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3D Bioprinted Biomimetic Bone Scaffolds for Osteoporotic Fracture Repair

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Abstract:

With the aging of the population and the increase of traumatic events, traditional bone repair materials are facing problems such as insufficient donors, immune rejection and mechanical mismatch, and are particularly difficult to meet the repair needs of osteoporotic fractures. 3D bioprinting technology provides an innovative solution for bone tissue engineering through the bionic strategy of "component-structure-function". This article focuses on the scenario of osteoporotic fractures in the elderly, systematically exploring the material design logic, functional verification system and clinical transformation path of 3D bioprinted bionic bone scaffolds, aiming to break through the traditional technical bottlenecks and promote precise bone regeneration. Existing studies have shown that the boron ions released from the degradation of BBG stents can activate osteogenic signals. The survival rate of human bone marrow mesenchymal stem cells is as high as 95%, the in vitro ALP activity is increased by 3.8 times, and the vascularized bone volume in vivo is doubled compared with the single-cell group. The multi-nozzle parallel printing technology will significantly increase production capacity, and the supercritical CO_2 sterilization technology retains more than 90% of the growth factor activity. Despite the current challenges such as material homogenization and high individualized costs, in the future, by integrating gene editing, dynamic metabolic regulation materials, and AI optimization, it is expected to drive the transformation of bone tissue engineering from a "static replacement" paradigm to a "dynamic regeneration" one, laying the foundation for large-scale clinical application.

Keywords: 3D bioprinting; osteoporotic fracture repair; biomimetic bone scaffold.

1. Introduction

Bones, as important supporting tissues and calcium and phosphorus metabolism organs in the human body, their integrity and functionality are crucial to the quality of life. With the aging of the population and the increase of accidental trauma, bone defect repair has become a major challenge in clinical medicine. Every year, there are more than 20 million new cases of bone defect patients worldwide. Traditional bone repair materials have problems such as insufficient donors, immune rejection, and mismatched mechanical properties, making it difficult to meet the demands of complex bone tissue regeneration. Especially for patients with osteoporotic fractures, the repair materials need to simultaneously meet the requirements of biocompatibility, bone inductance and mechanical compatibility with fragile bone tissue [1], which puts forward higher requirements for the bionic design of scaffolds.

In recent years, 3D bioprinting technology has opened up a new path for bone tissue engineering with its three-dimensional construction strategy of „component bionics - structure bionics - function bionics“ [2]. Bionic bone scaffolds, as the core carrier of 3D bioprinting, have the core innovation of precisely replicating the hydroxyapatite/collagen composite system of natural bones at the material level. The microstructure simulates the multi-level pore network of bone units (micropores smaller than 5μm promote nutrient exchange, and macropores ranging from 100 to 500μm guide angiogenesis); And the sequential controlled release of bioactive factors to simulate the microenvironment of bone repair. Among them, bio-borosilicate glass (BBG) has shown unique advantages in the field of elderly fracture repair due to its Ca/P ratio similar to that of bone minerals, controllable degradability, angiogenic promotion properties, as well as excellent biological activity and osteogenic induction ability, significantly improving the porosity, mechanical strength and angiogenic ability of the stent.

However, behind the advanced nature of bionic design, there are still technical challenges in clinical transformation that need to be urgently broken through. Although materials such as BBG highly simulate the composition of bone minerals, the uniformity of the dispersion of their nanoparticles and the biosafety of the long-term degradation products still need to be strictly verified; The bionic construction of multi-level pore networks relies on high-precision printing processes, but the existing technologies are difficult to achieve both structural fidelity and stable mechanical properties simultaneously at the millimeter to micrometer scale. Although the sequential controlled release of growth factors can simulate the microenvironment of bone repair, there is still a lack of universal solutions on how to precisely match the individualized healing cycle of patients.

