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EFFECTIVENESS OF HYDROXYAPATITE ON BONE RENOVATION

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ABSTRACT
Tissue damage caused by trauma, fracture or disease requires restoration to restore its function to its original state. According to data from the Hospital Information System (SIRS) 2010, cases of bone fractures in Indonesia have increased every year. Bone healing requires cells to form new bone. Hydroxyapatite (HA) is a ceramic biomaterial that is widely used because it has chemical and structural characteristics similar to the inorganic components of bones and teeth, its osteoconductivity/inductivity is very good, biocompatible and does not cause an inflammatory response. The main source of HA is synthetic materials that are chemically and biologically natural (eggshells and cuttlefish, coral, natural calcite and cow bones). In previous studies, eggshells have a higher ability in bone formation. To explain the effectiveness of hydroxyapatite in bone remodeling. Analyzing journals sourced from the PubMed, Ebsco, Google Scholar data bases taken from 2012 to 2024. There are 15 references that have been found and cover the topic of the effectiveness of hydroxyapatite on bone remodeling. Conclusion: Hydroxyapatite is effective in bone remodeling because it has a main mineral composition that resembles the mineral composition of bones, has biocompatible properties and does not cause an inflammatory response.

INTRODUCTION

Bone is a highly adaptive biomaterial, structurally dynamic, metabolically active, and superior in strength and hardness to all other biomaterials.(Hart et al., 2020) Bone also provides shape to the body. Osteoblasts, osteoclasts, osteocytes; minerals, matrix, and water are bone cells that are elements to form bones. In dentistry, bone damage can be caused by disease or trauma, including periodontal disease, post-extraction mechanical trauma, pre-prosthetic surgical trauma, trauma during dental implant application, and other pathological conditions. (Ramadhani et al., 2016)

Bone damage (bone defect) will cause damage to cells, bone matrix, and also blood vessels. There are 3 stages in the bone healing process, namely the inflammatory phase, the reparative phase, and the bone remodeling phase.(Ramadhani et al., 2016) Remodeling is a continuous homeostatic and restorative process that replaces old and damaged bones with new and healthy materials to maintain and improve structural integrity and mechanical competence. (Hart et al., 2020)

The ideal bone substitute material must at least meet the requirements, including supporting the growth of blood capillaries, perivascular tissue, and osteoprogenitor cells; interconnected pores at a size sufficient to assist bone growth; supporting osteoblast differentiation; and has calcium ion complex from body fluids. (Vidyahayati IL, Dewi AH, 2016)

According to Vidyahayati et al (2016), it is stated that one of the bone substitute materials that meets the requirements is hydroxyapatite (HA). (Vidyahayati IL, Dewi AH, 2016) HA is a bioactive ceramic material that is widely used in the medical world, one of which is used as a bone graft material (bone substitute). HA has very good biocompatibility properties because chemically and physically, the HA mineral content is the same as human bones and teeth. There are two main sources of hydroxyapatite, namely chemically synthetic materials and natural biological sources, such as eggshells, natural gypsum, cuttlefish shells, natural calcite, and also cow bones. (Hengky, 2012)

METHOD

This paper was meticulously prepared using a wide range of relevant and similar references that were gathered from various academic sources. These sources include textbooks, peer-reviewed scientific journals, scholarly articles, and credible websites, all of which were accessed through well-established and reputable databases such as PubMed, EBSCO, and Google Scholar. The primary keywords utilized in the search process were "tissue damage," "effectiveness," "hydroxyapatite," "bone remodelling," and "biocompatibility," ensuring that the search focused on highly relevant content. The inclusion criteria for selecting the literature were quite specific: only publications from 2012 to 2024 were considered, and these had to be eitherin English or Indonesian. Additionally, the selected studies needed to be directly related to the central theme of the discussion, which is the effectiveness of hydroxyapatite in the bone remodelling process. This approach ensured that the literature used was both current and aligned with the topic, providing a strong foundation for the analysis and conclusions drawn in this writing.

