ACS OMEGA

http://pubs.acs.org/journal/acsodf

Review

# Biodegradable Implants for Internal Fixation of Fractures and Accelerated Bone Regeneration

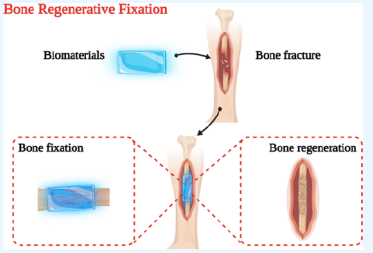
Pei Wang, Yan Gong, Guangdong Zhou,* Wenjie Ren, and Xiansong Wang*

Cite This: *ACS Omega* 2023, 8, 27920−27931

Read Online

ACCESS | Metrics & More | Article Recommendations

**ABSTRACT:** Bone fractures have always been a burden to patients due to their common occurrence and severe complications. Traditionally, operative treatments have been widely used in the clinic for implanting, despite the fact that they can only achieve bone fixation with limited stability and pose no effect on promoting tissue growth. In addition, the nondegradable implants usually need a secondary surgery for implant removal, otherwise they may block the regeneration of bones resulting in bone nonunion. To overcome the low degradability of implants and avoid multiple surgeries, tissue engineers have investigated various biodegradable materials for bone regeneration, whereas the significance of stability of long-term bone fixation tends to be neglected during this process. Combining the traditional orthopedic implantation surgeries and emerging tissue engineering, we believe that both bone fixation and bone regeneration are indispensable factors for a successful bone repair. Herein, we define such a novel idea as bone regenerative fixation (BRF), which should be the main future development trend of biodegradable materials.




## 1. INTRODUCTION

Bone fractures, as the most common traumatic injuries to humans,[1] are companied with numerous complications, especially infections. In addition, about 5−10% of fractures end up with delayed union and nonunion.[2−4] A successful bone repairment, mainly involving inflammatory, repair, and remodeling phases, is highly dependent on the fixation stability and regeneration of the fracture area.[5,6] Fracture reduction, fixation, and functional exercise are three basic principles of bone fracture treatment. On the basis of these principles, traditionally, the therapeutic strategies of bone fractures have been focused on orthopedic surgeries.[7] However, except for their incapability of promoting tissue growth, operative treatments usually contribute to implant-associated infections which may further inhabit the healing of bone fractures.[8−10] Recently, some commercial bone adhesives have been gradually used as substitutions for implants, since their applications are more convenient. Unfortunately, most current adhesives only possess relatively low biodegradability which might hamper cell in-growth resulting in weakened therapeutic efficacy[11] and only possess insufficient adhesive strength, contributing to instable bone fixation.

To reduce the risk of implant-associated infections and the limited biodegradability of current adhesives, various biodegradable materials, with suitable mechanical strength resembling natural bones, have been investigated as bone fixation implants.[12−16] Meanwhile, other studies tend to concentrate on some bioactive factors functioning as inflammatory regulators,[17−23] angiogenesis promoters, or osteogenesis accelerators,[24−28] for promoting the regeneration of bone fracture.

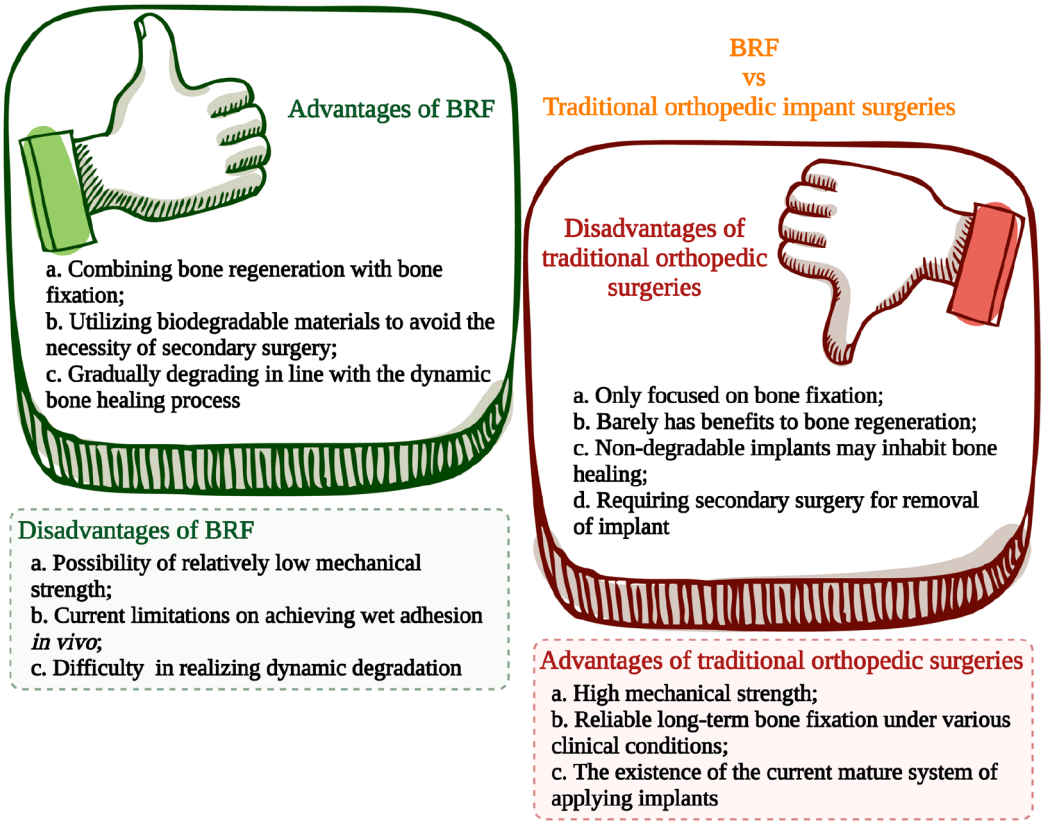
During our further studies on bone fracture repairment, we gradually realized that utilizing only bone fixation or only bone regeneration in treating fractures is insufficient for a successful bone repairment. Herein, we propose a novel concept: bone regenerative fixation (BRF). BRF represents two main aspects concerning bone fracture fixation. For one thing, biomaterials should possess outstanding adhesive properties and mechanical strength for realizing stable bone fixation. Meanwhile, the biodegradability of biomaterials would also be regulated for achieving the long-term bone fixation and matching the dynamic bone healing process. For another, the pathological microenvironment of bone fractures would also be reversed by those biomaterials, and thereby the bone regeneration would be highly enhanced. In conclusion, BRF combining the idea of bone fixation and bone regeneration is a great improvement for treating bone fractures, compared to the traditional treatments (Scheme 1). Therefore, we believe that BRF raises a novel goal for the future design of biomaterials and provides a novel strategy for treating bone fractures in clinics.

## 2. TRADITIONAL TREATMENT OF BONE FRACTURE

The basic principle of treating fractured bones is stable fixation.[7] The current external and internal fixation strategy

**Received:** April 20, 2023
**Accepted:** July 12, 2023
**Published:** July 26, 2023

Scheme 1. Comparison between Bone Regenerative Fixation (BRF) and Traditional Orthopedic Implant Surgeries




applied in the clinic were generated from this principle.[29] External fixation refers to a surgical treatment associated with the application of pins, wires, clamps and rings, or external fixation rods, which is usually applied for open fractures accompanied by extensive soft-tissue injuries.[7,29] In addition, temporary external fixation can serve as the pretreatment of internal fixation.[30] Internal fixation, referring to the surgical application of implants for bone fixation,[31] can be divided into open reduction internal fixation (ORIF) and closed reduction internal fixation (CRIF). Internal fixation has an advantage in realizing functional reduction and anatomical reduction simultaneously, whereas it also tends to result in more severe and increased risk of complications, such as damage to muscle and nerve, chronic pain, nonunion or mal-union of bones, and arthritis or tendinitis. In particular, implant-associated infections, one of the most severe complications of orthopedic internal fixation surgeries,[32] has happened even more frequently, resulting in prolonged pain of patients.[33,34]

Currently, numerous titanium (Ti) alloys have been applied for bone defect restoration.[35] Nevertheless, their mismatched mechanical properties with natural bones,[36] low biodegradability, and insufficient biocompatibility retain the risk of bone nonunion and bone resorption, which results in more suffering to patients. Therefore, most recent studies about metals have been concentrated on incorporating metals with biomaterials for better application or investigating novel topological design for matching the mechanical properties of natural bones.

Tian et al. integrated magnesium (Mg) screw coated with a polymer film with a Ti plate (Mg/Ti hybrid fixation system) for enhanced biodegradability and shared loading stress (Figure 1a).[37] The results of finite element analysis demonstrated that the integration of the Mg screw lowered the maximum stress compared to pure Ti implants (Figure 1b). Meanwhile, *in vivo* experiments and their corresponding quantification results also indicated the certain therapeutic efficacy of the Mg/Ti hybrid fixation system (Figure 1c−e). In comparison, Ma et al. fabricated porous Ti-6Al-4 V (PT) loaded with mineralized collagen (MC) (MC/PT) for bonelike mechanical strength and enhanced vascularized bone formation (Figure 1f).[36] The MC/PT scaffold was fabricated via 3D printing and then implanted into the radius of rabbits for testing its *in vivo* therapeutic efficacy (Figure 1g), and results showed that MC/PT scaffold significantly promoted bone regeneration (Figure 1h).

As substitutions for implants, currently, kinds of surgical glues have been investigated and applied in clinics which are mainly divided into the following five types: (blood) fibrin glue, cyanoacrylates, collagen glue, glutaraldehyde composite glue, and hydrogel glue. Surgical glues have demonstrated their efficacy on preventing postoperative tissue adhesion and realizing wound closure with lower infection rate and no stitches, possessing great advantages over traditional surgery treatment. Therefore, we summarized the advantages and disadvantages of bone adhesives compared to traditional treatments,[15,38] which is presented in Table 1.

