ISSN 2616-5791 Vol.5, Issue 2: 62-68, DOI: 10.25236/AJMHS.2024.050210

Research Progress of Bone Repair Materials for Bone Defects

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Abstract: *Bone defects remain a challenge for orthopedic treatment. At present, there are various treatment methods at home and abroad. Bone grafting and bone transport have become the main clinical techniques. However, there are some defects. In recent years, the rapid development of bone tissue engineering (BTE) technology and materials has brought new ideas and strategies for the treatment of bone defects. An ideal BTE material should be nonimmunogenic, biocompatible, controllable, accessible, and have mechanical properties similar to those of natural tissue materials. In addition, it must have a suitable structure and pore size to guarantee cell survival. Combined with the latest clinical application results, this article will deeply analyze the advantages and disadvantages of organic bone materials and inorganic bone materials, and explore the ideal effect of composite materials in the field of bone repair. This is important for promoting the development of bone defect repair.*

Keywords: *Bone defect; bone tissue engineering; biomaterials*

1. Introduction

Bone is a kind of connective tissue mainly composed of minerals, and bone is also a dynamic self-repairing organ. However, large bone defects [1] caused by trauma, malignancy, infection and congenital diseases cannot be well remodeled, therefore, surgical intervention and bone substitutes are required. Currently, bone graft materials include autogenous bone, allogeneic bone and artificial bone [2]. Autologous bone is still the "gold standard" and preferred method for the treatment of bone defects [3], but it may cause excessive pain, blood loss, and damage to the normal structure of the donor site. Allografts contain bone morphogenetic proteins (BMPS) and other growth factors that promote bone progenitor cell formation by differentiating mesenchymal stem cells [4]. However, allogeneic bone may be nonunion, leading to re-rupture and revision surgery [5]. Diabetes is a metabolic disease with a wide range of patients. Due to its complex pathological microenvironment, its high oxidative stress state, high level of protease, and blood glucose fluctuation have a significant negative impact on the healing of autologous wounds and tissue defects. Experiments have shown that blood glucose fluctuation is more harmful to bone tissue than continuous hyperglycemia [6].

The mechanism of bone repair is a complex process, and bone repair is a process that restores its initial structural and mechanical properties through self-repair and regeneration. In this process, trace elements such as calcium and magnesium ions play an important role in regulating the proliferation and differentiation of various cells (such as mesenchymal stem cells, osteoblasts and osteoclasts) in the stage of bone repair, as well as promoting new angiogenesis and growth factor release. The synergistic action of multiple factors is required, among which the application of trace elements and biomaterials has important clinical value.

Therefore, the purpose of producing composite materials by BTE is to prepare biomaterials with excellent properties for applications in bone tissue engineering and other fields. The main goal of BTE is to reconstruct the normal function of damaged human bone tissue. BTE is built around four key components - (a) osteoblasts that generate bone tissue matrix, (b) biocompatible frameworks or scaffolds created from bioactive materials that mimic bone ECM, (c) vascularization that provides mass nutrient and waste transport, and (d) morphogenetic signals that guide cells [7]. The advantages and disadvantages of inorganic bone materials and organic bone materials are summarized to provide reference for subsequent research. The specific methods and contents are as follows:

ISSN 2616-5791 Vol.5, Issue 2: 62-68, DOI: 10.25236/AJMHS.2024.050210

2. Data and methods

2.1. Literature source

PubMed, PMC, China Biology Medicine Disc, China National Knowledge Infrastructure (CNKI) and Wanfang Database were used to retrieve the literature related to bone defect repair materials published from May 2010 to May 2013. Bone tissue engineering; "bone defect, bone repair" was used as the English search keywords, and "biomaterials, bone repair materials, bone tissue engineering, bone defect, bone repair" was used as the Chinese search keywords.

2.2. Inclusion and Exclusion criteria Inclusion criteria

(1) Literature related to bone defect materials; (2) The latest literatures or published in authoritative journals in the same field were selected. 0 Exclusion criteria: repeated studies; Studies not less than 5 years old and no new findings highlighted.

2.3. Quality assessment

340 literatures were retrieved, including 150 English literatures and 190 Chinese literatures. Literatures with low correlation with research, old research content and repeatability were excluded, and 53 literatures met the criteria were finally included.