RESULT AND DISCUSSION

The results obtained from the comprehensive literature search included a total of 17 references. Subsequently, a detailed analysis was conducted using specific inclusion and exclusion criteria to ensure the relevance and quality of the sources. As a result of this thorough evaluation, 7 references were deemed suitable and selected for further review, while 10 references did not meet the criteria and were therefore excluded from consideration. Additionally, another 10 references were removed from the list due to their publication dates; these references were either published more than 5 years ago in the case of journals or more than10 years ago in the case of textbooks. This rigorous selection process was essential to ensure that only the most current and relevant literature was included in the study, thereby enhancing the credibility and accuracy of the research findings.

Table 1. List of references and summary.

Reference	Aim	Method	Sample	Result
Ramadhani *et al* (2016)	To test the effectiveness of the combination of lemuru fish oil (Sardinella longiceps) and hydroxyapatite application on the expression of fibroblast growth factor 2 (FGF-2)	The experiment was conducted on 20 male rats divided into 2 groups (Control and treatment). The treatment group was given lemuru oil and the control group was not	20 male wistar rats	The combination of lemuru fish oil (Sardinella longiceps) and hydroxyapatite application is significantly effective against the expression of fibroblast growth factor-2

	in the bone healing process	given it. All samples that had been given 2 defects in the right femur, some were applied with hydroxyapatite and some were not applied with hydroxyapatite		FGF-2 in the bone healing process on day 7
Kamadjaja *et al.* (2020)	To prove the effectiveness of hydroxyapatite from crab shells in increasing the area of bone trabeculae, changing growth factor-beta 1 (TGF-β1), and alkaline phosphatase (ALP)	Crab shell-based hydroxyapatite gel was given after the extraction of the post-socket of the lower left central incisor of Wistar rats, observing the trabecular area, TGF-β1, and ALP on the 14th and 28th days. Hydroxyapatite is made from the process of calcining crab shells into powder, then carrageenan and distilled water are added to form a gel preparation.	36 samples of wistar rats and crab shell-based hydroxyapatite gel	There is a significant difference in TGF-β1 between the control group and the treatment group given hydroxyapatite gel on days 14 and 28. It can be concluded that the application of hydroxyapatite derived from crab shells (P. pelagicus) in the post-extraction socket of Wistar rats increases TGF-β1, ALP, and trabecular bone area.
Suci *et al.* (2020)	To synthesize hydroxyapatite from ale-ale shells, and to characterize it.	HAp synthesis by the Double Stirring precipitation method (Ultrasonic-Magnetic)	Ale-ale clam shell	It is known that this shell has a high calcium content of 98.81%
Firdaus *et al.* (2021)	To determine the effect of nanocrystalline hydroxyapatite implantation on the number of osteoblasts in the post-extraction bone healing process	By measuring the effect of treatment on the treatment group and the control group with a population of male Wistar white rats.	Male mice aged 8-16 weeks, weighing 200-300 g, and without anatomical abnormalities.	Implantation of nanocrystalline hydroxyapatite increases the formation of the number of osteoblasts in bone healing after tooth extraction
Vidyahayati *et al.* (2016)	To determine the effect of bone substitution with hydroxyapatite (HAp) on the histological image of bone in the	Each treatment was given hydroxyapatite implantation on the right tibia defect and the left tibia as a control site	15 male Sprague Dawley rats, 3 months old, with defects made in the right tibia and left tibia.	Bone substitution with hydroxyapatite (HAp) increases new bone formation activity in tibia bone defects in rats

