

# GelMA-Based Nanocomposites for Bone Defect Regeneration: Design, Performance, and Clinical Translation Potential

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**Abstract:** This narrative review summarizes recent advances in gelatin methacryloyl (GelMA)-based nanocomposites for bone defect regeneration, addressing the persistent clinical need for effective and customizable bone repair strategies. As an extracellular matrix (ECM)-mimicking hydrogel, GelMA offers favourable biocompatibility, tunable mechanics, and photo-crosslinkability, enabling integration with light-based 3D printing platforms to fabricate patient-specific scaffolds and, more recently, skeletal organoid-inspired constructs. Nevertheless, key barriers to translational advancement remain, including limited load-bearing capacity without reinforcement, insufficient vascularization, lack of intrinsic antibacterial activity, and a shortage of large-animal validation and well-designed clinical trials. We synthesize how formulation and processing parameters translate into scaffold properties and biological outcomes, and we discuss representative optimization strategies—such as composite reinforcement with hydroxyapatite/bioglass, bioactive molecule delivery, and immunomodulatory design—to address these limitations. We further highlight application-oriented evidence across major bone-loss-related conditions and summarize practical translational bottlenecks, including batch-to-batch reproducibility, scalable, GMP-compliant pathways that may be required, sterilization compatibility, and the need to synchronize degradation kinetics with new bone formation. By integrating material design, mechanistic considerations, and translational constraints, this review provides a framework to guide the rational development of GelMA-based systems toward clinically relevant bone regeneration.

**Keywords:** bone defect, GelMA, bone regeneration, 3D printing

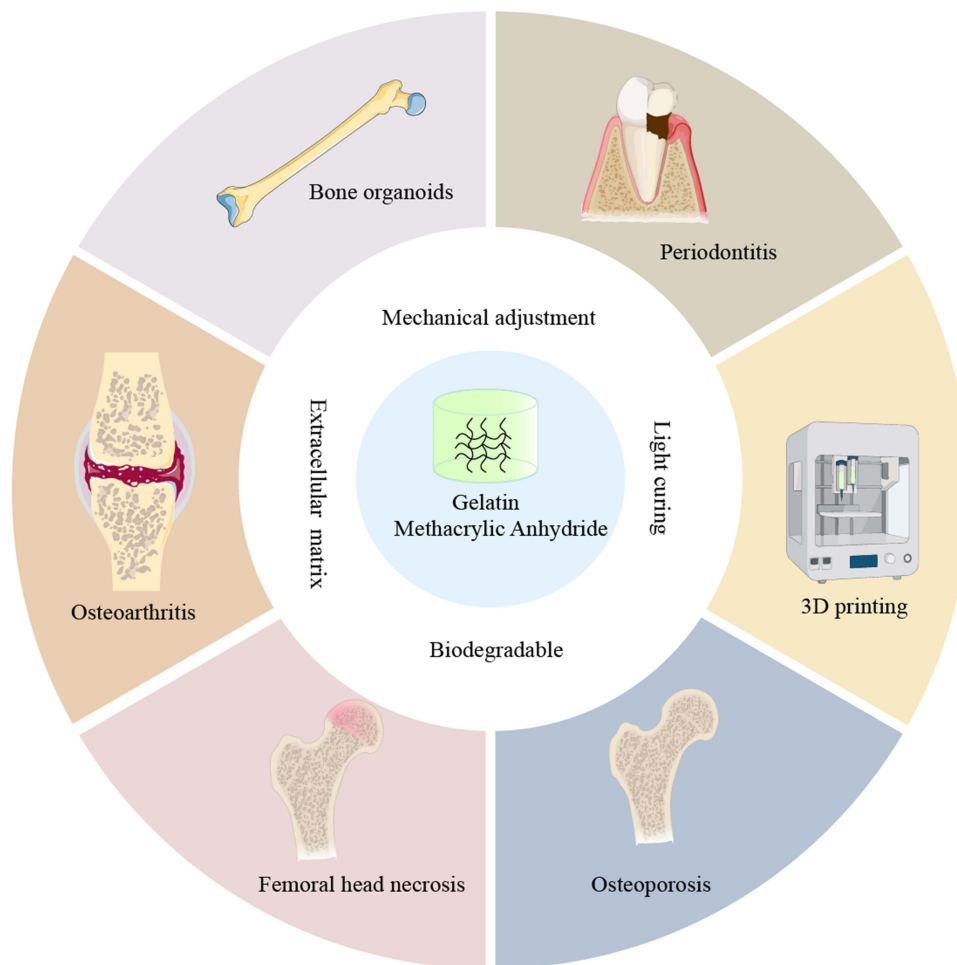
## Introduction

Bone defect repair remains a long-standing clinical challenge, particularly for significant or irregular defects where functional restoration is difficult to achieve.<sup>1,2</sup> Current clinical options, such as autografting and allografting, are constrained by limited graft availability, donor-site morbidity, and procedure-related complications. Consequently, biomaterial-enabled bone tissue engineering has gained increasing attention as an alternative strategy. Among candidate biomaterials, gelatin methacryloyl (GelMA) has attracted substantial interest due to its extracellular matrix (ECM)-mimicking characteristics and favourable processability.<sup>3,4</sup> In addition, a growing body of evidence suggests that appropriately designed biomaterial scaffolds can provide structural support and bioactive cues to promote osteogenic cell activity and new bone formation.<sup>5,6</sup>

GelMA is a methacrylated gelatin derivative that forms a hydrated three-dimensional network upon photocrosslinking, enabling tunable mechanical properties and good biocompatibility for tissue engineering applications.<sup>7,8</sup> As a highly hydrophilic hydrogel, GelMA can retain large amounts of water while maintaining structural integrity, thereby supporting cell adhesion, proliferation, and matrix deposition within defect sites. Moreover, GelMA can be crosslinked under mild conditions and has been widely explored as a platform for drug delivery and regenerative medicine.<sup>9-11</sup> However,



## Graphical Abstract



GelMA alone typically lacks sufficient mechanical strength for many load-bearing bone applications and often requires reinforcement or functional modification to achieve robust osteogenic performance and translational feasibility.

Combining GelMA with inorganic components such as hydroxyapatite, bioglass, or organic macromolecules like chitosan and hyaluronic acid to simulate the organic-inorganic hybrid structure of natural bone tissue can significantly enhance its osteogenic efficacy.<sup>6,10,12,13</sup> In addition, by loading Bone marrow mesenchymal stem cells (BMSCs)<sup>14</sup> and combining them with VEGF<sup>15</sup> and BMP-2<sup>15</sup> gene modifications, GelMA can be endowed with multiple biological functions, thereby synergistically promoting vascularization and ossification of tissue-engineered bone. In bone regeneration and repair, processing GelMA into appropriate structures can significantly promote bone repair. Among them, light-curing 3D printing technology not only enables personalized customization of the macroscopic structure of the GelMA scaffold but also precisely regulates the pore structure, porosity, and pore-size distribution at the microscopic scale, thereby influencing cell behaviour and metabolic efficiency.<sup>16–18</sup> Although most current research remains at the animal-experiment stage, some results indicate promising effects of GelMA-based scaffolds in repairing bone defects.<sup>19</sup> In the future, GelMA is increasingly being explored for a more significant role in repairing complex bone defects and constructing bone organoids by combining genetic engineering, microfluidic moulding, and biomimetic material design concepts.

Despite showing significant potential in bone tissue engineering, GelMA faces several challenges in practical application, including insufficient mechanical strength (ie, load-bearing mechanical performance such as strength/

modulus needed to maintain structural integrity in the target defect), a mismatch between degradation and osteogenic rates, limited vascularization capacity, and the absence of intrinsic antibacterial properties. In addition, how to achieve intelligent responses to the microenvironment through material functionalization, such as regulating the sequential controlled release of bioactive substances by adjusting the crosslinking degree of GelMA hydrogels, remains a key focus in current biomaterial research. In this narrative review, we summarize and synthesize recent advances in GelMA-based nanocomposites for bone defect regeneration, with an emphasis on material design strategies, structure–property–function relationships, and translational considerations. The literature reviewed was selected to represent and highlight influential studies in this rapidly evolving field, with an emphasis on applications relevant to bone repair and emerging biofabrication approaches. We further organize the review around (i) GelMA fundamentals and tunable properties, (ii) nanocomposite design and functionalization strategies, (iii) application-oriented evidence across bone-loss–related conditions, and (iv) practical barriers and opportunities for clinical translation.