3. Results

3.1. Inorganic bone material

3.1.1. Biological ceramics

In the past years, Bioceramics are a class of ceramic-based materials that are similar to the main components of human bone and have been studied for application in bone tissue replacement implants. Bioceramic nanomaterials, especially those based on calcium phosphate, have been widely used in orthopedics. Hydroxyapatite (HA) is considered to be the main inorganic component of human natural bone, and its good biocompatibility and biological activity has been widely studied and applied [8], calcium phosphate has the advantages of bone conductivity and porosity. However, the traditional HA has the disadvantages of high brittleness, low toughness, low biological activity, slow degradation, etc. Calcium phosphate has the disadvantages of limited mechanical strength and high brittleness. Qiao et al [9] showed that the composite material composed of 3D printed β-tricalcium phosphate scaffold combined with rifampicin and isoniazid sustained-release microspheres had good anti-inflammatory and osteogenic effects, and was a potential material for the treatment of infectious bone defects.

3.1.2. Bioglass

Bioglass (BG) used for bone repair materials includes silicate bioglass, phosphate bioglass and bioactive glass. BG has advantages of good biocompatibility and mechanical properties. However, BG has lower mechanical strength and brittleness compare to human bone tissue, which cannot meet the needs of clinical orthopedic patients [10]. Recent studies have shown that. The degradation kinetics of PCL/ BG bone scaffold was enhanced when the pore size increased from 500 μm to 200 μm [11]. Degradable scaffolds can release chemicals to stimulate cell growth and differentiation during degradation, thereby promoting tissue regeneration. It can also be used as a drug carrier to slowly release the drug to the lesion site, so as to achieve the purpose of long-term treatment. Duan et al. [12] developed a high-strength dual-function scaffold, which combined the high mechanical strength and controllable biodegradability of surface modified magnesium alloy with the excellent biocompatibility and bone conductivity of bioglass - magnesium phosphate bone cement to provide support for load-bearing bone defects and thus achieve bone regeneration. In the New Zealand white rabbit model of radius defect, the expressions of bone formation related proteins BMP2, Collagen, type I, alpha 1(COL1a1)and Osteocalcin(OCN) were increased by X-ray, Micro-CT and histological analysis.

3.1.3. Metallic material

Metal materials are the most widely used implants in orthopedics. Metal materials have sufficient corrosion resistance, mechanical properties and machinability, and are mainly used as artificial joints and implant firmware. [13] The main metal materials are stainless steel, titanium and titanium alloys, cobalt-

ISSN 2616-5791 Vol.5, Issue 2: 62-68, DOI: 10.25236/AJMHS.2024.050210

based alloys, nickel-titanium alloys, etc. Titanium and titanium alloys are the most commonly used materials [14]. The advantages are non-toxic, harmless, and have good corrosion resistance. The disadvantages are that the elastic modulus is too high, the surface is too smooth for cell attachment, and there are toxic corrosion products and allergens. Therefore, it is necessary to find a kind of composite bone tissue engineering material with good biocompatibility, mechanical properties and degradability.

3.2. Organic bone material

In the current biomedical field, natural polymer organic bone repair materials have attracted much attention. This kind of material is an ideal choice for repairing bone defects due to its biocompatibility, biodegradability, excellent mechanical properties and extracellular matrix that can mimic bone. Common natural biological materials are: collagen, cellulose, alginate, chitosan and so on. However, there are also some defects: insufficient mechanical strength, porosity problems, fast degradation, limited bearing capacity, complex production process, etc. Therefore, a composite system is constructed to meet the required functions of bone defect repair.

3.2.1. Natural biomaterials

In recent years, different types of chitosan based complexes have been developed that could have potential application value in implant bone graft devices. LEMOS and CORREIA et al. [15] added bioactive glass nanoparticles prepared by sol-gel method to chitosan matrix and prepared bioactive glass/chitosan composites by freeze-drying method. KUMAR et al. took polypyrrole/chitosan as raw material and conducted in-situ electrochemical polymerization in oxalic acid medium to synthesize composite materials with biological activity [16]. LEE et al. [17] prepared alginate - catecol hydrogel by covalently cross-linking, which had low cytotoxicity. The mechanical strength could be adjusted by adjusting the mass fraction of alginate - catecol in the gel. Bayer et al. [18] designed the alginate gel/calcium phosphate composite scaffold to control the release of bone morphogenetic protein 2 and platelet-derived growth factor BB, which has a synergistic effect on bone regeneration. In recent years, the research on composite scaffolds has been deepened, which provides more possibilities for the clinical treatment of bone defects.

