engineering and tissue engineering [30, [31], [32], [33] because of its non-toxic and biological inertness, ability to preserve its shape and mechanical strength, and convenient adjustment of mechanical, chemical, and biophysical properties [34], [35], [36]. Hydroxyapatite , on the other hand, is not biodegradable and can be removed and remodeled in the host. If implanted directly, it can move within the tissue [37].

The results obtained suggest that the introduced scaffolds are comparable to bone trabeculae from the compositional, structural and mechanical point of view and have a great potential as a bone substitute. It can be concluded that cytocompatible and non-toxic scaffolds are potentially useful in biomedical applications.

The second addresses the association of rifamycin for local microbiological control associated with hydroxypatite, it is known that antimicrobial agents applied together with the grafts could minimize the risks of initial infection, reducing adverse effects and toxicity of high doses of systemic antibiotics that would be necessary. The association tested in the study demonstrated superiority in local microbiological control, formation speed, and total final amount of bone matrix deposition. Together, these results suggest that the combination of mechanical properties and infection control may be crucial to the success of bone repair materials [38].

In the articles, Nano-Hydroxyapatite for Bone Regeneration vs. Biphasic Phychogenic Biomaterial was used in the Elevation of the Maxillary Sinus Floor. Both studies explore the use of materials of natural origin (eggshell-derived nanohydroxyapatite and biphasic phycogenic biomaterial).

However, while nano-hydroxyapatite shows improvements in bone regeneration, it does not demonstrate the distinct advantage of the use of nano-hydroxyapatite due to abundant availability, the absence of antigenic response and biocompatibility, low risk of contamination, and high rates of positive results with ease of use [39].

The biphasic phycogenic biomaterial has good resorbable properties over time, with a large surface area for protein binding, absorption and adsorption of amino acids [40]. This comparison highlights the importance of careful selection of biomaterials, considering not only their origin but also their specific properties.

One of the articles addresses the use of bioabsorbable hydroxyapatite and Calcium Sulfate Cement vs. Autologous Bone Grafts, the comparison between these two methods of bone repair indicates advantages in the use of bioresorbable hydroxyapatite and calcium sulfate cement. The significant reduction in blood loss and pain levels in the early postoperative period highlights immediate benefits, while the comparable efficacy in fracture healing and defect remodeling suggests that hydroxyapatite may be an effective and less invasive alternative compared to autologous grafts.

These studies contribute to the advancement of the field of bone regeneration by introducing new materials and associations that show promising efficacy and safety. The prospects of these approaches to bone repair are optimistic, with the potential to transform how we deal with orthopedic conditions and surgical procedures related to bone tissue. However, it is important to highlight the need for further clinical research to validate these findings in broader and more diverse settings, ensuring their widespread applicability and long-term safety in patients.

CONCLUSION

Advances in research into materials for bone regeneration represent a promising milestone in orthopedic medicine. The categories of allografts, xenografts and alloplastic materials, especially synthetic hydroxyapatite, demonstrate remarkable biocompatibility and efficacy in promoting osteoconduction.

The application of bioabsorbable hydroxyapatite and calcium sulfate cement shows significant advantages over autologous grafts, suggesting a less invasive and effective approach. While these studies feed into an optimistic outlook for the future of bone regeneration, it is imperative to conduct more diverse clinical research to validate these findings, ensuring their broad applicability and long-term safety in patients.

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