This article will focus on the scenario of osteoporotic fractures in the elderly, systematically analyze the material design paradigm, functional verification system and clinical transformation path of bionic bone scaffolds, and provide theoretical support for promoting precise bone regeneration.

2. The Design Logic of Bionic Materials and Their Clinical Adaptation

2.1 Three Dimensions of Bionic Design of Bone Tissue

The outstanding performance of natural bone tissue stems from its unique component-structure-function coupling system.

In terms of component coupling, the complementary synergy between inorganic and organic has been achieved. Among them, the inorganic component hydroxyapatite (HA, accounting for 60-70% of the backbone weight) is arranged in the form of nanocrystals to provide rigid support, the organic component is type I collagen (accounting for 20-30%), forming a fibrous network, which endows toughness through cross-linked structure, and trace proteoglycans regulate the mineralization process [3].

In terms of structural coupling, multi-scale voids are compatible with mechanical load-bearing. From a macroscopic structural perspective, the compact bone (Haves system) forms axial force-bearing channels with an elastic modulus of 15-25 gpa to resist daily loads [4]; Cancellous bone disperses stress through anisotropic pores (with a porosity of 50-90%) to prevent stress concentration [5]. Looking at the microstructure again, the periodic arrangement of nanoscale collagen fibers (67nmD cycle) and the directional deposition of HA crystals enhance the interface bonding. The micron-sized bone cave-bone tubule system (with diameters ranging from 5 to 20μm) forms nutrient transport channels and maintains cell activity [6]. In conclusion, the multi-level pore structure not only meets the mechanical bearing requirements but also provides space for cell migration and vascular growth, thus having unique advantages.

In terms of functional coupling, dynamic repair and metabolic regulation are integrated and constructed. Bone tissue is dynamically remodeled through “Wolff’s Law”, with increased bone density in high-stress areas and bone resorption in low-stress areas [7], achieving real-time matching of structure and load, and having mechanical adaptability. Meanwhile, osteoclasts and osteoblasts work

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collaboratively to maintain the balance of calcium and phosphorus metabolism, and the gradient distribution of growth factors coordinates osteogenesis and vascularization processes. The dynamic adjustment of components and structures ensures the unity of mechanical functions and metabolic functions, achieving a closed loop of "damage - repair - regeneration".

According to the coupling system of natural bones, the design of 3D printed bionic bone scaffolds needs to break through the traditional single dimension of "component bionics" or "structure bionics", and shift towards the collaborative optimization of components and structures, functional dynamic response, and the integration of multi-scale manufacturing processes. Only by achieving deep coupling can the trinity characteristics of "performance - function - lifespan" of natural bones be approached.

2.2 Introduction to Bio-ink Materials

Bio-ink is the core carrier of 3D bioprinting, composed of biocompatible materials, cells, growth factors and functional additives. It needs to meet the characteristics of printability, biological activity, mechanical adaptability and controllable degradation. Typical components of bio-ink include inorganic materials such as HA, bio-glass (such as BBG), calcium phosphate (TCP), etc. Some organic polymers such as collagen, silk fibroin, gelatin, polylactic acid (PLA), and polylactic acid-glycolic acid copolymer (PLGA); As well as functional additives such as vascular endothelial growth factor (VEGF), bone morphogenetic protein-2 (BMP-2) growth factor, nano-clay (enhancing rheology), and gold nanorods (photothermal response) [8]. Bioinks are used to construct a natural bone microenvironment, such as inorganic-organic composite systems. Among them, the BBG-silk fibroin composite ink has a high HA content on the surface layer to enhance the initial stability, and the inner layer BBG sustained-release boron ions to promote osteogenic differentiation, thereby increasing the activity of alkaline phosphatase (ALP) [9]. In addition, bio-ink can intelligently respond and conduct biological regulation. BMP-2 is encapsulated with PLGA microspheres and released only in the local acidic environment of the fracture (pH 5.5-6.5), thereby constructing ph-responsive microspheres and improving the osteogenesis efficiency. VEGF was loaded on gold nanorods and precisely released under near-infrared light irradiation [10], achieving a photothermal trigger system and forming a functional vascular network within 48 hours. The thermosensitive hydrogel /PLA composite ink self-expands at 37°C and adheres to the irregular fracture surface [11], reducing the operational difficulty of the surgery.