However, present surgical glues come with some inherent shortcomings: (a) glues may cause severe allergic reactions which pose a threat to the wound healing; (b) most glues would inhabit cell in-growth and therefore slow down the wound healing, let alone promoting tissue regeneration; (c) most commercial surgical glues tend to have low biocompatibility with certain cytotoxicity, especially fibrin glue and cyanoacrylates;[39,40] (d) the current glues only have limited adhesiveness and provide transient adhesion, which is


https://doi.org/10.1021/acsomega.3c02727
ACS Omega 2023, 8, 27920−27931

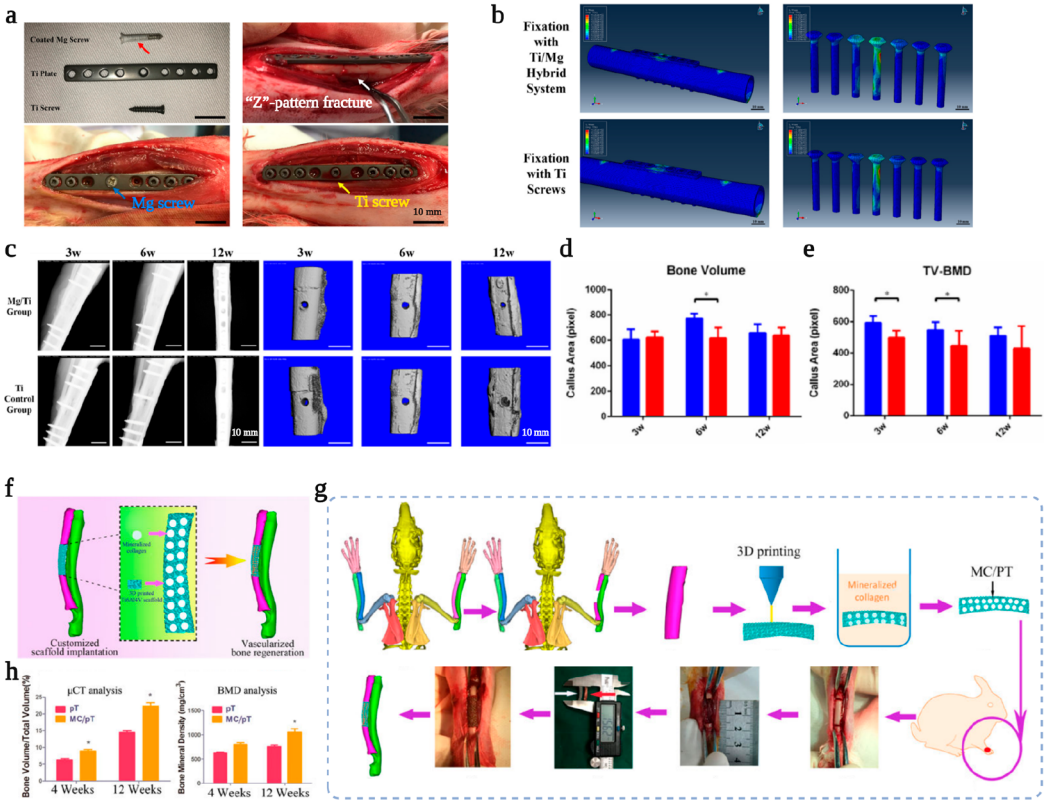



**Figure 1.** (a–e) Morphology, mechanical properties, and therapeutic efficacy of the Mg/Ti hybrid fixation system.[37] Reprinted with permission from ref 37. Copyright 2018 Elsevier. (a) Morphology of Mg/Ti hybrid fixation system and pure Ti implants. (b) Finite element analysis of the Mg/Ti hybrid fixation system and pure Ti implants. (c) X-ray images and 3D reconstructed images of bone fracture repair of rabbits implanted with a Mg/Ti hybrid fixation system and pure Ti implants within 12 weeks. (d,e) Quantification results of bone formation in the Mg/Ti hybrid fixation system group and pure Ti implant group. (f–h) Scheme illustration of fabrication and application of porous MC/PT scaffold, along with its bone regenerative efficacy.[36] Reprinted with permission from ref 36. Copyright 2018 American Chemical Society. (f) Description of the design of porous MC/PT scaffold. (g) Scheme illustration of fabrication of porous MC/PT scaffold and the *in vivo* application. (h) Quantification of bone formation rate of porous MC/PT scaffold.

**Table 1. Advantages and Disadvantages of Bone Adhesives Compared to Traditional Treatments**

| surgical glues compared to traditional orthopedic implant surgeries | |
|---|---|
| advantages | disadvantages |
| more convenient, faster, and safer | relatively low mechanical strength |
| shortened operation time | relatively poor biocompatibility and degradability |
| decreased infection rate | possible cytotoxicity |
| less invasive | unstable fixation |
| fewer complications | later functional exercise after surgery |
| no need for a second operation to remove implants | |

insufficient for long-term bone fixation;[41] and (e) glues can be ineffective in wet or moist microenvironments which limit their application in deep tissue.

In conclusion, traditional orthopedic implant surgeries highlight the significance of bone fixation, yet neglect the value of promoting bone regeneration. In contrast, although the surgical glues may weaken the complications of implants, they still have various deficiencies, as mentioned above. In particular, surgical glues are even incapable of proving sufficient mechanical strength for bone fixation, especially when it comes to tissues demanding a long-period fixation. Therefore, currently, neither implants nor surgical glues are suitable for realizing BRF.

## 3. TISSUE ENGINEERING FOR BONE FIXATION AND BONE REGENERATION

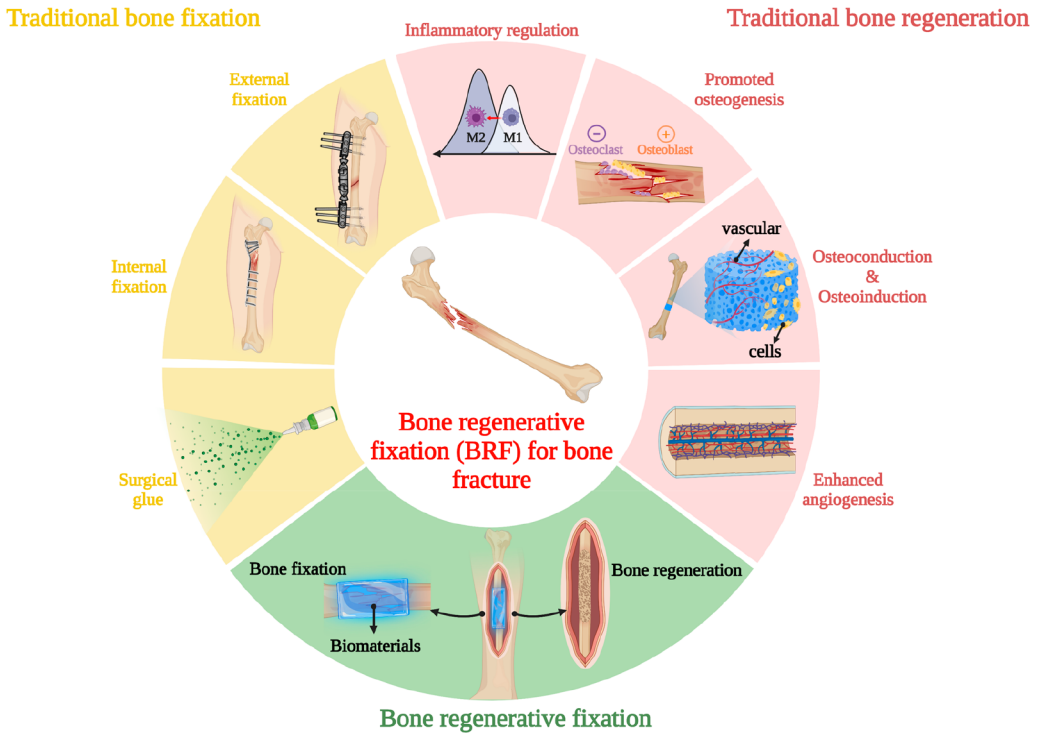
In tissue engineering, scientists have been mainly focused on fabricating biodegradable scaffolds simultaneously functioning as bone substitutes and promoting bone regeneration via regulating the inherent microenvironment.[42,43]

In the aspect of providing sufficient mechanical strength, tissue engineers tend to utilize porous scaffolds with great osteoconductivity and osteoinductivity. For this purpose, various demineralized bone matrix (DBM) hybrid scaffolds or DBM particles and nanocoatings have been studied,[21,44−47] since DBM alone can only function as a filling material instead of a bone graft. In the aspect of promoting bone regeneration, most tissue engineers are inclined to incorporate tissue-growth factors, such as VEGF and BMP-2, or stem cells into scaffolds.[48−51]

Since both mechanical support and growth-promoting effects are indispensable for bone fracture repair, most existing tissue engineered scaffolds have tried to combine them, which is a great improvement over traditional treatments. However, the obvious shortcoming of current scaffolds is that they tend to emphasize in one aspect and neglect in another one more or less. For example, applying biomodified metals can provide sufficient mechanical support for bone fixation, yet the low degradation rate of metals may inhabit the new bone formation in return. In comparison, utilizing biodegradable scaffolds


https://doi.org/10.1021/acsomega.3c02727
ACS Omega 2023, 8, 27920−27931

Scheme 2. Detailed Concept Description of Bone Regenerative Fixation (BRF)




integrated with regeneration-promoting cytokines can be very beneficial to the osteogenesis, yet most biodegradable scaffolds are incapable of providing enough mechanical strength especially for long-period bone fixation.

On the basis of previous studies, we propose a novel strategy for treating bone fracture: bone regenerative fixation, denoted as BRF. BRF refers to applying novel biodegradable materials based on tissue engineering which can not only provide sufficient mechanical strength for long-period bone fixation but also facilitate bone regeneration via regulating the pathological microenvironment and dynamically degrading, according to the bone healing process (Scheme 2). To our belief, BRF should be the ultimate goal for tissue engineers who fabricate bioscaffolds to realize bone fracture repair.

