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Review

Biologically modified implantation as therapeutic bioabsorbable materials for bone defect repair

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ABSTRACT

For decades, researches have concentrated on the mechanical properties, biodegradation, and biocompatibility of implants used in the therapy of large size bone defect. *In vivo* studies demonstrate that bioabsorbable bone substitute materials can reduce the risk of common symptoms such as inflammation and osteonecrosis caused by bio-inert materials after long-term implantation. Several organic, inorganic, and composite materials have been approved for clinical application, based on their unique characteristics and advantages. Although some artificial bioabsorbable bone substitute materials have been used for years, there are still some disadvantages existing, such as low mechanical strength, high brittleness, and low degradation rate. Therefore, novel bioabsorbable composite materials biomaterials have been developed for bone defect repair. In this review, we provide an overview of the development of artificial bioabsorbable bone substitute materials and highlight the advantages and disadvantages. Furthermore, recent advances in bioabsorbable bone substitute materials used in bone defect repair are outlined. Finally, we discuss current challenges and further developments in the clinical application of bioabsorbable bone substitute materials.
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1. Introduction

Bone defect caused by congenital dysplasia, infection, trauma or bone tumors are commonly in clinic [1]. The treatment of bone defects with critical size can be achieved by primary healing/direct healing which involves internal remodeling, or secondary healing/indirect healing through callus formation [2]. Autogenous bone graft and allogeneic bone graft are considered alternatives in bone defect therapy. However, these will be accompanied by several complications, such as chronic pain, disease transmission and immune rejection [3]. Furthermore, traditional non-bioabsorbable implants, including titanium alloy, poly-ether-ether-ketone (PEEK), and polymethyl methacrylate (PMMA), are reported to lead to long-term *in-situ* problems like osteolysis [4–9]. Traditional non-bioabsorbable materials are removed via secondary surgery, while bioabsorbable bone substitute materials are biodegradable and can be further metabolized without harmless substantial.

New chemical bonds, chemical decomposition and reabsorption can be found between bioabsorbable materials and surrounding tissues [10]. Bone tissue usually grows into the bioabsorbable scaffolds, as the implant materials degrade. Meanwhile, the grafts' mechanical properties decrease gradually. There has been a shift of body's biological stress from the grafted material to new bone tissue, which not only stimulates tissue regeneration but also avoids the stress-shielding effect [11]. Controlling the degradation rate precisely is essential to balance the rate of bone regeneration. Some basic properties of bioabsorbable biomaterials include porosity and pore size can also influence the treatment for bone defect. Therefore, advanced bioabsorbable materials with biological activity are the main focus of current research.

2. Properties of bioabsorbable materials

A summary of the bioabsorbable materials for bone defect repair is shown in Fig. 1.

2.1. Bioabsorbable metal materials

The *in vivo* degradation rate of magnesium (Mg) is high compared with iron (Fe) and zinc (Zn), thus, the integrity of the scaffolds is often completely lost due to its rapid degradation. Md Saad et al. [12] prepared three types of cuboid samples of varying porosity (30%, 41%, 55%) using pure Mg rod, and with a pore size of 800 μm. In the dynamic immersion test, the degradation rate (mg/cm^2/d) of the sample with 55% porosity was the highest after pre-incubation for 72 h. However, matching the structure and rate of mass loss of the porous pure Mg with new bone formation is difficult while ensuring a porous structure. The degradation of Mg also produces hydrogen gas, which may cause adverse effect to the surrounding tissues [13]. Byun et al. [14] used a canine model of low horizontal maxillary fracture osteotomy and the experimental group was implanted with WE43 alloy. The swelling was observed 8 weeks after implantation due to the formation of hydrogen gas. Peripheral cells are difficult to adhere to the surface of Mg because of hydrogen gas. In addition, the newly formed bone's quality isn't to be taken lightly, because it may be affected if the new bone tissue space is occupied by hydrogen gas [15].

In a previous study, Kraus et al. [16] implanted pure Fe, as well as two Fe-based alloys, into the femurs of SD rats and examined after 52 weeks. They found that the degradation process was rather slow even no remarkable differences were detected among the metal implants. Additionally, the ferromagnetism of Fe-based materials affects MRI examination after implantation. Although Zn-based materials have a moderate degradation rate, the lack of mechanical properties limits the application of pure Zn materials in bone defect repair. Besides, premature failure of Zn scaffolds are mostly caused by low fatigue strength and inadequate ductility. Zn also has a low melting point and low plasticity, which limits the fabrication of bone repair scaffolds. It is important to note that, Zn contributes to the growth of bones, which can directly activate aminoacyl t-RNA synthetase in osteoblasts and stimulate protein synthesis. In addition, Zn can also inhibit the formation of osteoclasts [17]. The mechanical properties, advantages, and disadvantages of bioabsorbable metallic implants are listed in Table 1.

2.2. Bioabsorbable polymer materials

Collagen (Col)'s unique triple-helical structure is considered to provide mechanical stability [18], and interstrand hydrogen bonds influence collagen triple-helix stability. However, in bone repair, Col can promote bone formation, initiate and induce mineralization. Elango et al. [19] confirmed that p38MAPK is a crucial component dependent Runx2 signalling pathway that triggered by collagen peptide (CP) during osteoblast differentiation. Pawelec et al. [20] created recombinant peptide scaffolds from Col. After co-culturing with mesenchymal stem cells for 4 weeks, the expression of osteogenic markers (Runx2, Osteocalcin) and mineralization were up-regulated. Similarly, Akhir et al. [21] demonstrated that Col was capable of inducing spontaneous osteogenesis of amniotic membrane mesenchymal stem cells (AM-MSCs) in exogenous inductors-free conditions. These studies demonstrate that Col could effectively induce bone regeneration.

Higher degree of deacetylation (DD) increases the number of positive charges, promotes the interaction between Chitin (Ct) and cells, thus, improves biocompatibility [22]. Ct and Chitosan (Cs) are reported to have antibacterial properties due to their cationic nature. Besides, their cationic properties could adjust and control growth factors by binding with anions and exert a physiological role [23]. Cs could facilitate cell adhesion, proliferation and differentiation, recruits or maintains cells and fluid to the defect site, and

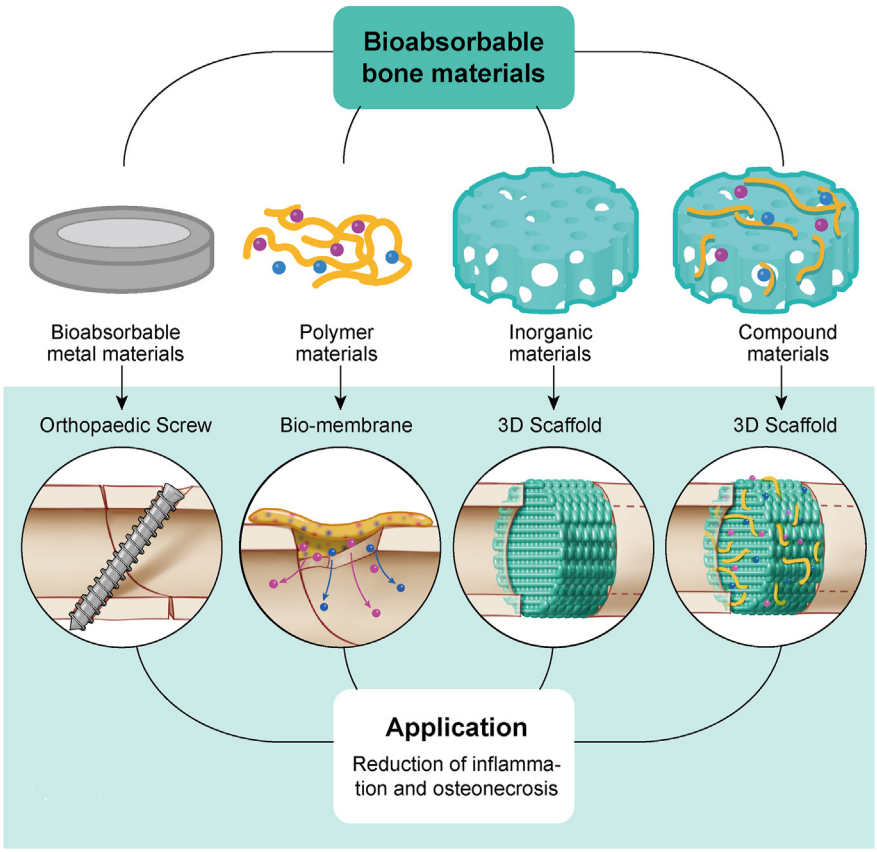

Fig. 1. Schematic presentation of bioabsorbable materials for bone defect repair. Implantation of bioabsorbable substitute materials are commonly used in the treatment of bone defect and can reduce the risk of common symptoms such as inflammation and osteonecrosis caused by bio-inert materials after long-term implantation.

also combines with the cell membrane to act as a bridge in bone defect repair because of its hydrophilic surface. Besides, it boosts the amount of osteopontin promoting attachment and infiltration of a diversity of cell types [24].

