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Original Article

Research Progress of Bone Tissue Regeneration Scaffolds

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Abstract:

Background: As a completely regenerated tissue, bone tissue has strong regeneration and healing capabilities. However, nonunion and malunion caused by large bone defects and complex fractures are still major challenges facing the medical community.

Objective: To review the current known related literature, summarize the research progress of bone tissue regeneration scaffolds, understand the mechanism of bone tissue regeneration scaffolds in osteogenesis, and provide theoretical references for new osteogenesis programs.

Results and Conclusions: Traditionally, bone defects are usually treated with bone grafts. Today, synthetic biomaterials are gradually replacing traditional bone grafts. Initially, based on the biomechanical properties of these materials, they were applied to structural support and repair. With the development of science and technology, bioactive or bioabsorbable materials are used in the construction of structural scaffolds to promote the growth of bone tissue. At present, the design of structural scaffolds is usually used to induce bone formation and vascularization of bone tissue. These scaffolds are usually designed as porous structures and are made of biodegradable materials containing different growth factors and stem cells. They not only have good biomechanical properties, but also promote the healing and repair of bone defects.

Keywords: Bone defects; Osteoblasts; Bone tissue regeneration; Regeneration scaffolds; Biomaterials; Bioactivity; Tissue compatibility; Biodegradability; Mechanical mechanics

Keywords: Ericaceae, *Pogonanthum*, new species, compare, taxonomy

1. Introduction

Bone regeneration is a complex and dynamic process with multiple systems interacting. First, the migration and recruitment of bone stem cells, then through cell proliferation, differentiation, matrix formation, and finally bone remodeling[1]. The main functions of bone tissue engineering scaffolds are achieved through the expression of growth factors, drugs and genes. Bone scaffolds are usually made of porous degradable materials to perform bone repair and regeneration at damaged or diseased sites, and provide mechanical support[2] in the process. Due to the complexity of bone structure and biomechanics, the requirements for an ideal scaffold for bone tissue regeneration are very stringent. Biohistocompatibility is one of the basic properties of bone regeneration scaffolds. The biocompatibility of scaffolds means that they can support normal cellular activities, such as the transmission of cellular and molecular signaling systems, without any local or systemic toxic effects[3] on the host. An ideal scaffold for bone regeneration must have good bone conductivity. The scaffold can promote the adhesion, proliferation, and formation of extracellular matrix on the surface and pores of bone cells.

Such scaffolds should also be able to recruit osteoprogenitor cells through molecular signals to induce bone formation, that is, osteoinduction. In addition, an ideal scaffold for bone tissue regeneration should form new blood vessels within a few weeks after implantation to facilitate the exchange[4] of nutrients, oxygen, and substances for bone tissue regeneration.

The mechanical properties of an ideal scaffold should match the biomechanical properties of the host bone to achieve appropriate stress dispersion. The biomechanical properties of bone tissue vary greatly from cortical to cancellous bone. The Young's modulus of cortical bone ranges from 15 to 20gpa, while that of cancellous bone ranges from 0.1 to 2gpa. The compressive strength of cortical bone ranges from 100 to 200 mpa and that of cancellous bone ranges from 2 to 20 mpa, and the complex mechanical properties and geometry make it very difficult[5] to design an "ideal scaffold for bone tissue regeneration". Bone tissue regeneration scaffolds must have a certain porosity, and the pore diameter should usually not be less than 100 mm, in order to successfully diffuse the nutrients and oxygen[6] required for cell survival. However, it has been found that scaffolds with pore sizes of 200-350 mm are most suitable for bone tissue growth[7]. In addition, recent studies have shown that porous scaffolds involving both microscopic and macroscopic pores perform better[8] than scaffolds involving only macroscopic pores. However, porosity reduces the mechanical properties of scaffolds, such as compressive strength, and increases the complexity of scaffold fabrication. Researchers have explored porous scaffolds using polymers, ceramics, composites, and metals. The strength of dense bioceramic materials approaches that of cortical bone, and the strength of different polymers approaches that of cancellous bone, but the strength of ceramic-polymer composite scaffolds is generally lower than the mechanical strength of bone. Porous metal scaffolds can meet the mechanical properties of bone, but they cannot provide the necessary implant histocompatibility and increase the potential risks[9] caused by metal ion liberation.