## 4. BONE REGENERATIVE FIXATION

**4.1. Metallic Alloys.** Metallic alloys mainly refer to biodegradable metals,[52] which can provide enough mechanical strength when bone fixation is required and gradually degrade *in vivo* to avoid a secondary surgery. Therefore, we mainly introduce the new development of metallic alloys in this paragraph.

Metallic alloys can be gradually corroded *in vivo*, but the biodegradability of them depends on the ratio of different ingredients which has been the focus of recent studies about alloys. Mg is biocompatible with rather low cytotoxicity which can release $Mg^{2+}$ and hydrogen for therapeutic effects, including enhancing angiogenesis and regulating an inflammatory reaction.[53,54] In particular, the *in vivo* biodegradability of Mg alloys avoids surgical intervention for removing implants.[55−58] Unfortunately, the excessive corrosion rate of pure Mg alloys would contribute to hydrogen accumulation and decreased mechanical integrity which restricts their physiological application.[55,59] The addition of coating,[60] other alloy elements, and rare-earth elements have been testified as practical solutions for realizing controlled corrosion rate and enhanced mechanical strength of Mg alloys. Hou et al. fabricated a MgZnCa alloy,[59] within which 0.7 wt % zinc (Zn) was used for enhanced mechanical strength and 0.6 wt % calcium (Ca) was incorporated for increased castability (Figure 2a). The MgZnCa alloy was studied in a rolled form and in an annealed form, and the results showed that the annealed MgZnCa alloy possesses better mechanical integrity and decreased degradation rate (Figure 2b−d). Similarly, Sommer et al. also fabricated MgZnCa alloy and applied it on osteoporotic (Osteo), old healthy (OH), and juvenile healthy (JH) SD rats to test its biodegradability.[61] The results showed that implants in all three groups experienced a volume decrease after a 24-week implantation, where the Osteo group had the most significant total volume loss of 40.89 ± 3.53% (Figure 2e−g). The histological experiments also revealed a homogeneous pit corrosion of MgZnCa alloy after 24-week implantation (Figure 2h). Except for integrating Mg with Zn and Ca, the incorporation of gallium,[62] gadolinium (Gd),[63] and silicon (Si)[64] also facilitate to avoid the inhomogeneous biodegradation and high corrosion rate of pure Mg alloy.

In addition, Zn-based implants are also a promising biodegradable material with great biocompatibility and functionality.[65−68] Zn-based implants can release zinc ions for affecting cell adhesion and promoting new bone formation.[69] Unfortunately, the yield strength and elongation of pure Zn alloy is extremely low, and thereby Zn-based alloys were integrated with other elements for better mechanical performance.[70] Qu et al. integrated Zn alloy with different concentration of silver (Ag).[71] Pure Zn, Zn-0.5Ag alloy, Zn-1Ag alloy, and Zn-2Ag alloy were applied in that study. Zn-2Ag alloy demonstrated enhanced efficacy on new bone formation and biodegradability compared to the commercially used Ti-6Al-4 V alloy (Figure 2i−k).



https://doi.org/10.1021/acsomega.3c02727
ACS Omega 2023, 8, 27920−27931

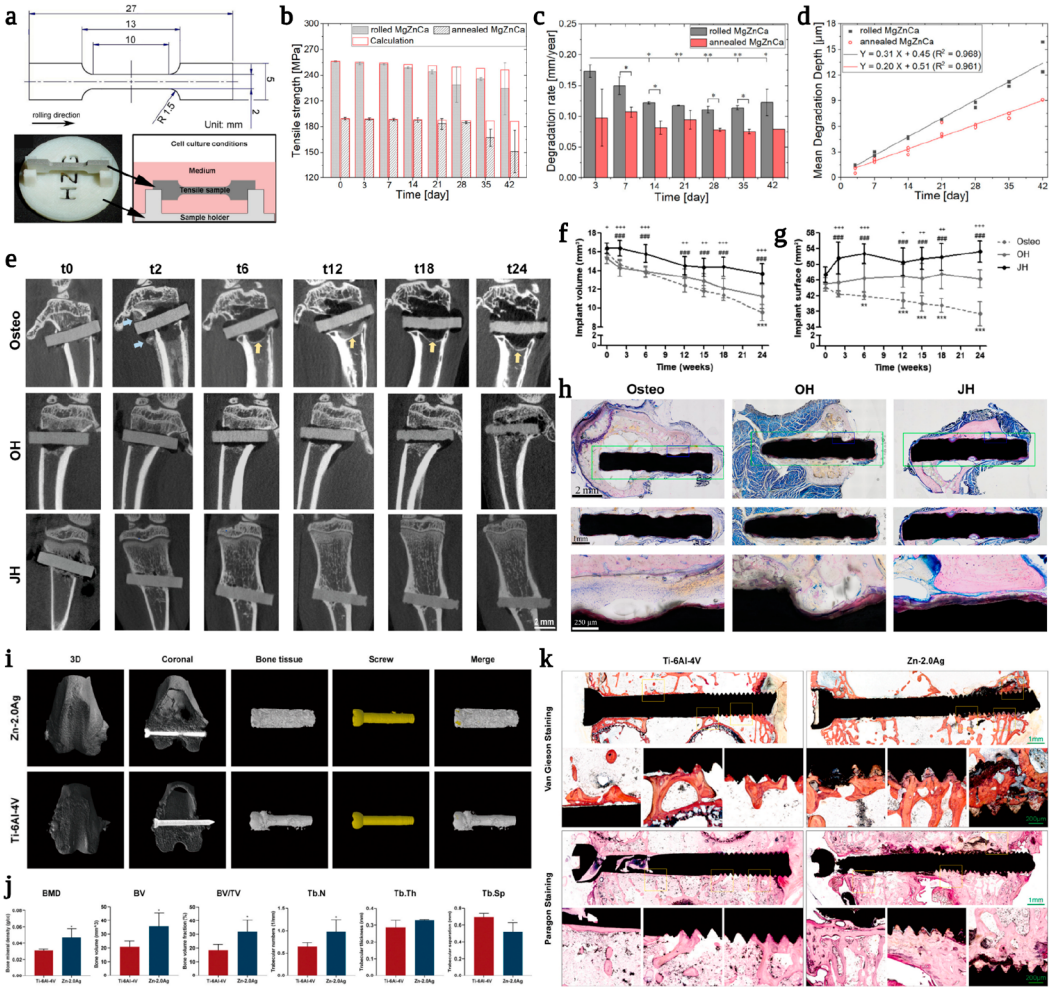



**Figure 2.** (a–d) Dimension, tensile strength, and degradation rate of rolled and annealed MgZnCa alloy.[59] Reprinted with permission from ref 59. Copyright 2019 Elsevier. (a) Dimension of tensile sample of MgZnCa alloy and scheme illustration of immersion test of tensile sample. (b) Tensile strength of rolled and annealed MgZnCa alloy. (c) Degradation rate of rolled and annealed MgZnCa alloy. (d) Mean degradation depth of rolled and annealed MgZnCa alloy. (e–h) *In vivo* degradability of MgZnCa alloy implanted in Osteo, OH, or JH rats.[61] Reprinted with permission from ref 61. Copyright 2022 Elsevier. (e) $\mu$CT images of implants after being implanted in Osteo, OH, or JH rats for 0, 2, 6, 12, 18, and 24 weeks. (f) Change of volume of implants in different groups. (g) Change of surface of implants in different groups. (h) Histological evaluation of MgZnCa alloy in different groups after 24 weeks of implantation. (i–k) Bone formation efficacy and degradability of Zn-2Ag alloy and Ti-6Al-4 V alloy after 3-month implantation.[71] Reprinted with permission from ref 71. Copyright 2021 Elsevier. (i) Results of 3D reconstruction of specimens of femoral condyles implanted with Zn-2Ag alloy or Ti-6Al-4 V alloys. (j) Quantification results of new bone formation. (k) Van Gieson and Paragon staining sections of femoral condyles three months after the implantation. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, and ****$p < 0.0001$ (same for the other marks # and +). * represents significant difference between Osteo and OH; # and + mean significant difference between Osteo and JH and between OH and JH, respectively.

In conclusion, metallic alloys are promising implants for orthopedic surgeries. Metallic alloys can not only release metal ions for bone formation via slow degradation but also provide enough mechanical strength for bone fixation and eventually achieve BRF. However, most metallic alloys still need to be further studied before their clinic usage. For example, the degradation rate of pure Mg alloy is uncontrollable, which may lead to the accumulation of Mg ions and hydrogen. Despite that many scientists have tried to integrate other metal elements and rare-earth elements to weaken the inherent disadvantages of the Mg alloy, Mg-based alloys with suitable biodegradation rates and enough mechanical properties for long period mechanical support have not been successfully fabricated, which demands further investigation.

**4.2. Bioceramics.** Bioceramics have been studied as implants for bone fixation, due to their successful simulation of bone microenvironment and direct new bone formation capability.[72,73] In addition, bioceramics also possess great therapeutic efficacy in promoting bone regeneration due to its outstanding osteoconduction and hierarchical porosity, including macro-, micro-, and nanoscales.[74−76] However, most bioceramics, including calcium silicate, hydroxyapatite (HA), tricalcium phosphate, and bioactive glass, have very low biodegradability and rather high brittleness which have limited their further application.