The degradation of polylactic acid (PLA) does not depend on enzymes, but through the hydrolysis of the ester bonds. For polylactic acid, the lack of hydrophilic groups in its structure makes the surface of the material hydrophobic. Low hydrophilicity is not conducive for cell adhesion, proliferation, and differentiation [25]. Although PLA has good absorbability and biocompatibility, it produces acidic degradation products. The accumulation of lactic acid cannot be metabolized within a short time and resulting in a pH as low as 3.0 within 4 weeks, this may also dissolve some bone components as well [26]. Maia-Pintoet al [27] established skull defect models via a semilunar incision in 45 Wistar rats and PLA materials were implanted. Histological evaluations showed that the connective tissues interspersed with PLA pieces and inflammatory cells at 1 month. Hence, the inflammatory effect of PLA degradation products should not be ignored. Polycaprolactone (PCL) appears like a rubber colloid in the physiological environment and with high toughness. It is same as PLA, non-toxic but hydrophobic. The mechanical properties, advantages, and disadvantages of bioabsorbable polymer materials are listed in Table 2.

2.3. Inorganic materials

Hydroxyapatite (HA) has the ability to induce new bone formation. Dissolving hydroxyapatite *in vivo* can create space for bone growth, increase the local concentration of Ca^{2+}, activate the proliferation of osteoblasts, and promote the differentiation of mesenchymal stem cells [28]. Bio-ceramic materials have stronger compression resistance compared with human bone, but lower tensile resistance (6–10 Mpa) due to their porous structure, and cracks appear firstly at the pore site. The high brittleness of bioceramic materials is related to the primary ionic bonds [29]. As mentioned earlier, high porosity makes HA scaffold brittle, and this may be one of the reasons for poor mechanical properties. The degradation rate of inorganic materials is relatively low. A previous study demonstrated that hydroxyapatite degraded slowly

Table 1
Mechanical properties, advantages and disadvantages of bioabsorbable metallic materials.

Bioabsorbable metallic materials	Modulus of elasticity (GPa)	Density ($g/cm^{3)}$	Standard electrode potential	Advantages	Disadvantages
Mg	40–45Gpa	1.74 ~ 2.0 g/cm^3	−2.37v	Reduce stress shielding, promote osteogenesis	Low mechanical strength and corrosion resistance
Fe	211.4Gpa	7.8 g/cm^3	−0.44v	High wear resistance	Low degradation rate, high modulus of elasticity
Zn	1.2–2.1Gpa	7.14 g/cm^3	−0.76 v	High biocompatibility, promote osteogenesis	Low strength and plasticity

Table 2
Mechanical properties, advantages and disadvantages of bioabsorbable polymer materials.

Bioabsorbable polymer materials	Young's modulus (GPa)	Melting point (°C)	Elongation (%)	Advantages	Disadvantages
Collagen	\	\	\	Can be cross-linked or blended, high biocompatibility	Low mechanical strength
Chitin/Chitosan	\	\	\	Non-toxic, promote cell adhesion	Poor stability and mechanical properties
Polylactic acid	4.8	175	5–10	Non-toxic, good elongation	High brittleness, low crystallinity, and hydrophilicity
Polycaprolactone	0.4	57	300–500	High biocompatibility, easy to process	Low degradation rate and strength

Table 3
Mechanical properties, advantages and disadvantages of bioabsorbable inorganic materials.

Bioabsorbable inorganic materials	Component	Pore size (μm)	Porosity (%)	Advantages	Disadvantages
Hydroxyapatite	$Ca_{10}(PO4)_6(OH)_2$	average2-5	29.4	Can be cross-linked or blended, high biocompatibility	Low mechanical strength
Bio-glass	Oxide of Si, Na, Ca, P	\	\	High biological activity, can combine with host bone	Low toughness and high brittleness

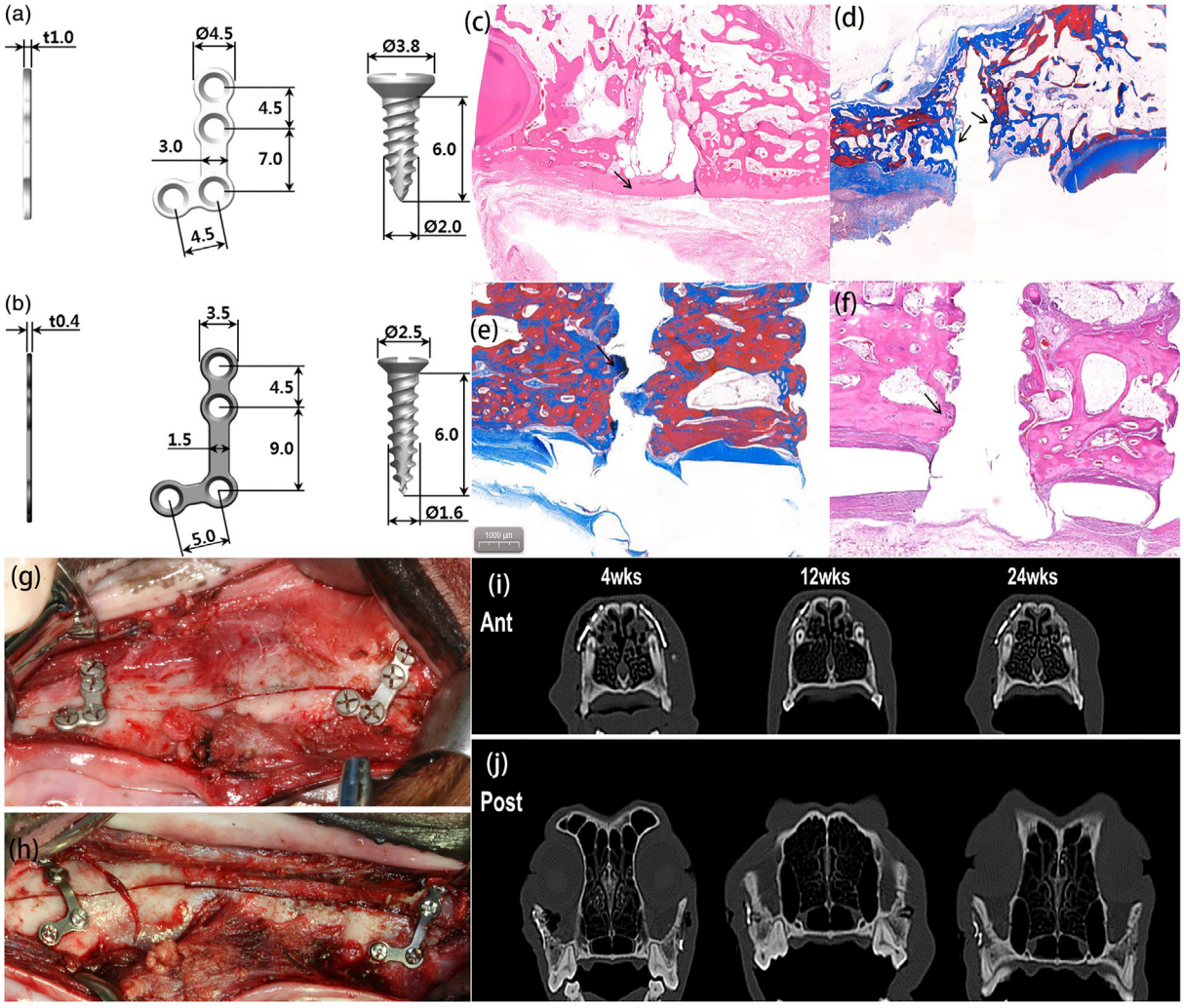

Fig. 2. Specifications and dimensions of the screws and plates (WE43 and Ti). (a) WE43 Mg alloy screws and plates. (b) Ti screws and plates. WE43 plate is slightly thicker and larger than titanium plate. These plates are designed as L-shaped with four holes. The WE43screw diameter is also slightly larger than that of titanium alloy. (c, d) WE43 plate. (e, f) Ti plate. The black arrow represented the new bone. There was no inflammation in any of the groups. Soft tissue formation between the screw and bone was not found. Histologic examination after 2 years showed no specific differences between WE43 and Ti (Scale bar, 1 mm). (g) Intraoperative photograph of the WE43 screws and plates fixation. (h) Intraoperative photograph of the Ti screws and plates fixation. 2 WE43plates,2 Ti platesand 16 screws are fixed on the preformed holes. (i, j) Radiological evaluation of the WE43 group. The plates were completely degraded at 2 years. The osteotomy line was clearly visible at 4 weeks and had slightly disappeared at 12 weeks. At 24 weeks, the osteotomy line was not observed, and complete bone healing was observed [32]. Copyright 2020, Wiley.