Bioabsorbability is another key factor[10] for bone tissue regeneration scaffolds. An ideal scaffold should not only have similar mechanical properties to the host tissue, but also be able to degrade over time in vivo, preferably at a controlled resorption rate, and ultimately create space for the growth of new bone tissue. The degradation behavior of the scaffold should vary according to the actual situation, for example, the degradation time of the spinal fusion scaffold is 9 months or longer. Of course, designing and fabricating porous scaffolds with desirable components, including targeted biomolecules, mechanical properties, and bioabsorbability, is currently a major challenge[11] in the bioengineering of bone tissue.

2. Scaffolds for Bone Tissue Regeneration

2.1.1 Molecular Transport

Bone tissue regeneration scaffolds are used to deliver biomolecules that promote bone tissue regeneration. The biomolecules integrated into the scaffold are usually proteins and growth factors, such as transforming growth factor-β (TGF-β), bone morphogenetic protein (BMPP), and bone morphogenetic protein (BMPP). BMP, insulin like growth factor (IGF), IGF), fibroblast growth factor (FGF) and vascular endothelial growth factor (VEGF). These growth factors act on osteoprogenitor cells to regulate bone tissue regeneration and extracellular matrix formation[12, 13] by recruiting and differentiating into bone cells of specific lineages. Therefore, it is promising to incorporate different growth factors and other biomolecules into bone tissue regeneration engineering research. For example, IGF contributes to the migration[14] of different osteocytes during bone healing, while BMP and

TGF-β induce the early proliferation and differentiation[15] of osteoprogenitor cells. Studies in animal models have shown that the use of biomolecules or growth factors can promote the healing of nonunion or delayed union[16] fractures. The application of biomolecules and growth factors in scaffolds can promote wound healing, thereby promoting the recovery of patients.

2.1.2 Angiogenesis

Bone tissue is highly vascularized, so its substitute bone tissue regeneration scaffold must have a strong ability[17] to induce neovascularization. Under in vivo conditions, the supply of oxygen and nutrients is essential[18] for the growing cells and tissues inside the scaffold. Inflammatory factors can induce blood vessel formation after stent implantation, and it takes several weeks to form a complex vascular network[17]. Studies have shown that VEGF can induce the formation of complex vascular network on the entire scaffold, and it can be added to the scaffold structure without neovascularization properties to promote angiogenesis[19].

2.2 Design and Manufacture of Scaffolds for Bone Tissue Regeneration

2.2.1 Design of Bone Tissue Regeneration Scaffold

Bone is a natural composite of collagen and hydroxyapatite, which has a porous hard outer layer (cortical bone) of 10-30%. And 30-90% porous and loose inside, called cancellous bone. The mechanical properties of bone vary greatly from cancellous to cortical bone, coupled with the complex geometry, making it difficult to design an ideal bone scaffold structure. The key factors for an ideal bone tissue engineering scaffold are: (1) Pore size: Macropores (pore size >100mm) and micropores (pore size <20mm), (2) interconnecting openings for in vivo tissue growth, (3) adequate mechanical strength and controlled degradation kinetics, "(2) sufficient mechanical strength and controlled degradation kinetics for transfer of load to adjacent host tissues, (4) initial strength and sterile environment[20] for safe handling during sterilization, packaging, transportation to surgery, and survival by in vivo physical forces."

2.2.2 Fabrication of Scaffolds for Bone Tissue Regeneration

Among various fabrication techniques, Solid freeform fabrication (SFF) -based 3D interconnected porous scaffolds have been[12] the most widely studied. Solid freeform fabrication (SFF) is a general method for fabricating three-dimensional (3D) structures layer-by-layer based on Computer Aided Design (CAD). There are various materials that can be used with solid free forming technology, such as metal and polymer materials. Laser engineered net shaping (LENS^{TM}) : a layer-by-layer SFF technology,