## Chemistry and Design Space of GelMA

### Synthesis and Characterization

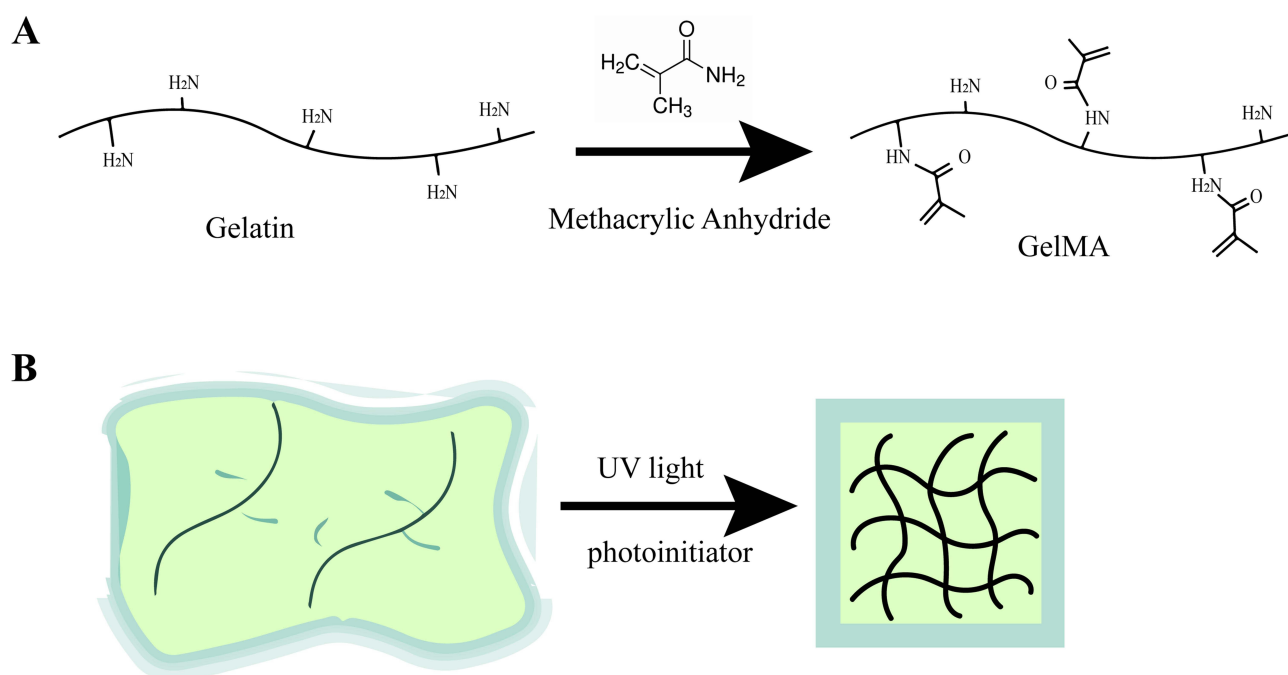
GelMA is a hydrogel chemically modified from gelatin, produced by the reaction of gelatin with methacrylate anhydride in the presence of a photoinitiator. This modification replaces the amino ( $-\text{NH}_2$ ) and hydroxyl ( $-\text{OH}$ ) groups on the gelatin side chains with methacryloyl groups, enabling GelMA to undergo photopolymerization under ultraviolet light to form a stable hydrogel network.<sup>13,20</sup> GelMA has tunable mechanical properties, biocompatibility, and a structure similar to ECM.<sup>21</sup> Compared with materials such as traditional gelatin or chitosan, GelMA can more precisely simulate the extracellular matrix, making it highly suitable for cell adhesion, proliferation, and differentiation, and providing a favourable microenvironment for bone regeneration. GelMA, as a suitable candidate material for tissue engineering applications, can be processed using a variety of techniques, including micromolding, photomasking, bioprinting, self-assembly, and microfluidics, to produce precisely controllable structures for specific application environments.<sup>22</sup> Studies have shown that GelMA is widely applicable across multiple fields, including bone, cartilage, cardiovascular, and vascular tissue engineering.<sup>23–26</sup> Based on the fact that GelMA retains the hydrophilicity and biodegradability (ie, tunable degradation of GelMA matrices into biocompatible by-products under physiological conditions, matching tissue ingrowth/remodelling), of gelatin while also exhibiting photocuring capabilities, it shows great potential for 3D printing. The light-curing properties of GelMA make it particularly suitable for integration with 3D printing technologies such as stereolithography (SLA) and Digital light processing (DLP).<sup>27,28</sup> These techniques can produce high-resolution, customizable scaffolds that simulate the natural microenvironment of bone tissue. In addition, GelMA's chemical structure enables functionalization, such as the incorporation of nanoparticles or bioactive molecules, to enhance its mechanical properties and biological functions.

### Mechanistic Framework Underlying GelMA-Mediated Bone Regeneration

Beyond serving as a structural scaffold, GelMA-based systems actively regulate bone regeneration through multiple interconnected mechanisms. First, the intrinsic extracellular matrix (ECM)-mimicking properties of GelMA, including arginine–glycine–aspartic acid (RGD) motifs and collagen-derived domains, facilitate cell adhesion, survival, and lineage commitment of osteoprogenitor cells.<sup>29–31</sup> Second, the tunable mechanical properties of GelMA hydrogels provide critical biomechanical cues that influence mechanotransduction pathways, such as YAP/TAZ and Wnt/ $\beta$ -catenin signalling, thereby directing osteogenic differentiation and matrix mineralization.<sup>32,33</sup> In addition, GelMA-based composites modulate the immune microenvironment by regulating macrophage polarization and inflammatory signalling, which are increasingly recognized as key determinants of successful bone regeneration.<sup>17,34,35</sup> The incorporation of bioactive nanoparticles, ions, or cytokines further enables spatiotemporal control over angiogenic and osteogenic signalling, supporting the coupling of vascularization and bone formation.<sup>36</sup> Collectively, these biochemical, biomechanical, and immunomodulatory mechanisms position GelMA not merely as a passive carrier, but as a dynamic regulatory platform for orchestrating bone repair processes.

## Crosslinking and Processing

GelMA is synthesized by reacting gelatin with methacrylate anhydride to introduce methacryloyl groups, followed by cross-linking to form a three-dimensional network under ultraviolet or visible light irradiation with photoinitiators.<sup>37</sup> The specific mechanism of methacryloyl group grafting onto gelatin and the process of photopolymerization-induced hydrogel formation are illustrated in Figure 1, which clearly shows the transformation of gelatin into GelMA and the subsequent formation of a 3D network. Various factors, including gelatin quality, GelMA concentration, photocrosslinking conditions, and auxiliary chemical components, influence its performance. The photocuring properties enable GelMA to form a stable three-dimensional structure rapidly, making it suitable for applications such as 3D bioprinting. Greater ultraviolet light exposure or longer exposure time could promote cross-linking reactions in GelMA, thereby enhancing the hydrogel's structural stability and mechanical strength and maintaining the integrity of the 3D structure.<sup>38–40</sup> However, studies suggest that prolonged exposure may cause burst release, that is, rapid initial release of the drug, which is not conducive to long-term controlled-release.<sup>41,42</sup> Although high crosslinking slows GelMA degradation, studies have found that it instead accelerates drug release, which contradicts the expected sustained release.<sup>42–44</sup> Higher GelMA concentrations typically increase crosslinking density, thereby enhancing mechanical strength. The mass concentration of GelMA, such as 5%–20% w/v, can increase the elastic modulus from a few kPa to tens of kPa.<sup>29</sup> High concentrations of GelMA combined with optimized crosslinking parameters can significantly increase its stiffness, making it suitable for load-bearing tissue engineering applications. However, an excessively high degree of methylacrylylation (DoM) or crosslinking density may reduce the binding capacity of growth factors, thereby weakening their slow-release and biological functions.<sup>42,45</sup> Increasing methylacrylylation may reduce the net positive charge of gelatin, thereby affecting electrostatic interactions with negatively charged drugs and loading and release efficiency. Increasing the initiator LAP concentration can enhance free-radical generation efficiency, thereby increasing crosslinking extent and improving mechanical properties.<sup>46</sup> LAP demonstrates good cell compatibility, even at higher concentrations, under appropriate crosslinking conditions, with cell survival rates exceeding 75% in long-term cultures.<sup>47</sup> The use of a visible light initiation system for LAP can avoid cytotoxicity and functional damage caused by ultraviolet initiators.<sup>48</sup> Lin et al found that using a UV lamp system with wavelengths between 320 and 500 nm, excluding the more harmful UVB and UVC light, GelMA hydrogels only need 15 seconds of transdermal UV irradiation to complete



**Figure 1** Schematic of GelMA and the fabrication of its hydrogels. **(A)** Chemical modification of gelatin to form GelMA. **(B)** Photopolymerization of GelMA into hydrogels.

polymerization, and this rapid photo-curing property is closely related to the free radical polymerization reaction of the methyl acryloyl group under light exposure.<sup>40</sup> In summary, adjusting the intensity and duration of light curing can optimize GelMA performance; however, it is necessary to balance mechanical strength, drug release, cytocompatibility, and biological function. In addition, combining GelMA with other functional materials can further enhance its photopolymerization performance, offering new possibilities for personalized medicine. This flexible modulating ability broadens the application prospects of GelMA in tissue engineering and regenerative medicine.