	tibia of rats (Rattus Sprague Dawley).	without implantation. Subjects were decapitated after 1, 2, 3, 4, and 8 weeks. The defect area was taken and histological images were made, then observations and counting of the number of osteoblasts and osteoclasts were carried out using a phase contrast microscope.		(Rattus Sprague-Dawley)
Febriani et al (2024)	To determine the use of marine products as a source of basic materials for bone graft replacement which is believed to provide better results than chemical materials.	Collecting references from articles about marine biota as bone grafts in dentistry	Articles are from PubMed and Google Scholar published in the last 5 years. Inclusion criteria are articles with the topic of marine biota utilized as bone grafts in dentistry.	Marine biota as bone graft materials such as pearl and snail shells, fish scales and bones, and algae has been proven to contain micronutrients including minerals and vitamins that can accelerate bone healing.
Irene Rieuwpassa et al (2024)	To determine the use of Chlorella vulgaris in bone regeneration in dental implant treatment.	Collecting references from articles about Chlorella vulgaris in bone regeneration	Articles are from PubMed and Google Scholar published within the last 5 years.	C.vulgaris is a microalgae that plays an important role in bone mineralization. Therefore, this microalgae has the potential as a material that can help in the bone regeneration process including regeneration that occurs after dental implant procedures.

Bone remodeling is a lifelong process in which the destruction of old bone (resorption) and bone formation. This process is regulated by different types of cells that form bone (osteoblasts), regulate bone homeostasis (osteocytes), and bone resorption (osteoclasts), and influence bone resorption and formation (innate and adaptive immune cells). Several pathological processes can affect bone remodeling which are shown in postmenopausal osteoporosis, arthritis, periodontal disease, and microgravity. (Xiao et al., 2016)

Osteoclasts are terminally differentiated myeloid cells that are uniquely adapted to remove mineralized bone matrix. They are found in pits within the bone surface called resorption bays, also known as Howship's lacunae. Osteoclasts resorb bone by producing acids that dissolve the mineral content and enzymes that remove the organic matrix. Mature osteoclasts anchor to the bone via RGD-binding sites to create a sealed microenvironment. (Xiao et al., 2016)

Osteoblasts are bone-forming cells that arise from osteoprogenitor cells. RUNX2 (runt-related transcription factor 2) and other transcription factors control osteoblast differentiation. (Jiao et al., 2015) During bone formation, a subpopulation of osteoblasts undergoes terminal differentiation and is engulfed by osteoid, at which point they are referred to as osteoid osteocytes. Osteocytes in lacunae are the most abundant cell type in mature bone and are long-lived. They have dendritic processes that interact with other osteocytes and bone-lining cells on the bone surface. Osteocytes respond to mechanical loading. Under resting conditions, osteocytes express sclerostin, which directly inhibits Wnt signaling. Sclerostin expression can be inhibited by parathyroid hormone signaling to remove this inhibitor of Wnt signaling and allow Wnt-directed bone formation to occur. Under basal conditions, osteocytes secrete transforming growth factor β (TGF-β), which inhibits osteoclastogenesis. However, upon stimulation osteoblasts and osteocytes produce osteoclastogenic factors such as macrophage colony-stimulating factor-1 (CSF-1) and receptor activator of the NF-κB ligand (RANKL) to induce bone remodeling. (Xiao et al., 2016)

The bone remodeling phase is the longest phase of bone healing which is characterized by slow changes in bone shape to a normal or nearly normal function and strength. In this phase, bone apposition and formation occur by osteoblasts and resorption of damaged bone by osteoclasts. (Ramadhani et al., 2016)

Hydroxyapatite (HA) is the main mineral component of bone minerals and hard tissue in mammals which has osteoconductive and biocompatible properties that integrate with host bones and act as bone substitutes by forming a framework (scaffold). FGF-2 is a control signal in bone formation that functions to regulate the replication of osteoprogenitor cells, differentiation of fibroblasts in the periosteum into osteoblasts, and apoptosis as a filler of the scaffold. Progenitor cells will attach to the scaffold and differentiate into osteoblasts and provide a place for bone matrix deposition and blood vessel pathways as a nutrient supply. Fibroblast growth factor (FGF) has been shown to stimulate bone growth, and collagen synthesis in bone healing both in vitro and in vivo. (Ramadhani et al., 2016)