To overcome these problems, recent studies about bioceramics were mainly focused on the enhancement of their bioactivity and biocompatibility.[77−80] Zamani et al. integrated Mg and Zn into alginate powder containing different weights of bioactive glass to fabricate different Alg/BG composite scaffolds (including pure alginate scaffold, Alg-0.3BG, Alg-1BG, and Alg-1.5BG) (Figure 3a).[81] Alg/BG


https://doi.org/10.1021/acsomega.3c02727
ACS Omega 2023, 8, 27920−27931

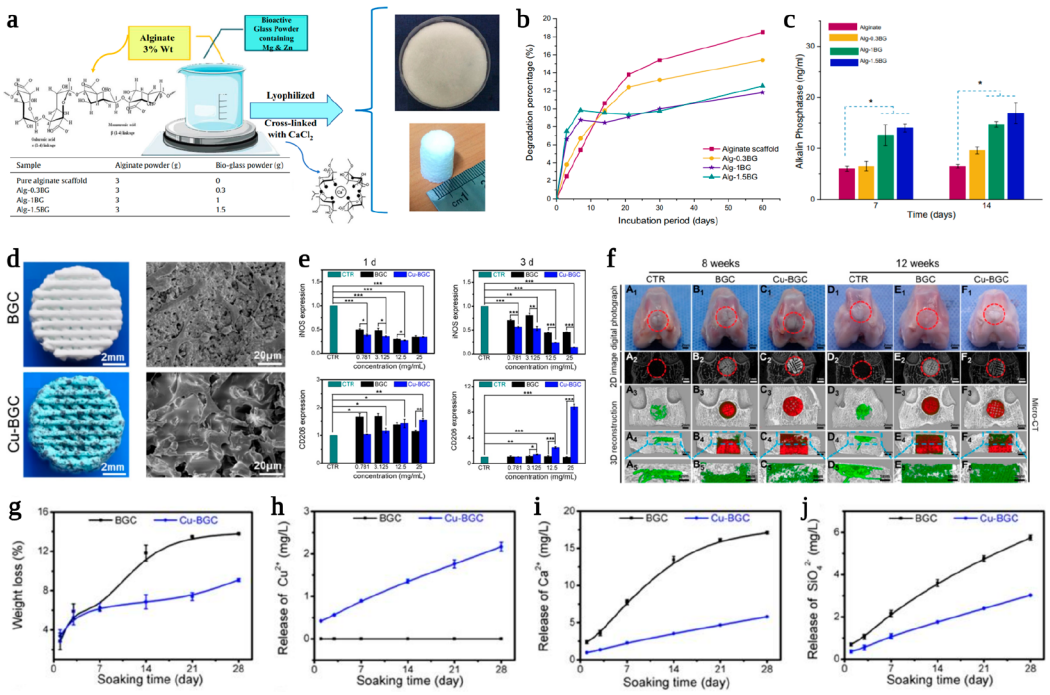


**Figure 3.** (a–c) Fabrication, degradability, and bone formation efficacy of Alg/BG composite scaffolds.[81] Reprinted with permission from ref 81. Copyright 2019 Elsevier. (a) Fabrication of different Alg/BG composite scaffolds. (b) Degradability of Alg/BG composite scaffolds in PBS for 60 days. (c) ALP activity promoting the efficacy of Alg/BG composite scaffolds. (d–j) Morphology and therapeutic efficacy of Cu-BGC scaffolds.[82] Reprinted with permission from ref 82. Copyright 2019 Ivyspring International Publisher. (d) Photographic and SEM images of BGC scaffold and Cu-BGC scaffold. (e) Inflammatory regulation effects of Cu-BGC scaffolds. (f) Bone recovery efficacy of Cu-BGC scaffolds. (g) Degradability of BCG and Cu-BCG in Tris-HCl solution for 28 days. (h) Release profile of $Cu^{2+}$ from BCG and Cu-BCG within 28 days. (i) Release profile of $Ca^{2+}$ from BCG and Cu-BCG within 28 days. (j) Release profile of $SiO_4^{2+}$ from BCG and Cu-BCG within 28 days.

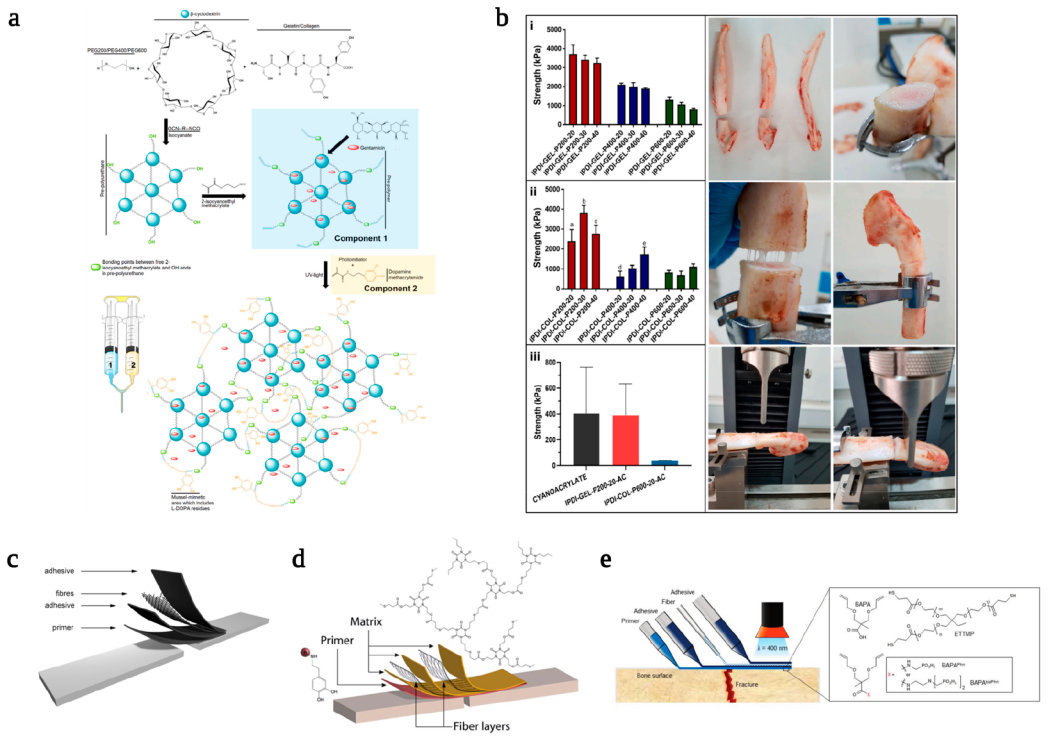


**Figure 4.** (a,b) Fabrication and adhesive strength tests of IPDI-GEL-PEG or IPDI-COL-PEG.[90] Reprinted with permission from ref 90. Copyright 2021 Elsevier. (a) Scheme illustration of fabrication of IPDI-GEL-PEG or IPDI-COL-PEG. (b) Adhesive strength tests of IPDI-GEL-PEG or IPDI-COL-PEG. (c–e) Structure of different FRAPs.[91−93] Reprinted with permission from ref 91. Copyright 2010 American Chemical Society. Reprinted with permission from ref 92. Copyright 2016 Royal Society of Chemistry. Reprinted with permission from ref 93. Copyright 2018 Wiley-VCH.



https://doi.org/10.1021/acsomega.3c02727
ACS Omega 2023, 8, 27920−27931

Table 2. Basic Materials and Adhesive Strength of Several Representative Bone Adhesives

| adhesives | basic materials | shear strength (MPa) |
|---|---|---|
| fiber-reinforced adhesive patch (FRAP)[91] | primer: 3,4-dihydroxyphenyl-L-alanine (DOPA) | 3.8 |
| | adhesive: histoacryl | |
| | fiber: E-glass fibers | |
| fiber-reinforced-adhesive-patch (FRAP)[92] | primer: dopa-thiol with either dopa-methacrylamide or dopa-allyl | 0.29 |
| | NaOH | |
| | matrix: Tris[2-(3-mercaptopropionyloxy)ethyl] isocyanurate (TAT) | |
| | 1,3,5-triallyl-1,3,5-triazinane-2,4,6-trione (TAA) | |
| | fiber: E-glass fibers | |
| Fiber-reinforced adhesive patch (FRAP)[93] | primer: 3-(allyloxy)-2-((allyloxy)-methyl)-2-methylpropanoic acid (BAPA) | 9 |
| | ethoxylated-trimethylolpropane tri-3-mercapto-propionate (ETTMP) | |
| | lithium phenyl-2,4,6-trimethylbenzoylphosphinate (LAP); adhesive: Tris[2-(3-mercapto propionyloxy) ethyl] isocyanurate (TEMPIC) | |
| | 1,3,5-triallyl-1,3,5-triazine-2,4,6(1H,3H,5H)-trione (TATATO) | |
| | hydroxyapatite (HA) particles | |
| | fiber: poly(ethyleneterephthalate) (PET) fiber mesh | |
| PSC/PEG/OCA adhesives[94] | 2-octyl cyanoacrylate (OCA); | 4.4 ± 0.2 (15 min) |
| | 10.8%$P_2O_5$-54.2%$SiO_2$-35.0%CaO, mol % (PSC) | 4.6 ± 0.3 (24 h) |
| | Poly(ethylene glycol) (PEG) | |
| SUP-SDBS glue system[95] | cationic supercharged polypeptides (SUPs) | 16.5 (K144-SDBS) |
| | surfactant sodium dodecylbenzenesulfonate (SDBS) | |

composite scaffolds were gradually degraded in PBS, albeit to varying degrees (Figure 3b). Meanwhile, the application of Alg/BG composite scaffolds also promoted the expression of ALP which is in line with the osteoblastic differentiation and bone regeneration rate (Figure 3c). Similarly, Lin et al. incorporated copper (Cu) into bioactive glass-ceramics (BGC) to create a Cu-BGC scaffold (Figure 3d).[82] The Cu-BGC scaffold would gradually degrade by 9.08% immersed in Tris-HCl solution for 28 days, while it slowly releases $Cu^{2+}$, $Ca^{2+}$, and $SiO_4^{2+}$ for therapeutic efficacy (Figure 3g−j). The release of $Cu^{2+}$ from Cu-BGC scaffolds can decrease the inflammatory response and promote the healing of the osteochondral interface (Figure 3e,f). In addition, 3D-printed bioceramics for mimicking the complicated structure of bones are also quite prevalent recently.[77,83,84]

In conclusion, porous bioceramics, especially bioactive glass, can provide sufficient osteoconduction and mechanical strength for fracture fixation, along with releasing ions for facilitating bone regeneration, which can be a suitable material for BRF. However, most current bioceramics can not fully degrade after bone fracture union, which may pose an adverse effect to the bone healing. It seems rather difficult to change the inherent inadequate properties of bioceramics. Therefore, we believe that incorporating bioceramics into biodegradable materials and maintaining the positive characteristics of bioceramics simultaneously can be a feasible method for eventually achieving BRF.

