Academic Journal of Science and Technology
ISSN: 2771-3032 | Vol. 23, No. 2, 2026

Nano-hydroxyapatite/Polylactic Acid Composite Scaffolds for Bone Tissue Regeneration: Preparation, Modification, and Clinical Translation Challenges

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Abstract: Bone defect repair has long been a core challenge in clinical orthopedics and maxillofacial surgery. Nano-hydroxyapatite/polylactic acid (nHA/PLA) composite scaffolds, which combine the processability of polylactic acid with the biological activity of hydroxyapatite, are a highly regarded material system in the field of bone tissue engineering. This paper analyzes from four levels: material preparation, functional modification, bioperformance and transformation bottleneck, systematically reviews the applicable boundaries of mainstream preparation techniques such as 3D printing and electrospinning, and compares the advantages and disadvantages of three modification strategies: ion doping, active factor loading, and multi-component compounding. The study found that nHA/PLA composite scaffolds have accumulated sufficient positive evidence in non-load-bearing bone repair, but problems such as nHA dispersion, degradation-regeneration matching, and the lack of load-bearing bone application data still restrict their clinical translation. In particular, there is a lack of consensus on the dynamic equilibrium of acid production from PLA degradation and alkaline neutralization of nHA, as well as the immune-osteogenic coupling mechanism. Future research will continue to advance in three areas: multi-scale design, immune regulation, and large animal evaluation.

Keywords: Nano-hydroxyapatite; Polylactic acid; Bone tissue engineering; Composite scaffold; Osteogenic differentiation.

1. Introduction

Trauma, tumor removal, etc. can all cause bone defects, and the number of patients undergoing bone repair surgery worldwide is huge each year. Autologous bone grafting is still regarded as the gold standard in clinical practice, but the donor site is painful, infected and has limited sample availability. Allogeneic bone and xenogeneic bone face immune rejection, pathogen transmission and ethical controversies [1]. As a result, artificial bone replacement materials have become a persistent hotspot in the intersection of materials science and regenerative medicine. An ideal bone repair scaffold needs to meet multiple requirements such as biocompatibility, biodegradability, appropriate mechanical strength, three-dimensional connected pore structure, and bone conduction/bone induction activity.

Polylactic acid (PLA), a biodegradable polyester approved by the FDA in the United States, has excellent thermoplasticity and can be prepared by technologies such as 3D printing and electrospinning. However, its degradation product lactic acid may induce inflammation, its surface hydrophobicity leads to poor cell adhesion and spreading effect, and PLA itself lacks osteogenic bioactivity and can only provide structural support [2]. The chemical composition and crystal structure of nano-hydroxyapatite (nHA) are highly similar to the inorganic phase of natural bone, and the high specific surface area and surface activity can provide a bone-like mineral microenvironment. Introducing nHA into the PLA matrix to construct an organic- inorganic composite system could theoretically achieve the triple goals of mechanical enhancement, acid-base regulation and biological activity improvement simultaneously [3].

Existing studies have accumulated a large amount of data on the optimization of the preparation process and functional modification of nHA/PLA composite scaffolds, but the horizontal comparability is insufficient. Some studies tend to report the osteogenic superiority of the material, while discussions on its intrinsic defects, the uncertainty of its mechanism of action, and transformation obstacles are relatively weak. This paper selects representative research results in recent years and presents an objective picture of the field in four levels: material preparation - functional modification - biological performance - transformation bottleneck, and discusses the controversial issues specifically.

2. Advances in the Preparation Technology of nHA/PLA Composite Scaffolds

The microstructure of the scaffold directly affects cell behavior and bone regeneration effect, and the preparation technique is the core factor determining pore structure characteristics. Different preparation processes have different focuses, and the selection should be based on the specific repair target.

2.1. 3D printing forming process

3D printing enables personalized design of scaffolds. Fused Deposition Modeling (FDM) is most widely used because of its low cost and high material utilization rate. Li et al. [1] prepared nHA/PLA scaffolds loaded with β -cyclodextrin-chlorhexidine and acellular matrix hydrogels using FDM, which had both antibacterial and cell-inducing functions. The core advantage of 3D printing lies in the precise control of pore size (200-500 μm) and porosity. The nHA content is usually controlled at 5% to 20%. Below 5%, the effect is not obvious, and above 20%, it is prone to print filament breakage and uneven output. Jiang et al. [4] also observed in the

nHA/PA66 study that the interlayer strength decreased after the inorganic phase content exceeded the threshold, indicating that particle agglomeration is a common problem. Selective laser sintering (SLS) does not require a support structure, but the equipment and materials are costly and the high temperature is not friendly to heat-sensitive factors. Overall, FDM is still dominant, but the optimal match of print parameters to nHA content has not been standardized.

