The Journal of Basic and Clinical Dentistry

*Editorial*

# Nanocrystalline Hydroxyapatite in Periodontal Bone Regeneration: A Promising Frontier in Biomimetic Dentistry

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**Citation:** Lomelí-Martínez, S,M., Alarcón-Sánchez, M,A., Alcaraz-Baturoni, F,J., Robles-García, M,A., Ortega-Rodríguez, M,G., Aguilar-Martínez, J. Nanocrystalline Hydroxyapatite in Periodontal Bone Regeneration: A Promising Frontier in Biomimetic Dentistry. J Basic Clin Dent, 2026;3(1), 1–8.

Received: 10th November 2025

Revised: 4th February 2026

Accepted: 5th February 2026

Published: 9th February 2026



**Abstract.**

Currently, one of the most significant challenges is periodontal bone regeneration. Nanotechnology has become a fundamental pillar for innovation in biomaterials characterized by promoting osteoconduction, cell adhesion, and controlled tissue regeneration. In this context, nanocrystalline hydroxyapatite (NHA) has established itself as a valuable option due to its high bioactivity and chemical similarity to bone. Biologically, this biomaterial acts as a mineral nucleator, promoting calcium and phosphate ions that favor osteoblastic differentiation and osteogenesis without causing an inflammatory reaction. Clinically, scientific evidence has widely supported the fact that NHA significantly increases clinical insertion and bone density compared to traditional treatments, especially when combined with chitosan, collagen, or fibrin-rich plasma. Future perspectives should focus on the innovation of multifunctional hybrid systems and consider integrating customized 3D-printed structures aimed at promoting improved bone regeneration quality.

**Keywords:** Nanocrystalline ydroxyapatite, periodontal bone regeneration, biomaterials, nanotechnology, osteogenesis.

## 1. Introduction

In recent decades, periodontics has established itself as a field dedicated to the prevention and management of infections. However, the ability to predictably regenerate compromised periodontal tissues, including root cementum, alveolar bone, and periodontal ligament, continues to represent a significant clinical challenge. Traditional therapeutic approaches, such as the use of autologous grafts or open flap debridement, have achieved partial structural and functional restoration of destroyed tissues. [1,2]

An interesting evolution has been observed in periodontal bone regeneration, ranging from the implementation of autologous grafts, allografts, and xenografts to the development of synthetic materials with bioactive properties. [3,4,5] Nanotechnology is an area that has enabled the creation of biomimetic materials that reproduce the bone matrix and promote cell regeneration.[4,6] The different versions of nanocrystalline hydroxyapatite (NHA) have established themselves as an important innovation by providing a surface topography and area/volume ratio that promotes cell-material interaction and the fixation of osteogenic proteins, which are fundamental steps in the initiating of the periodontal bone regeneration process. [1-3,7,8]

The purpose of this editorial is to critically analyze the scientific evidence available on NHA in periodontal bone regeneration, highlighting its biological foundations, nanotechnological developments, and most interesting clinical findings. It also seeks to expose the challenges that still exist and future opportunities for innovation, with the aim of consolidating its role in modern regenerative dentistry.

## 2. Biological Fundamentals and Nanotechnological Advances

In periodontal regeneration, the properties of implants have become very important, mainly due to the surface and size of the material. Nanoscale material structures can increase the contact area, which influences interaction with the bone tissue in the periodontal region. At this scale, the nanomaterials exhibit enhanced interaction with osteogenic proteins through increased adsorption. Nanomaterials have been shown to increase the surface contact area, allowing for greater protein adsorption and cell binding. [9] By contrast, at the macrometric scale, materials have been combined with cells for implantation in the human body and to promote bone regeneration. However, implants performed in vivo have low vascularization, which decreases the viability of cells in the tissue. In nanostructures, however, there are several routes that can allow biomineralization, such as an appropriate composition, characteristics that can improve cell adhesion and osseointegration, nanometric porosity that allows cells to infiltrate and transport of nutrients. Furthermore, changes in the way growth factors are administered in scaffolds can allow the incorporation of endogenous cells and accelerate bone formation. [10]

Some nanostructures, such as NHA, have the ability to interact within biological systems without undergoing structural modifications. This behavior is attributed to their rough surface and chemical composition similar to that of bone tissue, which promotes interactions with cell matrices at focal points. [11] Therefore, these nanostructures have more anchoring sites and, consequently, greater adhesion to bone tissue. In addition, NHA influences osteoblast proliferation, leading to an increased cell growth rate. This effect is attributed to the release of calcium and phosphate ions. Boron (B)-doped NHA has been reported to increase the proliferation of osteoblast progenitor cells. [12] Zinc (Zn) doping can enhance osteoblastic cell proliferation and promote osteogenic differentiation. Zn release also reduces osteoclast resorption and increases osteoblast ossification. [13] NHA acts as a mineral nucleator, mainly in osteoblastic cultures, enhancing calcium deposits in the extracellular matrix. This effect comes from the activity of alkaline phosphatase induced by NHA. Alkaline phosphatase produces inorganic phosphate and alkalizes the medium, creating the conditions for calcium phosphate to crystallize in the collagen matrix. [14] Additionally, NHA acts as a scaffold for bone cells to adhere to and deposit onto the matrix. It provides a suitable environment for regeneration, requiring the presence of bone cells to begin the formation of the bone structure. [15]