It has been used in the production[21] of titanium (Ti), tantalum (Ta) and their alloy porous scaffolds. In this process, a high-power laser locally melts the metal powder particles injected at the laser focus on the substrate, using liquid metal to build the structure layer by layer, and repeating the process until a 3D porous scaffold[22] is formed. The common methods for preparing 3D composite scaffolds include **Thermally Induced Phase Separation** (TIPS), solvent casting/particle leaching, microsphere sintering, and scaffold coating[23]. Electrospinning technology, as another method for constructing polymer scaffolds, shows great prospects. The polymer solution is sprayed through a needle under the action of an electric field to form a scaffold structure[24] on the rotating surface. Although it is mainly used for the construction of polymer scaffolds, ceramic-polymer composite scaffolds can also be constructed[25] by such techniques.

2.3. Types of Bone Tissue Regeneration Scaffolds (Table I)

2.3.1 Metal Scaffolds

In view of the demanding mechanical strength requirements of bone substitutes, metal scaffolds are widely used as bone substitutes in clinical practice. However, mechanical strength mismatch between metallic scaffolds and natural bone can lead to bone resorption and treatment failure. It is difficult to obtain metal scaffolds with personalized shape and complex internal structure by traditional methods. Therefore, scientific and technological innovation is needed to develop scaffolds with bionic structure and mechanical properties. With the rapid development of 3D metal printing technology, metal scaffolds that match the porosity and modulus of human bone have been constructed. These scaffolds can not only restore the mechanical function of bone structure, but also promote bone tissue regeneration. Titanium has been widely used in bone tissue engineering as a metal material with good immune tolerance. In order to improve the biocompatibility and bone conductivity of titanium scaffolds, Garot et al.[26] conducted a series of strategies to modify titanium scaffolds, including electrochemical deposition, heat treatment, and alkali treatment. Compared with titanium, the elastic modulus of tantalum is closer to that of human bone, which can reduce complications caused by stress shielding. To fabricate 3D-printed tantalum scaffolds for bone regeneration, Wang et al.[27] reported a strategy based on selective laser sintering (SLS). Compared with Ti scaffolds fabricated by the same method, the 3D printed tantalum scaffolds showed superior biological properties. The topological structure of 3D printed porous scaffolds can be precisely fabricated. The printed porous scaffolds have good topological structure and mechanical properties, which can better simulate human bone and enhance osteogenic activity and bone regeneration[28]. Dong et al. reported a room temperature 3D printing method for the preparation of porous Mg scaffolds with topological structure as bone replacement implants, that is, after solvent casting, the binder in the ink was removed by defatting and sintering, and then the Mg scaff[29]olds with multi-stage interconnected pores were prepared by liquid phase sintering. In the study of Li et al., the porous metal scaffold with topologically ordered structure was directly fabricated from metal materials, and the results showed that the porous metal scaffold with topologically ordered structure had bone-like mechanical strength and biodegrad[30]ability. In summary, 3D porous scaffolds with customized topology have a broad application prospect in bone tissue engineering. However, the printing resolution and lack of materials need to be solved urgently.

Integrating ceramics, hydrogel materials, or other bioactive ingredients into 3D printed metal scaffolds can regulate their mechanical strength, biocompatibility, and osteogenic effect. To improve biocompatibility and bone conductivity, Yang et al. introduced a 3D printed scaffold with hydroxyapatite (HA) -coated macropores and surface structure. Hydroxyapatite (HA) and 3D printed iron scaffolds with the mechanical strength of human bone can promote the osteogenic[31] differentiation of bone marrow mesenchymal stem cells (BMSCs). Along with the integration of the hydrogel, the researchers found the feasibility of loading the cells in the 3D printed metal scaffold. The bioactive hydrogel containing sodium alginate, gelatin, and hydroxyapatite (HA) was injected with osteoblasts to construct a composite scaffold that effectively promoted bone tissue regeneration[32].