**4.3. Bone Adhesives.** As we discussed above, both metallic alloys and bioceramics have inherent shortcomings, especially their limited bioactivity and low biodegradability. In comparison, bone adhesives pose a new strategy for fixing bone fragments which circumvent problems of traditional implants.[85,86] Bone adhesives can not only realize stabilized fracture with minimized surgical trauma[87] but also promote bone regeneration via delivery growth-promoting factors. Therefore, we are mainly focused on two characteristics of bone adhesives which need to be improved.

On the one hand, for *in vivo* application, the biocompatibility of adhesives requires improvement. Molecular-modification, such as dopamine-modification,[88,89] has been used in much research for enhanced biocompatibility. Balcioglu et al. fabricated a photo-cross-linkable aliphatic isophorone diisocyanate (IPDI) bone adhesive based on gelatin or collagen integrated with different weights of PEGs (P200, P400, and P600) (IPDI-GEL-PEG or IPDI-COL-PEG) (Figure 4a).[90] The adhesive strength of IPDI-GEL-PEG or IPDI-COL-PEG was also tested (Figure 4b). Results demonstrated that the adhesive strength of IPDI-GEL-P200-20-AC (390 kPa) is comparable to that of cyanoacrylate (403 kPa, a commercial adhesive).

On the other hand, for long-term bone fixation, the adhesive strength requires testing and strengthening which is usually determined by tensile strength, peeling strength, and shear strength. Normally, the strength needs to reach mepa level for bone fixation. Before, fiber-reinforced adhesive patch (FRAP) fixations with enough mechanical strength and the typical multilayered structure were studied by many groups (Figure 4c−e).[91−93] Recently, with the development of tissue engineering, various adhesive systems with higher adhesive strength were also fabricated. Hence, in this article, we summarized several qualified bone adhesives made of high polymer with their basic materials and shear strength on Table 2.

To sum up, tissue engineers have witnessed numerous advancements in fabricating better bone adhesives. However, the normal function of glues under a moist microenvironment remains a major problem when it comes to the long-term healing process of bone fractures. Meanwhile, despite the existing advancement on enhancing adhesive strength, it still


https://doi.org/10.1021/acsomega.3c02727
ACS Omega 2023, 8, 27920−27931

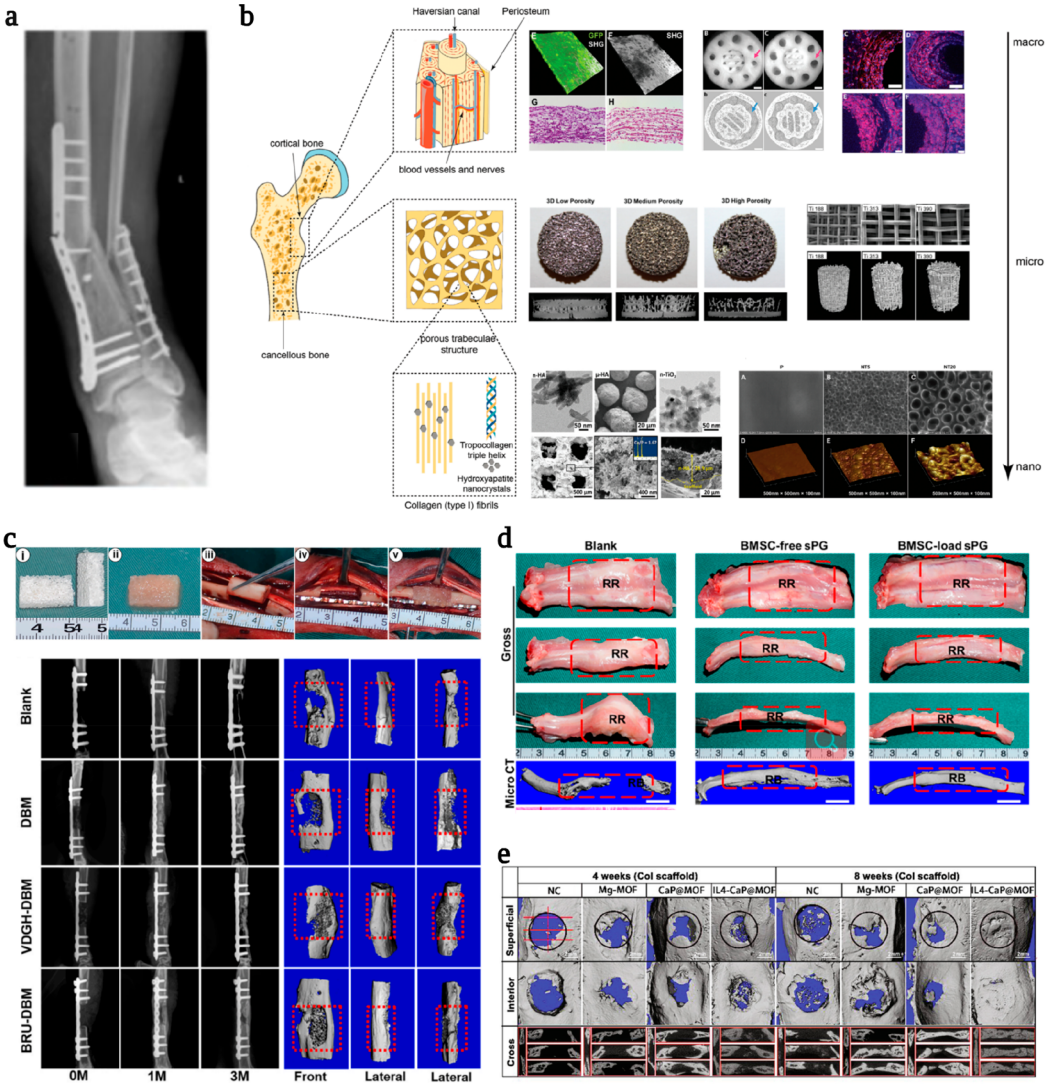



**Figure 5.** (a) X-ray images of representative case of bone nonunion at 7 months after surgery.[97] Reprinted with permission from ref 97. Copyright 2019 Multidisciplinary Digital Publishing Institute. (b) Tissue-engineered different-sized scaffolds for simulating corresponding bone structures.[100] Reprinted with permission from ref 100. Copyright 2021 Wiley-VCH. (c) Scheme illustration of implanting surgical procedures and the regenerated bone tissue after implantation of BRU-DBM scaffold. VDGH: VEGF/DBM-loaded GelMA/HAMA.[101] Reprinted with permission from ref 101. Copyright 2022 Elsevier. (d) Therapeutic efficacy of BMSCs-loaded sPG on large-sized bone defects.[102] Reprinted with permission from ref 102. Copyright 2022 American Chemical Society. (e) Therapeutic efficacy of IL4-MOF@CaP on large-sized bone defects.[103] Reprinted with permission from ref 103. Copyright 2020 Elsevier.

has not met the standard of mechanical strength of natural bones.

**4.4. Bio-Scaffolds.** Bone nonunion is one of the most severe complications of bone fractures.[96] In most situations, the treatment of bone nonunion requires bone grafting and several revision surgeries, which put great pressure on the health and socio-economic situation of patients (Figure 5a).[97−99] Traditionally, autogenous bone graft and bone allograft were applied in the clinic for fulfilling bone defect areas, whereas the autogenous bone graft tends to be limited by insufficient bone reservation and bone allograft may result in immunological rejection. Under this circumstance, simple regeneration-promoting fixators seem to be insufficient since that bone nonunion is usually accompanied by bone defects which require fulfilling. Therefore, biodegradable materials which can fill bone defects and serve as bone regeneration-promoting fixator simultaneously should be further studied.

Recently, bioscaffolds with different sizes have been studied and used as bone grafts due to their outstanding properties in simulating the native structure and microenvironment of bones (Figure 5b).[100] We believe that tissue engineered bioscaffolds can not only serve as bone substitutes for filling bone defects in bone nonunion but also function as the growth promoter for facilitating bone regeneration. In addition, bioscaffolds would not be taken as the block of bone regeneration due to their great biodegradability.

On the basis of this idea, we fabricated several bioscaffolds and investigated their therapeutic efficacy on critical-sized bone defects. In our previous studies, we constructed bone regeneration units (BRUs) via loading bone marrow mesenchymal stem cells (BMSCs) on photo-cross-linkable microgel (GelMA and HAMA containing vascular endothelial growth factor).[101] Afterward, the mixture was loaded on DBM scaffolds as BRU-DBM scaffolds. BRU-DBM scaffolds demonstrated great therapeutic efficacy on treating large


https://doi.org/10.1021/acsomega.3c02727
ACS Omega 2023, 8, 27920−27931

bone defects (Figure 5c). Similarly, we also constructed a 3D printed bone biomimetic scaffold (BBS) (sPG) which was then integrated with BMSCs (BMSCs-loaded sPG).[102] BMSCs-loaded sPG was implanted in the rib defects of rabbits and demonstrated satisfactory bone regeneration effects (Figure 5d). In addition, we also studied the effect of the regulated pathology microenvironment on bone regeneration via a building bone regeneration multicellular unit (BRMU).[103] The BRMU was made of magnesium metal−organic framework (Mg−MOF), a calcium phosphate (CaP) shell, and IL4 (IL4-MOF@CaP) which promoted successful repairment of large bone defects (Figure 5e).

In conclusion, bioscaffolds demonstrated outstanding superiority on bone non-union which demands the implantation of bone grafts. Unfortunately, despite their satisfactory biocompatibility, biodegradability, and osteogenic effects, most bioscaffolds are still incapable of realizing bone fixation alone, meaning their incapabile of achieving successful BRF and thereby need traditional internal fixation surgeries. Therefore, bioscaffolds with enhanced efficacy on bone fixation which can fulfill the bone defects and realize BRF simultaneously should be the focus of our future studies.

