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(Review Article)

Nano hydroxyapatite in bone regeneration: A literature review

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Abstract

Background: The tissue engineering technique to bone and periodontal tissue regeneration therapy that makes use of one or more of three key factors: signaling molecules, scaffold or supporting matrix, and cells. The graft works as a scaffold and a framework for forming a structure to aid tissue regeneration. One of the most generally used graft substances is hydroxyapatite (HAp). Hydroxyapatite (HAp) is a calcium phosphate derivative that is commonly utilized in bone coatings and cements due to its exceptional biocompatibility. The topic of nano- hydroxyapatite (nHAp) in tissue regeneration therapy will be discussed in this publication.

Methods: The method used in writing this article review was a literature review sourced from Google Scholar, Science Direct, and PubMed (MEDLINE).

Result: The identification results from a search on Google Scholar, Science Direct, and PubMed (MEDLINE) in which the title contains one or more keywords being searched for, from the article, 55 articles are obtained that have appropriate titles and 14 data are obtained from the results of the review.

Discussion: Hydroxyapatite (HAp) is a bioceramic material formed from strong chemical bonds and is included in the bone components of living organisms (in vivo). Conclusion: Hydroxyapatite (HAp) is a bioceramic substance made up of a strong chemical link that is a derivative of calcium phosphate. It is commonly used in coatings or cements on bone because of its excellent biocompatibility.

Keywords: Bone Graft; Hydroxyapatite; Nano Hydroxyapatite; Medicine

1. Introduction

Bone graft is a support material that has been extensively studied and advanced rapidly to acquire periodontal tissue regeneration[1]. Graft is a synthetic or natural material that acts as a filler that also functions as a scaffold and is able to begin the method of bone formation[2]. In the primary phase of regeneration, bone grafts aid in the attachment and proliferation of cells in the defect area, as well as the stability of blood clots to prevent tissue injury[2,3,4]. Autograft, allograft, xenograft, and alloplast are the several varieties of graft materials, each having its private set of advantages and disadvantages. As a result, researchers are continually looking for alternative replacements that have more predictable regeneration outcomes and less side effects[5,6]

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2. Methods

The method used in writing this article review was a literature review sourced from Google Scholar, Science Direct, and PubMed (MEDLINE). The strategy used in data collection was in the form of writing keywords that were used to find articles to be reviewed with a publication period between 2011-2021. The keywords used were bone graft, hydroxyapatite, nano hydroxyapatite, medicine.

Table 1 Tracking scientific articles

No.	Keywords	Year	Database	Number of Articles
1.	Bone Graft	2011-2021	Google Scholar	7700
			Science Direct	941
			PubMed	624
2.	Hydroxyapatite		Google Scholar	3800
			Science Direct	974
			PubMed	998
3.	Nano Hydroxyapatite		Google Scholar	2.103
			Science Direct	571
			PubMed	420
4.	Medicine		Google Scholar	2400
			Science Direct	607
			PubMed	959

3. Results

The identification results from a search on Google Scholar, Science Direct, and PubMed (MEDLINE) in which the title contains one or more keywords being searched for, from the article, 55 articles are obtained that have appropriate titles and 14 data are obtained from the results of the review. There are 3 Indonesian journal articles and 66 international journal articles. The next step is the process of screening the search results data, the results of data types that have similarities in the research theme are obtained. The eligibility stage is carried out to determine which articles enter the inclusion and exclusion criteria based on the suitability of the title and content of the article. Then the include stage is a search with inclusion criteria, namely articles with a time limit of the last eleven years that have been set by the author in the form of studies related to the topic: Nano Hydroxyapatite in Bone Regeneration.

4. Discussion

4.1. Hydroxyapatite

Hydroxyapatite (HAp) is a bioceramic material formed from strong chemical bonds and is included in the bone components of living organisms (in vivo)[7]. Hydroxyapatite (HAp) is a derivative of calcium phosphate which is most widely used in coatings or cements on bone because it has excellent biocompatible properties[8]. The Ca/P ratio of calcium phosphate hydroxyapatite ($Ca_{10}(PO_4)_6(OH)_2$) is 1.67[9,10]. Biomaterials made from HAp consist of HAp cement, HAp nonporous, HAp porous, nano HAp, and bioceramics (which has a greater compact structure when compared to different formations)[8].

