REVIEW ARTICLE

CONTENTS

Nanohydroxyapatite as the key factor in bone regeneration

Paweł Kamiński[1], Mateusz Kaczmarski[1], Marta Żerebiec[1], Natalia Saj[1], Aleksandra Bełżek[1], Zuzanna Rupeć[1], Karolina Turżańska[2], Małgorzata Drelich[2]

[1]STUDENT SCIENTIFIC ASSOCIATION OF THE LABORATORY OF LOCOMOTOR SYSTEMS RESEARCH, MEDICAL UNIVERSITY OF LUBLIN, LUBLIN, POLAND

[2]DEPARTMENT OF REHABILITATION AND ORTHOPEDICS , MEDICAL UNIVERSITY OF LUBLIN, LUBLIN, POLAND

ABSTRACT

Bone tissue is a complex material with remarkable durability, elasticity and resistance to mechanical forces, playing a key role in the musculoskeletal system. Hydroxyapatite, a naturally occurring bone-like mineral, is used in a variety of medical applications due to its compatibility with bone tissue. However, synthetic hydroxyapatite has some limitations, such as fragility and low resistance to mechanical straining. Recent developments in nanotechnology have led to the invention of nanohydroxyapatite, which improves bone regeneration and integration with surrounding tissues. The aim of the study is to draw attention to the growing potential of nanohydroxyapatite in clinical practice, especially in the treatment of bone defects. A comprehensive literature review was conducted using PubMed and Google Scholar based on specific criteria to identify relevant studies on the clinical application of nanohydroxyapatite and evaluate its effectiveness and applicability with other organic and inorganic materials. Nanohydroxyapatite has been extensively studied in vitro, in vivo and in clinical trials, showing enhanced bone regeneration and integration. Studies in animal models show promising results for nanohydroxyapatite in bone healing and infection prevention. Clinical studies also confirm its effectiveness in bone grafts, showing comparable results to autografts and fewer complications than other synthetic materials. Nanohydroxyapatite represents a promising biomaterial in modern medicine. Demonstrating effectiveness comparable to natural bone tissue in clinical applications, it exhibits great promise in bone regeneration, implant integration and tissue healing.

KEY WORDS: synthetic scaffolds, bone defects, bone infections, osteomyelitis

Wiad Lek. 2025;78(3):551-558. doi: 10.36740/WLek/202331 DOI

INTRODUCTION

Bone tissue is an exceptional material that surpasses most artificial materials in strength. It is also flexible and resistant to various mechanical stresses. Bone tissue undergoes constant metabolic and structural changes, driven by the activity of osteoclasts, which break down bone, and osteoblasts, which build new bone. This process prevents damage accumulation, maintains mechanical strength, and regulates calcium metabolism [1]. Bone tissue also contains osteocytes and an extracellular matrix, which enable bones to perform essential functions in the body [2]. Both bones and muscles arise from the paraxial mesoderm, developing together to form the musculoskeletal system, which functions as an integrated unit [3].

Hydroxyapatite, a complex material with the chemical formula $Ca_{10}(OH)_2(PO_4)_6$, shares a structure similar to the inorganic matrix of bone. Due to its similarity to natural bone, hydroxyapatite has been explored as a potential bone substitute [4]. Bone is primarily composed of minerals, with hydroxyapatite being the dominant component. The physicochemical properties of hydroxyapatite affect the characteristics of bone. However, natural hydroxyapatite differs significantly from its synthetic counterpart, particularly in the presence of trace elements like strontium and magnesium. Synthetic hydroxyapatite offers benefits such as chemical purity and structural predictability, but it has drawbacks, especially in surgical settings where it may exfoliate. It is also brittle and has low resistance to cracking and stretching, leading to its reduced use in clinical practice [5].

Nanotechnology has advanced the development of inorganic transplantation methods, enabling the production of nanohydroxyapatite (nHA). This technology enhances the predictability of the material's regenerative properties, allowing for more accurate and long-lasting bone defect repairs and improved integration with surrounding bone tissue [6]. In vivo studies have shown that nHA can also serve as a carrier for antimicrobial drugs, offering controlled antibiotic release while providing a scaffold for bone repair at defect sites.