## Parameter-Performance-Outcome Mapping

Mechanical property testing is a key step in evaluating the suitability of GelMA scaffolds for biomedical applications. Standard testing methods include compression, tensile, and three-point bending tests, among others. These methods can effectively measure essential parameters, such as the elastic modulus, compressive strength, and flexural strength, of GelMA scaffolds. Compression tests can be used to assess the scaffold's deformation and load-bearing capacity under stress by applying progressively increasing loads.<sup>49</sup> In addition, dynamic mechanical analysis (DMA) is also widely used to evaluate the viscoelastic properties of GelMA, providing information on the mechanical response of the material at different frequencies and temperatures. The combined use of these testing methods provides a comprehensive understanding of GelMA's mechanical properties, which is essential for its application in fields such as bone tissue engineering. There is a close relationship between the mechanical properties of GelMA and its biological functions. Studies have shown that appropriate mechanical strength can promote cell attachment, proliferation, and differentiation, thereby enhancing tissue regeneration.<sup>49,50</sup> For example, in bone tissue engineering, the mechanical strength of GelMA scaffolds must match that of natural bone to support osteocyte growth and bone tissue formation.<sup>51</sup> In addition, the mechanical properties of GelMA also affect its degradation rate *in vivo*, which in turn affects the formation and growth of new tissue. Therefore, optimizing the mechanical properties of the GelMA scaffold not only enhances its load-bearing capacity but also promotes tissue regeneration, ultimately leading to more effective clinical applications (Table 1).<sup>52</sup>

The mechanical properties of GelMA are typically weak, which limits its use in load-bearing bone applications.<sup>57</sup> In addition, the Bloom strength of the gelatin raw material used in the preparation is equally crucial. Gelatin with higher Bloom strength can produce GelMA hydrogels with higher stiffness and a higher viscoelastic ratio, and can alter their diffusion properties and pore size.<sup>53,54</sup> The toughness of GelMA can also be significantly enhanced by adding different concentrations of toughening agents or fillers such as graphene and nano-hydroxyapatite. In addition, altering the degree of crosslinking in GelMA has been shown to be an effective optimization strategy. By adjusting the photopolymerization conditions, researchers can control the crosslinking density of GelMA and thereby modify its mechanical properties. The higher the crosslinking density, the greater the scaffold's stiffness and strength; however, it may also affect its

**Table 1** Influencing Factors of GelMA Mechanics

Influencing Factors	Specific Conditions or Types	Effects on Mechanical Properties	References
Light crosslinking conditions	Light intensity, exposure time, and photoinitiator concentration	Directional prediction and "tunability" of mechanical properties such as elastic modulus can be achieved by regulating the rate of crosslinking reaction.	[38]
Additive	A variety of additives (nanoparticles, polymers, etc.) in combination with GelMA concentrations	Mechanical properties are improved at different GelMA concentrations ( $\leq 5\%$ , 5–10%, $\geq 10\%$ ), but the effects are heterogeneous	[49]
Bloom strength of gelatin feedstock	High Bloom strength (corresponding to high molecular weight)	It leads to increased stiffness and viscoelastic ratio of the hydrogel, and affects its diffusivity, permeability, and pore size	[53, 54]
Nanocomposite	Embedding nanin liposomes and adding graphene oxide	Significantly increase the elastic modulus and compressive modulus of the hydrogel	[55, 56]
GelMA itself concentration	High concentration	Form a tighter network structure, thereby enhancing mechanical strength	[57]

biocompatibility and degradation rate.<sup>51</sup> Therefore, optimizing the mechanical properties of GelMA scaffolds requires finding a balance between strength and biocompatibility.

Despite the versatility of GelMA, a persistent “stiffness-permeability paradox” remains a critical unsolved problem in scaffold design. While increasing the degree of methacryloyl substitution or crosslinking density enhances mechanical load-bearing capacity, it inevitably reduces hydrogel porosity and limits nutrient diffusion, often leading to necrotic cores in large-volume constructs. Current reinforcement strategies, such as adding inorganic fillers (eg, HAP, graphene), improve stiffness but usually introduce interface incompatibility or stress-shielding effects. Furthermore, most studies optimize these parameters in static environments, failing to account for the dynamic degradation rates that occur under physiological loading conditions. Achieving a balance in which degradation kinetics precisely match the rate of new bone formation remains a significant bioengineering challenge that has not yet been fully resolved.

## Basic Properties of GelMA Hydrogel with Light-Curing 3D Printing Technology

### Principles and Advantages of GelMA Light-Curing 3D Printing

3D printing is a manufacturing process that builds three-dimensional objects by adding materials layer by layer. The basic principle is to generate a three-dimensional model using computer-aided design (CAD) software, then slice the model into layers to guide the printer to deposit material layer by layer. Standard 3D printing techniques include SLA,<sup>58</sup> Selective Laser Melting (SLM),<sup>59</sup> Fused Deposition Modelling (FDM),<sup>60</sup> and Selective Laser Sintering (SLS), among others. Each technology has distinct material requirements and printing methods. SLA uses photosensitive resin to build objects layer by layer via ultraviolet curing, whereas FDM builds objects layer by layer by heating extruded filaments.<sup>61</sup> Light-curing 3D printing techniques, such as SLA and DLP, produce fine bone tissue scaffolds by initiating polymerization reactions with ultraviolet light and layer-by-layer curing of GelMA hydrogels. The advantage of light-curing 3D printing lies in its high degree of design flexibility and customization, enabling the fabrication of complex geometries to meet the demands of personalized medicine and bioengineering. One of the main advantages of light-curing 3D printing technology is its high print resolution, which can achieve micron- or even sub-micron precision. This high precision is crucial for manufacturing orthopedic scaffolds, particularly when fine porosity and complex geometries are required. Light-curing 3D printing can precisely simulate the ECM of natural bone tissue, thereby providing an ideal growth environment that promotes the adhesion, proliferation, and differentiation of osteoblasts.<sup>17,62</sup>

### Comparison of the 3D Printing Process Compatibility

The light-curing properties of GelMA enable its compatibility with 3D printing technology, producing high-precision personalized scaffolds that simulate the microstructure of bone tissue. GelMA, a commonly used photocuring material, exhibits good biocompatibility and tunable degradability, thereby providing favourable support for bone tissue engineering. 3D printing supports a variety of photocurable biomaterials, such as GelMA, PEGDA, and their composites.<sup>63,64</sup> These materials not only have excellent biocompatibility, but also mechanical properties, and degradation rates can be adjusted according to clinical needs. Compared with light-curing 3D printing technology, FDM mainly uses thermoplastics such as PLA and PCL, which lack biological activity and are not suitable for supporting cell growth.<sup>65–67</sup> SLS technology, though capable of manufacturing metal or ceramic scaffolds, requires additional surface modification to be biocompatible;<sup>68,69</sup> Inkjet printing is mainly used in soft tissue engineering and does not meet the mechanical requirements of orthopedic applications. Light-curing 3D printing technology enables the integration of biological factors, such as cells and growth factors, into scaffolds during printing, thereby producing multifunctional scaffolds that support bone tissue regeneration.<sup>26,70</sup> In contrast, technologies like FDM and SLS have limited capabilities in this regard. FDM typically has lower resolution, is constrained by nozzle size, and cannot produce complex microscale structures; SLS technology is limited by powder particle size and lower print precision, making it difficult to achieve complex bone tissue scaffold structures (Table 2).

**Table 2** Types of 3D Printing

Feature	(SLA/DLP) <sup>28,71</sup>	FDM <sup>72</sup>	SLS <sup>73</sup>	Inkjet Printing <sup>74</sup>
Resolution	High (micron to submicron level)	Moderate (100–300 μm)	Moderate to low (100 μm)	High (micron level)
Material compatibility	Photocurable polymers (eg, GelMA, PEGDA), composites	Thermoplastics (eg, PLA, PCL), limited biopolymers	Polymers, metals, ceramics	Liquid polymers, biomaterial suspensions
Structural complexity	Excellent; supports intricate designs and internal porosity	Moderate; limited by nozzle size	Moderate; limited by powder resolution	High; suitable for soft biomaterial layers
Mechanical properties	Tunable; adjustable by crosslinking density and material	Good for load-bearing applications	Excellent for metals, moderate for polymers	Moderate; depends on the material formulation
Biocompatibility	High; suitable for cell-laden materials and tissue scaffolds	Moderate; limited by material choices	Low to moderate; often requires post-treatment	High; used for bio-inks and cell printing
Speed	Fast; layer-by-layer solidification with minimal post-processing	Moderate; dependent on heating/cooling cycles	Slow, prolonged sintering process	Fast; ideal for soft materials
Cost	Moderate; higher initial investment, lower material cost	Low; widely accessible	High; requires specialized powders	Moderate; limited to specific bio inks
Applications in orthopedics	Excellent; personalized scaffolds with biomimetic structures	Limited; primarily for prototypes and models	Excellent, durable metal implants	Limited; soft tissue engineering focus

**Abbreviations.** SLA, Stereolithography; DLP, Digital Light Processing; FDM, Fused Deposition Modelling; SLS, Selective Laser Sintering; PEGDA, Polyethylene Glycol Dimethacrylate; PLA, Polylactic Acid; PCL, Polycaprolactone.

## Advantages of GelMA Application in Bone Scaffolds

GelMA, as a novel biomaterial, is widely used in 3D printing technology due to its favourable biocompatibility and adjustable mechanical properties. The advantage of GelMA lies in its ability to cure rapidly via photopolymerization, forming a stable hydrogel structure, making it suitable for cell culture and tissue engineering.<sup>75</sup> Moreover, the chemical structure of GelMA allows it to be combined with a variety of functional materials, which gives it significant application potential in areas such as bone tissue regeneration. When GelMA is combined with materials such as nano-hydroxyapatite (nHA), black phosphorus (BP), and nano-graphene oxide (rGO), it can enhance the scaffold's mechanical properties and promote osteogenic differentiation and bone cell regeneration, thereby synergistically promoting bone tissue repair.<sup>76,77</sup> In addition, GelMA can be combined with drug delivery systems to achieve local, sustained drug release, thereby facilitating the healing of bone defects. 3D printing technology using GelMA as a bioink not only improves printing accuracy but also supports cell growth and functional maintenance, thereby providing a suitable scaffold material for bone tissue regeneration.