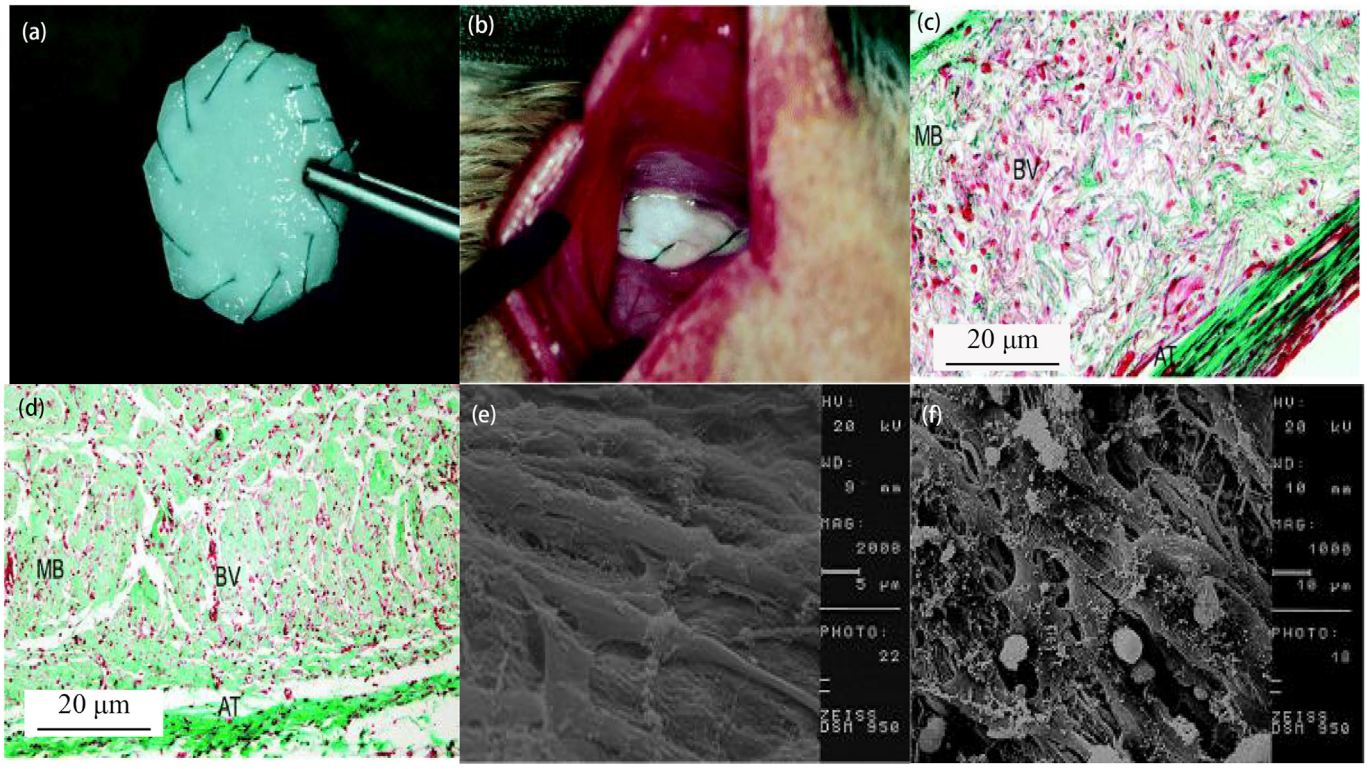

Fig. 3. (a) Folded collagen membrane. Each collagen membrane was trimmed to an uniform size (octagon shaped specimens of 1.7 cm2). (b) Bio-Gide® was implanted into the subcutaneous pouches on the back of the rat. (c) The membrane body of Bio-Gide® seemed to be structured like an interconnective porous system. Complete vascularization (2 weeks). (d) Entire biodegradation (4 weeks). AT, adjacent tissue. BV, blood vessels. MB, membrane body. Goldner Trichrome Stain [36]. Copyright 2005, Wiley. (e) SEM view of human periodontal ligament fibroblasts adherent to Bio-Gide® (7 days). Fibroblasts were spindle shaped and slender. (f) SEM view of human SaOs-2 osteoblasts adherent to Bio-Gide® (7 days). Osteoblasts were star shaped [37]. Copyright 2004, Wiley.

following treatment of large femoral bone defects in rats, 12 weeks after surgery [30].

Hydroxyapatite carbonate degraded from bioglass (BG) in the physiological environment can rapidly interact with surrounding normal bone tissue to promote new bone formation. However, the clinical use of bioactive glass is limited and implants fail due to instability of the crystal phase boundaries in the glass-ceramic [31]. The premise of making porous bone scaffold with BG is to crystallize during sintering. However, the rise of novel technologies, in particular gel-cast foaming, has achieved the goal of mimicking the structure of porous bone. As a consequence, the porous scaffolds can only be used in places with little or compressive load [31]. The mechanical properties, advantages, and disadvantages of bioabsorbable inorganic materials are listed in Table 3.

3. Application of bioabsorbable materials and associated problems

Because of the non-absorbability of titanium (Ti) plates and screws, the postoperative infection rate may be raised as a result. Fig. 2 shows the size and intraoperative application of Ti and Mg screws and plates. In 2013, the world's first commercial Mg-based screw called MAGZENIX by Syntellix was launched in Germany, marking the initial success of biodegradable Mg-based internal fixation materials [32]. A retrospective analysis by May et al. [33] found that bioabsorbable Mg and Ti screws had similar therapeutic efficacy in medial malleolar fracture fixation. All patients with Mg screws achieved fracture healing without any serious complications. Therefore, bioabsorbable Mg implants are as safe and effective as traditional implants in this case. However, the use of bioabsorbable metal faces several challenges, for instance, lower corrosion resistance.

Nevertheless, when the bone defect is over sized, new bone tissue tends to form in the marginal stable area, while the central area is often occupied by loose connective tissue [34]. The membrane made of Col can protect the blood clot in the defect area, block the connective tissue, and induce new bone formation. Geistlich Bio-Gide®, a kind of double-layer bioabsorbable Col membrane has good vascularization and tissue integration, and could promote the attachment and proliferation (Fig. 3) [35,36]. In addition, Remaix™ (RX; Matricel GmbH, Herzogenrath, Germany) and Ossix Plus® (Datum Dental Biotech, Lod, Israel) are also commercially available Col membranes used as a treatment of alveolar bone defect [37]. Allan et al. [38] developed a new Col membrane called CelGro™. Compared with commercially available Col membrane Bio-Gide®, CelGro™ showed better cortical arrangement and fewer pores at the defect interface.

Injectable hydrogel is an effective treatment for bone defects, especially irregular bone defects. Peng et al. [39] prepared a new Cs-based porous hydrogel and found that it could promote cell proliferation in the repair of cartilage defects in New Zealand white rabbits. Li et al. [40] incorporated bone morphogenetic protein-2 (BMP2) plasmid DNA (pDNA-BMP2)-loaded Cs nanoparticles (Cs/Csn(pDNA-BMP2)-GP) into thermosensitive hydrogel scaffold. They injected the Cs/Csn-GP solution into the muscle pouches of rats, but non-specific inflammation occurred after gelation *in situ*, finally proved that Cs nanoparticles can promote the endogenous repair of alveolar bone.

Moreover, Fairag et al. [41] prepared three types of PLA scaffolds with different pore sizes (1000 μm, 750 μm, 500 μm) by 3D printer technology, and seeded hBMSCs on PLA scaffolds. The research