Since ancient times, clinicians have struggled with treating intramedullary defects, which are challenging to manage due to their location. Hydroxyapatite presents a promising solution because of its ease of use, resistance to mechanical damage, and strong adhesion. It is also useful for filling bone cavities left after the surgical removal of infected bone or tumors. While autogenous grafts remain the most effective option, their limited availability poses a significant challenge. Allogeneic transplantation is another possibility, but it carries the risk of disease transmission from donor to recipient. Inorganic transplantation, however, offers significant advantages, including nearly unlimited availability and no risk of pathogen transmission [7].

This review will examine the potential clinical applications of nanohydroxyapatite, comparing its effectiveness and applicability with other organic and inorganic materials. It will also assess its use in treating bone defects. Encouraging results from animal studies and applications in various medical fields suggest that nanohydroxyapatite holds great promise for orthopedic use [8].

MATERIALS AND METHODS

A comprehensive review of the literature was conducted using PubMed and Google Scholar to identify relevant studies on nanohydroxyapatite, synthetic scaffolds, bone defects, bone infections, and osteomyelitis. The search strategy employed a combination of keywords, such as "nanohydroxyapatite" and "bone defect," "nanohydroxyapatite" and "synthetic scaffolds," and related terms to capture a wide array of studies within the scope of bone repair and regeneration.

Articles were included in the review based on specific criteria:

- Studies that involved nanohydroxyapatite or synthetic scaffolds in relation to bone defects, bone infections, or osteomyelitis.
- Articles published within the last 15 years to ensure the inclusion of the most up-to-date research.
- Studies published in English.
- Full-text articles available for review.

We excluded:

- Studies that were available only as abstracts.
- Articles in languages other than English.
- Articles published more than 15 years ago to maintain relevance and ensure the use of recent findings.

SEARCH RESULTS AND STUDY SELECTION

The initial search yielded approximately 1,000 articles across both databases. After applying the exclusion criteria, the pool was narrowed down to 25 studies most relevant to the specific focus of this review. Due to the limited availability of studies specifically focused on the clinical use of nanohydroxyapatite for bone defects and infections, we prioritized studies that met the outlined criteria and provided meaningful insights.

CLASSIFICATION OF STUDIES

The selected studies were then divided into two main categories:

1. In-vitro studies: These included experiments conducted in laboratory settings, often involving cell cultures or synthetic bone environments to test the properties of nanohydroxyapatite and synthetic scaffolds.
2. In-vivo studies: These were further subdivided into studies conducted on animals and humans. Animal studies provided valuable insights into the biological responses to nanohydroxyapatite in living organisms, while human studies focused on clinical outcomes and the material's effectiveness in treating bone defects or infections.

This methodological approach ensured that the review included a balanced representation of preclinical and clinical research, providing a broad perspective on the potential applications of nanohydroxyapatite in bone repair and infection management.

REVIEW

NANOHYDROXYAPATITE

SYNTHESIS AND PROPERTIES OF NANOHYDROXYAPATITE

The formation process of nanohydroxyapatite (nHA) varies based on the synthesis method employed, with each approach influencing the resulting material's properties. One of the most commonly used methods for synthesizing nHA is wet chemical precipitation, a process favored for its simplicity and lack of reliance on organic solvents. This method typically involves extracting calcium and phosphorus from inexpensive and readily available inorganic salts. The simplicity of the process and the minimal use of complex chemicals enable the production of nanohydroxyapatite at a relatively low cost [9].

During wet chemical precipitation, calcium and phosphate ions are combined in an aqueous solution under controlled pH and temperature conditions. The resulting nanohydroxyapatite crystals are highly uniform, with properties such as size, morphology, and crystallinity being carefully regulated by adjusting parameters like reaction time, temperature, and ionic concentrations. Wet precipitation is advantageous for its scalability and the ability to produce high yields of nanohydroxyapatite with consistent properties, making it an ideal method for large-scale production [9].

MODIFICATION OF NANOHYDROXYAPATITE

The properties of nHA, such as crystallinity, solubility, and morphology, can be significantly influenced by introducing various inorganic ions into its structure. This ion substitution allows researchers to tailor the material for specific biomedical applications without altering the crystal configuration of hydroxyapatite. For instance, the addition of magnesium ions (Mg^{2+}) to nHA has shown promise in inhibiting cancer cell proliferation, making it a potential candidate for bone regeneration in cancer patients [10]. Magnesium-modified nHA exhibits lower crystallinity and increased solubility, which enhances its biodegradability and bioactivity, promoting better integration with natural bone tissue.