## Design and Optimization of GelMA Structures

### Effects of Bone Scaffold Structures on Bone Regeneration

GelMA, as a biomaterial, offers significant advantages for bone defect regeneration, particularly for the design of highly adjustable bone scaffold structures. The structural design of bone scaffolds, including porosity, pore size, shape, and overall geometry, directly determines the effect of bone regeneration. GelMA exhibits excellent structural adaptability and can modulate porosity and pore size as needed to optimize the cell growth environment, thereby improving bone regeneration efficiency. Porosity is crucial for the migration, proliferation, and differentiation of bone cells. Proper porosity provides sufficient space to facilitate nutrient and oxygen diffusion and channels for waste removal, thereby accelerating bone regeneration.<sup>61</sup> The porosity of GelMA can be precisely controlled by adjusting the print parameters, crosslinking degree, or material formulation. Studies have shown that GelMA bone scaffolds with moderate porosity can provide good support for the proliferation and differentiation of bone mesenchymal stem cells (BMSCs), thereby promoting bone tissue formation.<sup>75</sup> GelMA bone scaffolds can be customized to meet the repair requirements of various bone defects. In addition to porosity, the size of the stent's aperture is also an essential factor affecting bone regeneration. Proper pore size can effectively simulate the microstructure of bone tissue, providing better attachment surfaces and growth space for cells. By precisely controlling the pore size of the GelMA scaffold, a bone scaffold similar to the natural bone structure can be created to support the normal function of bone cells and promote the formation of new bone. The

geometry and overall three-dimensional structure of bone scaffolds also significantly affect cell behaviour.<sup>64</sup> 3D printing technology enables the fabrication of complex geometries that simulate the microenvironment of natural bone. These structures not only enhance cell attachment and expansion but also improve the scaffold's mechanical properties, providing sufficient support to withstand loads encountered during bone tissue repair. Studies have shown that GelMA scaffolds employ structures with stratified pores and reticular or porous designs that more effectively promote cell differentiation and mineralization and improve vascularization, thereby accelerating bone regeneration.<sup>36,78</sup> Optimizing the structural design of GelMA scaffolds, particularly the adjustment of porosity, pore size, and geometry, can significantly improve their biocompatibility and mechanical properties. By adjusting the degree of GelMA cross-linking and incorporating bioactive molecules, the scaffold's bioactivity (the ability to actively elicit pro-regenerative responses, including osteogenic support and angiogenic–osteogenic signalling modulation, rather than acting as a passive carrier) can be enhanced, thereby further improving the adhesion, proliferation, and differentiation of bone cells. The tunability of this structure makes GelMA an ideal bone scaffold material that can be customized to meet diverse clinical needs and the characteristics of bone defects, thereby providing more effective support and repair.

## Optimization and Simulation of 3D Printing Design Parameters

In the design of GelMA 3D-printed scaffolds, optimizing design parameters is a key step toward improving scaffold performance. The design parameters include material concentration, print speed, layer thickness, and scaffold geometry, all of which affect the physical and biological properties of the final scaffold. Using computer simulation, design parameters can be systematically analyzed to predict their impact on the performance of 3D-printed personalized heart stents, thereby optimizing stent structure and improving therapeutic efficacy. Finite element analysis (FEA) is a widely used numerical simulation method that assesses the impact of design parameters, such as porosity, stent shape, and layer thickness, on mechanical properties by simulating stent behaviour under various loading conditions.<sup>79,80</sup> FEA can analyze the stress distribution and deformation of honeycomb and mesh scaffolds under applied forces, ensuring that the scaffolds provide the necessary mechanical support without adversely affecting biocompatibility.<sup>81</sup> The response surface method (RSM) is to explore the impact of multi-parameter combinations on stent performance by establishing a multivariable regression model, and to accelerate the optimization process while maintaining the balance between stent biocompatibility and mechanical performance by finding the optimal parameter combinations in the design space.<sup>82</sup> Topological optimization methods can automatically adjust the material distribution and structural shape of scaffolds to maximize scaffold performance based on mechanical requirements, especially with significant advantages in the design of porous scaffolds.<sup>83</sup> In recent years, machine learning and artificial intelligence technologies have also begun to be applied to the optimization of GelMA scaffolds, by analyzing a large amount of experimental data to predict the effects of different design parameters and automatically adjust the design scheme, further improving design efficiency and accuracy.<sup>84</sup> In summary, these computer simulation and optimization methods not only improve the design accuracy of GelMA scaffolds, but also accelerate their clinical translation. For example, in the treatment of intervertebral disc degeneration, 3D cyclic-gradient GelMA hydrogel scaffolds, designed using computer-aided design, demonstrated good biocompatibility and degradability and showed significant therapeutic effects in experimental studies. In addition, numerical simulation methods have been widely applied to the study of intracranial flow-directed close-mesh scaffolds, thereby enhancing experimental efficiency by simulating mechanical properties and fluid dynamics, providing strong technical support for tissue engineering and regenerative medicine.

## Applications

Bone tissue is a dynamic organ that is continually undergoing reconstruction. During this process, Osteoclasts (OCs) resorb aged bone tissue, whereas Osteoblasts (OBs) promote bone formation by synthesizing new bone matrix. They maintain bone metabolic balance by alternating between bone resorption and bone formation. The balance is not only dependent on the synergy between the two cell types. Still, it is also regulated by active factors, including RANKL and M-CSF, to ensure the steady progression of bone remodelling.<sup>85,86</sup> OCs originate from hematopoietic stem cells and degrade bone by secreting acids and proteolytic enzymes, such as cathepsin K, which dissolve collagen and other gelatinous proteins during bone resorption. OBs are bone-forming cells that, under the guidance of transcription factors,

are derived from BMSCs and differentiate into OBs. OBs secrete extracellular proteins, including osteocalcin, alkaline phosphatase, and type I collagen, and unmineralized bone-like secreted extracellular matrix, which then accumulates and mineralizes the calcium phosphate secreted by bone cells in the form of hydroxyapatite to produce bone tissue.<sup>38,87</sup> But when the defect area exceeds the critical value for self-repair and reconstruction of bone tissue, the defect area will not heal on its own. Many factors influence bone defect repair and rebuilding, including gene expression regulation, cell migration, cell morphogenesis, and cell cycle progression. Effective coordination of the balance among osteoblasts, osteoclasts, and angiogenic cells within biological bone scaffolds is critical for promoting bone regeneration. GelMA, when combined with osteogenic agents or angiogenic factors, can enhance the osteogenic function of currently used composites. In addition, bone tissue, as a mineralized tissue, exhibits a specific elastic modulus, and the mechanical stiffness of GelMA is limited. By incorporating inorganic minerals with osteogenic-inducing functions into GelMA, the hydrogel's elastic modulus can be increased to a certain extent. Therefore, it is vital to prepare mixed hydrogels from mixtures of two or more components to combine the unique advantages of individual elements within the composite hydrogel system.<sup>88,89</sup>

## Research Progress of GelMA in Osteoarthritis (OA)

Osteoarthritis (OA) is characterized by progressive degeneration of articular cartilage, subchondral bone sclerosis, and osteophyte formation, which leads to pain and functional limitation. It is one of the high-burden diseases in an aging society.<sup>90,91</sup> Existing treatment options, such as NSAIDs, intra-articular hyaluronic acid injection, and end-stage replacement, are mostly inclined towards analgesia and lubrication. They are challenging to reverse cartilage damage, with complications and life expectancy issues coexisting.<sup>92,93</sup> GelMA, which combines ECM similarity, degradability, and tunability of mechanical and pore structures, can support and permeate the complex microenvironment of the joint, providing a material basis for the “anti-inflammatory + regenerative” combination treatment.