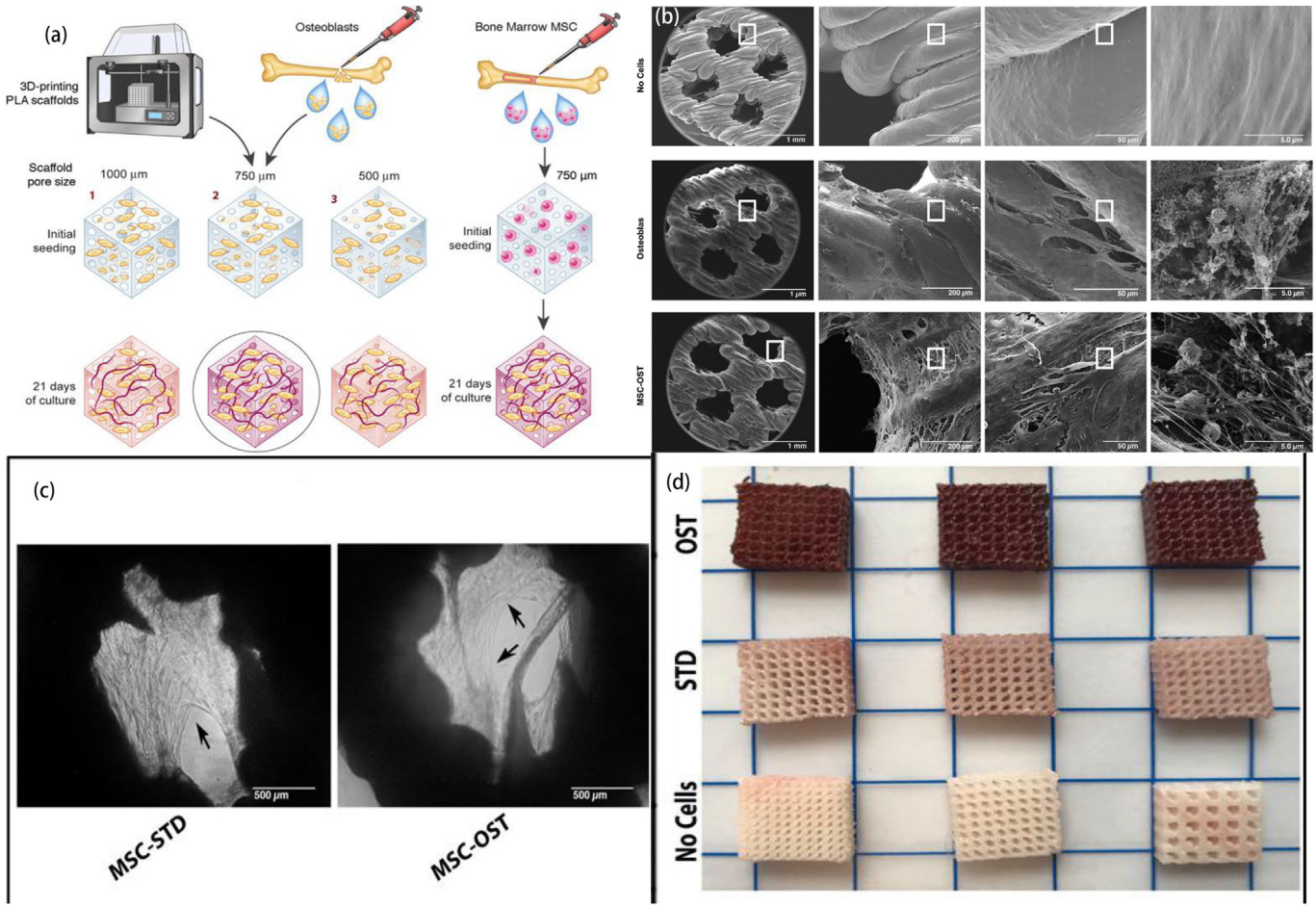

Fig. 4. (a) Schematic representation of PLA scaffolds with different pore sizes by 3D printing (1000μm, 750μm, 500μm). (b) Representative SEM images of acellular scaffold, osteoblasts and MSC–OST seeded scaffold from top to bottom. Representative SEM images of 80×, 450×, 1500×, and 22 000× magnifications respectively from left to right. The cells always start at the edge of the pores, but with the extension of culture time, the cells grew to the pore center. (c) Representative images of Bright field microscopy (phase contrast) of MSC-seeded scaffolds during the culture period at 10× magnification. Black arrows indicate cell growth and neo-tissue deposition (Scale bar, 500 μm). MSC had a strong tendency to form multilayer structures, covering the scaffold surface with matrix like tissues, which penetrated into the pores over time. (d) Fixed acellular and MSC-seeded PLA scaffolds stained with Alizarin Red-S stain after 21 days of culture. MSC culturesshowed a significantly more calcified matrix. MSC, mesenchymal stem cells. STD, standard culture. OST, osteogenic culture [42]. Copyright 2019, American Chemical Society.

detected that the 750 μm porous scaffold could be used for bone defect repair (Fig. 4). Honeycutt et al. [42] used a biobioabsorbable poly-L lactic acid (PLLA) screw to treat pediatric tibial eminence fracture, which not only mitigated the possible need for hardware removal but also reached a rigid fixation. Whereas numerous problems need to be solved, such as poor biocompatibility caused by the inert hydrophobic surface, uncontrollable degradation rate, acidic degradation by-products, etc.

Pharmacologic agents like hormones and antibiotics are attached to the HA by chemical, physical, or mechanical linking [43]. In a previous study, HA beads were loaded with gentamicin/amoxycillin-clavulanate/vancomycin, and the drug eluent levels were well above bactericidal levels [44]. HA's capacity can be harnessed to carry tailor-made pharmaceutical agents into the bone defects, effect adequate elution, and allow for osteoconduction, thereby promoting osseous healing. Li et al. [45] developed and designed a kind of HA nanorod bioabsorbable material which had less crystalline structure by simulating the structure of natural bone (Fig. 5). This rod-shaped HA bone implant not only showed good biocompatibility but also significantly improved the osteogenic ability.

Wu et al. [46] found that the exosome production secreted by hBMSCs was increased when received much stimulation of 45S5 Bioglass® (BG). This could be related to the fact that BG upregulated neutral sphingomyelinase-2 (nSMase2) through nSMases pathway and Rab27a through Rab GTPases pathway (Fig. 6). Xu et al. [47] used cyanoacrylates as a biological adhesive to combine porogen poly (ethylene glycol) and PSC-BG (PSC stands for 10.8%P_2O_5–54.2% SiO_2–35.0% CaO, mol%), and good bone regeneration was observed after implantation into the mouse skull. Although, BG's biomechanical properties and brittleness remain unsatisfactory, it plays a significant biological effect, to induce osteogenesis and indirectly promote bone healing.

4. Formation of composites to optimize material properties

4.1. Alloying of bioabsorbable metals

Kawamura et al. [48] confirmed adding aluminum (Al) or Zn to Mg alloys could facilitate the corrosion resistance of Mg alloys to simulated body fluid (Fig. 7). The degradation rates of Fe–35Mn alloy (0.42 ± 0.03 mm/year vs 0.062 mm/year) and Zn–4Ag (silver) alloy (17.38 ± 0.78 μm/year vs 4.80 ± 0.82 μm/year) were significantly higher than those of their pure metals respectively [49,50]. For quaternary alloys, a study by Trincă et al.'s [51] showed the ability of FeMnSiCa alloys to degrade at higher corrosion rate when