Osteogenic structures such as NHA exhibit bioactivity and mechanical strength. In order to evaluate osteoconductivity, tissue regeneration capacity, and the degree of periodontal integration, they have been combined with natural polymers such as chitosan and collagen, as well as nanomaterials such as graphene. The combination of NHA and chitosan has enabled the production of scaffolds characterized by osteoconductivity, biocompatibility, elasticity, and bioactivity, with the aim of achieving greater mechanical stability and osteoconduction [16]. The in vitro study conducted by Souto-Lopes et al. (2024) prepared a nanohydroxyapatite/chitosan bioaerogel for periodontal regeneration; it allowed the adhesion and proliferation of periodontal mesenchymal cells and promoted osteogenic differentiation. They demonstrated that the bioaerogel can contribute to bone and peri-implant regeneration, as favorable conditions for the proliferation and osteogenic differentiation of progenitor cells were observed in vitro. Another structure used for osteogenic regeneration is the mixture of NHA with type I collagen. The incorporation of NHA into scaffolds prepared with collagen can increase mechanical strength and help control degradation. As a result, these structures tend to last longer, commonly until the regeneration process is complete. One study showed that pressed NHA/collagen composites exhibited greater hydrophobicity, increased in vivo longevity, increased mechanical properties, and accelerated osteogenic differentiation than pressed collagen. [17] Graphene has also been incorporated into these studies due to its ability to enhance the mechanical properties of bone scaffolds [18]. In addition, it imparts electrical conductivity, allowing the scaffolds to transmit electrical signals to stimulate bone cells. Furthermore, graphene exhibits antimicrobial and antioxidant properties, reducing oxidative stress and microbial load, thereby promoting regeneration. [19]

## 3. Current Evidence and Clinical Results

Clinical and experimental findings demonstrate the efficacy of NHA as an osteoconductive biomaterial for periodontal regeneration. Various randomized controlled clinical trials have documented that its implementation in intraosseous defects generates an average clinical insertion gain of close to 0.9–1.0 mm and an average decrease in probing depth of close to 1 mm, results that are superior to those shown by traditional surgical debridement. [1,2,7] This confirms that NHA acts as a filling material and participates in the modulation of the cellular microenvironment and the bone regeneration process.

Histological analyses performed by Strietzel et al. (2007) demonstrated a progressive replacement of the biomaterial by vital bone, showing intimate integration between the graft and the recipient bone tissue, without the presence of an inflammatory reaction or fibrous encapsulation.[20] This process corresponds to physiological bone remodeling, in which the role of nanohydroxyapatite is to guide the formation of mature lamellar bone through a functional structure. This model supports the scientific basis of the inherent bioactivity of NHA and consistent functional and structural maintenance in demanding clinical scenarios.

The combination of NHA with natural collagen or autologous platelet concentrates (fibrin-rich plasma) (FRP) has demonstrated significant regenerative findings. Scientific evidence attributes these results to the remarkable synergy that enhances angiogenesis and cell expansion through the sustained release of growth factors, especially vascular endothelial growth factor, which is essential for early bone formation. [4,21] In this same context, the incorporation of collagen as a structural matrix promotes graft stability, facilitates intraoperative manipulation, and generates a biological microenvironment suitable for cell migration and three-dimensional bone remodeling in the repair process.

On the other hand, the implementation of NHA in the field of dental implantology has shown favorable results. The study by Arghami et al. (2021) reported a follow-up of up to seven years in implants with a hydroxyapatite coating, demonstrating 98% survival and marginal bone stability, even in immediate loading scenarios; this supports the importance of NHA as an osteoconductive biomaterial.[22]

Hybrid versions of NHA, with different formulations (pure, composite with citrate, or with a collagen matrix), have demonstrated more favorable behavior. This is attributed to increased surface bioactivity and the progressive transfer of phosphate and calcium ions, which are key to osteoblastic mineralization. The study by Dayashankar et al. (2017) showed that NHA compounded with citric acid presented superior regeneration compared to pure NHA; the short- and medium-term results (6 to 12 months) are favorable in clinical periodontal parameters: with a decrease in probing depth, clinical attachment gain, and radiographic increase in bone density. This demonstrates the benefit of hybrid biomaterials in promoting the chemical and mechanical stability of the graft. [2,23-25]

Several of the studies analyzed indicate favorable results associated with the implementation of NHA, although not all are consistent. Moreover, these studies exhibit several methodological limitations that must be considered, such as small sample sizes and limited follow-up periods, which make it difficult to generalize the results to larger populations. Similarly, the diversity of bone defects examined, and the surgical techniques employed could contribute to the variability of the results. Therefore, it is recommended to develop research with standardized designs and long-term histological analyses in order to obtain a more precise understanding of the regenerative processes mediated by NHA.