2.3 Comparison of Bionic properties of Common Bio-Ink Materials

Table 1. Comparison of Bionic Properties of Common bio-ink Materials

Material type	Bionic characteristics	Mechanical properties	Degradation cycle	Clinical application scenarios
BBG	Ca/P=1.67 Bone-like minerals	Compressive strength 35-50MPa	3-6months	Osteoporotic fracture repair
PLGA	Adjustable pore structure bone-like trabeculae	Elastic modulus 1-3GPa	6-24months	Temporary support for weight-bearing bone defects
HA	The composition is highly consistent with the inorganic phase of bone	High brittleness (bending resistance <10MPa)	More than 2 years	Bone filling in the non-load-bearing area
Silk fibroin protein	Collagen-like fiber structure imitates ECM	Excellent toughness (elongation at break >200%)	Adjustable	Flexible components of composite support

As shown in Table 1, this paper conducts a comprehensive comparison of common bio-ink materials in terms of characteristics, explanation cycles and other dimensions. The comparison results show that BBG, as an inorganic phase with medium-speed degradation and strong osteogenic induction ability, is an ideal core component of the bone scaffold in the scenario of fracture repair in the elderly.

3. Systematic Verification of the Function of Bionic Bone Scaffolds

In order to verify the regulatory ability of the bionic microenvironment on cell behavior, the functions of the bionic bone scaffold were experimentally verified. This also facilitates the optimization of the parameters of the bionic microenvironment and supports the feasibility of clinical transformation. The biological safety and functional ef-

fectiveness of the bionic scaffold were verified through in vitro and in vivo experiments, providing data support for subsequent clinical trials. The functional verification of bionic bone scaffolds will be carried out from three aspects: biological safety, osteogenic ability and angiogenesis ability. Combined with in vitro and in vivo experimental data, it will provide a scientific basis for its clinical transformation.

3.1 Biological Safety Verification

Biological safety is the primary prerequisite for the clinical application of bionic stents. Studies have shown that the concentration of boron ions released by the bioboron-based glass (BBG) scaffold during degradation is 0.5-1.5ppm [12], which can effectively activate the osteogenic differentiation signaling pathway without causing cytotoxic reactions. The survival rate of human bone marrow mesenchymal stem cells (hBMSCs) is > 95%. Real-time monitoring by quartz crystal microbalance (QCM-D) revealed that the binding kinetics of integrin receptors on the scaffold surface was highly similar to that of natural bone, indicating its good biocompatibility. In addition, the supercritical CO_2 sterilization technology can retain the porosity of the scaffold, with a control error of less than 3% and a retention rate of growth factor activity VEGF greater than 90%, solving the problem of decreased mechanical properties caused by traditional sterilization methods.

3.2 Assessment of Osteogenic Ability

The osteogenic induction ability is the core of the function of bionic scaffolds. In vitro experiments showed that the BBG/ silk fibroin protein composite scaffold significantly increased the ALP activity and osteocalcin (OCN) expression level by 3.8 times through the sustained release of boron ions [13]. In large animal models, after 12 weeks of implantation of BBG stably in femoral defects of osteoporotic sheep, the bone volume fraction (BV/TV) reached 62.3%, which was 50% higher than that of the PLGA group (41.2%), and the maximum torsional strength recovered to 78% of the healthy bone, meeting the early weight-bearing needs of elderly patients. Histopathological analysis further confirmed that the proportion of mature lamellar bone was > 50%, indicating that the scaffold has the ability of dynamic bone remodeling.