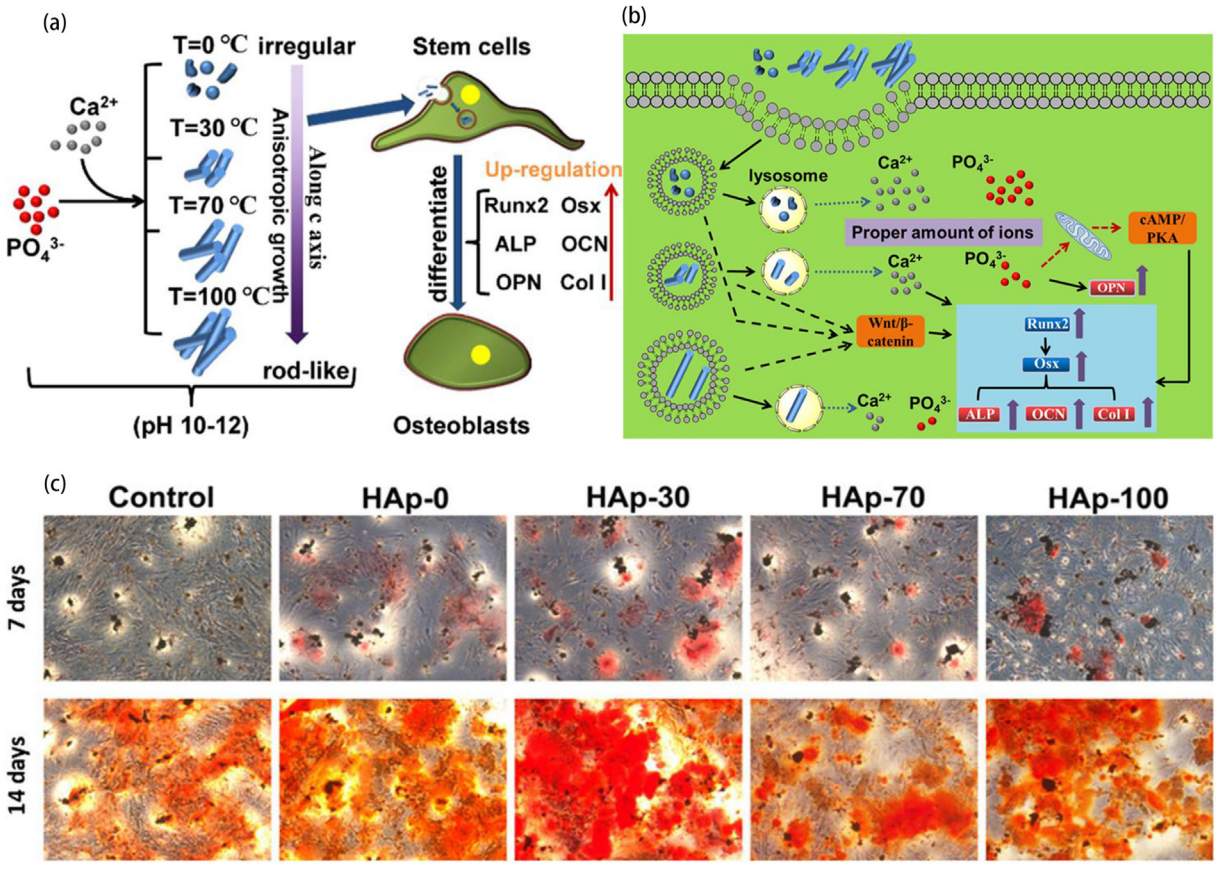

Fig. 5. (a) Preparation of bone-mimicking HA nanorods via a simple chemical precipitation approach in combination with mild temperature treatment for mediating rat bone marrow-derived mesenchymal stem cells (rBMSCs) osteogenesis. (b) rBMSCs' possible mechanisms of osteogenic differentiation varies with the aspect ratios of HA nanoparticles. Calcium ions promote the expression of Runx2 and Osx, and phosphate ions increase the expression level of OPN through cAMP / PKA pathway. (c) Alizarin Red-S staining of rBMSCs co-cultured with different HA nanoparticles (7 and 14 days). HA-30 provided the highest expression level of calcium tuberculosis, indicating that HA nanorods with medium ratio could better promote the mineralization of rBMSCs. HA-0, the reaction was maintained at 0 °C for 32 h. HA-30, 30 °C (24 h). HA-70, 70 °C (4 h). HA-100, 100 °C (2 h) [46]. Copyright 2020, American Chemical Society.

compared with base FeMnSi alloys. The degradation of metals *in vivo* is not catalyzed by enzymes but through electrochemical corrosion. The addition of alloy elements could enhance degradation rate and switch the electrode potential, which is an effective measure to improve the degradation rate of bioabsorbable metals.

According to Wolff's law, high strength leads to stress shielding and weakening of the surrounding bone. A study by Erdmann et al.'s reported that the biocompatibility and biomechanical properties of MgCa0.8 alloy screw implanted into rabbit tibia [52] were better than those of stainless steel (S316L). Without changing the metal degradability, Bryła et al. [53] added 4%Ag to pure Mg, then found that the ultimate compressive strength of Mg–4%Ag alloy rose by 30%. Similarly, Xue et al. [54] maked an as-cast Zn1Fe1Mg alloy, which yield strength (146 MPa), tensile strength (157 MPa), elongation (2.3%) and hardness (105 HB) were higher than those of pure Mg. Alloying can effectively increase the load-bearing capacity and promote bone regeneration.

Osteoinductive activity is the key role of the ideal scaffold materials for bone repair. Han et al. [55] showed that there was bone formation around the bioabsorbable magnesium alloy, thus, revealing that Mg ions released in the degradation process of Mg alloy could promote angiogenesis, and recruit bone progenitor cells to promote osteogenesis. Tian et al. [56] found that Mg ions promoted the release of calcitonin gene-related peptide (CGRP), which binded to receptors on the surface of periosteal stem cells to stimulate new bone formation. Jia et al. [57] used Zn-0.8Sr alloy scaffold to repair femoral condylar defects in rats and reached a conclusion that Zn-0.8Sr alloy had satisfactory osteogenic properties and biocompatibility not only *in vitro* but also *in vivo*. Much attention which gained much importance has been drawn to the addition of Ca, Mg, strontium (Sr), and lithium (Li) to Zn. Yang et al. [58] confirmed that cytocompatibility, osteogenesis, and osseointegration of the new alloy would be improved. Hence, it could enhance the remodeling ability of bone and enhance osteoinductive activity.

4.2. Modification of polymer materials blends

Col-based materials could mimic the microenvironment of native bone *in vivo*. This similarity with natural bone tissue makes mineralized collagen (MC) material not only have good biocompatibility but also good bone conduction. In a study by Xu et al.'s [59], hMSCs were cultured on HA and MC, and the study found that MC could promote osteogenic differentiation of hMSCs. Song et al. [60] added zinc silicate to HA/Col scaffold to form 10ZS/HA/Col (zinc silicate/nanohydroxyapatite/collagen) scaffold, and its ability of angiogenesis and bone regeneration *in vivo* was enhanced significantly. Zhou et al. [61] developed a HA/Rgo (reduced graphene oxide) composite scaffold with nano surface morphology and hierarchical pore structure, moreover, HA/Rgo could greatly accelerate bone ingrowth. The blending of HA and various high molecular polymers such as polylactic acid, poly (butylene succinate), can be optimized to improve mechanical stability, osteogenic ability, and biocompatibility [62,63]. Quercetin (Qtn) [64], Carbon

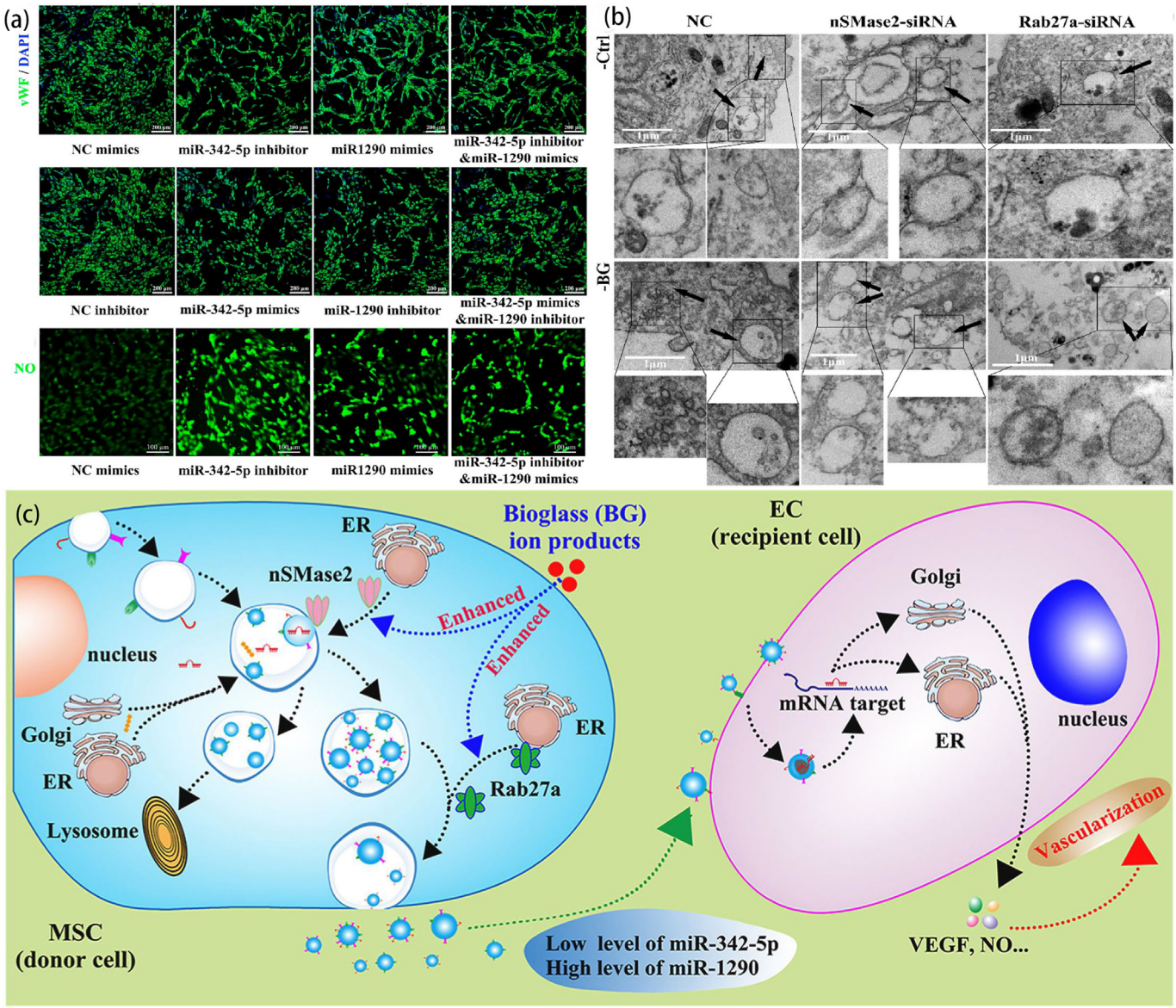

Fig. 6. (a) The vWF staining images showed that the Lipofectamine® 2000 treatment, negative control siRNA transfection (NC) mimics and inhibitor had no significant effects on the growth and distribution of ECs. When miR-342-5p inhibitor, miR-1290 mimics and their combination were transfected into ECs, clear semicircular structure, capillary-like networks and more NO were observed. (b) After MSCs were treated with nSMase2-siRNA or Rab27a-siRNA for 6 hours and stimulated with BG ion products respectively for 48 hours, the representative transmission electron microscope images of MSCs (arrows showed clear MVBs, ILVs referred to the small particles contained in MVBs). (c) BG products' mechanisms of promoting the production and modification of MSCs-derived exosomes. BG ion products could upregulate the expression of nSMase2 and Rab27a in MSCs, which subsequently enhanced the numbers of intracellular MVBs and ILVs as well as the exosome particle concentration in the culture supernatant. ILVs, intraluminal vesicles. ECs, endothelial cells. MVBs, multivesicular bodies. MSCs, bone marrow mesenchymal stem cells [47]. Copyright 2020, The Authors.

nanotube [65], BMP-2, and alendronate [66] have become new HA/Col scaffolds in recent years, which promote bone regeneration.