HA with the chemical formula $Ca_{10}(PO4)_6(OH)_2$ is included in the category of bioactive materials that are rich in calcium (Ca) and phosphate (PO_4) so it can respond to specific biology between tissue and material. HA has high biocompatibility properties so it is expected to have the ability to be bioactive as well. (Vidyahayati IL, Dewi AH, 2016) This biocompatibility property is the ability of HA to adapt to the body and there is no rejection by body tissue. The bioactive properties of HA are able to bind to bone tissue and provide a specific biological response, which is stimulating osteoblast cells to form new bone tissue so it can facilitate the bone regeneration process. (Supangat & Cahyaningrum, 2017) In addition, HA also has interconnected pore properties at a size that is sufficient for bone growth. (Vidyahayati IL, Dewi AH, 2016) Interconnected porous HA forms a very strong bond between bones and can accelerate the vascularization process. Pore size and shape are important factors in the osteointegration process. HA interconnected between pores with rough surfaces will facilitate osteoblast cell penetration and become a good medium for osteoblast cell attachment. (Hengky, 2012)

Other advantages of HA are good osteoconductive and osteoinductive properties, which can support the growth of perivascular tissue, the growth of blood vessel capillaries bioresorption, and biodegradation properties. (Vidyahayati IL, Dewi AH, 2016)

HA also has disadvantages. It has poor mechanical properties, such as low tensile strength and compressive strength, therefore, special reinforcing materials are usually added, such as collagen, chitosan, polyacrylamide and graphene oxide so hydroxyapatite achieves better performance.(Ielo et al., 2022) Collagen will provide flexibility, while chitosan will provide pores so the resulting bone graft can be passed through body tissue and the bone rehabilitation process can occur. (Khoiriyah & Cahyaningrum, 2018)

Some materials contain hydroxyapatite, one of which is eggshell, which is the synthesis of hydroxyapatite from eggshell. There are several methods to produce hydroxyapatite from eggshells. Previous research hydroxyapatite in eggshells can be obtained including by hydrothermal methods, microwave irradiation, and mechanical chemical activation. (Suprianto et al., 2019)

Hydrothermal method

The hydrothermal method is the most widely reported method for HA production from eggshells. This method has been proven to be the easiest method to use for HA. The method of synthesizing HA from eggshells in phosphate solution at high temperature is a new way to produce useful biomedical materials. In this method, fine hydroxyapatite single crystals were synthesized by hydrothermal method with $Ca(OH)_2$ and $CaHPO_4(2H_2O)$ as the starting materials. H. Khandelwal, S. Prakash (2016) conducted the synthesis of hydroxyapatite powder from eggshells by this hydrothermal method. In the study, good eggshells (not crushed) were taken in bulk and cleaned by hand with deionized water, then boiled in water for about half an hour in an oven, after which they were stored in a porcelain vessel and calcined in a tube furnace at 900˚C for one hour. At 850˚C, the eggshells become carbon dioxide and then convert to calcium oxide. The expected reaction is as follows: CaCO2 à CaO + CO2↑. After obtaining a measured amount of the strength of the calcined shell, it is taken in a glass and dispersed in distilled water. The stoichiometric amount is decided according to the quantity of calcium present in the calcined eggshell. In this reaction, CaO changes to $Ca(OH)_2$. (Khandelwal & Prakash, 2016)

Mechanochemical Activation Method

This method has been reported to involve the use of two mechanochemical activation processes, namely attrition milling and ball milling. The mechanochemical reaction supplies sufficient hydroxyl groups to the initial powder to form one HA phase. Hamidi et al. (2017) conducted a comparative study in the synthesis of hydroxyapatite from eggshells by mechanochemical activation and succeeded in obtaining HA powder with crystals and particle sizes in the range of 8–47 nm and 250–550 nm. It was observed from this study that increasing the rotational speed of the mill increased the purity of the HA sample phase. The higher heating temperatures of HA samples resulted in higher degree of HA crystallinity and the emergence of β-tricalcium phosphate(β-TCP) as a secondary phase. (Khandelwal & Prakash, 2016)