3D printed scaffolds constructed by nanodiamond with bioinert and pericore functional groups (such as -COOH, -NH2 and -OH) can stimulate cell proliferation and differentiation[33]. Rifai et al. printed scaffolds containing nanodiamond coatings, which increased the cell density of human fibroblasts and osteoblasts by 32% and 29%, respectively, and reduced the detected

Staphylococcus aureus on their substrates by 88%, paving[34] the way for biomedical implantation of antifouling 3D printed titanium scaffold structures. In order to enhance the biological properties of 3D printed titanium scaffolds, the researchers used autologous platelet-rich plasma, which can promote the proliferation and differentiation of bone marrow mesenchymal stem cells (BMSCs), to construct a composite 3D printed titanium scaffold. The rabbit femoral model experiment was carried out. The survival rates of BMSC in ordinary titanium scaffold, traditional PRP-coated pTi scaffold, and freeze-dried PRP-coated titanium scaffold were 89.52± 1.64%, 90.67± 1.51%, and 93.69± 1.77%, respectively. The relative bone volumes of the three groups were 8.69± 1.10%, 13.53± 2.24% and 19.08± 2.31% at 6 weeks, and 12.19± 1.46%, 17.04± 1.31% and 23.80± 3.03% at 12 weeks, respectively. The results showed that PRP coated scaffolds significantly promoted bone tissue regeneration[35]. In conclusion, surface modification of 3D printed metal scaffolds with ceramics, hydrogel-based materials, or other bioactive ingredients can give them better biocompatibility and osteogenic properties.

2.3.2 Ceramic Scaffolds

As a major component of bone, calcium phosphate has been widely studied in bone tissue engineering. Among different calcium phosphates, most studies have focused on hydroxyapatite (HA), tricalcium phosphate (β-TCP), or a mixture of hydroxyapatite and tricalcium phosphate, namely biphasic calcium phosphate (BCP), which have long been used in the study[36] of porous scaffolds for bone tissue engineering. A biphasic calcium phosphate (BCP) scaffold (80±3% HA and 20±3% tricalcium phosphate) with 70% interconnecting porosity (68% pore size 400μm, 3% pore size 0.7μm) can be prepared by polymer recombination method, which can successfully promote bone regeneration and repair bone formation[37]. Woodard et al.[38] compared the changes in relative bone conductivity and mechanical properties of a hydroxyapatite (HA) scaffold with multi-scale porosity to a scaffold with a single pore size. The results showed that hydroxyapatite (HA) scaffolds with a combination of macroscopic (250-350μm) and microscopic (2-8μm) pore sizes had significant formation of compact bone and cancellous bone, while the scaffolds without microscopic pore sizes did not have this change. The results showed that the compressive strength of TCP scaffold increased significantly by 46% to 69% when the porosity of TCP scaffold was between 42% and 63%, and the compressive strength of TCP scaffold could reach 10.95±1.28MPa. When applied to human osteoblasts for in vitro cell-material experiments, an increase in cell density was observed. Histomorphological analysis in a rat femoral defect model also showed that the combination of micropores and macropores promoted bone formation[39]. Studies have shown that incorporation of dopants into scaffolds can control dissolution rate, compaction, mechanical strength, and biocompatibility[40]. Doping SiO2 (0.5%) and ZnO (0.25%) into TCP scaffolds can increase the compressive strength of the scaffold by 2.5 times, and significantly improve the mechanical strength and cell proliferation[41] of the scaffold. Silicon doping can significantly enhance the expression of collagen type I (COL-I) gene and the secretion of extracellular signal-regulated kinase (ERK), thereby positively regulating angiogenesis, osteoblast proliferation, differentiation and bone morphogenetic protein formation[42].

2.3.3 Polymeric Scaffolds

Polymer scaffolds have been widely used in bone tissue regeneration research. Through appropriate processing and modification, polymers can obtain good biocompatibility[43] in bone regeneration. Bose et al., using polycaprolactone (PCL) mixed with polyethylene glycol (PEG) to construct a