3.3 Validation of Angiogenesis Function

Vascularization is the key to the construction of the microenvironment for bone regeneration. Rats aged 6-8 weeks were selected to establish a critical bone defect model of the femoral condyle. Scaffolds co-printed with VEGF-loaded microspheres were implanted into the rats and compared with the control group. Stents co-printed with VEGF-loaded microspheres induced the formation of functional vascular networks in HUVEC within 48 hours. Micro-ct quantitative analysis showed that the density of neovascularization was ≥15 vessels/mm² [14]. Eight weeks after the operation, Prussian blue staining solution was perfused into the left ventricle of rats. After death and sample collection, the distribution of blue perfusion vessels in the stent and their anastomosis with the host vessels were observed to evaluate the formation of functional vascular networks. In vivo experiments have shown that the multi-cell co-printing technology significantly increases the vascularized bone volume compared with the single-cell group. Moreover, the blood vessels are mainly distributed radially along the microchannels, anastomosed with the host blood vessels, and achieve synchronous regeneration of “bone-blood vessels” through microchannel interconnection.

To verify the regulatory ability of bionic bone scaffolds on cell behavior and the feasibility of clinical transformation, this paper conducted a systematic verification from three aspects: biological safety, osteogenic ability and angiogenesis ability. In terms of biosafety, the boron ions released by the degradation of the BBG scaffold can activate the osteogenic signaling pathway without cytotoxicity, and its surface integrin receptor has good biocompatibility. The assessment of osteogenic ability showed that the BBG/ silk fibroin protein composite scaffold increased the activity of ALP and the expression of OCN in vitro experiments by slowly releasing boron ions, and had the ability of dynamic bone remodeling. In the verification of angiogenesis function, the scaffold co-printed with VEGF-loaded microspheres induces the formation of a functional vascular network to achieve synchronous regeneration of “bone-blood vessels”. Thus, the regulatory ability of the bionic bone scaffold function on cell behavior and the feasibility of clinical transformation have been fully verified.

4. Construction of an Intelligent Bionic system

With the in-depth development of 3D bioprinting technology, the construction of intelligent bionic systems has become a key direction to break through the existing technical bottlenecks and achieve precise bone regeneration. By integrating artificial intelligence, dynamic material response and multi-cell collaborative technology, bionic bone scaffolds have gradually evolved from static structures to intelligent systems with the ability of „perceiving - responding - adapting“, further approaching the dynamic repair mechanism of natural bones.

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4.1 Bionic design driven by Artificial Intelligence

Traditional bionic design relies on empirical trial and error and is difficult to efficiently analyze the complex coupling relationship of „component - structure - function“ of natural bones. Artificial intelligence provides a new paradigm for material selection, structural design and functional prediction through deep learning and multi-objective optimization algorithms [15]. For example, for the optimization of material combination, a bioink database is established based on the Generative Adversarial Network (GAN). Combined with clinical data such as the bone density and defect morphology of patients, the optimal material ratio scheme is generated. Studies show that the BBG/ silk fibroin composite ratio predicted by AI has an increased compressive strength and a reduced porosity error compared with the traditional trial-and-error method. Furthermore, a growth factor release kinetics model was established through AI, combined with the individual healing cycle of patients, and the sequential controlled-release curve of BMP-2/VEGF was optimized through reinforcement learning algorithms, significantly improving the synchronization rate of osteogenesis and vascularization processes [16].

4.2 4D Printing Dynamic Bionic System

4D printing, by introducing environmentally responsive materials, endows the scaffold with the ability to dynamically evolve over time or in response to external stimuli, simulating the „Wolf‘s Law“ adaptive remodeling characteristics of natural bones. Temperature-sensitive PLA/ silk fibroin composite ink can be adopted. After being implanted in the body and triggered by body temperature, the scaffold self-expands from the flat pre-formed state to a three-dimensional network structure, adhering to the irregular bone defect surface, reducing the need for manual shaping during the operation, and constructing shape memory materials. Piezoelectric ceramic nanoparticles can also be embedded in HA-based scaffolds. Under the action of load, microcurrents are generated to activate calcium ion channels in osteoblasts, promote the expression level of ALP, and simulate the microenvironment of bone regeneration under mechanical stimulation.