2.2. Electrospinning and other preparation approaches

Electrospinning can prepare ultrafine fiber membranes, whose topological morphology is similar to that of extracellular matrix. Fallah et al. [5] verified the promoting effect of the PCL/nHA system on bone regeneration. For PLa-based electrospinning, nHA dispersion also poses challenges. The inherent limitation is that the products are mostly two-dimensional films, making it difficult to construct large three-dimensional scaffolds, which are more suitable for guiding bone regeneration membranes. The freeze-drying process is mild but has an irregular pore structure; Solvent casting is low-cost but has the problem of organic solvent residue and irregular pores.

Overall, 3D printing is suitable for three-dimensional scaffolds of load-bearing parts; Electrospinning is suitable for film-type products; Freeze-drying, etc. can be used during the laboratory exploration stage.

3. Functionalization Modification Strategies and Material Design

The osteogenic activity of the pure nHA/PLA binary system is mainly based on bone conduction. Modification can confer additional functions, which can be roughly summarized into three pathways: inorganic ion doping, bioactive factor and cell loading, multi-component compounding and surface modification, each with its own emphasis and limitations.

3.1. Inorganic ion doping modification

Introducing bioactive ions such as strontium (Sr) into the nHA lattice can endow functionality at the elemental level. Strontium promotes osteogenesis and inhibits osteoclasts, and is of great value in osteoporosis repair, with substitution ratios typically ranging from 5% to 10% molar fraction. Shaikh et al. [3] prepared Sr-nHA/PLA composites with improved mechanics and osteogenic differentiation. Attention should be paid to the kinetics of strontium ion release: too fast is cytotoxic, too slow is ineffective. Research on long-term release patterns and cumulative effects in vivo is still insufficient. Magnesium, zinc and copper ions also have their own potential, and multi-ion co-doping is an emerging direction, but the complexity and the difficulty of explaining the mechanism increase accordingly.

3.2. Bioactive factors and co-culture systems of cells

Loading growth factors such as BMP and SDF-1 is a direct approach to enhancing osteogenic induction. Li Xueying [6] constructed SDF-1-loaded HA nanowire /PLA composite membranes for periodontal bone regeneration and verified good results. Growth factors face common problems such as poor stability, high cost, and risk of ectopic osteogenesis. Some studies have turned to natural active substances such as chamomile extract [5], which are low-cost, multi- target, but complex in composition and difficult in quality control. The cell-scaffold combination strategy is more effective. Ekrampoor et al. [7] combined functionalized PLA/nHA scaffolds with dental pulp stem cells for mandibular defects in rats and significantly improved bone regeneration, but the conversion threshold and cost of the cell scheme are much higher than those of the simple material.

Horizontal comparison: Ion doping is the simplest but has limited gain; Active factors have a direct effect but are risky; Cell regimens are the best but the most complex.

3.3. Multi-component compounding with surface functionalization

Jia et al. [8] prepared PLA/nHA/ human acellular amniotic membrane ternary scaffolds with improved biological activity. The "hard skeletons-soft matrix" composite structure of hydrogel and 3D printed scaffold was also shown in the study by Li et al. [1], which can play an advantage in vascularization repair, but attention should be paid to the synchronization of two- phase degradation and interface binding. Surface functionalization (plasma treatment, dopamine coating, etc.) can improve cell adhesion, but the long-term stability of the coating and the foreign body shedding reaction are difficult to be fully exposed in short-term experiments.

4. Evaluation of Osteogenic Biological Properties

The osteogenic properties of the material need to be verified layer by layer from the in vitro cellular level to the in vivo tissue level, with different evaluation levels having different focuses and limitations. Establishing a systematic evaluation system from in vitro to in vivo is the basis for accurately judging the osteogenic potential of materials.

4.1. In vitro cytocompatibility and osteogenic differentiatio

In vitro experiments are the first screening. Song et al. [2] used three-dimensional microtissue models and found that the geometry of PLA-nHA composite microparticles and the distribution of nHA affect osteogenic differentiation, suggesting the importance of microscopic topological morphology. The limitations of in vitro evaluation lie in the large differences between static culture and the real physiological environment, the inability of single-cell models to reflect multi-cell synergy, and the differences in laboratory conditions affecting comparability. The development of dynamic culture and multi-cell co-culture is a way to narrow the transformation gap.