4.2. Hydroxyapatite Sources

In addition to human bones and teeth (allograft), the source of this hydroxyapatite is obtained from animal bones or other sources (xenograft) in inorganic and organic forms. Inorganic sources such as rocks containing phosphate. While organic sources, for example, come from chicken egg shells, clam shells, fish bones and cow bones[11,12,13]. HAp may be made with the synthetic substances used within the sol-gel technique. However, based on the results of research that has been carried out, hydroxyapatite made from natural materials is better in terms of crystal size, biocompatible and non-toxic to cells, besides that it is also more economical in terms of raw materials[14].

4.3. Advantages of Hydroxyapatite

Biocompatible, bioactive, and bioresorbable are only a several of the properties of hydroxyapatite (HAp). Biocompatibility is the property where the material does not cause a rejection reaction from the human immune system. The bioactive properties will cause the material to be slightly soluble but help form a biological surface layer before directly interacting with tissue and forming chemical bonds with bone[15]. The material's bioresorbable characteristics aid in the formation and reabsorption of bone tissue, allowing it to be used as a scaffold or filler to fill and repair the tissue[15,16,17,18,19].

The chemical similarity of the mineral phase to bone is HAp's most unique feature, resulting in excellent osteoconductive ability and biocompatibility[20,21,22,23]. Examples of the use of HAp composite materials and in the field of periodontics are used as bone graft materials[24]. Biocompatibility, cell adhesion, and functional support are all advantages of hydroxyapatite made from natural materials[25,26,27,28].

HAp has inelastic and brittle properties which can limit its synthesis ability in the desired shape or structure, so that it can affect the capacity of bone regeneration. Several methods can be used to solve HAp's weaknesses: to improve osteoconduction, the size and porosity of HAp can be modified; to overcome brittleness and improve osteoconduction even greater, it's far combined with other polymers; combined with growth factors, cells and/or molecules for better osteoinductivity (Bal et al, 2019)[28,29].

4.4. Nano Hydroxyapatite

Nanoparticle materials are increasingly developing in medicine. One of the materials that is being developed into nanoparticles is hydroxyapatite.

Bioactivity, osteoconductivity, osteoinductivity, degradation rate, porosity, and material surface properties are all elements to consider in bone regeneration[31]. Cell-to- cell communication, cell mobility, cellular adhesion, proliferation, differentiation, and biodegradation are all affected by porosity size, at the same time as bioactivity and cell adhesion are affected by material surface characteristics[28,32,33,34,35,36]. Increased porosity will improve the amount of body fluids that come into contact with each surface area, as well as the material's bioactivity[28,32,37].

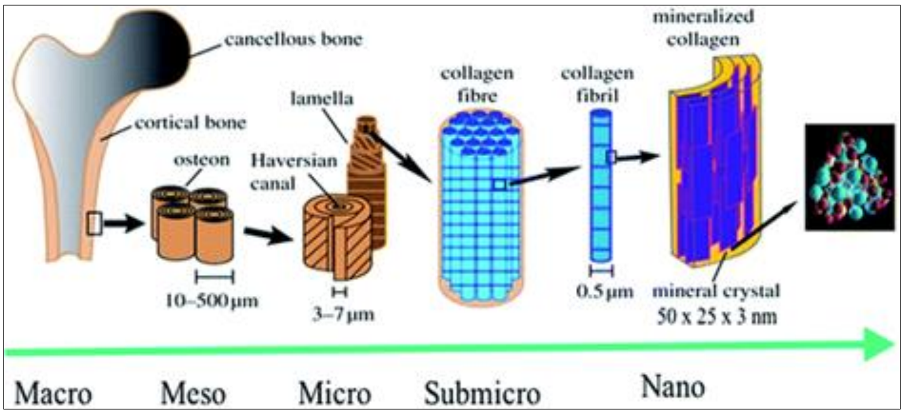

Figure 1 Bone structure at all scales, from macro to micro[30]