Similarly, the incorporation of silicon ions (Si^{4+}) into the nHA matrix has been observed to enhance the proliferation and differentiation of osteoblasts, the cells responsible for bone formation. Silicon plays a crucial role in bone metabolism and regeneration, and its presence in nHA stimulates cellular activity, leading to faster bone growth and repair. Additionally, the substitution of iron ions (Fe^{3+}) has been explored to improve osteoblast adhesion to the nHA surface. This modification enhances the material's interaction with bone-forming cells, increasing its effectiveness as a scaffold for bone regeneration [10].

APPLICATIONS AND RESEARCH FOCUS

Due to its favorable properties and potential applications in bone repair and regeneration, nanohydroxyapatite has garnered significant interest from researchers in the fields of biomaterials and tissue engineering. The ability to modify the material's surface structure with various ions enables the fine-tuning of its biological performance, allowing for applications beyond traditional bone substitutes. For example, ion-doped nHA has been studied for its potential use in drug delivery systems, where its surface can be functionalized to release therapeutic agents like antibiotics or anticancer drugs in a controlled manner.

As a result of these promising modifications, nanohydroxyapatite has been the focus of numerous in-vitro studies, which have demonstrated its bioactivity and compatibility with human cells. These laboratory studies have laid the foundation for further in-vivo experiments on animal models, where researchers have explored nHA's performance in bone regeneration, wound healing, and infection management. The successful outcomes from these preclinical studies have led to clinical trials in human patients, where nHA-based scaffolds and implants are being tested for their effectiveness in treating bone defects, osteomyelitis, and other orthopedic conditions.

NANOHYDROXYAPATITE IN *IN-VITRO* STUDIES

To date, two notable *in-vitro* studies have investigated the effects of nanohydroxyapatite (nHA) in various biological contexts, providing insights into its biocompatibility and potential applications in tissue regeneration.

In a 2022 study conducted by Gusmão et al., the researchers explored the cytotoxicity of nanohydroxyapatite, titanate nanotube (TiNT), and their combination (nHA-TiNT) on mouse fibroblasts. The study evaluated the viability of fibroblasts exposed to these materials at different concentrations – 1%, 2%, 3%, and 10% – comparing the results with a control group of untreated cells. The results showed that at all tested concentrations, no cytotoxic effects were observed against the mouse fibroblasts. This indicates that both nHA and TiNT, as well as their combination, are biocompatible with fibroblasts and do not adversely affect cell viability, even at higher concentrations. The lack of cytotoxicity is a crucial finding, as it supports the potential use of nHA-based materials in medical applications such as bone regeneration, where cell survival is critical [11].

In another study, Zhang et al. investigated the effects of nanohydroxyapatite-doped gelatin (Gel-nHA) on mouse articular chondrocytes, cells responsible for cartilage production. This study aimed to compare Gel-nHA with non-doped gelatin (Gel) to assess their effectiveness in treating osteoarthritis. The study found that both Gel and Gel-nHA enhanced the migration and proliferation of chondrocytes, confirming their potential in forming acellular matrix scaffolds for cartilage regeneration. However, Gel-nHA demonstrated superior performance in promoting chondrocyte activity compared to the control Gel.

Moreover, chondrocytes cultured in Gel-nHA exhibited increased secretion of critical cartilage matrix components, such as type II collagen and glycosaminoglycans (GAG), which are essential for cartilage formation and integrity. Importantly, nHA also stimulated chondrocyte mineralization and the production of type X collagen, which is involved in the process of endochondral ossification and contributes to the overall strength and stability of the cartilage. These findings suggest that the presence of nHA in the Gel scaffold not only enhances cartilage regeneration but also improves the quality and durability of the repaired tissue by promoting bone-cartilage integration. This positions Gel-nHA as a potentially superior material for articular cartilage repair over traditional Gel [12].

Both studies provide encouraging evidence for the biocompatibility and regenerative potential of nanohydroxyapatite in different cell types, laying the groundwork for future research on its clinical applications in tissue engineering and regenerative medicine.

NANOHYDROXYAPATITE IN ANIMAL STUDIES

We reviewed eight animal studies exploring the application of nanohydroxyapatite in various species, including rabbits, rats, and sheep. These studies highlight the material's promising effects in promoting bone healing and regeneration.

In a preclinical study conducted by Júnior et al., female rats were used to compare the effectiveness of nanohydroxyapatite (nHA) and dual acid-etched (DAE) surfaces as implant coatings. The study also evaluated the addition of leukocyte-platelet-rich fibrin (L-PRF) to the nHA coating. Results from histological and micro-imaging analyses revealed that nHA, both with and without L-PRF, significantly enhanced bone-implant contact, increased bone surface area, and improved trabecular bone separation compared to DAE, indicating better osseointegration [13].