DISCUSSION

In 2016, Ramadhani et al. conducted a study discussing the application of hydroxyapatite obtained from eggshells for the bone healing process. The object of the study used male Wistar rats and the results showed that rats given hydroxyapatite were faster in the bone healing process than rats not given hydroxyapatite. It can be concluded from the different FGF-2 excretion between male Wistar rats given hydroxyapatite and male Wistar rats not given hydroxyapatite. (Ramadhani et al., 2016) FGF is responsible for signal stimulation in the early cell development process (such as pattern determination, proliferation, differentiation, and migration) to form a network. (Dewi et al., 2016)

Several studies stated that there are differences between groups of objects given hydroxyapatite and groups of objects not given hydroxyapatite, such as research by Kamadjaja et al. in 2020 which stated that the application of hydroxyapatite derived from crab shells (P. pelagicus) to the post-extraction socket of Wistar rats increases TGF-β1, ALP, and trabecular bone area. The results showed a significant difference in TGF-β1 between the control group and the treatment group given hydroxyapatite gel, both on the 14th and 28th days. This is due to the effect of hydroxyapatite gel on the treatment group. The porous hydroxyapatite mineral structure, which is interconnected and osteoconductive, will bind cytokines when bone damage occurs, and these cytokines will stimulate mesenchymal stem cells found in the pores of the hydroxyapatite mineral to differentiate into osteoblasts, chondroblasts, and fibroblasts. Osteoblasts and chondrocytes will produce TGF-β1 during the healing process. (Kamadjaja et al, 2020)

There is also a study conducted by Ida Ayu Suci et al in 2020, using ale-ale clam shells which are a potential natural resource in Ketapang Regency, West Kalimantan Province, but most of the ale-ale clam meat in this area is used as culinary and the shell waste has not been utilized optimally. The use of clam shells until now has only been limited to handicraft materials, even though clam shells have a high calcium carbonate composition. It is known that these clam shells have a high calcium content of 98.81%, then the EDX results showed that the calcium content in the clam shells is much greater than the elements oxygen and carbon. (Suci & Ngapa, 2020)

The study of Firdaus et al in 2021 using synthetic hydroxyapatite, one example of which is nanocrystalline hydroxyapatite (HAN) because it has the same shape as natural HA in bones. HAN material has closer contact with the surrounding tissue, its nature is reabsorbed faster than conventional HA so it can be replaced by new bones and has a high number of molecules on its surface. The use of synthetic HA in the formation of alveolar bone aims to induce and stimulate stem cells and osteoblasts to proliferate and differentiate to form new bone or the bone regeneration process. (Firdaus et al., 2021)

However, there is a study that obtained different results from the above study conducted by Vidyahayati et al. In 2016 regarding the effect of bone substitution with hydroxyapatite on the bone remodeling process, the results of the study showed that there was no significant effect of hydroxyapatite substitution treatment on the treatment object and control object. Bone has the most inorganic material in the form of Ca and PO_4 in bone hydroxyapatite which has a hexagonal group. However, bone apatite minerals are not pure crystalline substances. Chemical hydroxyapatite is included in the category of bioactive materials that are rich in calcium and phosphate which are expected to be developed as bone substitute materials. The synthetic form of hydroxyapatite showed chemical similarities and crystal images that are similar to bone hydroxyapatite but are not identical to natural hydroxyapatite in bone. This is likely a factor that influences the process of new bone formation after hydroxyapatite implantation and does not have a significant effect on osteoblast activity. (Vidyahayati IL, Dewi AH, 2016)

P.cochlidium is a hard-shelled gastropod that lives in the mangrove ecosystem in Indonesia. *P.cochlidium* is also found in substrates near the coast, muddy areas, or near estuaries. Tiger snails (*Babylonia spirata, L*) have high economic value and considerable potential for cultivation. This snail is one of the marine animals that has long been known to the public as a source of animal protein, rich in calcium and essential amino acids (arginine, leucine, lysine), but until now the shells or snails have not been widely traded. (Febriani et al., 2024)