In terms of material design and loading strategies, GelMA is commonly used in combination with natural matrix dECM or MSC-ECM to enhance cell adhesion and an anti-inflammatory microenvironment. The former, when combined with microfracture surgery, can fill osteochondral defects, inhibit chondrocyte pyroptosis, and promote hyaline cartilage regeneration. The latter supports cartilage repair by regulating macrophage metabolism through soluble factors, promoting M2 polarization, and alleviating synovitis.<sup>94</sup> To address issues such as low systemic efficacy and significant side effects, GelMA was developed as a long-acting controlled-release platform, for example, by loading astragalus polysaccharides (APS) to activate Fgfr2 for proliferation and matrix synthesis and by loading curcumin to achieve “anti-inflammatory-chondrogenic differentiation” dual effects and increase local bioavailability.<sup>95</sup> In cell therapy, GelMA can enhance cell retention and activity. Hypoxic pretreatment of CPCs, in combination with GelMA scaffolds, can activate the HIF-1 $\alpha$  pathway, adapt to the joint's hypoxic environment, and enhance repair.<sup>96</sup> In addition, the three-dimensional microstructures constructed by GelMA can amplify the paracrine effects of MSC cells and promote cartilage regeneration.<sup>97</sup> Signals such as MMP/ROS/acidity/mechanical stress can be “programmed” as release switches around the OA lesion. A microenvironment-responsive, physical-trigger GelMA response system can be constructed within the OA-specific pathological environment to trigger drug release during joint movement or under high MMP expression, thereby precisely targeting the lesion and reducing systemic exposure.<sup>98</sup> He et al constructed ultrasensitive-piezoelectric microspheres with GelMA as the carrier and successfully achieved the dual effects of non-invasive analgesia and immunomodulation.<sup>99</sup> Yu et al designed ROS-responsive, lubricated-surface injection microspheres to reduce oxidative damage and improve tribological performance in OA mice. In response to the observation that elevated intra-articular oxidative stress exacerbates chondrocyte damage, preventing chondrocyte apoptosis is an important step in the treatment of early OA.<sup>100</sup> Yu et al developed strontium lanate SrR/GelMA composite hydrogels based on the Wnt/ $\beta$ -catenin signalling pathway in OA pathology. SrR/GelMA achieves early intervention by inhibiting Wnt/ $\beta$ -catenin and promoting chondrogenic differentiation of BMSCs.<sup>101</sup> Drawing on the lubrication mechanism of synovial fluid, GelMA hydrogel microspheres with enhanced lubricity and controllable drug release were designed to significantly reduce the coefficient of friction between articular surfaces and mechanical damage. Meanwhile, the GelMA network within the microspheres can load anti-inflammatory drugs and enable local drug release via slow degradation, thereby alleviating inflammation.<sup>24,102</sup> Overall, these regimens generally led to an increase in OARSI scores, upregulation of type II collagen/proteoglycans, improvements in cartilage thickness and microvessel density, and reductions in pain indicators in animal models.

At present, GelMA-based OA treatment research has developed in multiple directions and at multiple levels, including material modification (eg, composite dECM), the introduction of responsive groups, functional integration (eg, drug-controlled release, cell carriers), and mechanism exploration (eg, metabolic regulation, signalling pathway intervention), with significant progress. These studies not only provide diverse and innovative strategies for OA treatment but also deepen the understanding of material-cell-microenvironment interactions. However, there are still bottlenecks to be broken through in this field: first, some studies are still at the animal model stage, and there is a lack of human clinical trial data, which requires further verification of the safety and efficacy of the GelMA system in the human body; The complex physiological environment within the joints, such as frequent mechanical stress and immune cell infiltration, places higher demands on the long-term stability and functional persistence of GelMA; Third, the compatibility of GelMA degradation rate with cartilage repair cycle and the standardization process for large-scale production still need to be further optimized. In the future, promoting the clinical translation of GelMA-based treatment regimens through multidisciplinary intersections such as materials science, cell biology, and clinical medicine will become a core research direction, which is expected to bring new therapeutic hope to patients with OA (Table 3).

## Steroid-Induced Femoral Head Necrosis

Hormone-induced femoral head necrosis (SONFH) is a condition in which bone tissue dies due to the disruption of the blood supply to the femoral head. As the condition progresses, the femoral head collapses, eventually leading to loss of hip joint function, often accompanied by joint pain and limited movement.<sup>103,104</sup> Conventional conservative treatment has limited efficacy, and joint replacement is inevitable in the late stage. Tissue engineering repair offers new hope for patients with early-stage femoral head necrosis. The key to SONFH treatment lies in addressing three core issues: alleviating oxidative stress damage, restoring local blood supply, and promoting bone regeneration. Current research on GelMA focuses on these issues. Long-term hormone use leads to a substantial accumulation of reactive oxygen species (ROS) in the femoral head, which not only impairs mitochondrial function in BMSCs and inhibits their osteogenic differentiation but also activates pro-inflammatory macrophages (M1 type), intensifying the local inflammatory response and creating a vicious cycle. Conventional regimens lack targeted ROS-clearing mechanisms, leading to continuous deterioration of the bone repair microenvironment.

To address this issue, the Bai team constructed a composite scaffold of “metal-organic framework MOF-818 GelMA hydrogel + demineralized bone matrix (DBM)” to achieve the triple effect of “ROS clearance - immune regulation - bone vascular regeneration”.<sup>105</sup> The study showed that when MOF-818 was modified with zinc, the activities of superoxide dismutase (SOD) and catalase were significantly enhanced, which helped to efficiently eliminate excessive reactive oxygen species (ROS) in the femoral head, thereby reducing mitochondrial damage in BMSCs and promoting the expression of osteogenic difference-related genes RUNX2 and OCN. This result is consistent with studies on the mechanisms by which IGF1 and melatonin regulate osteogenic differentiation of BMSCs. Meanwhile, the composite scaffold promotes the conversion of M1-type macrophages to M2-type macrophages and significantly reduces the secretion of pro-inflammatory factors, such as IL-1 $\beta$ . DBM, as a natural bone matrix, provides bone morphogenetic protein (BMP) and binds to the mechanical support of GelMA to guide new bone growth along the scaffold, increasing trabecular bone density of the femoral head in animal experiments and reducing the risk of bone collapse. In SONFH, the hormone inhibits HIF-1 $\alpha$  activity, thereby impairing angiogenic capacity. Deferoxamine (DFO) promotes angiogenesis by inhibiting the HIF-1 $\alpha$ -degrading enzyme and thereby activating the HIF-1 $\alpha$  pathway. However, DFO has a short half-life in the body, and direct injection is prone to “burst release”, and excessive local concentration can lead to BMSCs toxicity, limiting its clinical application. The sustained-release properties of GelMA hydrogel precisely address the “burst release problem” of DFO. By embedding DFO in GelMA hydrogel and adjusting the crosslinking degree of GelMA, the DFO release cycle is extended from 2 hours to 7 days, and the local concentration is maintained within the safe and effective range of 50–100 $\mu$ mol/L to avoid cytotoxicity. Sustained-release DFO continuously activates the HIF-1 $\alpha$  pathway, increases VEGF expression, and the number of new blood vessels in the femoral head. At the same time, GelMA supported BMSC adhesion, and the two together promoted “vascular-bone regeneration” coupling. In the rabbit ONFH model, the area of osteonecrosis was reduced compared with the DFO-alone injection group.

GelMA hydrogel, as an integrated platform for SONFH treatment, can specifically address ROS-induced injury and insufficient blood supply by combining with MOF, DFO, nanoparticles, and other agents. It also features injectable and

**Table 3** GelMA Studies for Osteoarthritis Treatment

Authors	Year	Keywords	Summary of Key Findings	Approach	Relevance to Osteoarthritis
Xinhe Li et al <sup>99</sup>	2025	Ultrasound, Piezoelectric, Osteoarthritis Pain, Analgesic	Ultrasound-activated piezoelectric microspheres generate electrical pulses to reduce OA pain via blockade of Nav1.7.	Microfluidics; piezo NP synthesis; in vitro/in vivo pain assays.	Ultrasound-responsive, controlled analgesic strategy for OA.
Ziqian Yu et al <sup>100</sup>	2025	Oxidative Stress, Lubrication, Osteoarthritis, Hydrogel	Redox/pH-responsive injectable microspheres deliver antioxidants and sustained lubrication to treat OA.	Hydrogel microspheres; stimulus-response tests; in vitro/in vivo OA.	Targets oxidative stress and lubrication loss in OA.
Qi Sun et al <sup>98</sup>	2025	Cartilage Regeneration, Matrix Metalloproteinases, OA, Hydrogel	Dual-responsive hydrogel releases therapeutics in response to MMPs/mechanical stress, promoting cartilage repair and alleviating OA symptoms.	MMP- and stress-responsive gel; release profiling; in vitro/in vivo.	Microenvironment-triggered therapy for OA cartilage healing.
Jiakai Wang et al <sup>95</sup>	2025	GelMA, Fgfr2, Cartilage Regeneration, Osteoarthritis	Astragalus polysaccharide-loaded GelMA microspheres enhance chondrocyte growth and cartilage repair via Fgfr2 activation.	Nanomaterials; drug delivery; in vitro/in vivo; bioinformatics.	Drug-loaded GelMA microspheres for OA cartilage regeneration.
Zhuolin Chen et al <sup>94</sup>	2025	Mesenchymal Stem Cells, Macrophage Polarization, Osteoarthritis	MSC-derived ECM-batch hydrogels shift macrophages and improve mitochondrial function, reducing inflammation and OA progression.	ECM functionalization; in vivo OA; mitochondrial assays; omics.	A promising material for modulating immune response in OA, focusing on mitochondrial health to target synovial inflammation.
Ying Han et al <sup>102</sup>	2021	Hydrogel Microspheres, Lubrication, Drug Release, Osteoarthritis	Injectable hydrogel microspheres enhance lubrication and sustain drug release, thereby reducing OA inflammation and cartilage damage.	Microspheres; photo-crosslinking; OA mo tribology tests.	Immunometabolic modulation to limit synovial inflammation in OA.
Xingchen Li et al <sup>97</sup>	2023	Hydrogel Microspheres, Paracrine Activity, Cartilage Regeneration, Osteoarthritis	Injectable porous hydrogel microspheres enhance MSC paracrine effects, promoting cartilage repair and lowering inflammation.	Freeze-drying microfluidics; MSC loading; in vitro/in vivo cartilage tests.	Cell-assisted microspheres to boost cartilage regeneration.
Kai Feng et al <sup>96</sup>	2023	Cartilage Progenitor Cells, Hypoxia, GelMA Microspheres, Osteoarthritis	Hypoxia-preconditioned CPCs in GelMA microspheres enhance chondrogenesis and cartilage repair in rat OA models.	Hypoxic 3D culture; GelMA encapsulation; rat OA in vivo.	Hypoxia-primed CPC delivery for OA cartilage restoration.

mechanically adjustable properties, making it suitable for minimally invasive surgical procedures. Significant results have been achieved in animal experiments, laying a foundation for clinical transformation. Clinical translation should focus on staging customized plans. In the future, it is expected to undergo clinical translation and serve as the core material for “head-preserving treatment” of early- and mid-stage SONFH, enabling most early- and mid-stage patients to avoid joint replacement and promoting progression from end-stage replacement to early, precise repair (Figure 2).