In another preclinical study by Han et al., female rabbits were utilized to compare two types of membranes – one made of polycaprolactone/nanohydroxyapatite/collagen (PCL/nHA/Col) and the other of PCL alone – for promoting healing after anterior cruciate ligament (ACL) reconstruction. The PCL/nHA/Col membrane showed a significant increase in failure load and stiffness compared to the control, suggesting that it facilitated stronger bone-ligament integration [14].

Radhakrishnan et al. conducted an experiment on male rabbits with segmental injuries to the ulna. The rabbits were divided into three groups: two received cylindrical scaffolds made from a nanohydroxyapatite composite (nHA, polyhydroxybutyrate, and polyε-caprolactone), with one group having an additional protein interface, while the third group acted as the control with no intervention. Both experimental groups exhibited bone regeneration by bridging the defect and better bone maturation compared to the control group, which developed sclerotic tissue instead [15].

In a separate study, Li et al. tested the efficacy of copper-lithium-doped nanohydroxyapatite (Cu-Li-nHA) in treating glucocorticosteroid-induced femoral head necrosis (ONFH) in male rabbits. Rabbits were divided into five groups, with various implant treatments, including nHA, Li-nHA, and Cu-Li-nHA, alongside a control and surgical group. Enhanced migration of bone mesenchymal stem cells (BMSCs) was observed in the Cu-Li-nHA group through activation of the HIF-1α/SDF-1 pathway, leading to accelerated osteogenesis and angiogenesis, thus improving bone formation [16].

Wang et al. conducted a study where rabbits were treated with nanohydroxyapatite-chitosan-gelatin micro-scaffolds (HaCGMs), gelatin scaffolds, or no intervention (control). HaCGMs significantly improved subchondral bone regeneration following knee injuries, showing superior results compared to gelatin scaffolds and controls [17].

Alegrete et al. investigated the use of nanohydroxyapatite as a vector for antimicrobial drugs in rabbits. They tested heparinized nHA/collagen biocomposites loaded with vancomycin (V-HEPHAPC) to evaluate the safety of the therapy. Rabbits were divided into three groups, with one receiving V-HEPHAPC, another HEPHAPC without vancomycin, and the control group receiving no treatment. Results showed no significant toxic effects on the liver or kidneys, despite elevated urinary urobilinogen levels in the V-HEPHAPC group. A subsequent study on sheep, where animals were infected with MRSA, demonstrated that the V-HEPHAPC group had no remaining bacteria and showed better bone integration than the control groups, which suffered from bacterial presence and joint destruction. The results indicate that nanohydroxyapatite, particularly in combination with vancomycin, can effectively prevent infections and promote bone regeneration in infected areas [18].

Lastly, Gusmão et al. conducted an additional study on osteopenic rats, in which nanohydroxyapatite combined with titanate nanotubes (TiNT) at different concentrations (1%, 2%, 3%, 10%) was used as an implant material after bone cavities were created. The best results were observed in the group with the 10% TiNT-nHA combination, which exhibited the highest rate of bone regeneration within 30 days compared to untreated control animals [11].

These animal studies provide valuable insights into the efficacy of nanohydroxyapatite in promoting bone regeneration and its potential for use as a scaffold in various bone-related conditions. The addition of antimicrobial drugs, protein interfaces, or specific dopants (e.g., copper and lithium) to nHA further enhances its performance, improving both osseointegration and the prevention of post-surgical infections.

NANOHYDROXYAPATITES IN CLINICAL TRIALS

Promising outcomes from *in-vitro* and animal studies have encouraged researchers to conduct more comprehensive human clinical trials. After an extensive search and analysis of scientific databases, we identified two notable studies focused on the clinical application of nanohydroxyapatite.

The first randomized clinical trial by Stacchi et al. involved 28 patients, including 10 women and 18 men aged between 39 and 79 years. Each patient underwent bilateral sinus floor elevation, using either sintered nanohydroxyapatite or anorganic bovine bone as an active control. After a six-month follow-up period, biopsies were taken to evaluate the percentage of vital bone through histophotometry. The results revealed no statistically significant differences between the study and control groups, indicating that the efficacy of nanohydroxyapatite implants was comparable to that of natural bone. Moreover, the use of nanohydroxyapatite avoided the risks associated with xenograft transplantation, supporting its viability as an alternative to traditional bone grafting techniques [19].