bone regeneration scaffold, have shown that the hydrophilic nature of PEG promotes the formation of porous structure and promotes cell proliferation. Higher cell density and protein secretion were observed in the PCL/PEG scaffold, indicating that the polymer has the function[44] of promoting osteogenesis. Conductive polymers are also widely used in bone regeneration, where electrical signals that stimulate cells can be transmitted[45] through conductive composites during osteogenesis. At present, conductive composites commonly used in bone tissue engineering research include polyaniline (PANI), polypyrrole (PPy) and poly (3, 4-ethylenedioxythiophene) (PEDOT)[46]. Poly (3, 4-ethylidene dioxythiophene) (PEDOT) is known for its excellent plasticity and biocompatibility, and is often used in bone tissue engineering[47]. Simon et al., constructed PCL scaffolds coated with poly (3, 4-ethylenedioxythiophene) and cultured mesenchymal stem cells (MSCs) directly on PCL scaffolds with or without PEDOT coating. The results showed that the PCL scaffolds coated with poly (3, 4-ethylenedioxythiophene) had good cytocompatibility with MSCs. Recent studies have reported that the combination of PEDOT:PSS with gelatin methacrylate anhydride (GelMA) can improve the plasticity and biocompatibility[48] of conductive materials. Bartolo et al. embedded polyaniline (PANI) microparticles into PCL polymers to enhance the conductivity of scaffolds, and also improved the mechanical properties of scaffolds to promote bone tissue regeneration. However, compared with natural hydrogels, their application in structural scaffolds is limited due to their cytotoxicity.

As a cross-linked three-dimensional polymer, hydrogel has also received extensive attention[49] in bone tissue engineering. They can be used to generate porous structures for embedding cells or proteins[50]. The cross-linked network of hydrogels can swell in the aqueous microenvironment, forming a structure rich in water and good tissue elasticity, which facilitates the incorporation[51] of bone regenerative cells. However, the low mechanical strength of hydrogels is a major challenge in bone regeneration applications. To address this problem, Kim et al. used silk fibroin (SF) as the main component of the hydrogel matrix to improve its mechanical strength. Decellularized extracellular matrix (dECM) extracted from osteoblasts (MC3T3-E1) was also added to provide signal guidance for cell differentiation and maintain a certain degree of plasticity. Compared with pure collagen scaffold, the 3D printed collagen /dECM /SF composite scaffold promoted the osteogenic activity of pre-osteoblasts by inducing the expression of early osteogenic marker alkaline phosphatase (ALP) and calcium deposition. Accelerated[52] cell proliferation was observed in collagen and matrix containing dECM compared to pure collagen or collagen containing dECM.

3D printing of ductile hydrogels is an emerging technology in bone tissue engineering. Hydrogel scaffolds with high strength have been used for bone regeneration, and high fracture resistance and toughness hydrogels that can withstand physiological mechanical loads have been developed[53]. Cui et al. synthesized a ductile polyionic composite (PIC) hydrogel for 3D printing, specifically, to directly exploit the innovative fabrication mechanism of sol-gel transition to develop a ductile hydrogel suitable for 3D printing. Multi-walled carbon nanotubes (MWNTs) were incorporated into the PIC hydrogel to promote the osteogenesis process. In this study, researchers took advantage of 3D printing to form porous PIC/MWNT nanocomposite scaffolds. The study showed that the scaffold not only promoted osteogenic differentiation of rat bone marrow mesenchymal stem cells (MSCs), but also promoted bone defect

repair and angiogenesis[54] at the bone defect site. These biocompatible hydrogel scaffolds, with good plasticity and mechanical properties, have shown great potential in bone tissue regeneration.