The standard methods used to synthesize HA (as bone graft material) are precipitation, hydrothermal, mechanochemical, and sol-gel. The sol-gel method can produce HA powder with relatively homogeneous grain size, high crystallinity, low process temperature, and the ability to produce nano-sized particles. In a study by Nasution et al. gave the result that HA used came from *P.cochlidium* and *B.spirata* shells synthesized by sol-gel method. Using calcium nitrate tetrahydrate as calcium source, HA was obtained with an average size of 50-200nm. This study obtained HA size of 5.589-7.393μm from *P.cochlidium* snail shells and 2.614-5.410 μm from tiger snail shells. It was concluded that the use of marine products as a source of basic materials for bone graft replacement is believed to provide better results. Materials derived from marine biota have been shown to accelerate bone healing, increase mineralization, and bone remodeling. (Febriani et al., 2024)

Another study conducted by Irene Rieuwpassa et al (2024) on the use of *Chlorella vulgaris* in bone regeneration. *Chlorella vulgaris* is a greenalgae that is widely distributed in freshwater, marine and terrestrial environments, and has high photosynthetic capabilities. Previous studies have also shown that the content in *C.vulgaris* can play an important role in the mineralization of bones, teeth, and regulation of calcium and phosphorus levels in the blood so that it can be used as a material to help the bone regeneration process after implants.(Rieuwpassa, 2024)

In the process of bone regeneration, nutrients are needed in the form of protein, carbohydrates, fats and micronutrients such as sodium, phosphorus, zinc, magnesium, vitamin A, vitamin K and vitamin B12. The human body cannot synthesize micronutrients in sufficient quantities so they must be obtained from external sources. *C.vulgaris* is one of the green microalgae that has the main content of protein, lipids, carbohydrates, pigments, vitamins and minerals. The bioactive components of microalgae have antimicrobial, antioxidant, antivirus, antifungal and anti-inflammatory activities. (Rieuwpassa, 2024)

C.vulgaris also contains bioactive components that can produce collagen that will support cell regeneration, for example in bone remodeling. Mineral content, such as calcium and iron and vitamin D in C.vulgaris can play an important role in the mineralization of bones, teeth, and regulation of blood calcium and phosphorus levels. (Rieuwpassa, 2024)

Therefore, this microalgae can be used as a material that can help the healing process and bone regeneration such as after implant installation in edentulous cases. Thus, according to Irene Rieuwpassa et al (2024) it can be concluded that this microalgae has the potential as a material that can help in the bone regeneration process including regeneration that occurs after dental implant procedures. (Rieuwpassa, 2024)

The components used are hydroxyapatite which has been used in bone tissue engineering for many years as a good bone replacement and replacement regeneration material so it has great potential for bone regeneration, gelatin which has a strong bonding affinity with hydroxyapatite so it can resemble real bone and can provide porous structure to increase cell attachment and growth, as well as rosella flower extract which has the potential to treat bone damage. (Auliadini, 2024)

CONCLUSION

One of the bone substitute materials that meets the requirements is hydroxyapatite (HA). (Vidyahayati IL, Dewi AH, 2016) HA is a bioactive ceramic material which is used as a bone graft material (bone substitute). HA has very good biocompatibility properties, bioresorption, and biodegradation properties, has good osteoconductive and osteoinductive properties, and can support the growth of perivascular tissue and blood vessel capillaries. (Hengky, 2012) HA also has disadvantages, including having poor mechanical properties, such as low tensile strength and compressive strength. (Ielo et al., 2022)

Some materials that contain hydroxyapatite are eggshells. Some study stated that the application of hydroxyapatite from crab shells can replace the position of damaged bones. However, synthetic hydroxyapatite materials, one example of which is nanocrystalline hydroxyapatite (HAN), also have the same shape as natural HA in bones. And some stated that ale-ale shells have a high calcium content, which is 98.81%. (Suprianto et al., 2019) Therefore, it can be concluded that hydroxyapatite is effective in helping the bone remodeling process.

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