## 5. FUTURE PERSPECTIVES FOR BRF

Novel biodegradable materials for bone fixation and regenerative factors for bone regeneration are constantly being studied. For successful and enhanced bone repair, both stable bone fixation and enhanced bone regeneration are indispensable. Therefore, we proposed a novel ideal: bone regenerative fixation (BRF). Biodegradable materials designed for BRM should be simultaneously capable of realizing stable bone fixation via providing sufficient mechanical strength and accelerating bone regeneration through inflammatory regulation, angiogenic promotion, and osteogenic enhancement.

Till now, many breakthroughs have been achieved on enhancing biocompatibility of bone adhesives, while there are several remaining problems that need to be resolved before the clinic application of BRM: (a) The adhesive strength of the current tissue-engineered biodegradable materials has not reached a similar level of the mechanical strength of natural bones. Therefore, biodegradable materials with sufficient mechanical strength (mainly including tensile strength, peeling strength, shear strength) should be further studied. (b) The healing process of bone fracture usually takes a long time, making long-term fixation an indispensable property of biodegradable materials which has not been fully achieved in present studies. (c) Current biodegradable materials, especially bone adhesives are incapable of functioning normally in a wet microenvironment which limits their application in the deeper layer of tissue and bone fixation. (d) For better realization of BRM, biocompatible adhesives and regenerative factors should be further combined to modulate bone regeneration. For example, various growth factors can be released into the microenvironment of fractures in a slow and accurately controlled way for regulating inflammatory reactions, osteogenesis, and angiogenesis. (e) Some bone fractures can result in bone ununion which need the implantation of bone grafts. Although most tissue-engineered scaffolds with great biodegradability can fulfill the bone defects and promote bone regeneration, most of them lack the ability to realize bone fixation. Therefore, biodegradable scaffolds for filling bone defects and achieving BRF should be investigated.

In conclusion, this novel BRF provides a new direction for the future fabrication of biodegradable materials and offers a promising strategy for clinic treatment of bone fractures. Although current biodegradable materials have successfully realized either long-term bone fixation or enhanced bone regeneration, most of them fail in fully achieving BRF. Therefore, future studies should be focused on resolving the existing problems of current biodegradable materials to eventually achieve BRF and realize successful bone fracture repairment.

## AUTHOR INFORMATION


### Corresponding Authors

**Guangdong Zhou** − *Department of Plastic and Reconstructive Surgery, Shanghai Key Laboratory of Tissue Engineering, Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai 200011, China; Institute of Regenerative Medicine and Orthopedics, Institutes of Health Central Plain, Xinxiang Medical University, Henan 453003, China;* orcid.org/0000-0003-2488-2733; Email: guangdongzhou@126.com

**Xiansong Wang** − *Department of Plastic and Reconstructive Surgery, Shanghai Key Laboratory of Tissue Engineering, Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai 200011, China; Institute of Regenerative Medicine and Orthopedics, Institutes of Health Central Plain, Xinxiang Medical University, Henan 453003, China;* orcid.org/0000-0001-5836-6601; Email: wonderluis@126.com

### Authors

**Pei Wang** − *Department of Plastic and Reconstructive Surgery, Shanghai Key Laboratory of Tissue Engineering, Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai 200011, China*

**Yan Gong** − *Department of Plastic and Reconstructive Surgery, Shanghai Key Laboratory of Tissue Engineering, Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai 200011, China*

**Wenjie Ren** − *Institute of Regenerative Medicine and Orthopedics, Institutes of Health Central Plain, Xinxiang Medical University, Henan 453003, China*

Complete contact information is available at: https://pubs.acs.org/10.1021/acsomega.3c02727


### Author Contributions

P.W.: Conceptualization, methodology, investigation, writing−original draft, review, and editing. G.Y.: Writing−review and editing. W.R.: Methodology and form analysis. G.Z.: Methodology and form analysis. X.W.: Conceptualization, supervision, and funding acquisition.

### Notes

The authors declare no competing financial interest.

## ACKNOWLEDGMENTS

This work was financially supported by the National Natural Science Foundation of China (no. 31971271)

## REFERENCES

(1) Einhorn, T. A.; Gerstenfeld, L. C. Fracture healing: mechanisms and interventions. *Nat. Rev. Rheumatol* **2015**, *11*, 45−54.

(2) Foulke, B. A.; Kendal, A. R.; Murray, D. W.; Pandit, H. Fracture healing in the elderly: A review. *Maturitas* **2016**, *92*, 49−55.