2.3.4 Biological Scaffolds

With the development of solvent-free printing technology and biocompatible inks, it has become possible[55] to directly print biological scaffolds containing living cells. By introducing bionic components to simulate the mechanical and mechanical properties of bone tissue, biological scaffolds can restore the biomechanical properties[56] of bone tissue at the defect site. Fischer et al. coated MSCs in a bioprinted collagen-based hydrogel and added agarose to the collagen to improve the mechanical strength of the scaffold. The results showed that the scaffold effectively promoted the differentiation of BMSCS and bone tissue regeneration. However, the plasticity limits the percentage of agarose in the hydrogel matrix. By optimizing the ratio of collagen to agarose, a 3D hydrogel with strong plasticity (AGx-Coly) was prepared. In vitro experiments showed that the cells embedded in AGx-Coly had better spreading and stretching properties than those embedded in agarose alone. In conclusion, the preparation of MSCS-loaded scaffolds has great potential[57] in bone tissue regeneration engineering. Different bioinks need to optimize different parameters to screen the best formulation for bone tissue engineering. Ouyang et al screened the best formula for bone tissue regeneration by using bio-ink made from polymers (including gelatin, hyaluronic acid, chondroitin sulfate, dextran, sodium alginate, chitosan, heparin and PEG). The composite bio-ink (GelMA+ gelatin) has high osteogenic activity and calcification effect[58] on osteosarcoma cell line (Saos-2). In order to improve the mechanical strength of the bioprinted hydrogel scaffold, a polymeric 3D printing structure with high strength was used. By using a fiber carving technique, grooves were carved on the surface of the PCL scaffold so that low-viscosity bioink was deposited into the grooves without lateral diffusion. Subsequently, the GelMA hydrogel loaded with fibroblasts was printed in the groove, and it was confirmed that the fibroblasts in the GelMA bioink still had cellular activity[59].

2.3.5 Hybrid Scaffold

Bone is composed of inorganic and organic components and forms a complex bone structure[60] with different functions. Therefore, the construction of hybrid scaffolds with materials with different characteristics is helpful to promote the research of bone tissue regeneration engineering. In order to further simulate the structure and composition of bone, inorganic materials with similar chemical and mechanical properties to human bone minerals were mixed into organic scaffolds to improve their mechanical properties. For example, hydroxyapatite (HA), which is similar to the major component of cap minerals in bones and teeth, has been widely used in bone substitutes or implants to enhance mechanical strength and bone conductivity. Chen et al. fabricated a degradable hybrid scaffold using hydroxyapatite (HA), carboxymethyl chitosan (CMCS), and polydopamine (PDA) to fix femoral condylar defects and demonstrated that 3D-printed HA/CMCS/PDA scaffolds could effectively promote new bone formation. In addition, the 3D printed HA/CMCS/PDA scaffold showed biodegrad[61]ability that matched the new bone formation. A 3D printing strategy using crosslinkable nanocomposite ink was proposed in the study by Yang et al., which consists of hydroxyethyl methacrylate (HEMA) functionalized hydroxyapatite nanoparticles (nHAMA) and lactide-propylene glycol-lactide-dimethacrylate (PmLnDMA). The researchers found that by cross-linking PmLnDMA and nHAMA, and adding inorganic components, inorganic-organic co-crosslinked nanocomposites with good mechanical properties could be formed. The bone grafts printed with this nanocomposite

showed excellent bone conductivity both in vitro and in vivo, with a nearly 10-fold increase in compression modulus (from 40 MPa to 400 mpa)[62].