4.3 Breakthrough in Multi-cell co-printing technology

Natural bone repair relies on the synergistic effect of osteoblasts, vascular endothelial cells and immune cells. Multi-cell co-printing constructs biomimetic cell communities through spatial positioning and microenvironment regulation to enhance regeneration efficiency.

For this, researchers can adopt a dual-nozzle system. The outer layer prints BBG/ collagen ink loaded with hBMSCs to promote bone formation, while the inner layer prints thermosensitive hydrogel /VEGF ink loaded with HUVECs to guide angiogenesis. The two are interconnected through microchannels to achieve synchronous regeneration of „bone-blood vessels“. Experiments on large animals have shown that at 12 weeks, the volume of vascularized bone is twice that of the single-cell printing group.

For the regulation of the immune microenvironment, the macrophage regulation module was introduced. The surface of the scaffold was modified by M2-type macrophage exosomes to inhibit the secretion of the inflammatory factor IL-6 and promote the expression of the anti-inflammatory factor IL-10, accelerating the transition of the repair phase. Finally, in order to construct the intercellular communication network, the intercellular signal factor gradient was preset through microfluidic technology to guide the directional migration of mesenchymal stem cells to the defect core. The migration efficiency was increased by three times compared with the random distribution, and the healing cycle was shortened [17].

5. Challenges and Solutions in Clinical Transformation

5.1 Challenges in Industrialized Preparation

The composition of bio-ink is complex, and nanoparticles are prone to agglomeration, resulting in fluctuations in the mechanical properties of the scaffold. Traditional production schemes also have certain limitations. Mechanical stirring or ultrasonic dispersion has low efficiency and is prone to destroying bioactive components, resulting in a growth factor inactivation rate of more than 30%, which leads to serious material homogenization problems [18]. To solve this problem, microfluidic chip homogenization technology can be used to achieve monodispersion of BBG nanoparticles through the laminar shear force of microchannels while protecting biological activity. Meanwhile, the cryogenic ball milling process was used to grind the HA/ collagen composite powder in a liquid nitrogen environment, avoiding collagen denaturation caused by high temperature. The uniformity of particle size was significantly better than that of conventional ball milling.

Insufficient stability of the printing process is also a major pain point for industrialization bottlenecks [19]. 3D bioprinting involves multi-parameter collaboration. Environmental fluctuations can easily lead to structural defects,

such as interlayer misalignment and pore collapse. In addition, during continuous 8-hour operation of the industrial-grade bioprater, the elastic modulus of the support fluctuated by ±15% due to temperature drift (±2℃). To solve this problem, a closed-loop feedback control system can be set up, integrating infrared temperature and pressure sensors to adjust the nozzle temperature and extrusion pressure in real time, reducing the printing error from 200μm to 50μm, and maintaining a constant temperature and humidity printing environment to reduce the standard deviation of the porosity of the support from 8% to 2%.

In the laboratory, it takes 4 to 6 hours to print a single piece, which cannot meet the demands of large-scale production. It can carry out interdisciplinary integration and improve the multi-nozzle parallel printing technology with other specialties such as mechanical design and manufacturing. In the experiment, researchers upgraded the traditional single-nozzle printing platform to a 4×4 array nozzle module based on the Cartesian coordinate system structure in mechanical design. Using array nozzles, 16 brackets were printed simultaneously, and the nozzle positions were monitored in real time through intelligent path planning. Achieve load balancing to avoid collisions. The experimental results show that the printing time of a single bracket has been shortened from 4-6 hours to 1.2-1.5 hours, and the production capacity has increased by 400%. In addition, there was no significant difference in porosity and average pore diameter between the row printing bracket and the single-nozzle printing group, and the mechanical property tests also met the requirements of cancellar bone mechanics. Bio-ink can also be pre-coated on a flexible substrate and rapidly formed through laser cutting and lamination technology. It is expected that the daily output can be significantly increased.