Besides, it can also be made into hydrogel loading growth factors, which indirectly promote bone healing. Moeinzadeh et al. [67] reported a BMP-2 loaded alginate (Alg)/Col hydrogel, which repaired a critical size calvarial bone defect in rats after 8 weeks of injection. Lately, Wu et al. reported that Col-based hydrogels are sequentially mineralized to induce bone regeneration [68]. Besides, they demonstrated the regeneration capability of the Col hydrogel mineralized scaffolds, an indication that this is a promising approach in bone defect repair.

Furthermore, by blending Ct/Cs with some biomaterials can effectively enhance their mechanical properties and improve their biological activity. The combination of chitosan (C), hydroxyapatite (HAp), gelatine (G), fibrin (F) and bone ash could form a composite bioabsorbable material (HApGCF) with good biocompatibility, in addition, the surface of HApGCF could effectively promote the adhesion of osteoblasts [69]. Chakravarty et al. [70] prepared Ct/PLA/nHA composites, and cell growth studies showed that the composite materials supported the growth and proliferation of Ocy 454 osteocyte cells, and had minimal cytotoxicity and biodegradability. If supplemented with other biomaterials, Ct/Cs are expected to become ideal bone repair composite materials.

Unlike the corrosion degradation of metals, PCL and PLA are hydrolyzed *in vivo*. In general, copolymerization and blending with other polymers or inorganic materials is used to adjust the absorption rate, to enhance osteogenesis and stable hydrolysis in the degradation cycle, or to construct 3D scaffolds to change their microstructure, and improve the degradation performance. Liu et al. [71] reported new Ag nanoparticles-loaded PLA electrospun

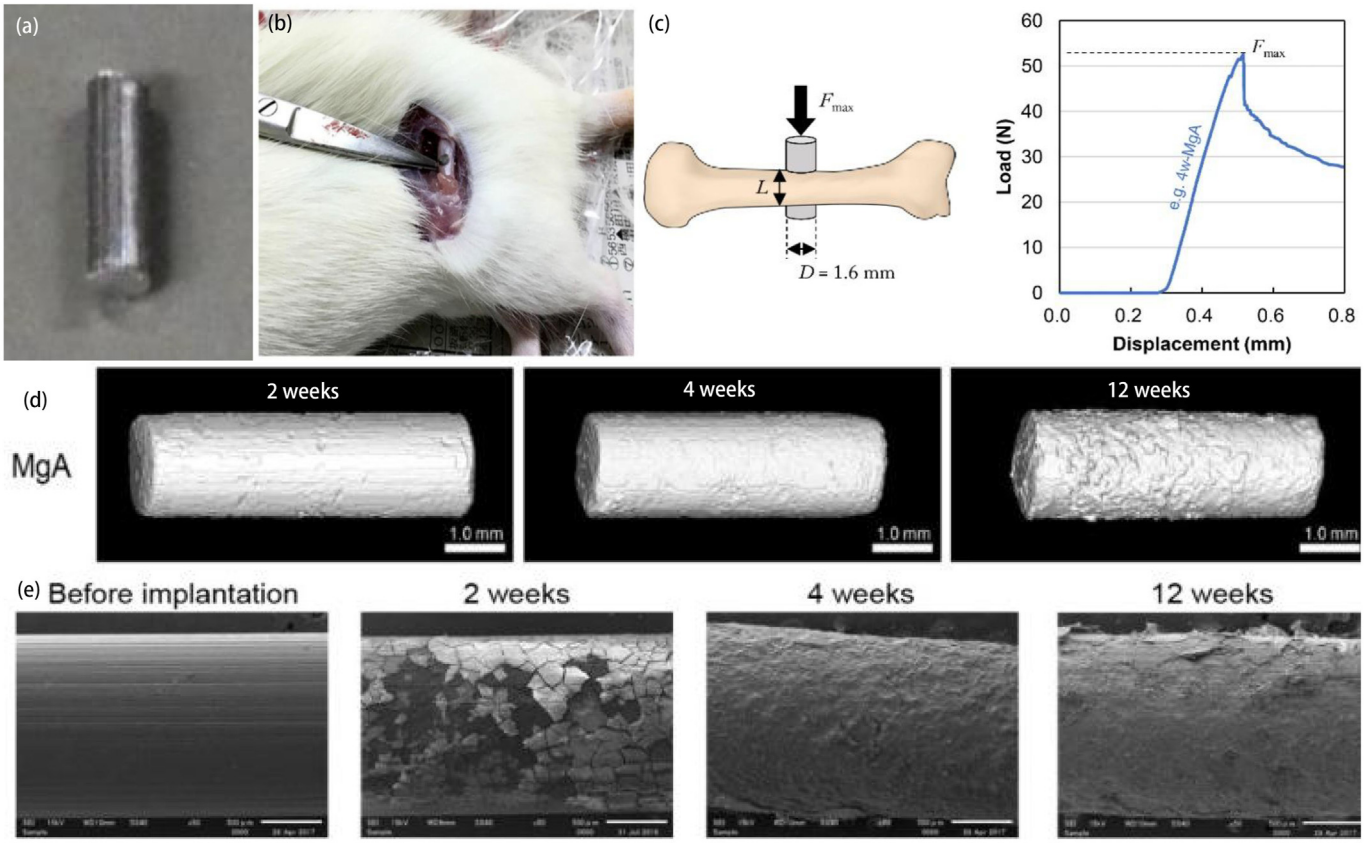

Fig. 7. (a) Photograph of AZ31 MgA (magnesium alloy). Diameter, 1.6 mm. Length, 4.0 mm. (b) Photograph of the femur and the implant. The mid-diaphyseal region of the femur was exposed and the cylindrical implant was inserted by gentle tapping. (c) Schematic diagram of biomechanical push-out testing. Fmax (N), maximum push-out force. L (mm), mean length of bone in contact with the implant. D (1.6 mm), diameter of the implant. Typical load-displacement curve of 4-week MgA group. (d) Three-dimensional reconstructions of implants based on the micro-computed tomography (CT) data.In the MgA group, the degradation of the surface layer was increased with time. (e) Representative SEM images (100x) of the implant surface removed during biomechanical push-out testing (Scale bars, 500 μm). SEM and EDX (Energy Dispersive X-ray Detector) analyses revealed that calcium and phosphorus were enriched on the surface at 2 weeks after implantation. Mg was not detected after 2 weeks, suggesting the formation of a relatively thick calcium phosphate layer. At 4 weeks, the surface was exfoliated, leading to the loss of calcium and phosphorus, and internal Mg was detected [49]. Copyright 2020, The Authors.

fiber which prepared by electrospinning and covered with a polydopamine (PDA) membrane. The results showed that the composite fiber not only had good physiological stability but also had long-term antibacterial ability in order to inhibit bone infections. At present, in the preparation of bone materials, the hydrophilicity, mechanical strength, cytotoxicity and other aspects of PLA have been improved by compounding with different materials, which broadens its application.

As for PCL, the common problems, such as poor hydrophilicity and slow degradation rate can be improved by blending or copolymerization. Harikrishnan et al. [72] fabricated a PCL-nHA scaffold which composed of PCL and nanohydroxyapatite (nHA) by electrospinning, and PCL-nHA scaffold played a good role in the repair of rabbit femur bone defect model. Therefore, after introducing nHA, the PCL electrospun scaffold became more biomimetic and osteogenic. Park et al. [73] coated PDA on 3D PCL/HA scaffold, then added bone morphogenetic protein-2 (BMP-2) and HA nanoparticles to prepared a PCL/PDA/HA/BMP-2 composite scaffold which showed striking osteogenic differentiation.