To optimize scaffold material mechanical properties and osteogenesis ability, in addition to the hydroxyapatite (HA), also on decellularized bone matrix and other bioactive ceramics were studied. Tricalcium phosphate (beta TCP) as one of the most commonly used ceramic material, has excellent bone conductibility and biocompatibility. Bone remodeling using hydroxyapatite (HA) polyglycolic acid (PGA) and β-tricalcium phosphate (β-TCP) scaffolds in the study by Cao et[63] al., bone mineral density (mg/cm^3) within HAP, PGA /β-TCP (1:1) and PGA /β-TCP (1:3) scaffolds at 90 days after surgery were: 390.4 ± 18.1, 563.8 ±26.9 and 606.3 ±26.9, respectively. The new bone mineral density of PGA /β-TCP scaffold was higher than that of HA scaffold ($p < 0.001$), while the new bone mineral density of PGA /β-TCP (1:3) scaffold was higher than that of PGA /β-TCP (1:3) scaffold. 1) scaffold ($p < 0.05$). 90 days after HA, PGA/beta TCP (1:1) and PGA/beta TCP (1:3) stents biodegradation rate (%), respectively: 35.1 + / - 5.5, 99.0 + / - 1.0 and 96.2 + / - 3.3. Within 90 days after the surgery, the PGA/beta TCP scaffolds almost replaced by new long bone. Therefore, the PGA /β-TCP composite scaffold, especially the PGA /β-TCP (1:3) scaffold, has strong osteogenesis and biodegradability. In addition, magnesium (Mg) as the important component of natural bone material, not only promote calcium salt deposition, also strengthened the cell adhesion, proliferation and differentiation[64]. Lai et al.[65] performed scaffold printing and used it to treat steroid-associated osteonecrosis by using a novel ink containing TCP, Mg powder, and polylactic acid-coglycolic acid (PLGA). The study showed that blood perfusion increased and promoted the ingrowth of new blood vessels at 4 weeks after surgery. Meanwhile, new blood vessels with good structure were observed at 8 weeks. At 12 weeks postoperatively, through the Micro - CT, mechanical properties and morphology analysis showed that the drug-loaded PLGA/TCP/Mg (PTM) stent newborn bone mass than PLGA/TCP (PT) group, bone mass by 56.3%. Bioactive glass as biodegradable materials is commonly used in bone tissue engineering, and after soaking by implanted or simulated body fluids, induced hydroxyapatite (HA) sample surface formation, promote the combination[66] of soft tissue and bone tissue. A biodegradable scaffold with good mechanical properties was prepared by mixing silk fibroin (SF) with mesoporous bioactive glass (MBG). MBG/SF, stents can significantly enhance the osteoblast type I collagen (COL), osteocalcin (OCN) and bone protein (BMP - 2) expression of form. The MBG/ SF scaffold promoted ectopic bone formation[67] in vivo after the incorporation of BMSCS. In the past decade, more and more attention has been paid to extracellular matrix (ECM) scaffolds for bone tissue engineering. Join the tissue specificity of ECM can regulate cell biology behavior, research has shown that contain tissue specificity of ECM in 80% to 100% after 3 weeks can promote bone healing[68]. However, ECM-related hyperacute rejection from allogeneic or xenogeneic bone is a great challenge. Researchers for alpha 1, 3 - galactose caused by super acute rejection of transplantation, the alpha 1, 3 galactosyl transferase - defects of cell-free pig bones (DCB) as the scaffold material, the results show that the addition of DCB not only enhance the mechanical strength of the stent also promotes the bone regeneration[69].

Table 1. Summary of different scaffold material of bone tissue regeneration

Types	Materials	Biological properties	Citation

Metal brackets	titanium	In vitro for bone marrow mesenchymal stem cell adhesion, differentiation, proliferation, survival and development	(26)
	tantalum	In vitro on human bone marrow mesenchymal stem cell adhesion between the influence of differentiation, proliferation, survival, and development	(27)
	magnesium	It promotes calcium salt deposition and also enhances cell adhesion, proliferation, and osteogenic differentiation	(64)
	Titanium/nanodiamond	It can promote the attachment and proliferation of human fibroblasts and rat osteoblasts	(33)
	Titanium/autologous platelet-rich plasma	In vivo survival and osteogenic differentiation of bone marrow mesenchymal stem cells: regeneration of bone defects in rabbit osteoporotic model	(35)
Ceramic brackets	Hydroxyapatite (HA), tricalcium phosphate (β-TCP), or hydroxyapatite with tricalcium phosphate	It can effectively promote bone regeneration and repair	(37)
	TCP doped with SiO2 and ZnO	It can increase the compressive strength of the scaffold by 2.5 times, and significantly improve the mechanical strength and cell proliferation of the scaffold	(41)
	Mesoporous silica/bioactive glass	Can increase collagen type I (COL I) gene expression and extracellular signal regulating kinase (ERK) significantly enhanced secretion, thus positively regulating angiogenesis, osteoblast proliferation, differentiation and bone protein formation of form	(42)
Polymer scaffold	Polycaprolactone (PCL) mixed with polyethylene glycol (PEG)	Higher cell density and protein secretion were observed, which promoted bone regeneration and repair	(44)
	Polyaniline (PANI), polypyrrole (PPy) and poly (3, 4 - thiophene and ethyl 2 oxygen (PEDOT)	Stimulates the electrical signals of cells and promotes the information transmission of bone cells	(45)
	3, 4-ethylenedioxythiophene /PCL	It has good cell compatibility	(47)
	PEDOT: PSS/GelM)	It can improve the plasticity and biocompatibility of conductive materials	(48)
	Polyaniline (PANI) /PCL	It enhances the conductivity of the scaffold, improves the mechanical properties of the scaffold, and promotes bone tissue regeneration, but it has certain cytotoxicity	
	Silk fibroin	The mechanical strength of the stent was	