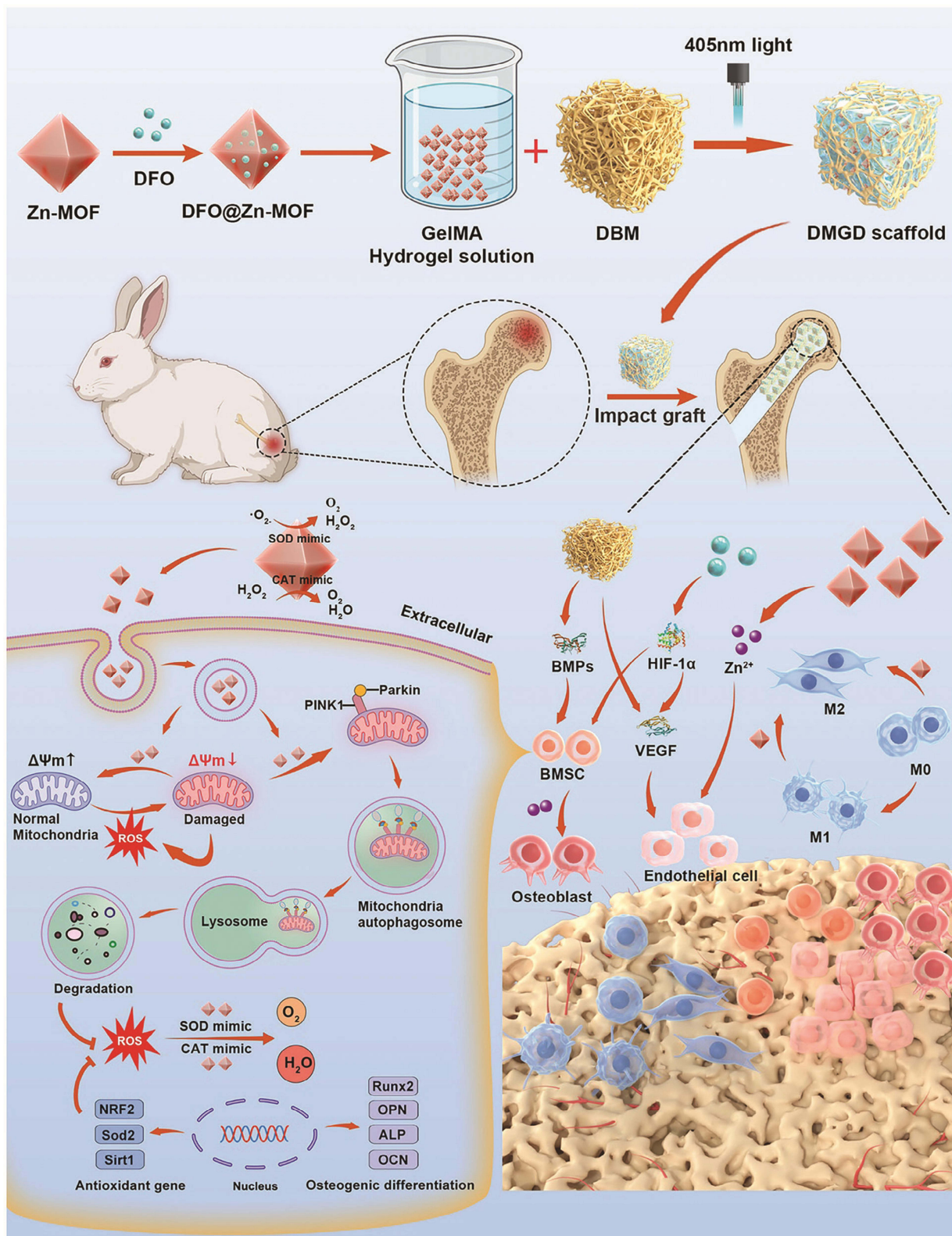
## Osteoporotic Defect

Osteoporosis (OP) is a metabolic bone disease with a high global prevalence. The imbalance between bone resorption and bone formation leads to decreased bone density, microstructural damage, and an increased risk of fragility fractures. The prevalence is 30% to 50% in women and 10% to 20% in men among people over 50 years old, imposing a heavy burden on the social medical system.<sup>106,107</sup> At present, treatment options for OP remain limited. Although drug therapy can slow bone loss, it cannot restore the damaged bone microarchitecture. In surgical management, conventional implants are prone to loosening and displacement because of low bone mass and reduced bone strength. Artificial bone exhibits insufficient biological activity and poor bone integration, and the risk of refracture after surgery is high. Traditional scaffold materials for tissue engineering repair have poor biocompatibility, are challenging to regulate the bone-formation microenvironment, and cannot be tailored to the patient’s bone-regeneration capacity.<sup>108</sup> GelMA hydrogel, with its similar composition to natural bone matrix collagen, excellent biocompatibility, porous structure conducive to cell colonization and drug factor release, and adjustable mechanical properties, can specifically address many difficulties in OP treatment and has become one of the core materials in OP treatment research. The key to OP treatment lies in restoring the balance between bone formation and resorption, promoting repair of bone defects, and enhancing the efficiency of bone integration around implants. Current research on GelMA is centred on these goals, resulting in innovative, multi-dimensional treatment regimens.

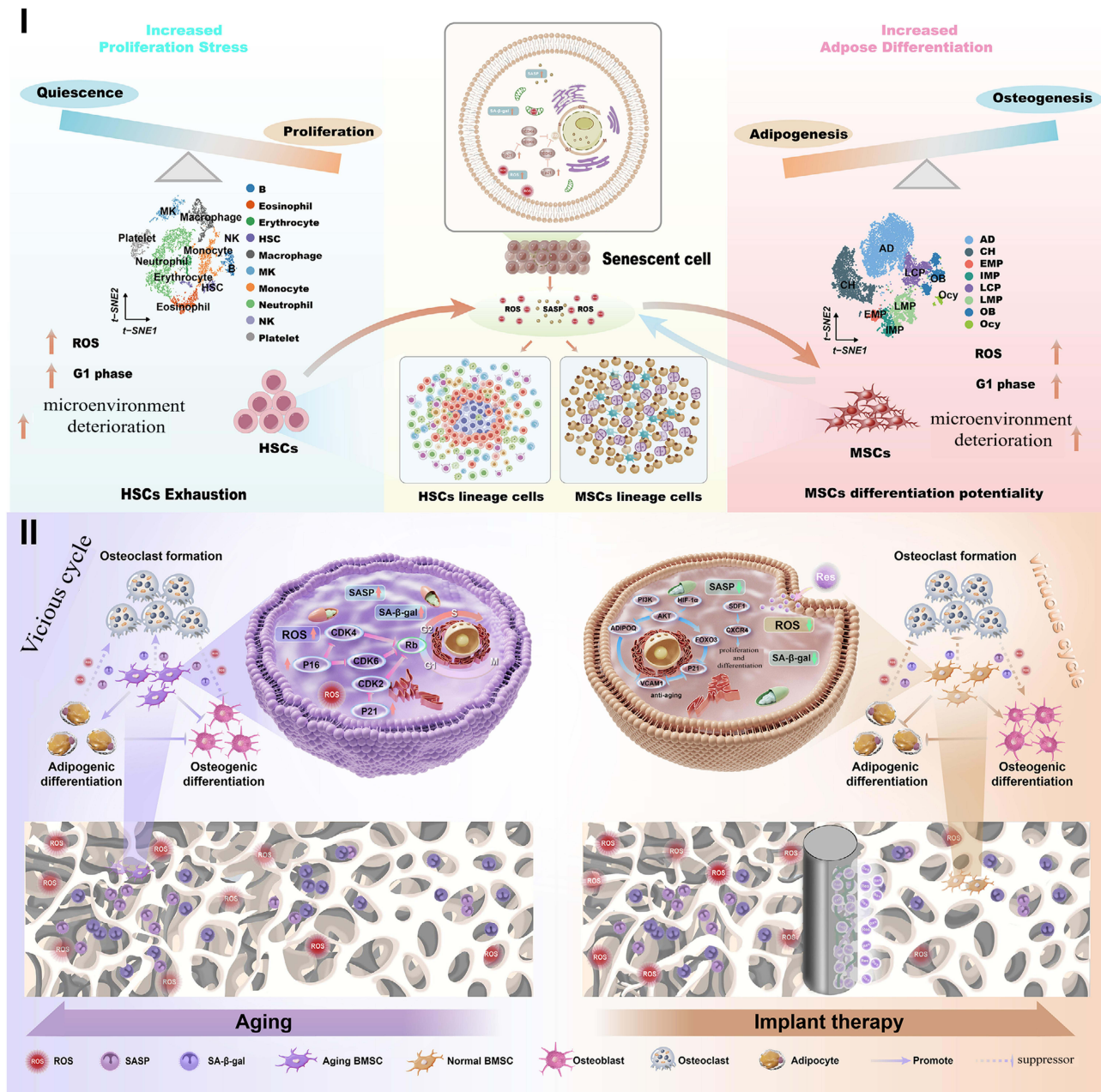
Senescent OP (A-OP), the primary type of OP in the elderly population, is characterized by BMSCs’ senescence.<sup>109</sup> With increasing age, the osteogenic differentiation capacity of BMSCs declines, and the secretion of inflammatory factors increases, further inhibiting bone formation. To address this challenge, the Fan team combined single-cell transcriptomics to precisely screen for key regulators of BMSCs’ senescence in A-OP and designed an A “GelMA hydrogel-modified titanium alloy implant” in which osteogenic gene expression in BMSCs was increased.<sup>109</sup> In terms of enhancing implant osseointegration, the GelMA hydrogel forms a “bioactive interface” on the titanium alloy surface, providing a colonization scaffold for BMSCs and continuously regulating the bone formation microenvironment by sustained-release resveratrol, increasing the peri-implant osseointegration effect and reducing the risk of loosening in the A-OP animal model. The study employed single-cell transcriptomics in material design to precisely target pathological mechanisms and avoid the drawbacks of blind dosing in traditional regimens, offering new approaches to the precise treatment of A-OP (Figure 3).