4.3. Inorganic materials

After implantation *in vivo*, bioactive inorganic materials can induce specific biological reactions at the interface of materials and tissues, to form a close combination with tissues. Wetzel et al. [74] substituted small amounts of Mg^{2+} or Zn^{2+} for Ca^{2+}. Mg or Zn

Table 4
Bioabsorbable bone substitute materials products.

Bioabsorbable bone substitute materials	Owner	Composition	Form	Approval time	Performance
Bongold™	Allgens, China	synthetic HA and Col I	strip, granule, and buck	2015	bioabsorbable, osteoconductive, osteogenesis, and osteoinduction
OsteoFlo®NanoPutty®	SurGenTec, USA	HA,α-TCP, β-TCP and BG	putty	2020	biocompatibility, osteoconductive
Sorrento™	Xenco, USA	β-TCP and Col I	strip, sponge	2019	biocompatibility
FIBERGRAFT® AERIDYAN	Prosidyan, USA	45S5 BG, boron BG, and Col I	putty	2018	osteoconductive, bioabsorbable, biocompatibility
Osteo-P™	Molecular Matrix, CA	porous hyper cross-linked polymeric carbohydrate	granules, sheets, cubes, wedges, and cylinders	2017	osteoconductive, biocompatibility, bioabsorbable

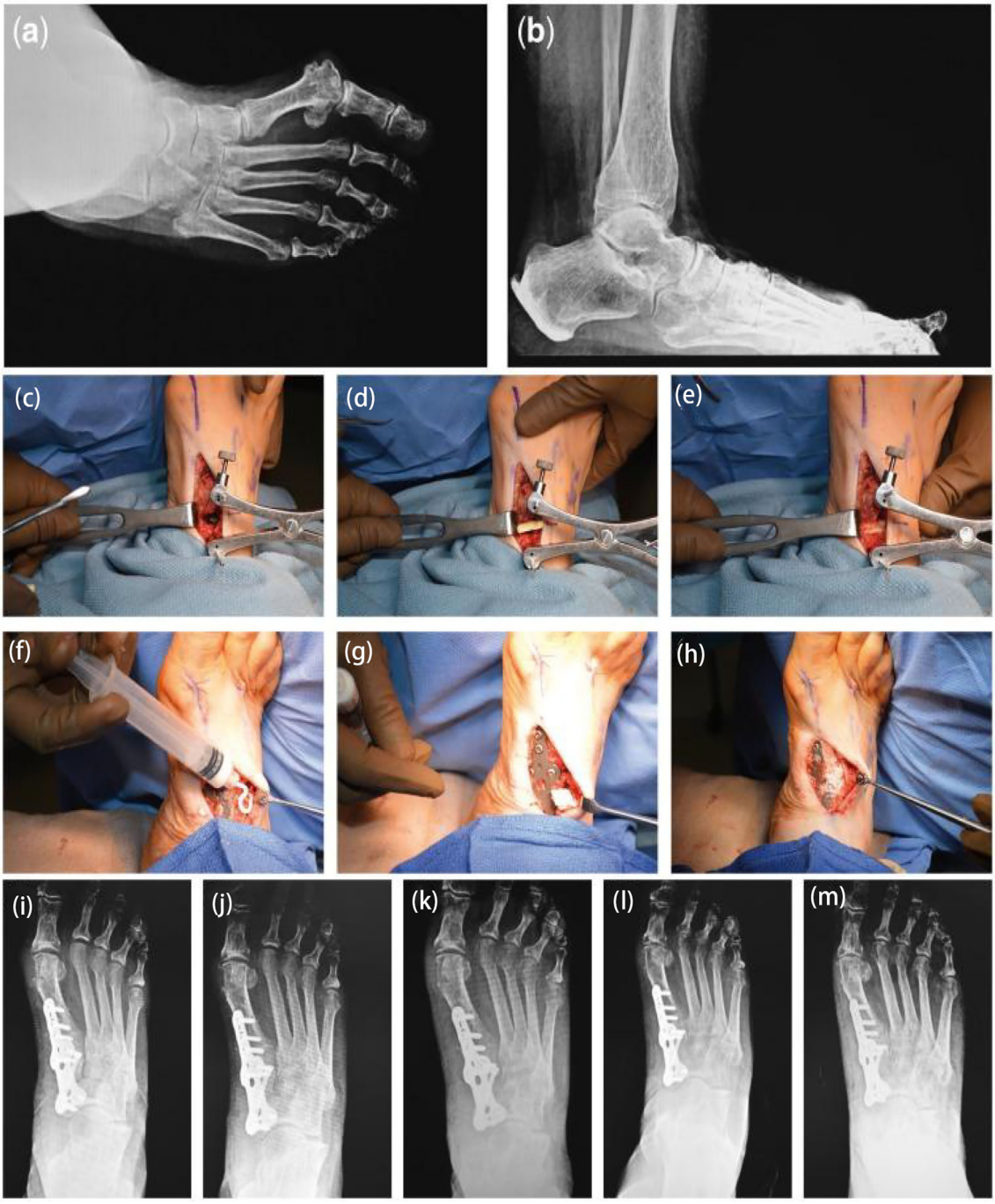

Fig. 8. (a-b) Transverse and sagittal section preoperative X-ray examination. Subluxated and collapsed medial arch was found out at the navicular-cuneiform, metatarsal-cuneiform joint with subluxed first metatarsophalangeal joint (MTPJ). (c-e) Pull open the incision and insert BongoldTM sponge. (f-h) The injured medial column was stabilized with an internal fixation plate and screws and the fusion site firmed up with BonGoldTM Bone Putty. (i-m) Transverse section X-ray examinations at the 2nd, 4th, 6th, 9th and 13th weeks after surgical operation were displayed from a to m. On part m, we can see complete consolidation of the medial column with excellent coalescence at the medial column without any lucency visible at the fusion sites [79]. Copyright 2017, Oxford University Press.

introduced into bioactive glasses significantly reduced BG degradation and ion release and inhibited apatite precipitation. Liu et al. [75] entrapped corticosteroid dexamethasone within porous mesoporous BG scaffold and immobilized biomimetic recombinant human bone morphogenetic protein (rhBMP). This scaffold mimicked human endochondral osteogenesis and provided novel bone repair materials. Ferreira et al. [76] added 45S5 BG to OssiMend® (carbonate apatite/Col) to produce a three-component porous composite bone graft material of OssiMend® Bioactive (45S5 BG/carbonate apatite/Col). The Ca ions and soluble silicon species released from 45S5 BG particles mediated the osteostimulatory effects. For modification of BG, it is important to accelerate the formation of HA and combine it with the mineralization and bone promoting effect of cofactors.