3.2.2. Copolymer materials

The copolymer components of organic bone repair materials mainly include the following: polycaprolactam (PCL), polylactic acid (PLA), polylactic acid-glycolic acid (PLGA), polyvinyl alcohol (PVA) and Polyether-ether-ketone (PEEK). These copolymers have a wide range of applications in biomedical fields, such as internal fixation of fractures, dental repair, soft tissue repair, etc. Copolymer materials have good biocompatibility and degradability, and with the continuous development of materials science and biomedical engineering, copolymer materials will be further optimized. Ortega-Yago et al. [19] designed a new filament based on the melting of PLA powder for fused deposition modeling (FDM) sheets on which tensile mechanical tests of bone composite materials were conducted. Hu et al. [20] synthesized a composite hydrogel for bone tissue using PVA and pectin as raw materials. The results show that the composite hydrogel can increase the activity of alkaline phosphate (ALP) and calcium biommineralization, up-regulate the expression of osteoblast gene, and accelerate the bone healing in vivo after femoral defect transplantation. PEEK has an elastic modulus similar to that of natural human bone, and has good thermal and chemical stability. PEEK is widely used in producing prosthesis and have gained great attention for repair of large bone defect in recent years with the development of additive manufacturing. PEEK has been used in BTE for a lot of years now. The mechanical properties of porous PEEK are close to those of cancellous bone, but the lower yield strength poses a design challenge [21].

3.3. Modification by cell growth factors

The ideal composite bone biological scaffold has excellent properties of bone induction, bone conduction and bone integration. At present, the commonly used composite scaffolds are loaded with traditional Chinese medicine, additive manufacturing technology, doped metal ions, added cytokines, nano hydrogels and so on

3.3.1. Compound cell growth factor

Natural scaffolds can also induce cell differentiation and vascular growth by adding small signaling molecules such as bone morphogenetic proteins (BMPs), fibroblast growth factors (FGFs), and vascular endothelial growth factors (VEGFs). VEGF is a major player in angiogenesis, which can stimulate the

ISSN 2616-5791 Vol.5, Issue 2: 62-68, DOI: 10.25236/AJMHS.2024.050210

migration and proliferation of endothelial cells and indirectly stimulate bone formation by regulating the release of osteoblastic growth factors and through paracrine signaling. The microspheres prepared by Liu et al. [22] found that BMP-2 and VEGF have sustained release and biocompatibility, and could promote osteoblast differentiation and proliferation of vascular endothelial cells.

3.3.2. 3d Printing technology

As a disruptive technology, 3D printing has great potential in the field of bone repair. Zhou et al. [23] prepared a MC/PLGA scaffold made by adding polylactic-glycolic acid copolymer (PLGA) and magnesium metal to the matrix of collagen matrix protein (MC). On the one hand, it has good biocompatibility similar to MC and has a strong effect on promoting fracture healing. The addition of PLGA made the scaffold have an interconnected porous structure, and the addition of magnesium made the scaffold have anti-inflammatory, osteogenic and angiogenic activities.

3.3.3. Traditional Chinese medicine stent

Traditional Chinese medicine (TCM) extracts are combined with BTE to promote cell proliferation and regulate bone metabolism [24]. BTE can be used as a delivery carrier to improve bioavailability, prolong residence time and maintain drug release [25], making scaffolds more capable of bone regeneration. Bioactive molecules commonly used in TCM include pueraria, icariin, gastrodia, etc. Puerarin has been shown to promote new bone formation in the β-tricalcium phosphate osteoblast complex [26]. Li [27] et al. prepared a new type of gaviin-PU /n-HA scaffold for bone repair and regeneration of immune regulatory materials. And Xie [28] et al. prepared icariin hydroxyapatite/alginate (IC/HAA) into a porous composite scaffold for sustainable release of icariin and bone regeneration. IC/HAA promoted the proliferation of rBMSCs, and also up-regulated the relative expression levels of osteogenic genes and Wnt signaling pathway genes.