OP patients exhibit insufficient synergy between bone and vascular regeneration during bone defect repair due to low bone mass and reduced vascular density, thereby limiting the efficacy of traditional repair materials.<sup>110</sup> The He team combined SR-LDH with GelMA hydrogel to construct a synergistic system that activated osteoblasts via  $\text{Sr}^{2+}$  to promote osteogenic differentiation and angiogenesis. It sustainably released  $\text{Sr}^{2+}$  through the porous structure of GelMA.<sup>111</sup> In the OP animal model, the composite hydrogel significantly increased bone density and the number of new blood vessels, shortened the repair cycle, and its injectability meets the minimally invasive treatment requirements of elderly patients with OP (Figure 4).

Following fractures in OP patients, an abnormal local immune microenvironment leads to macrophage polarization toward the pro-inflammatory M1 phenotype, with the release of inflammatory factors, which inhibit osteoblast activity and intensify bone resorption.<sup>112</sup> According to the study, this immune response pattern is particularly pronounced in patients with osteoporosis, resulting in significantly longer fracture-healing times than in healthy individuals, particularly among elderly patients. Conventional treatments focus on immobilization and calcium supplementation, neglecting immunomodulation and thereby impeding improvements in healing efficiency. The Zhou team designed an “IL-4 + bacterial exosome (BEVs) co-loaded GelMA hydrogel” to promote OP fracture repair through dual immunomodulation.<sup>113</sup> IL-4 induces macrophage polarization to the anti-inflammatory M2 phenotype; BEVs carry the



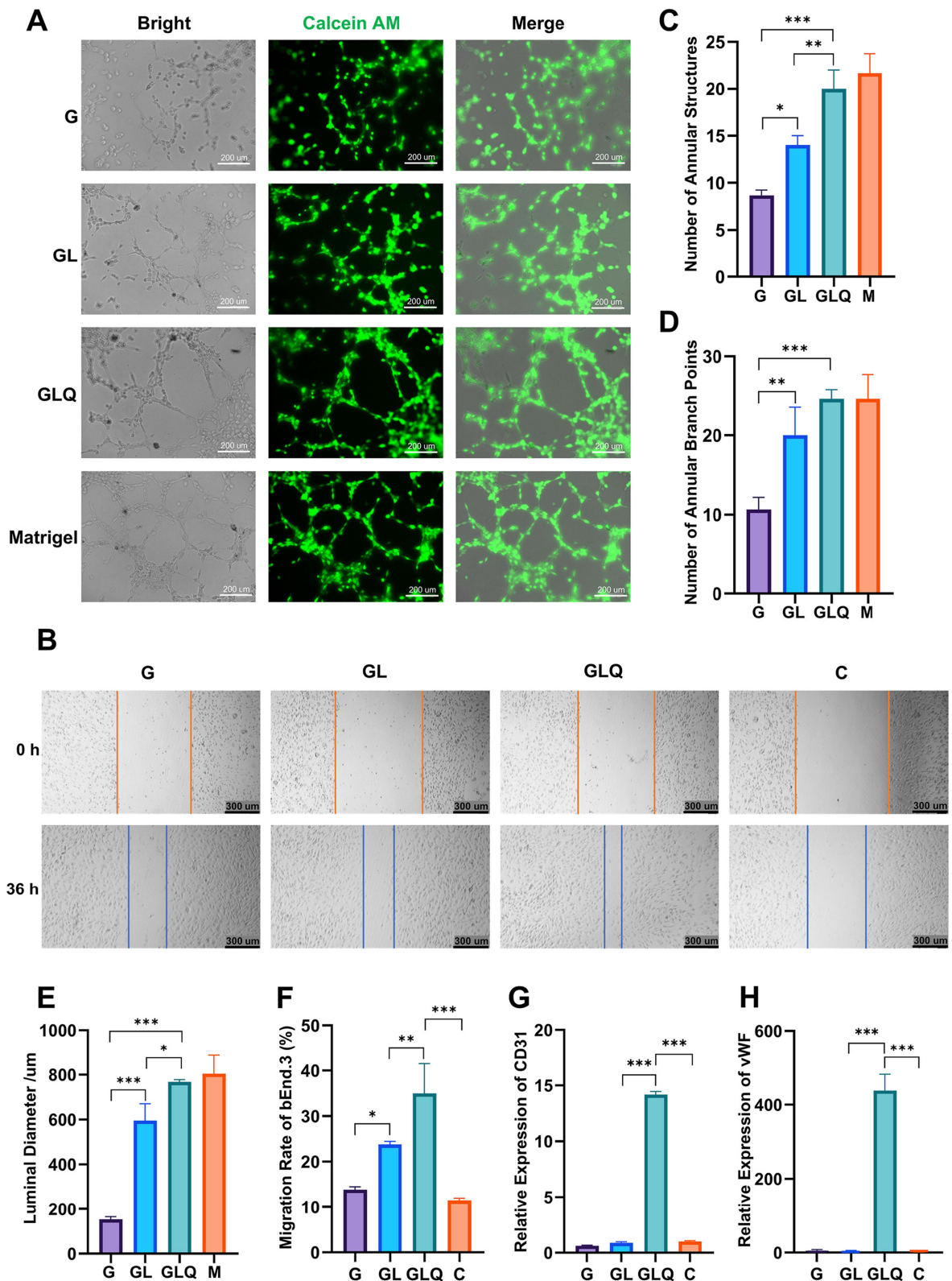
**Figure 2** Schematic illustration of the biomimetic multifunctional scaffold for the treatment of steroid-induced osteonecrosis of the femoral head. Reprinted from Bai L, Zhang X, Shen W et al Multifunctional Scaffold Comprising Metal-Organic Framework, Hydrogel, and Demineralized Bone Matrix for the Treatment of Steroid-Induced Femoral Head Necrosis. *Small*. Jan 2025;21(3): e2407758. doi:10.1002/smll.202407758.<sup>105</sup>