Another clinical study by Zhong et al. examined the effectiveness of different bone graft materials in 57 patients suffering from tuberculosis of the thoracic or lumbar spine, all of whom exhibited associated neurological symptoms. The patients were divided into three groups based on the type of material used for filling tubercular cavities: 13 patients received hip bone transplants, 26 were treated with titanium mesh bone grafts, and 18 received nanohydroxyapatite/polyamide-66 cage bone grafts. All patients showed improvements in neurological function, and no significant differences were found between groups in terms of erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), or visual analog scale (VAS) scores. Operative time, blood loss, postoperative hospitalization, and complications were also similar across the groups. However, patients in the nanohydroxyapatite/polyamide-66 group experienced less cage subsidence and significantly shorter graft fusion times, suggesting a faster recovery compared to the other two groups [20].

Additionally, Sotome et al. conducted a multicenter randomized controlled trial with 126 participants to compare the efficacy of a porous hydroxyapatite/collagen composite (HAp/Col) with porous β-tricalcium phosphate (β-TCP), which served as the control. The study found that HAp/Col showed superior bone regeneration compared to β-TCP. However, there was a higher incidence of non-serious adverse reactions with the HAp/Col group, although these reactions did not necessitate patient withdrawal from the study [21].

These clinical trials suggest that nanohydroxyapatite is an effective and safe alternative to traditional bone graft materials, offering comparable or even superior outcomes in terms of bone regeneration and recovery time. However, further research is required to better understand the potential for adverse reactions associated with some forms of nHA-based composites.

DISCUSSION

This review highlights the widespread use of nano-sized hydroxyapatite (nHA) in modern medicine, particularly in orthopedics and musculoskeletal traumatology. Nanohydroxyapatite is a molecular modification of hydroxyapatite, a well-known and extensively studied compound. As shown in this review, nHA has demonstrated considerable potential across various medical applications, often outperforming traditional treatment methods and providing significant benefits to patients. Comparisons between biomaterial-based treatments and conventional approaches show that nHA is at least as effective and, in many cases, superior.

A key area of interest is the integration of nHA with elemental ions such as magnesium (Mg), iron (Fe), silicon (Si), zinc (Zn), bismuth (Bi), copper (Cu), and lithium (Li). These combinations enhance nHA's properties and broaden its medical applications. For instance, doping nHA with silicon and iron ions positively affects graft integration with surrounding bone tissue, reducing recovery time and minimizing risks such as graft displacement or implant rejection. Although clinical applications are not yet fully defined, these early findings suggest promising future uses of nHA in medicine [10]. Additionally, combining zinc and bismuth with nHA imparts bactericidal and bacteriostatic properties, preventing the formation of biofilms and reducing the risk of infections, especially in perioperative settings. This combination also facilitates post-surgical wound healing [22]. Although these properties have been mostly tested in dental implants, there is a strong rationale for believing they could benefit orthopedic applications as well, though more research is required to confirm this [23].

The inclusion of magnesium ions in nHA has also shown anti-tumor effects on human osteoblast-like cells and rat mesenchymal stem cells. This opens up potential applications in oncology and oncologic surgery, particularly in managing musculoskeletal tumors [10,24]. Copper and lithium doping of nHA has been demonstrated to promote the migration of bone stem cells, enhancing bone regeneration within grafts [16].

In-vitro studies also provide promising results for cartilage regeneration. When used in hydrogels for treating osteoarthritis, nHA has been shown to stimulate chondrocytes, improve cartilage matrix quality, and enhance resistance to mechanical damage. This leads to faster and more durable cartilage regeneration [12]. Additionally, nHA has not shown cytotoxic effects on mouse fibroblasts, affirming its safety for further clinical investigation [11].

In-vivo animal studies, particularly on rats [11,13], rabbits [14-18], and sheep [18], further validate nHA's efficacy in promoting bone regeneration. The mechanical and molecular similarities between animal skeletal systems and humans allow for some conclusions to be extrapolated to human treatments. Studies on rodents, for example, have shown that implants using a combination of nHA and titanium nanotubes (TiNT) achieve the best results in bone integration and regeneration [11]. This is supported by findings from Júnior et al., who demonstrated that nHA significantly improves new bone formation when used as an implant surface material [13].