5.2 The Conflict between Individualized Adaptation and Large-Scale Production

The morphology of bone defects in each patient varies significantly. The production cost of customized stents is as high as $5,000 - $8,000 per piece, far exceeding the payment capacity of medical insurance. To reduce costs, the brackets can be decomposed into standardized units. By combining and adapting to different defect sizes, the time for customized modeling can be reduced and time costs can be saved. Based on the CT data of patients, doctors generate lightweight structures to reduce material consumption and printing time.

5.3 Sterilization Process

Traditional sterilization techniques have certain limitations. Although the ethylene oxide sterilization method can effectively sterilize, the residual toxicity leads to a passing rate of cytotoxicity tests of only 65%-70%, and the compressive strength of the scaffold decreases by 35%. In gamma irradiation, high-energy rays destroy polymer chains, accelerating the degradation rate of PLGA by 50% and causing conformational changes in growth factors, resulting in an activity loss of approximately 40% [20].

To avoid high-temperature damage, the method of low-temperature plasma sterilization can be adopted. Through the excitation of argon gas by radio frequency electric field, active particles are generated, which penetrate the pores of the scaffold to kill microorganisms. After testing, the retention rate of compressive strength and the cell survival rate of BBG scaffolds increased to 95% after plasma sterilization. In addition to sterilization with active ions, supercritical CO_2 also has both gas permeability and liquid solubility, which can efficiently inactivate spores and cause no structural damage to the HA/ collagen composite scaffold. After the silk fibroin protein scaffold was treated with supercritical CO_2, the porosity remained almost unchanged and the activity of VEGF was largely retained.

6. Conclusion

This review focuses on the application of 3D biopharmaceutical bionic bone scaffolds in the repair of osteoporotic fractures in the elderly and systematically analyzes the full-chain research from material design to clinical transformation. At the material design level, by mimics the „component - structure - function“ triple coupling system of natural bone, the inorganic-organic composite bio-ink constructed with BBG as the core not only achieves a Ca/P ratio and multi-level pore network similar to bone minerals, but also synergistically promotes osteogenic differentiation and angiogenesis through the sustained release of boron ions and the controlled release of growth factors. The functional verification experiments indicated that the BBG scaffold could activate the osteogenic signaling pathway in vitro and double the vascularized bone volume in vivo compared with the single-cell group, confirming its biological safety and functional effectiveness.

The exploration of the construction of intelligent systems and the challenges of clinical transformation further highlights the application value of the research. Through AI-driven material ratio optimization, 4D printing dynamic response and multi-cell co-printing technology, bionic bone scaffolds have evolved from static structures to intelligent systems of „perception-response-adaptation“, such as temperature-sensitive materials self-expanding to fit bone defects and multi-cell microchannel interconnection to achieve synchronous regeneration of „bone-blood-

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vessels“. In response to industrialization challenges, multi-nozzle parallel printing and laser cutting lamination technology will enhance production capacity, while supercritical CO_2 sterilization technology retains over 90% of the growth factor activity, providing an engineering solution for large-scale production.

Finally, through the integration of multiple disciplines, this study achieved the expected goals in three dimensions: theoretical innovation in bionic design, experimental support for functional verification, and technological breakthroughs in clinical transformation, providing a systematic solution to problems such as insufficient donors and poor mechanical matching of traditional bone repair materials. If the future can be deepened in gene editing and dynamic metabolic regulation materials, it is expected to promote the paradigm shift of bone tissue engineering from „static replacement“ to „dynamic regeneration“, and truly realize the clinical vision of precise bone regeneration.

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