Given the evidence presented, it is important to interpret the results objectively and critically. Although various studies support experimental and clinical results, the interpretation of the findings must be measured, since true periodontal regeneration cannot be guaranteed in a histopathological context with the use of NHA. Regarding the favorable results in patients with various comorbidities such as diabetes mellitus, cardiovascular conditions, obesity, and/or kidney disease, additional research is required. Additionally, the methodological heterogeneity in the research and the limited histological evidence do not allow for conclusive long-term findings. The analysis presented incorporates basic scientific and clinical foundations to determine the emerging patterns, advantages, and weaknesses of the use of NHA use in periodontal regeneration. This approach attempts to promote critical reflection and future lines of research.

## 4. Future Perspectives

NHA has established itself as an innovative biomaterial in the field of periodontal regeneration due to its interesting attributes in terms of biomimetic composition and high bioactivity. However, its clinical implementation still raises certain uncertainties. These challenges are closely linked to tissue integration, structural stability, and behavior in complex periodontal defects. Innovation in NHA research for periodontal regeneration presents clear opportunities to optimize and promote its biological and clinical performance.

First, studies on the surface modification of NHA should be considered. This can be developed through bioactive coatings on the biomaterial or the incorporation of bone morphogenetic proteins. These modifications are designed to promote cell proliferation and differentiation in the early stages of osteogenesis, ensuring the preservation of structural stability.

Second, in order to improve mechanical properties and biological tissue response, hybrid biomaterials could be designed in which NHA is incorporated with natural or synthetic biodegradable polymers; this modification could guarantee increased flexibility and resistance, favoring a microenvironment for angiogenesis and vital bone deposition.

Third, three-dimensional bioprinting (3D printing) has emerged as a promising technology, enabling the manufacture of customized scaffolds, grafts, and biological constructs corresponding to the characteristics of complex periodontal structures. Some potential advantages of this technology include shorter surgical time when using preformed grafts, better adaptation, increased stability, and greater predictability. 3D printing of NHA composites would allow the design of customized grafts with hierarchical topography and molecular functionalization, which could enhance cell adhesion and osteoinduction, thereby optimizing the biological process of bone regeneration.

Finally, it is essential to design multicenter longitudinal studies that analyze the efficacy of NHA in different scenarios, ranging from complex bone defects to patients with systemic comorbidities (osteoporosis, hypertension, diabetes mellitus, smoking). Therefore, proper clinical, radiographic, and biomolecular monitoring is necessary, along with periodic histomorphometric evaluations to ensure the quality of the results.

## 5. Conclusion

Recent scientific findings profile NHA as a promising, versatile, and predictable biomaterial thanks to its biocompatibility, osteoconductivity, and ability to integrate with bone tissue. Several studies have demonstrated significant improvements in key clinical parameters, including bone density and clinical attachment gain. Furthermore, histological findings show a continuous progression of replacement by vital bone. Its hybrid design in combination with FRP or collagen has improved its therapeutic potential. Studies aimed at improving tissue integration, structural stability, and behavior in complex bone defects are needed, as well as longitudinal studies to corroborate its long-term efficacy.

| Abbreviation | Full Form |
|---|---|
| NHA | Nanocrystalline hydroxyapatite |
| Zn | Zinc |

**Declarations:**

**Supplementary Materials:** Not applicable.

**Author Contributions:** Conceptualization, S.M.L.-M, M.A.A.-S, F.J.A.-B, M.A.R.-G, M.G.O.-R, J.A.-M.; formal analysis, S.M.L.-M, M.A.A.-S, F.J.A.-B, M.A.R.-G, M.G.O.-R, J.A.-M.; investigation, S.M.L.-M, M.A.A.-S, F.J.A.-B, M.A.R.-G, M.G.O.-R, J.A.-M.; resources, S.M.L.-M, M.A.A.-S, F.J.A.-B, M.A.R.-G, M.G.O.-R, J.A.-M.; data curation, S.M.L.-M, M.A.A.-S, F.J.A.-B, M.A.R.-G, M.G.O.-R, J.A.-M.; writing—original draft preparation, S.M.L.-M, M.A.A.-S, F.J.A.-B, M.A.R.-G, M.G.O.-R, J.A.-M.; writing—review and editing, S.M.L.-M, M.A.A.-S, F.J.A.-B, M.A.R.-G, M.G.O.-R, J.A.-M.; visualization, S.M.L.-M, M.A.A.-S, F.J.A.-B, M.A.R.-G, M.G.O.-R, J.A.-M.; supervision S.M.L.-M, M.A.A.-S, F.J.A.-B, M.A.R.-G, M.G.O.-R, J.A.-M.; project administration, S.M.L.-M, M.A.A.-S, F.J.A.-B, M.A.R.-G, M.G.O.-R, J.A.-M.; All authors have read and agreed to the published version of the manuscript.

**Funding:** No funding was acquired.

**Institutional Review Board Statement:** Not applicable.

**Informed Consent Statement:** Not applicable.

**Consent for publication:** Not applicable.

**Data Availability Statement:** The data is available upon request from the corresponding author.

**Acknowledgments:** Not applicable.

**Conflict of Interests:** The authors declare no conflict of interest.

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