In rabbit studies, nHA has proven effective as an inducer of bone regeneration [14-18]. Additionally, nHA-based implants prevent the development of sclerotic tissue, which enhances implant strength and resistance to mechanical stress [15]. Moreover, nHA plays a role beyond bone tissue, improving the strength of ligament-to-bone interfaces in procedures such as anterior cruciate ligament (ACL) reconstruction [14]. The combination of nHA with antimicrobial agents, such as vancomycin, also showed promising results in animal models, preventing surgical site infections and promoting better healing outcomes [18].

Nanohydroxyapatite has been successfully utilized in dentistry for many years, particularly as a bone defect filler. Compared to alternatives like xenografts or artificial materials, nHA shows superior clinical outcomes while reducing the risk of zoonotic disease transmission [19,25,26]. However, research on nHA in fields beyond dentistry remains limited. In one clinical study, nHA was compared to iliac bone grafts and titanium mesh grafts for treating spinal tuberculosis. The study showed that nHA accelerated wound healing and postoperative recovery while maintaining comparable safety profiles to other grafting methods [20]. Clinical trials have further confirmed the positive effect of nHA on bone regeneration [21].

Beyond orthopedics, nHA has been used in periodontology to replace periodontal bone defects, where it shows significant improvements in bone mineral density and tissue adhesion compared to other materials [25,26]. Given the successful track record of nHA in dental applications, there is strong justification for exploring its broader use in other fields such as orthopedics and musculoskeletal surgery.

In conclusion, nanohydroxyapatite offers immense potential in modern medicine, particularly for bone and tissue regeneration. Its versatility, combined with its ability to be enhanced through elemental doping, makes it an invaluable biomaterial in fields such as orthopedics, dentistry, and potentially oncology. However, further clinical studies are needed to validate these findings and ensure the safe and effective application of nHA across a broader range of medical treatments.

CONCLUSIONS

Nanohydroxyapatite (nHA) represents a promising biomaterial in modern medicine, particularly in the fields of orthopedics, musculoskeletal traumatology, and dentistry. Its molecular similarity to naturally occurring bone minerals makes it an ideal candidate for enhancing bone regeneration, implant integration, and tissue healing. The integration of elemental ions such as magnesium, iron, zinc, and copper into the nHA structure further enhances its properties, making it more versatile by adding antibacterial, anti-inflammatory, and osteogenic capabilities.

Extensive preclinical in-vitro and in-vivo studies have demonstrated nHA's efficacy and safety, showing that it not only supports but often improves tissue regeneration when compared to conventional materials. In particular, its ability to reduce recovery time, increase implant stability, and minimize the risk of infections highlights its potential clinical benefits. Moreover, animal studies, especially in rodents and rabbits, have revealed nHA's superiority in terms of bone formation and implant integration.

While nHA has long been established in dentistry, especially for filling bone defects and periodontology, its potential applications in orthopedics and other areas of medicine, including oncology, are beginning to emerge. However, there remains a need for more comprehensive human clinical trials to confirm its effectiveness across different medical fields. Early clinical studies, such as those involving spinal tuberculosis and sinus floor elevation, indicate that nHA is comparable to, if not better than, traditional materials like autologous bone grafts or titanium mesh.

The successful use of nHA in these various applications suggests that it could be increasingly employed as a biomaterial in medical practice. However, the transition from preclinical success to widespread clinical adoption requires further large-scale studies to confirm its long-term safety, efficacy, and versatility in human populations. Given its potential, nHA is poised to become a key material in regenerative medicine, offering innovative solutions for bone healing, tissue integration, and implant technology.