Porosity and pore length are crucial for touch with body fluids and tissue vascularization[28,32,38,39,40,41,42,43,44,45]. Improved porosity allows greater fluids to contact the composite, permitting growth factors like VEGF to penetrate the clot and promote vascularization and angiogenesis[28,44,45,46,47]. Advanced new bone growth, vascularity, protein and cell adhesion are all advantages of improved porosity. It additionally improves the biodegradability of the material to the specified stage. However, if the implant fails, the biocomposite's mechanical strength may be compromised, particularly in the load-bearing area[28,39,40]. Although the benefits increase due to the porosity of the material, care must be taken about the risk of loss of mechanical strength, and a balance must be found[28].

4.5. Advantages of Nano Hydroxyapatite

Bayani et al. (2017) published a take a look at in the journal on the properties of nanocrystalline hydroxyapatite as a bone graft material within the treatment of periodontal problems. In periodontal tissue regeneration, nano hydroxyapatite is probably a less high-priced possibility to autogenous bone grafts[48]. It is critical in tissue engineering to offer bioactive materials with the necessary mechanical characteristics and, in most cases, degradation rates that are identical to the tissue's original structure[28].

HAp nanoparticles are more similar to natural hydroxyapatite found in bone than micro- sized hydroxyapatite. Here are some advantages of nano HAp[49]:

- Have closer contact with the surrounding network
- Has properties that are more quickly absorbed and a high number of molecules on the surface
- The attachment of osteoblasts and osteoclasts is more formed on the nanocrystalline hydroxyapatite than conventional hydroxyapatite
- Have good bioaffinity
- This could help in the integration of bone, the expression of collagen I, and the differentiation of osteoblasts.

Nanomaterials have benefits in material stiffness, effective surface place, and location- volume ratio because of smaller particle length[50]. At the nanometric scale, natural bone is formed by a highly organized extracellular matrix (ECM), and the use of nano-scaffold can benefit tissue engineering methods[51,52,53]. Nanomaterials have the ability to solve difficulties with current bone regeneration scaffold, along with mechanical vulnerable factors, instability of released growth elements and the presence of impaired cell differentiation[50,51,54,56,57,58,59].

4.6. The Role of Nano Hydroxyapatite in Tissue Regeneration

Nanoparticles have a greater surface area to volume ratio and a higher strength gradient on the surface than microparticles. Three-dimensional modelling and simulation can be used to optimize the shape of the nanoparticles and the character of the scaffold to shape the scale and shape of the repaired bone defect[60].

Nutrition absorption and protein adsorption can improve the wettability of large-surface- area nanoparticles. When designing composite materials, nHAp is used as a strong filler material, to improve the mechanical stability of composite materials, increase cell proliferation, adhesion, and differentiation, consisting of stem cells, with the aid of increasing interactions among cells. Through selective protein adsorption, nHAp can also help cell surface contacts[60,61].

For bone regeneration and composite strength, porosity and stoichiometry are important. As the porosity of the composite improves, so does the ability to build bones, as does the integration of body fluids with the composite[28].

While nHAp has a tiny particle size and a wide surface area, it can resorb quickly and be replaced by essential bone more quickly. According to the preceding observation, whole nHAp resorption takes 12 weeks. Maintaining the post-extraction socket and minimizing the quantity of graft material around the dental implant is a good idea[48,62]. When Canullo et al. (2015) studied post- extraction sockets grafted with nHAp (including Mg), they discovered that the hard tissue around the graft had completely healed. Additionally, at the time of the study, the graft material had experienced significant resorption[48,63].