	(SF)/extracellular matrix	improved. It provides signal guidance for cell differentiation and maintains a certain degree of plasticity	
	Collagen /dECM /SF	It promotes the osteogenic activity of preosteoblasts by inducing the expression of early osteogenic marker alkaline phosphatase (ALP) and calcium deposition	(48)
	Polyion complexes (PIC)/ Multi-walled carbon Nanotubes (MWNTs)	Promoting osteogenic differentiation and angiogenesis of rat bone marrow mesenchymal stem cells (MSCs)	(54)
Biological scaffolds	Collagen with agarose (AGx-Coly)	It has better spreading and extensibility	(57)
	Gelatin/hyaluronic acid/chondroitin sulfate/dextran/alginate/chitosan/heparin/polyethylene glycol	It has high osteogenic activity on sarcoma cell line (Saos-2)	(58)
	PCL/GelmA/PLGA	Promotes fibroblast activity	(59)
Hybrid scaffold	Hydroxyapatite (HA), Carboxymethyl Chitosan (CMCS) and Polydopamine (PDA)	Promote tissue regeneration, and the biodegradation rate of well	(61)
	Hydroxyethyl methacrylate (HEMA) functionalized hydroxyapatite nanoparticles (nHAMA) and lactide-propylene glycol-lactide-dimethacrylate (PmLnDMA)	It has excellent bone conductivity and improved mechanical properties	(62)
	Hydroxyapatite (HA) polyglycolic acid (PGA) and β-tricalcium phosphate (β-TCP)	It has strong osteogenesis and biodegradability	(63).
	TCP, Mg powder and polylactic acid - glycolic acid (PLGA)	It can promote bone tissue regeneration and peripheral blood vessel reconstruction	(65)
	Silk fibroin (SF) and Mesoporous Bioactive Glass (MBG)	Enhanced the expression of human collagen type I (COL-1), osteocalcin (OCN) and bone morphogenetic protein (BMP-2) in osteoblasts	(67)
	Cell-free pig bone extracellular matrix (ECM) (DCB)	It not only enhances the mechanical strength of the scaffold but also promotes bone regeneration	(68)

3. Summary and Outlook

With the continuous development of scaffold

materials, great progress has been made in the construction of scaffolds that promote osteogenesis and angiogenesis. With the innovation of advanced construction technology, the controllable porosity and customizable properties of biological absorbable stents become possible. According to the characteristics of natural bone porosity, a gradient distribution of porosity from the center to the periphery of the scaffold can be achieved through complex design and fabrication, ensuring the mechanical integrity and interconnection of the scaffold. The bioabsorbability of scaffolds is also a major research challenge, which polymer-ceramic composite scaffolds were designed and constructed to address. However, polymeric materials degrade faster than most ceramic materials, thus making the scaffolds degrade unevenly, which also produces problems such as osteolysis. To achieve uniform scaffold absorption, the degradation rates of polymer and ceramic materials should be matched. Using amorphous amorphous calcium phosphate (ACP), which degrades faster than its crystalline counterpart, the degradation of ACP creates a high calcium environment for rapid deposition of hydroxyapatite to promote bone formation. The inorganic material and organic material components of stand not only maintained the original histocompatibility and osteogenesis ability, also improve its biomechanical properties.

Future research should better mimic natural bone tissue regeneration process, such as the coupling between angiogenesis and osteogenesis. The coordination performance of biological molecules and is essential for stent tissue for the successful development and optimization of bone tissue regeneration needs not only the combination therapy of biomolecules, its continued transfer and release is also vital, in the process, support the aperture size in terms of transmission efficiency and transmission rate plays an important role, the scaffolding of the microporous capillary tube to prevent the sudden release of biomolecules. The application of multidisciplinary knowledge will further promote the development of scaffolds for bone tissue regeneration.

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