REFERENCES

1. Hart NH, Newton RU, Tan J, Rantalainen T, Chivers P, Siafarikas A, Nimphius S. Biological basis of bone strength: anatomy, physiology and measurement. J Musculoskelet Neuronal Interact. 2020 Sep 1;20(3):347-371
2. Kim JM, Lin C, Stavre Z, Greenblatt MB, Shim JH. Osteoblast-Osteoclast Communication and Bone Homeostasis. Cells. 2020 Sep 10;9(9):2073. doi: 10.3390/cells9092073 DOI
3. Florencio-Silva R, Sasso GR, Sasso-Cerri E, Simões MJ, Cerri PS. Biology of Bone Tissue: Structure, Function, and Factors That Influence Bone Cells. Biomed Res Int. 2015;2015:421746. doi: 10.1155/2015/421746. Epub 2015 Jul 13 DOI
4. Battafarano G, Rossi M, Marampon F, Minisola S, Del Fattore A. Bone Control of Muscle Function. Int J Mol Sci. 2020 Feb 11;21(4):1178. doi: 10.3390/ijms21041178 DOI
5. Zhou H, Lee J. Nanoscale hydroxyapatite particles for bone tissue engineering. Acta Biomater. 2011 Jul;7(7):2769-81. doi: 10.1016/j.actbio.2011.03.019 DOI
6. Ryabenkova Y, Pinnock A, Quadros PA, et al. The relationship between particle morphology and rheological properties in injectable nano-hydroxyapatite bone graft substitutes. Mater Sci Eng C Mater Biol Appl. 2017 Jun 1;75:1083-1090. doi: 10.1016/j.msec.2017.02.170 DOI
7. Nobile S, Nobile L. Nanotechnology for biomedical applications: Recent advances in neurosciences and bone tissue engineering. Polym Eng Sci. 2017;57(7):644-650.
8. Chitsazi MT, Shirmohammadi A, Faramarzie M, Pourabbas R, Rostamzadeh An. A clinical comparison of nano-crystalline hydroxyapatite (Ostim) and autogenous bone graft in the treatment of periodontal intrabony defects. Med Oral Patol Oral Cir Bucal. 2011 May 1;16(3):e448-53. doi: 10.4317/medoral.16.e448 DOI
9. Li Y, Liao C, Tjong SC. Synthetic Biodegradable Aliphatic Polyester Nanocomposites Reinforced with Nanohydroxyapatite and/or Graphene Oxide for Bone Tissue Engineering Applications. Nanomaterials (Basel). 2019 Apr 10;9(4):590. doi: 10.3390/nano9040590 DOI
10. Rajula MPB, Narayanan V, Venkatasubbu GD, Mani RC, Sujana A. Nano-hydroxyapatite: A Driving Force for Bone Tissue Engineering. J Pharm Bioallied Sci. 2021 Jun;13(Suppl 1):S11-S14. doi: 10.4103/jpbs.JPBS_683_20 DOI
11. Gusmão SBS, Ghosh A, de Menezes AS, et al. Nanohydroxyapatite/Titanate Nanotube Composites for Bone Tissue Regeneration. J Funct Biomater. 2022 Dec 17;13(4):306. doi: 10.3390/jfb13040306 DOI
12. Zhang Y, Cui Y, Tian J, Chen X, Xu T, Liu J, Xu Y. Nanohydroxyapatite Hydrogel Can Promote the Proliferation and Migration of Chondrocytes and Better Repair Talar Articular Cartilage. Comput Math Methods Med. 2022 May 26;2022:8388473. doi: 10.1155/2022/8388473 DOI
13. Júnior JAG, Nóbrega F, Oliveira PG, et al. Evaluation of Implant Surface Modification with Nanohydroxyapatite Associated with the Use of L-PRF: In Vivo Study in Rats. J Funct Biomater. 2023 Jul 14;14(7):370. doi: 10.3390/jfb14070370 DOI
14. Han F, Zhang P, Sun Y, Lin C, Zhao P, Chen J. Hydroxyapatite-doped polycaprolactone nanofiber membrane improves tendon-bone interface healing for anterior cruciate ligament reconstruction. Int J Nanomedicine. 2015 Dec 7;10:7333-43. doi: 10.2147/IJN.S92099 DOI
15. Radhakrishnan J, Muthuraj M, Gandham GSPD, Sethuraman S, Subramanian A. Nanohydroxyapatite-Protein Interface in Composite Sintered Scaffold Influences Bone Regeneration in Rabbit Ulnar Segmental Defect. J Mater Sci Mater Med. 2022 Apr 9;33(4):36. doi: 10.1007/s10856-022-06657-4 DOI
16. Li Q, Yang Z, Wei Z, Li D, Luo Y, Kang P. Copper-Lithium-Doped Nanohydroxyapatite Modulates Mesenchymal Stem Cells Homing to Treat Glucocorticoids-Related Osteonecrosis of the Femoral Head. Front Bioeng Biotechnol. 2022 Jun 2;10:916562. doi: 10.3389/fbioe.2022.916562 DOI
17. Wang B, Liu W, Xing D, et al. Injectable nanohydroxyapatite-chitosan-gelatin micro-scaffolds induce regeneration of knee subchondral bone lesions. Sci Rep. 2017 Dec 1;7(1):16709. doi: 10.1038/s41598-017-17025-6 DOI
18. Alegrete N, Sousa SR, Padrão T, et al. Vancomycin-Loaded, Nanohydroxyapatite-Based Scaffold for Osteomyelitis Treatment: In Vivo Rabbit Toxicological Tests and In Vivo Efficacy Tests in a Sheep Model. Bioengineering (Basel). 2023 Feb 4;10(2):206. doi: 10.3390/bioengineering10020206 DOI
19. Stacchi C, Lombardi T, Oreglia F, Alberghini Maltoni A, Traini T. Histologic and Histomorphometric Comparison between Sintered Nanohydroxyapatite and Anorganic Bovine Xenograft in Maxillary Sinus Grafting: A Split-Mouth Randomized Controlled Clinical Trial. Biomed Res Int. 2017;2017:9489825. doi: 10.1155/2017/9489825. DOI
20. Zhong D, Lin L, Liu Y, Ke ZY, Wang Y. Analysis of Nanohydroxyapatite/Polyamide-66 Cage, Titanium Mesh, and Iliac Crest in Spinal Reconstruction of the Patients with Thoracic and Lumbar Tuberculosis. Neurol India. 2022 Sep-Oct;70(Supplement):S230-S238. doi: 10.4103/0028-3886.360908. DOI
21. Sotome S, Ae K, Okawa A, et al. Efficacy and safety of porous hydroxyapatite/type 1 collagen composite implantation for bone regeneration: A randomized controlled study. J Orthop Sci. 2016 May;21(3):373-80. doi: 10.1016/j.jos.2016.01.007 DOI
22. Kazimierczak P, Golus J, Kolmas J, Wojcik M, Kolodynska D, Przekora A. Noncytotoxic zinc-doped nanohydroxyapatite-based bone scaffolds with strong bactericidal, bacteriostatic, and antibiofilm activity. Biomater Adv. 2022 Aug;139:213011. doi: 10.1016/j.bioadv.2022.213011 DOI