4.2. In vivo bone defect repair effects

Animal models are an essential step. Ekrampoor et al. [7] confirmed the bone regeneration effect of functionalized scaffolds in mandibular defects in rats, and Li Xueying [5] reached similar conclusions in periodontal models. But existing studies have mostly used rodents, whose bone metabolism is much faster than that of humans, and the tendency of defect self- healing cannot be ignored; The observation period is mostly limited to 4 to 12 weeks, lacking long-term follow-up; There is a lack of data on weight-bearing bones, and the current positive results are mostly from non-weight-bearing parts. The extension to long bones still requires support from large animal experiments.

4.3. Immune microenvironment regulation mechanism

Macrophage polarization affects bone repair outcomes. Fan Xincheng [9] found that the morphology and ion release of HA can regulate the macrophage phenotype and thereby affect the osteogenic and osteoclastic balance, providing ideas for "immunomodulatory bone repair materials". Immunological research on the nHA/PLA system is still in its infancy, and a key controversy is whether PLA acid production may induce inflammation, while nHA has dual potential for alkaline neutralization and immunomodulation, and whether there is a simple superposition or complex interference between the two? Does the change in the acidic microenvironment reverse the release of nHA ions and immune effects? These questions await systematic clarification.

5. Existing Bottlenecks and Future Directions

Although significant research progress has been made in nHA/PLA composite scaffold, there are still several key bottlenecks that need to be overcome before they can be widely translated into clinical practice. These bottlenecks involve multiple aspects such as materials science, biology, manufacturing engineering and regulatory science.

5.1. Issues with interfacial compatibility and dispersion uniformity

The uniform dispersion of nHA particles in the PLA matrix is a fundamental prerequisite for determining the overall performance of the composite material. nHA is highly polar and PLA is non-polar, resulting in a naturally poor interface. Agglomerates can lead to mechanical weakness and uneven degradation. Silane coupling agents and surface grafting can improve, but increase costs and the need for biosafety assessment. Establishing a quantitative association of composition - process - structure - performance is key, and machine learning can boost it, but standardized data accumulation is required.

5.2. Dynamic matching of degradation rate to bone regeneration rate

The ideal scaffold should have a degradation rate that is dynamically synchronized with new bone formation. PLA degradation cycles vary greatly, while nHA neutralizes acid production and changes water diffusion pathways. The clinical significance of PLA acid production is controversial: one school holds that lactic acid accumulation interferes with bone remodeling; Another group believes that adequate fluid exchange can clear it in time, and the risk is overestimated. Quantitative data on the neutralizing effect of nHA and the temporal and spatial distribution of pH in the body are very limited. Current studies have focused more on mass loss and mechanical decay, with insufficient understanding of the dynamics of microenvironment pH and the biological effects of degradation intermediates.

5.3. Practical Obstacles to clinical translation

3D printed personalized stents face a series of thresholds such as registration, quality control, sterilization, and long-term safety. Yan Caiping [10] systematically examined the preparation process and biological properties of 3D printed bone repair materials in the nHA/PA66 system, and his research approach and transformation ideas are of reference value for the nHA/PLA system. Sterilization methods have their limitations: high temperature and high pressure are not suitable for PLA, gamma rays may cause degradation, and there is a risk of residual ethylene oxide. Long-term evaluation of large animals is the way to go, but it is costly, difficult to operate, and there are few related studies. Policy uncertainty in the regulatory path also affects the pace of transformation. In addition, the cost issue, like patent barriers, is a real obstacle that cannot be ignored: whether the production and quality control costs of 3D printed personalized scaffolds can be accepted by the medical insurance system, and whether core patents form technical barriers, both directly affect the prospects. In the future, efforts will be made in three areas: multi-scale structural design, regulation of immune microenvironments, and standardized evaluation of large animals.

6. Conclusions

nHA/PLA scaffolds demonstrate combined advantages in non-load-bearing bone repair through organic-inorganic complementarity. PLA's processability is compatible with 3D printing, and nHA gives bone conduction activity. Strontium doping, active factor loading, multi-component compounding and other modification strategies enhance performance at different levels, and the immune regulation perspective brings new ideas. However, issues such as particle dispersion, degradation matching, immune mechanisms, lack of large animal data, cost and patent barriers still need to be overcome. With the continuous cross-integration of materials science, cell biology and additive manufacturing technology, nHA/PLa-based composite scaffolds are expected to gradually expand from non-weight-bearing bone repair scenarios such as maxillofacial bones and periodontal bones to weight-bearing bone applications.

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