Webster et al. (2000) reported increased osteoblast and protein adhesion observed in the nanophase of alumina, titanium, and HAp compared to conventional forms due to reduced material size as well as increased surface area. As a result, the number of cells attaching to the surface of the material has improved[28,64,65,66]. According to Tavakol et al. (2013) the material's surface morphology and wettability were essential elements in bone regeneration[48,63].

4.7. Mechanism of Nano Hydroxyapatite Signaling

To understand the mechanism involved in nHAp signaling, the research conducted by Ha et al. (2015) was carried out in several stages so that the mechanism of nHAp was received by the FGF receptor (FGFR) and Phosphate Transporter (PiT), then received by the FRS 2α receptor, then continued to activate the center of the ERK to express the gene. The ERK 1/2 pathway is required for nHAp activation in OPN expression. Thus, OPN expression induced by nHAp involves the major components FGFR and PiT and is mediated by the MEK-ERK 1/2 pathway[28,67]. Expression genes that are activated by ERK 1/2 will produce 2 groups, namely Up-regulation and Down-regulation. Up regulation (Amyloid A3 and Lipocalin) and down regulation (VDR, IGF-1, IGF-2, and Osterix). Osterix will activate pre-osteoblasts to become osteoblasts[28,67].

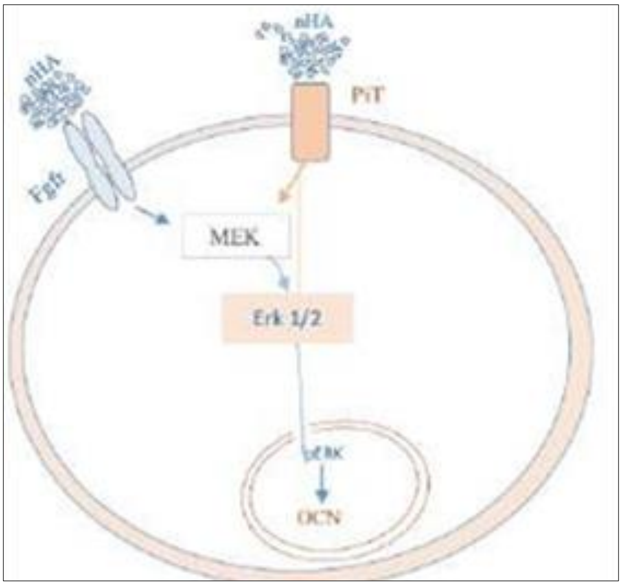

Figure 2 Signaling centers formed by nHAp that induce gene expression changes are shown in this image[28]

4.8. Nano Hydroxyapatite on Growth Factor Release

Lock and Liu (2011) suggested that n-HA present in scaffold nanocomposites might stimulate undifferentiated mesenchymal cell attachment and differentiation in a manner similar to shortening BMP-7 from bone. Zhou et al. (2008) compared the n-HA particle films to the hydroxyapatite particle films, found a lot of protein on the n-HA films[48,68]. Furthermore, Jain et al. (2012) showed that the degradation of calcium sulphate particles, which lowers local pH, would possibly lead to wall defect demineralization and the release of growth elements such BMP-2,

BMP-7, TGF-ß, and PDGF-BB[48,69]. The findings of a study by Pezzatini et al. (2007) showed that n-HA will increase endothelial cell proliferation through upregulating FGF-248,62. The outcomes of this study display that n-HA can enhance the response of cells to VEGF[48,69]

5. Conclusion

Hydroxyapatite (HAp) is a bioceramic substance made up of a strong chemical link that is a derivative of calcium phosphate. It is commonly used in coatings or cements on bone because of its excellent biocompatibility. Bioactive materials that can imitate the tissue's original structure are important in tissue engineering. Nano HAp proved to be better than micro particles because it has a rougher surface and a larger cross-sectional area. In addition, research has shown that nano- hydroxyapatite exhibits several advantages, including minimal toxicity and when applied with biological particles such as fibroblasts, osteoblasts and osteoclasts additionally cause a positive response inside the regeneration of periodontal tissue.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors declare that they have no conflict of interest.

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