(3) Maruyama, M.; Rhee, C.; Utsunomiya, T.; Zhang, N.; Ueno, M.; Yao, Z.; Goodman, S. B. Modulation of the Inflammatory Response and Bone Healing. *Front Endocrinol (Lausanne)* **2020**, *11*, 386.
(4) Hake, M. E.; Davis, M. E.; Perdue, A. M.; Goulet, J. A. Modern Implant Options for the Treatment of Distal Femur Fractures. *J. Am. Acad. Orthop Surg* **2019**, *27*, No. e867.
(5) Claes, L.; Recknagel, S.; Ignatius, A. Fracture healing under healthy and inflammatory conditions. *Nat. Rev. Rheumatol* **2012**, *8*, 133−143.
(6) Kusumbe, A. P.; Ramasamy, S. K.; Adams, R. H. Coupling of angiogenesis and osteogenesis by a specific vessel subtype in bone. *Nature* **2014**, *507*, 323−328.
(7) Taljanovic, M. S.; Jones, M. D.; Ruth, J. T.; Benjamin, J. B.; Sheppard, J. E.; Hunter, T. B. Fracture fixation. *Radiographics* **2003**, *23*, 1569−1590.
(8) Depypere, M.; Morgenstern, M.; Kuehl, R.; Senneville, E.; Moriarty, T.F.; Obremskey, W.T.; Zimmerli, W.; Trampuz, A.; Lagrou, K.; Metsemakers, W-J. Pathogenesis and management of fracture-related infection. *Clin Microbiol Infect* **2020**, *26*, 572−578.
(9) Foster, A. L; Moriarty, T F.; Trampuz, A.; Jaiprakash, A.; Burch, M. A; Crawford, R.; Paterson, D. L; Metsemakers, W.-J.; Schuetz, M.; Richards, R G. Fracture-related infection: current methods for prevention and treatment. *Expert Rev. Anti Infect Ther* **2020**, *18*, 307−321.
(10) Schmidt, A. H.; Swiontkowski, M. F. Pathophysiology of infections after internal fixation of fractures. *J. Am. Acad. Orthop Surg* **2000**, *8*, 285−291.
(11) Xu, L. Bioactive Pore-Forming Bone Adhesives Facilitating Cell Ingrowth for Fracture Healing. *Adv. Mater.* **2020**, *32*, No. e1907491.
(12) Seppänen-Kaijansinkko, R.; Lindqvist, C. In *Craniomaxillofacial Reconstructive and Corrective Bone Surgery*; Greenberg, A. M., Schmelzeisen, R., Eds.; Springer: New York, 2019; 121−128.
(13) Agarwal, R.; Garcia, A. J. Biomaterial strategies for engineering implants for enhanced osseointegration and bone repair. *Adv. Drug Deliv Rev.* **2015**, *94*, 53−62.
(14) Boker, K. O. Current State of Bone Adhesives-Necessities and Hurdles. *Materials (Basel)* **2019**, *12*, 3975.
(15) Zhang, M.; Liu, J.; Zhu, T.; Le, H.; Wang, X.; Guo, J.; Liu, G.; Ding, J. Functional Macromolecular Adhesives for Bone Fracture Healing. *ACS Appl. Mater. Interfaces* **2022**, *14*, 1−19.
(16) Shokri, M.; Dalili, F.; Kharaziha, M.; Baghaban Eslaminejad, M.; Ahmadi Tafti, H. Strong and bioactive bioinspired biomaterials, next generation of bone adhesives. *Adv. Colloid Interface Sci.* **2022**, *305*, 102706.
(17) Chen, Y.; Zhou, F.; Liu, H.; Li, J.; Che, H.; Shen, J.; Luo, E. SIRT1, a promising regulator of bone homeostasis. *Life Sci.* **2021**, *269*, 119041.
(18) Silfversward, C.-J.; Sisask, G.; Larsson, S.; Ohlsson, C.; Frost, A.; Ljunggren, O.; Nilsson, O. Bone formation in interleukin-4 and interleukin-13 depleted mice. *Acta Orthopaedica* **2008**, *79*, 410−420.
(19) Bastidas-Coral, A. P.; Hogervorst, J. M. A.; Forouzanfar, T.; Kleverlaan, C. J.; Koolwijk, P.; Klein-Nulend, J.; Bakker, A. D. IL-6 counteracts the inhibitory effect of IL-4 on osteogenic differentiation of human adipose stem cells. *J. Cell Physiol* **2019**, *234*, 20520−20532.
(20) Kroner, J.; Kovtun, A.; Kemmler, J.; Messmann, J. J; Strauss, G.; Seitz, S.; Schinke, T.; Amling, M.; Kotrba, J.; Froebel, J.; Dudeck, J.; Dudeck, A.; Ignatius, A. Mast Cells Are Critical Regulators of Bone Fracture-Induced Inflammation and Osteoclast Formation and Activity. *J. Bone Miner Res.* **2017**, *32*, 2431−2444.
(21) Guo, B.; Feng, X.; Wang, Y.; Wang, X.; He, Y. Biomimetic and immunomodulatory baicalin-loaded graphene oxide-demineralized bone matrix scaffold for in vivo bone regeneration. *J. Mater. Chem. B* **2021**, *9*, 9720−9733.
(22) Zheng, Z.-w.; Chen, Y.-h.; Wu, D.-y.; Wang, J.-b.; Lv, M.-m.; Wang, X.-s.; Sun, J.; Zhang, Z.-Y. Development of an Accurate and Proactive Immunomodulatory Strategy to Improve Bone Substitute Material-Mediated Osteogenesis and Angiogenesis. *Theranostics* **2018**, *8*, 5482−5500.
(23) Zheng, Z.; Chen, Y.; Hong, H.; Shen, Y.; Wang, Y.; Sun, J.; Wang, X.; et al. The ″Yin and Yang″ of Immunomodulatory Magnesium-Enriched Graphene Oxide Nanoscrolls Decorated Biomimetic Scaffolds in Promoting Bone Regeneration. *Adv. Healthc Mater.* **2021**, *10*, No. 2000631.
(24) Zhou, X.; et al. Spatiotemporal regulation of angiogenesis/osteogenesis emulating natural bone healing cascade for vascularized bone formation. *J. Nanobiotechnology* **2021**, *19*, 420.
(25) Ramasamy, S. K.; Kusumbe, A. P.; Wang, L.; Adams, R. H. Endothelial Notch activity promotes angiogenesis and osteogenesis in bone. *Nature* **2014**, *507*, 376−380.
(26) Su, W. Angiogenesis stimulated by elevated PDGF-BB in subchondral bone contributes to osteoarthritis development. *JCI Insight* **2020**, *5*, No. e135446, DOI: 10.1172/jci.insight.135446.
(27) Zhang, W.; Chang, Q.; Xu, L.; Li, G.; Yang, G.; Ding, X.; Wang, X.; Cui, D.; Jiang, X.; et al. Graphene Oxide-Copper Nanocomposite-Coated Porous CaP Scaffold for Vascularized Bone Regeneration via Activation of Hif-1alpha. *Adv. Healthc Mater.* **2019**, *8*, No. 1900067.
(28) Wang, C.; et al. Targeting angiogenesis for fracture nonunion treatment in inflammatory disease. *Bone Res.* **2021**, *9*, 29.
(29) Bible, J. E.; Mir, H. R. External Fixation: Principles and Applications. *J. Am. Acad. Orthop Surg* **2015**, *23*, 683−690.
(30) Dougherty, P. J.; Silverton, C.; Yeni, Y.; Tashman, S.; Weir, R. Conversion from temporary external fixation to definitive fixation: shaft fractures. *J. Am. Acad. Orthop Surg* **2006**, *14*, S124−127.
(31) Burns, G. T.; King, B. W.; Holmes, J. R.; Irwin, T. A. Evaluating Internal Fixation Skills Using Surgical Simulation. *J. Bone Joint Surg Am.* **2017**, *99*, No. e21.
(32) Pall, E.; Roman, A. Lactoferrin Functionalized Biomaterials: Tools for Prevention of Implant-Associated Infections. *Antibiotics (Basel)* **2020**, *9*, 522.
(33) Teixeira-Santos, R.; Lima, M.; Gomes, L. C.; Mergulhao, F. J. Antimicrobial coatings based on chitosan to prevent implant-associated infections: A systematic review. *iScience* **2021**, *24*, 103480.
(34) Dong, J.; et al. Immunomodulatory biomaterials for implant-associated infections: from conventional to advanced therapeutic strategies. *Biomater Res.* **2022**, *26*, 72.
(35) Wang, Z.; et al. The combination of a 3D-Printed porous Ti-6Al-4V alloy scaffold and stem cell sheet technology for the construction of biomimetic engineered bone at an ectopic site. *Mater. Today Bio* **2022**, *16*, 100433.
(36) Ma, L.; et al. Integrating 3D Printing and Biomimetic Mineralization for Personalized Enhanced Osteogenesis, Angiogenesis, and Osteointegration. *ACS Appl. Mater. Interfaces* **2018**, *10*, 42146−42154.
(37) Tian, L.; et al. An innovative Mg/Ti hybrid fixation system developed for fracture fixation and healing enhancement at load-bearing skeletal site. *Biomaterials* **2018**, *180*, 173−183.
(38) Farjam, P.; Hekman, E. E. G.; Rouwkema, J.; Verkerke, G. J. Bone fixation techniques for managing joint disorders and injuries: A review study. *J. Mech Behav Biomed Mater.* **2022**, *126*, 104982.
(39) Liu, Y.; Cheong Ng, S.; Yu, J.; Tsai, W. B. Modification and crosslinking of gelatin-based biomaterials as tissue adhesives. *Colloids Surf. B Biointerfaces* **2019**, *174*, 316−323.
(40) Lim, J. I.; Lee, W. K. Enhanced biocompatibility and adhesive properties by aromatic amino acid-modified allyl 2-cyanoacrylate-based bio-glue. *Colloids Surf. B Biointerfaces* **2014**, *122*, 669−673.
(41) Weber, S. C.; Chapman, M. W. Adhesives in orthopaedic surgery. A review of the literature and in vitro bonding strengths of bone-bonding agents. *Clin Orthop Relat Res.* **1984**, *December*, 249−261.
(42) Wei, H.; Cui, J.; Lin, K.; Xie, J.; Wang, X. Recent advances in smart stimuli-responsive biomaterials for bone therapeutics and regeneration. *Bone Res.* **2022**, *10*, 17.
(43) Wang, P.; Wang, X. Mimicking the native bone regenerative microenvironment for in situ repair of large physiological and pathological bone defects. *Engineered Regeneration* **2022**, *3*, 440−452.
(44) Kang, H. J.; Park, S. S.; Tripathi, G.; Lee, B. T. Injectable demineralized bone matrix particles and their hydrogel bone grafts