3.3.4. Nano hydrogel

Hydrogels consist of natural or synthetic polymer networks with high water absorption capacity that provide a microenvironment very similar to that of natural tissue extracellular matrix (ECM) [29] to stimulate cell adhesion, proliferation, and differentiation. The combination of polymer and nanomaterials through chemical crosslinking further enhances the toughness and strength of hydrogels, which can be used as a new generation of drug carriers to achieve functions such as magnetic response, targeted delivery and local temperature rise therapy [30]. Nanoscaffolds include porous scaffolds, hydrogels and fiber scaffolds [31]. Lu et al. [32] studied a composite hydrogel with methacrylate gelatin (GelMA) and methacrylate hyaluronic acid (HAMA) introduced appropriate nano-hydroxyapatite (nHAP) to improve its mechanical properties. Yao et al. [33] developed PH-sensitive gelatin methylacrylyl (GelMA) -sodium alginate oxide (OSA) hydrogel for double-release gentamicin sulfate (GS) and phenamil (Phe) to enhance antibacterial activity and promote large bone defect repair. GelMA-HAMA/nHAP composite hydrogel as a drug delivery system has been shown to promote osteogenesis of bone marrow mesenchymal stem cells (BMSCs) and endothelial progenitor cells (EPCs) angiogenesis in vitro.

3.3.5. Metal ions

Metal ions directly affect human metabolism and regeneration of damaged tissues. Strontium (Sr), zinc (Zn) and magnesium (Mg) are considered to be essential trace elements for bone growth and mineralization, and play an important role in immune regulation, bone development and bone reconstruction [34].

Strontium is an alkaline earth metal element, and studies have shown that strontium regulates the function of osteoblasts and osteoclasts through the BMP-2/Smad1 and OPG/RANKL signaling pathways [35], thus affecting bone remodeling. Sr is thought to have both osteogenic (anabolic) and anti-absorption (catabolic) effects [36]. Zhao et al. [37] developed a new type of doped strontium (Sr) photocrosslinked sodium methacrylate alginate (SR-PMA) hydrogel. Sr-pma stimulated the expression of osteogenic genes and proteins, and significantly improved the osteogenic differentiation and mineralization. The new alginate/collagen composite scaffold [38] with 2-20mg/mL of 1% strontium-calcium polyphosphat(SCPP) provides adjustable long-term degradation and material characteristics suitable for potential in vivo critical size defects CSD applications. HASSAN et al. [39] synthesized strontium Zn-doped nano-hydroxyapatite by sol-gel technology, and used polylactic acid-glycolic acid copolymer as the matrix to prepare a composite scaffold. The scaffold had a good porous structure with an average pore size of 189-406μm, which was conducive to cell adhesion and proliferation.

Inadequate zinc intake (less than 3 mg/day) may be a risk factor for fractures, osteopenia, and osteoporosis [40]. Zinc supplementation (40-50 g/day) can maintain bone density and accelerate bone

ISSN 2616-5791 Vol.5, Issue 2: 62-68, DOI: 10.25236/AJMHS.2024.050210

healing, on the one hand, zinc can stimulate runt-related transcription factor 2 (Runx2), promote osteoblast differentiation. On the other hand, zinc was found to inhibit osteoclast-like cell formation and reduce bone resorption. In addition, zinc regulates the RANKL pathway, thereby promoting bone remodeling.

Magnesium is an important trace element in the inorganic components of bone tissue, and lack of magnesium will lead to bone dysplasia, osteoporosis and bone fragility [41]. Zhao et al. [42] used the coordination reaction of metal ion ligands to construct a bisphosphate-functionalized injectable hydrogel microsphere (GelMA-BP-Mg). Magnetically stimulated Mg2+ trapping composite microspheres stimulate osteoblasts and endothelial cells, inhibit osteoclasts, facilitate osteogenesis and angiogenesis, and ultimately effectively promote cancellous bone regeneration. The beneficial effects of PLGA/Exo-Mg-GA MOF composite scaffold designed and synthesized by Kang et al. [43] on osteogenesis of human bone marrow mesenchymal stem cells (hBMSCs) and angiogenesis of human umbilical endothelial cells (HUVECs). The elastic modulus of Mg is close to that of cortical bone, effectively reducing the occurrence of stress shielding [44]. However, at present, the research of various kinds of trace elements is still in the animal experiment stage, and there are no clinical research results.

4. Summary and Prospect

BTE is a new type of material, which has problems such as poor biocompatibility, cell migration, and adhesion. The precise control of cell differentiation, gene expression and growth factors, as well as the safety of clinical application still need to be further studied. With the integration and development of multiple disciplines, it is possible to construct new bone repair substitutes or directly construct bioactive bone tissues in vitro. After clarifying the efficacy, complications, and mechanisms of action of existing treatments, well-designed randomized controlled clinical trials are needed to further accelerate the translation of these treatments to clinical application.

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