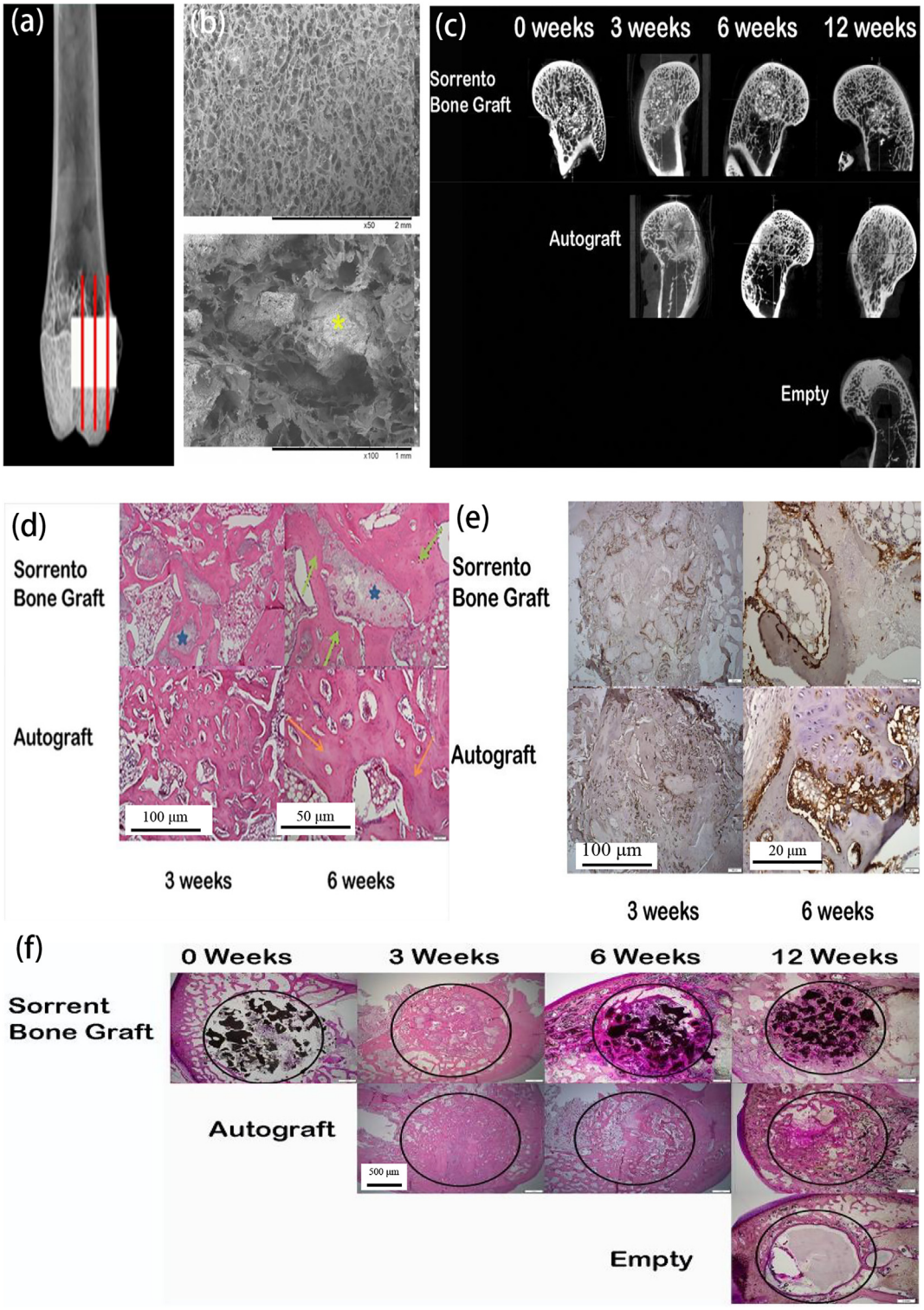

Fig. 9. (a) Schematic diagram of the defect in the distal femur. Section preparation for Micro-CT, polymethylmethacrylate (PMMA) and paraffin histology. (b) Stereoscopic zoom and electron microscopy images of implant. The CaP component in SorrentoTM material seemed to be covered by collagen matrix. SorrentoTM material presented a uniform collagen pore structure along the surface which was impregnated with CaP granules when viewed in cross section. (c) Micro-CT images. The signal intensity increased at the edges of the defect and extended to the center of the defect with the SorrentoTM Bone Graft Substitute for 3 weeks, indicating the newly formed bone. With the passage of time, the repair effect of the autograft group was good, but the defect still existed in the empty group. (d) Histologic images of the defect center (4x, 10x, H&E). The star represents TCP. The green arrows and orange arrows represent the osteogenic reaction of SorrentoTM Bone Graft Substitute and autogenous bone graft respectively. SorrentoTM material supported new bone formation with direct bone formation on the surface of the calcium phosphate phase (star) and newly formed bone (green arrows) marrow spaces at 6 weeks.(e) Immunohistochemistry results for alkaline phosphatase (1.25x, 20x). ALP expression in the osteoblasts throughout the defects for defect treated with SorrentoTM as well as autograft at 3 weeks. The remodeled bone in the SorrentoTM treated defects with continued expression in the osteoblasts lining the newly formed bone at 6 weeks. (f) Histology demonstrated the Micro-CT findings for new bone formation and implant degradation with time (1.25x). The defect repaired by autograft and SorrentoTM healed well over time, but the vacancy was still vacant [82]. Copyright 2017, The Authors.

5. Commercially available bioabsorbable bone substitute materials

Nowadays, with the increasing acceptance of bioabsorbable bone substitute materials, increasing number of bone repair materials have been applied in clinical practice. Table 4 summarizes bioabsorbable bone substitute materials products available in the market.

Bongold™ Bone Graft Material [77] is composed of synthetic HA and Col I. This bone graft substitute contains approximately 45% mineral by weight. The degradation rate can reach 40% in 10 weeks. Its porosity $\geq$70% with pores between 25 and 600 μm and its compressive strength is $\geq$ 0.5 MPa. Ghate et al. [78] employed Bongold™ for the first time and it had a critical influence on podarthral joint defect repair (Fig. 8). The postoperative 13-weeks follow-up showed that the joint healed well with no inflammatory reactions.

OsteoFlo® NanoPutty®-Quadphasic Synthetic Bone Graft [79] is an osteoconductive, non-hardening bone graft solution. OsteoFlo® is applied as a premixed putty, and the synthetic binder is resorbed to expose quadphasic particles. The particles act as osteoconductive scaffolds for new bone formation as they are slowly resorbed. Smaller particles used in OsteoFlo® NanoPutty® are smaller than most artificial bone grafts available in the market. This helps to maintain fluidity during minimally invasive surgery. The combination of four different particles can maximize the bone promoting effect. At the same time, nano-surface technology can pomote the attachment of bone cells.

Sorrento™ Bone Graft Substitute [80] is an absorbable bone void filler. Walsh et al. [81] developed a cancellous bone defect model of critical size and evaluated its ability to form new bone and the local reaction of Sorrento™ Bone Graft Substitute in New Zealand rabbits. The results showed Sorrento™ Bone Graft Substitute's ability to promote bone formation, and its completion of the repair of the empty defect which was not completed by autologous bone transplantation (Fig. 9).

After hydration with bone marrow aspirate, the FIBERGRAFT® AERIDYAN Matrix Bone Graft Substitute [82] can be applied directly to the defect site or molded into the desired shape and gently packed into the defect site as a non-setting putty. The pores are continuous, and the connection of fibers provides an uninterrupted channel for cells. The antibacterial test of FIBERGRAFT® shows that it has good antibacterial activity against *Staphylococcus aureus in vitro* [83].

Osteo-P™ Bone Graft Substitute [84] is composed of a porous, osteoconductive polymeric carbohydrate. This bone graft substitute could also simulate the structure of cancellous bone. Although it is osteoconductive and biocompatible, its mechanical properties are insufficient to produce load bearing effect on bone defects. This product is not available in the market yet, and its clinical effect remains unknown.

6. Summary and perspective

The ideal scaffold for bone defect repair should possess following characteristics: (1) maintain a specific three-dimensional structure; (2) act as the bone conductive matrix for osteoblasts; (3) have fine biocompatibility and biodegradable; (4) provide certain mechanical strength; (5) have appropriate matrix absorption rate which matches the new bone formation rate [85]. Due to the limitations of traditional methods in the treatment of large bone defects, it is particularly important to develop better bone repair materials.

With the recent developments in medicine and material science, as well as the in-depth study of bone regeneration mechanisms, more new bioabsorbable materials have been developed. No matter single component or composite materials, they reflect the urgent need for load-bearing, degradation, and biocompatibility in large bone defect repair. Bioabsorbable metal materials are used to manufacture bioabsorbable sutures, bioabsorbable screws, intramedullary needles, and other implants. Bioabsorbable polymer materials play a role in coating anti electrolysis, orthopaedic splint, and used as drug carriers in the treatment of osteomyelitis or bone tuberculosis. Bioabsorbable inorganic materials as injectable bone cement can be used in vertebroplasty and kyphoplasty by rapid prototyping.

Natural bone has incomparable advantages in composition, multi-level hierarchicalstructure, and biological activity. In terms of composition, nano HA and Col fiber are the basic components of natural bone. The Ca–P (phosphorus) system and its rich Mg, Zn, and other trace elements can greatly improve the biocompatibility of materials, enhance the proliferation and adhesion of mesenchymal stem cells, and regulate the osteogenic differentiation potential of the cells. In terms of structure, natural bone is highly interconnected at the nanoscale and microscale. The three-dimensional porous structure with gradual gradient distribution and rich three-dimensional capillary network is the transport channels of nutrients and metabolites. The topological structure and vascular network of the microenvironment are very conducive to the differentiation, proliferation and adhesion of stem cells, and can effectively stimulate gene expression in osteoblasts. Another important function of the natural bone matrix is to carry a variety of growth factors. It has unique 'osteoinductive activity' and induces BMSCs to differentiate into osteoblasts. These aspects should be considered important for the design and development of artificial materials.

At present, some methods such as 3D printing, surface coating and cross-linking modification can effectively improve the physical and chemical properties of the materials. In the future, with more advanced manufacturing technologies, such as fabrication method based on microfluids, ideal artificial bioabsorbable bone substitute material that meet the requirements of bone defect repair will be achieved, and provide a new therapy for clinical bone defect repair and benefit more patients.

Statement of originality

This material has not been published and is not currently under consideration with another journal.

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Authorship confirmation statement

CL and HZL performed literature research and writing of the manuscript. YWD, WBZ and WJY contributed to editing and writing of the manuscript. XMW, JW and WC critically reviewed the intellectual content of the article. All authors who participated in the creation of this manuscript are listed.

Declaration of competing interest

The authors declare no conflict of interest.

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