loaded with beta-tricalcium phosphate powder and granules: A comparative study. *Mater. Today Bio* **2022**, *16*, 100422.
(45) Jin, Y. Z.; Zheng, G. B.; Lee, J. H.; Han, S. H. Comparison of demineralized bone matrix and hydroxyapatite as carriers of Escherichia coli recombinant human BMP-2. *Biomater Res.* **2021**, *25*, 25.
(46) Mehta, S.; et al. Cost-Effectiveness Analysis of Demineralized Bone Matrix and rhBMP-2 versus Autologous Iliac Crest Bone Grafting in Alveolar Cleft Patients. *Plast Reconstr Surg* **2018**, *142*, 737−743.
(47) Yuan, B.; Wang, Z.; Zhao, Y.; Tang, Y.; Zhou, S.; Sun, Y.; Chen, X.; et al. In Vitro and In Vivo Study of a Novel Nanoscale Demineralized Bone Matrix Coated PCL/beta-TCP Scaffold for Bone Regeneration. *Macromol. Biosci* **2021**, *21*, No. 2000336.
(48) Zha, Y.; et al. Progenitor cell-derived exosomes endowed with VEGF plasmids enhance osteogenic induction and vascular remodeling in large segmental bone defects. *Theranostics* **2021**, *11*, 397−409.
(49) Zhang, J.; Tong, D.; Song, H.; Ruan, R.; Sun, Y.; Lin, Y.; Wang, J.; Hou, L.; Dai, J.; Ding, J.; Yang, H.; et al. Osteoimmunity-Regulating Biomimetically Hierarchical Scaffold for Augmented Bone Regeneration. *Adv. Mater.* **2022**, *34*, No. 2270257.
(50) Fitzpatrick, V.; et al. Functionalized 3D-printed silk-hydroxyapatite scaffolds for enhanced bone regeneration with innervation and vascularization. *Biomaterials* **2021**, *276*, 120995.
(51) Liu, X.; et al. Immunopolarization-regulated 3D printed-electrospun fibrous scaffolds for bone regeneration. *Biomaterials* **2021**, *276*, 121037.
(52) Ibrahim, H.; Esfahani, S. N.; Poorganji, B.; Dean, D.; Elahinia, M. Resorbable bone fixation alloys, forming, and post-fabrication treatments. *Mater. Sci. Eng. C Mater. Biol. Appl.* **2017**, *70*, 870−888.
(53) Zhu, W. Y.; et al. Biodegradable magnesium implant enhances angiogenesis and alleviates medication-related osteonecrosis of the jaw in rats. *J. Orthop Translat* **2022**, *33*, 153−161.
(54) Wang, P.; et al. Intelligent microneedle patch with prolonged local release of hydrogen and magnesium ions for diabetic wound healing. *Bioact Mater.* **2023**, *24*, 463−476.
(55) Weng, W.; Biesiekierski, A.; Li, Y.; Dargusch, M.; Wen, C. A review of the physiological impact of rare earth elements and their uses in biomedical Mg alloys. *Acta Biomater* **2021**, *130*, 80−97.
(56) Chaya, A.; et al. In vivo study of magnesium plate and screw degradation and bone fracture healing. *Acta Biomater* **2015**, *18*, 262−269.
(57) Shan, Z.; Xie, X.; Wu, X.; Zhuang, S.; Zhang, C. Development of degradable magnesium-based metal implants and their function in promoting bone metabolism (A review). *J. Orthop Translat* **2022**, *36*, 184−193.
(58) Chen, Y.; et al. Rotator cuff repair with biodegradable high-purity magnesium suture anchor in sheep model. *J. Orthop Translat* **2022**, *35*, 62−71.
(59) Hou, R.; et al. In vitro evaluation of the ZX11 magnesium alloy as potential bone plate: Degradability and mechanical integrity. *Acta Biomater* **2019**, *97*, 608−622.
(60) Zhang, Y.; et al. 3D gel-printed porous magnesium scaffold coated with dibasic calcium phosphate dihydrate for bone repair in vivo. *J. Orthop Translat* **2022**, *33*, 13−23.
(61) Sommer, N. G.; et al. Implant degradation of low-alloyed Mg-Zn-Ca in osteoporotic, old and juvenile rats. *Acta Biomater* **2022**, *147*, 427−438.
(62) Drobyshev, A. Bone Remodeling Interaction with Magnesium Alloy Implants Studied by SEM and EDX. *Materials (Basel)* **2022**, *15*, 7529.
(63) Tong, X.; et al. Impact of gadolinium on mechanical properties, corrosion resistance, and biocompatibility of Zn-1Mg-xGd alloys for biodegradable bone-implant applications. *Acta Biomater* **2022**, *142*, 361−373.
(64) Li, W.; Qiao, W.; Liu, X.; Bian, D.; Shen, D.; Zheng, Y.; Wu, J.; Kwan, K. Y. H.; Wong, T. M.; Cheung, K. M. C.; Yeung, K. W. K. Biomimicking Bone-Implant Interface Facilitates the Bioadaption of a New Degradable Magnesium Alloy to the Bone Tissue Microenvironment. *Adv. Sci. (Weinh)* **2021**, *8*, No. e2102035.
(65) Shao, X.; et al. In vivo biocompatibility and degradability of a Zn-Mg-Fe alloy osteosynthesis system. *Bioact Mater.* **2022**, *7*, 154−166.
(66) Tong, X.; et al. A biodegradable in situ Zn-Mg(2)Ge composite for bone-implant applications. *Acta Biomater* **2022**, *146*, 478−494.
(67) Jia, B.; et al. Biodegradable Zn-Sr alloy for bone regeneration in rat femoral condyle defect model: In vitro and in vivo studies. *Bioact Mater.* **2021**, *6*, 1588−1604.
(68) Gopal, N. In Vitro Degradability, Microstructural Evaluation, and Biocompatibility of Zn-Ti-Cu-Ca-P Alloy. *Nanomaterials (Basel)* **2022**, *12*, 1357.
(69) Mao, M.; et al. An Extracellular Matrix-like Surface for Zn Alloy to Enhance Bone Regeneration. *ACS Appl. Mater. Interfaces* **2022**, *14*, 43955−43964.
(70) Liu, Y.; Du, T.; Qiao, A.; Mu, Y.; Yang, H. Zinc-Based Biodegradable Materials for Orthopaedic Internal Fixation. *J. Funct Biomater* **2022**, *13*, 164.
(71) Qu, X.; et al. Zinc alloy-based bone internal fixation screw with antibacterial and anti-osteolytic properties. *Bioact Mater.* **2021**, *6*, 4607−4624.
(72) Samavedi, S.; Whittington, A. R.; Goldstein, A. S. Calcium phosphate ceramics in bone tissue engineering: a review of properties and their influence on cell behavior. *Acta Biomater* **2013**, *9*, 8037−8045.
(73) Bouler, J. M.; Pilet, P.; Gauthier, O.; Verron, E. Biphasic calcium phosphate ceramics for bone reconstruction: A review of biological response. *Acta Biomater* **2017**, *53*, 1−12.
(74) Diaz-Rodriguez, P.; Lopez-Alvarez, M.; Serra, J.; Gonzalez, P.; Landin, M. Current Stage of Marine Ceramic Grafts for 3D Bone Tissue Regeneration. *Mar Drugs* **2019**, *17*, 471.
(75) Gao, C.; et al. Current progress in bioactive ceramic scaffolds for bone repair and regeneration. *Int. J. Mol. Sci.* **2014**, *15*, 4714−4732.
(76) Ma, H.; Feng, C.; Chang, J.; Wu, C. 3D-printed bioceramic scaffolds: From bone tissue engineering to tumor therapy. *Acta Biomater* **2018**, *79*, 37−59.
(77) Saberi, A.; et al. 3D direct printing of composite bone scaffolds containing polylactic acid and spray dried mesoporous bioactive glass-ceramic microparticles. *Int. J. Biol. Macromol.* **2022**, *207*, 9−22.
(78) Liu, X.; et al. 3D-printed bioactive ceramic scaffolds with biomimetic micro/nano-HAp surfaces mediated cell fate and promoted bone augmentation of the bone-implant interface in vivo. *Bioact Mater.* **2022**, *12*, 120−132.
(79) Bellucci, D.; Scalzone, A.; Ferreira, A. M.; Cannillo, V.; Gentile, P. Adhesive Bioinspired Coating for Enhancing Glass-Ceramics Scaffolds Bioactivity. *Materials (Basel)* **2022**, *15*, 8080.
(80) Ogihara, N.; et al. Biocompatibility and bone tissue compatibility of alumina ceramics reinforced with carbon nanotubes. *Nanomedicine (Lond)* **2012**, *7*, 981−993.
(81) Zamani, D.; Moztarzadeh, F.; Bizari, D. Alginate-bioactive glass containing Zn and Mg composite scaffolds for bone tissue engineering. *Int. J. Biol. Macromol.* **2019**, *137*, 1256−1267.
(82) Lin, R.; et al. Copper-incorporated bioactive glass-ceramics inducing anti-inflammatory phenotype and regeneration of cartilage/bone interface. *Theranostics* **2019**, *9*, 6300−6313.
(83) Plantz, M. A.; et al. Osteoinductivity and biomechanical assessment of a 3D printed demineralized bone matrix-ceramic composite in a rat spine fusion model. *Acta Biomater* **2021**, *127*, 146−158.
(84) Tian, B.; et al. A 3D-printed molybdenum-containing scaffold exerts dual pro-osteogenic and anti-osteoclastogenic effects to facilitate alveolar bone repair. *Int. J. Oral Sci.* **2022**, *14*, 45.
(85) Sanchez-Fernandez, M. J.; Hammoudeh, H.; Felix Lanao, R. P.; van Erk, M.; van Hest, J. C. M.; Leeuwenburgh, S. C. G. Bone-Adhesive Materials: Clinical Requirements, Mechanisms of Action, and Future Perspective. *Advanced Materials Interfaces* **2019**, *6*, 1802021.


https://doi.org/10.1021/acsomega.3c02727
*ACS Omega* 2023, 8, 27920−27931

(86) Sun, X. Three-dimensional bioprinted BMSCs-laden highly adhesive artificial periosteum containing gelatin-dopamine and graphene oxide nanosheets promoting bone defect repair. *Biofabrication* **2023**, *15*, 025010.
(87) Hu, S. A Mechanically Reinforced Super Bone Glue Makes a Leap in Hard Tissue Strong Adhesion and Augmented Bone Regeneration. *Adv. Sci. (Weinh)* **2023**, *10*, No. e2206450.
(88) Zhou, D.; et al. Dopamine-Modified Hyaluronic Acid Hydrogel Adhesives with Fast-Forming and High Tissue Adhesion. *ACS Appl. Mater. Interfaces* **2020**, *12*, 18225−18234.
(89) Li, Z.; et al. Bioinspired polysaccharide hybrid hydrogel promoted recruitment and chondrogenic differentiation of bone marrow mesenchymal stem cells. *Carbohydr. Polym.* **2021**, *267*, 118224.
(90) Balcioglu, S.; et al. Photocrosslinkable gelatin/collagen based bioinspired polyurethane-acrylate bone adhesives with biocompatibility and biodegradability. *Int. J. Biol. Macromol.* **2021**, *192*, 1344−1356.
(91) Nordberg, A.; et al. Highly Adhesive Phenolic Compounds as Interfacial Primers for Bone Fracture Fixations. *ACS Appl. Mater. Interfaces* **2010**, *2*, 654−657.
(92) Olofsson, K.; Granskog, V.; Cai, Y.; Hult, A.; Malkoch, M. Activated dopamine derivatives as primers for adhesive-patch fixation of bone fractures. *RSC Adv.* **2016**, *6*, 26398−26405.
(93) Granskog, V.; Garcia-Gallego, S.; von Kieseritzky, J.; Rosendahl, J.; Stenlund, P.; Zhang, Y.; Petronis, S.; Lyven, B.; Arner, M.; Hakansson, J.; Malkoch, M. High-Performance Thiol-Ene Composites Unveil a New Era of Adhesives Suited for Bone Repair. *Adv. Funct. Mater.* **2018**, *28*, 1800372.
(94) Xu, L. Bioactive Pore-Forming Bone Adhesives Facilitating Cell Ingrowth for Fracture Healing. *Adv. Mater.* **2020**, *32*, e1907491.
(95) Ma, C.; et al. Ultra-strong bio-glue from genetically engineered polypeptides. *Nat. Commun.* **2021**, *12*, 3613.
(96) Tam, W. L.; et al. Human pluripotent stem cell-derived cartilaginous organoids promote scaffold-free healing of critical size long bone defects. *Stem Cell Res. Ther* **2021**, *12*, 513.
(97) Schlickewei, C. W. Current and Future Concepts for the Treatment of Impaired Fracture Healing. *Int. J. Mol. Sci.* **2019**, *20*, 5805.
(98) Ekegren, C. L.; Edwards, E. R.; de Steiger, R.; Gabbe, B. J. Incidence, Costs and Predictors of Non-Union, Delayed Union and Mal-Union Following Long Bone Fracture. *Int. J. Environ. Res. Public Health* **2018**, *15*, 2845.
(99) Wildemann, B.; et al. Non-union bone fractures. *Nat. Rev. Dis Primers* **2021**, *7*, 57.
(100) Xie, C.; Ye, J.; Liang, R.; Yao, X.; Wu, X.; Koh, Y.; Wei, W.; Zhang, X.; Ouyang, H.; et al. Advanced Strategies of Biomimetic Tissue-Engineered Grafts for Bone Regeneration. *Adv. Healthc Mater.* **2021**, *10*, No. 2100408.
(101) Hao, J.; et al. Large-sized bone defect repair by combining a decalcified bone matrix framework and bone regeneration units based on photo-crosslinkable osteogenic microgels. *Bioact Mater.* **2022**, *14*, 97−109.
(102) Bai, B.; et al. Repair of Large-Scale Rib Defects Based on Steel-Reinforced Concrete-Designed Biomimetic 3D-Printed Scaffolds with Bone-Mineralized Microenvironments. *ACS Appl. Mater. Interfaces* **2022**, *14*, 42388−42401.
(103) Zheng, Z. Magnesium-organic framework-based stimuli-responsive systems that optimize the bone microenvironment for enhanced bone regeneration. *Chemical Engineering Journal* **2020**, *396*, 125241.


https://doi.org/10.1021/acsomega.3c02727
*ACS Omega* 2023, 8, 27920−27931