23. Ciobanu G, Harja M. Bismuth-Doped Nanohydroxyapatite Coatings on Titanium Implants for Improved Radiopacity and Antimicrobial Activity. Nanomaterials (Basel). 2019 Nov 27;9(12):1696. doi: 10.3390/nano9121696 DOI
24. Zhao Z, Espanol M, Guillem-Marti J, Kempf D, Diez-Escudero A, Ginebra MP. Ion-doping as a strategy to modulate hydroxyapatite nanoparticle internalization. Nanoscale. 2016 Jan 21;8(3):1595-607. doi: 10.1039/c5nr05262a DOI
25. Koduru S, Aghanashini S, Nadiger S, Apoorva SM, Bhat D, Puvvalla B. A Clinical and Radiographic Evaluation of the Efficacy of Nanohydroxyapatite (Sybograf™) versus Bioactive Calcium Phosphosilicate Putty (Novabone®) in the Treatment of Human Periodontal Infrabony Defects: A Randomized Clinical Trial. Contemp Clin Dent. 2019 Jan-Mar;10(1):16-23. doi: 10.4103/ccd.ccd_52_18 DOI
26. Vani TMS, Paramashivaiah R, Prabhuji MLV, et al. Regeneration of Intrabony Defects with Nano Hydroxyapatite Graft, Derived from Eggshell along with Periosteum as Barrier Membrane under Magnification—An Interventional Study. Applied Sciences. 2023; 13(3):1693. doi.org/10.3390/app13031693.

CONFLICT OF INTEREST

The Authors declare no conflict of interest.

CORRESPONDING AUTHOR

Małgorzata Drelich
Department of Rehabilitation,
Medical University of Lublin,
Lublin, Poland;
e-mail: malgorzata.drelich@umlub.pl

ORCID AND CONTRIBUTIONSHIP

Paweł Kamiński: 0009-0003-9322-6374 A B D
Mateusz Kaczmarski: 0009-0000-9215-5656 A B D
Marta Żerebiec: 0009-0003-7438-238X A B D
Natalia Saj: 0009-0006-3069-6573 B D
Aleksandra Bełżek: 0000-0001-5543-877X B D
Zuzanna Rupeć: 0009-0001-3767-5090 B D
Karolina Turżańska: 0000-0001-7359-9622 D E
Małgorzata Drelich: 0000-0001-6709-0440 A D E F

A – Work concept and design, B – Data collection and analysis, C – Responsibility for statistical analysis, D – Writing the article, E – Critical review, F – Final approval of the article

RECEIVED: 10.11.2024
ACCEPTED: 15.02.2025