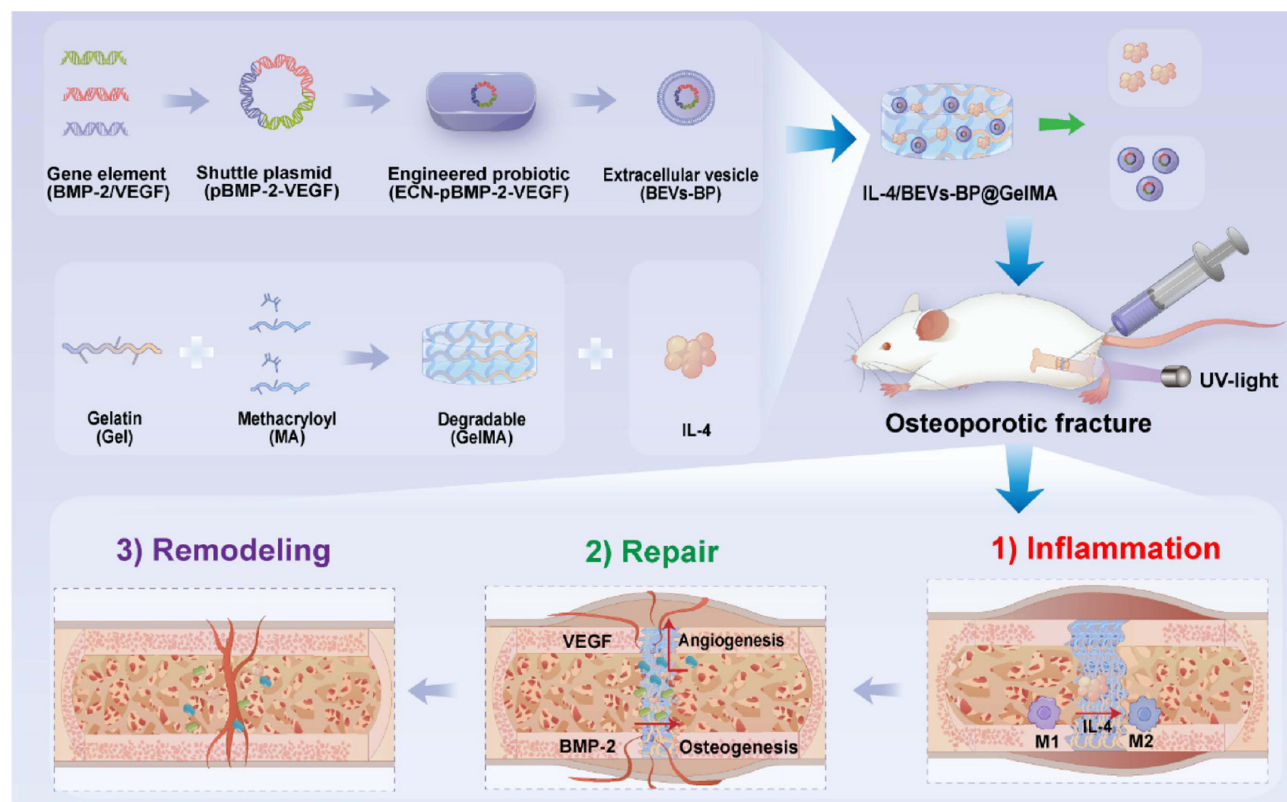
**Figure 3** Schematic representation. (I) The dynamics of the skeletal stem cell and (II) its application to the design of a titanium implant for the treatment of senile osteoporosis. Reprinted from Fan W, Zheng T, Mao M et al A Study of Skeletal Stem Cell Dynamics and Its Potential Applications in the Design of a Titanium Implant for Senile Osteoporosis. *Adv Sci (Weinh)*. Sep 2025;12(34): e06982. doi:10.1002/advs.202506982.<sup>109</sup>

anti-inflammatory factor TGF-β to regulate the immune microenvironment; and their nanostructures enhance the stability of IL-4. GelMA hydrogel provides mechanical support and sustained-release IL-4 and BEVs, synergistically promoting osteoblast proliferation and angiogenesis (Figure 5). In OP animal fracture models, the regimen shortens fracture healing time. This study, for the first time, combines immunomodulation with bone regeneration, overcoming the limitations of traditional regimens and providing a new strategy for the efficient healing of OP fractures.

With the increasing demand for precision in OP treatment, there is an urgent clinical need for smart stents that can respond to microenvironmental changes and precisely regulate bone formation. Some researchers have pointed out that nanomaterials can mimic the nanostructure of the natural bone matrix, enhance their affinity for bone tissue, and deliver growth factors precisely, thereby informing GelMA modification.<sup>114</sup> Growth factors are key to bone regeneration, but their direct use poses risks.



**Figure 4** GelMA-QK/Sr-LDH@PDA hydrogel enhances vascularization in vitro. **(A)** Tube formation assay of bEnd.3 cells on different hydrogels, with Matrigel as the control group. **(B)** Representative images of the migration assay of bEnd.3 cells at zero h and 36 h, and blank cell plate set as the control. **(C)** Quantification of annular structures in tube formation assay. **(D)** Quantification of annular branch points in tube formation assay. **(E)** Quantification of luminal diameter in the tube formation assay. **(F)** Quantification of bEnd.3 cell migration. **(G and H)** qRT-PCR results of vascularization-related marker genes. All groups are with the following designations: M for Matrigel, G for pure GelMA hydrogel, GL for GelMA/Sr-LDH@PDA composite hydrogel, GLQ for GelMA-QK/Sr-LDH@PDA composite hydrogel and C for control. Significant differences were indicated as \* $p < 0.05$ , \*\* $p < 0.01$  and \*\*\* $p < 0.001$ . Reprinted from He Y, Zeng F, Quan H et al Strontium-loaded multifunctional gelatin methacryloyl hydrogels for type-II vascularized bone regeneration under osteoporotic conditions. *Mater Today Bio*. Jun 2025;32: 101909. doi:10.1016/j.mtbio.2025.101909.<sup>111</sup>



**Figure 5** Schematic representation of engineered probiotic EVs in a composite hydrogel for temporally controlled repair of OPF. Reprinted from Zhou G, Zhou Q, Li R et al Synthetically Engineered Bacterial Extracellular Vesicles and IL-4-Encapsulated Hydrogels Sequentially Promote Osteoporotic Fracture Repair. *ACS Nano*. Apr 29 2025;19-(16):16,064–16083. doi:10.1021/acsnano.5c03106.<sup>113</sup>

Combining them with GelMA to design sustained-release systems can enhance osteogenic effects. Future innovative scaffolds require multi-signal integration capabilities, and GelMA, owing to its high compatibility, is expected to serve as the core carrier. Currently, GelMA hydrogels have demonstrated remarkable efficacy in OP treatment research, with breakthroughs in implant modification, bone defect repair, and immune microenvironment regulation. The core advantage lies in its robust carrier properties, which enable the integration of multiple functional modules, achieve coordinated multi-mechanism regulation, and adapt to complex pathological environments. Future research could develop personalized GelMA systems based on pathological differences among OP subtypes.

## Periodontitis and Alveolar Bone Regeneration

Periodontitis is a chronic inflammatory disease characterized by progressive alveolar bone defects, often accompanied by symptoms such as swollen gums and loose teeth. If the disease progresses, it will ultimately result in tooth loss.<sup>115</sup> The core objective of current clinical treatment is to achieve the regeneration of dental supporting tissues, including alveolar bone, periodontal ligament, and cementum, as well as the formation of functional new attachments. However, traditional techniques such as bone grafting, guided tissue regeneration, and growth factor addition face limitations, including limited indications, poor adhesion of the binding epithelium, and easy collapse of the guiding membrane, which make them challenging to meet clinical needs.<sup>116</sup> In contrast, the GelMA hydrogel offers significant advantages for the treatment of periodontitis. Its excellent biocompatibility can reduce immune rejection and create favourable conditions for tissue repair. With its customizable properties, it can precisely regulate mechanical properties and degradation rates to account for individual patient differences. Its robust functional adaptability supports the loading of growth factors, stem cells, and other active ingredients to target and promote periodontal tissue regeneration. The core advantage of GelMA hydrogel is its ability to be precisely adapted to the individual morphological characteristics of alveolar bone defects in

patients. Through 3D printing, scaffolds with complex geometric structures can be fabricated to provide stable spatial support for periodontal tissue regeneration.

Zhu Y et al designed 3D bioprinted biomimetic periodontal modules with high structural integrity using GelMA/ECM as the cell-loading bioink.<sup>117</sup> The module is not only mechanically stable, but also enables cell orientation guidance through high-precision terrain prompts, creating a favourable biochemical environment for the proliferation and differentiation of encapsulated cells. Meanwhile, the potent immunomodulatory activity of ECM reduces the release of pro-inflammatory factors TNF- $\alpha$  and IL-6 from M1-type macrophages, thereby alleviating local inflammation in the periodontal defect area and clearing environmental obstacles to bone regeneration.<sup>118,119</sup> Periodontal Ligament Stem Cells (PDLSCs) are the primary seed cells for periodontal tissue regeneration and exhibit multi-directional differentiation potential.<sup>120,121</sup> GelMA is an ideal carrier for the proliferation and differentiation of PDLSCs. Scaffolds prepared by bioprinting with 10% high-concentration GelMA hydrogel exhibit a higher compressive modulus and a lower swelling rate, although they slightly reduce the survival rate of PDLSCs. However, it can significantly enhance osteogenic differentiation ability by activating the eprinB2/EphB4 signalling pathway.<sup>117</sup> Low-stiffness GelMA can optimize the microenvironment for cell survival and proliferation. The Wang team found that although low-stiffness GelMA hydrogels provide weaker mechanical support, they significantly increase PDLSC survival and are more conducive to cell proliferation, migration, and the expression of osteogenic genes RUNX2, COL1A1, and ALP.<sup>122</sup>

By constructing GelMA composite systems, the mechanical microenvironment can be precisely regulated, and the application of 3D bioprinting technology further enhances the precision with which the mechanical properties of GelMA are controlled. Yufei Ma et al prepared GelMA/PEGDA composite hydrogel microarrays by adjusting the ratio of GelMA to polyethylene glycol dimethacrylate (PEGDA).<sup>121</sup> In vitro experiments confirmed that the composite system was most conducive to osteogenic differentiation of PDLSCs, and in vivo animal experiments also showed that its effect on new bone formation in rat alveolar bone defect models was significantly better than that of the single GelMA hydrogel control group.

Exosomes have immunomodulatory and tissue-regenerative activities and are emerging as functional biomarkers for periodontitis treatment; however, their short half-life and rapid clearance limit their clinical application.<sup>123,124</sup> GelMA hydrogel can serve as an efficient carrier for exosomes, prolonging their retention time and biological activity within the periodontal lesion and thereby achieving a synergistic therapeutic effect. Immune-cell-derived exosomes regulate the periodontal inflammatory microenvironment. The Ya Cui team developed melatonin loaded m2-type macrophage-derived exosomes (Mel@M2-exos) and embedded them in injectable GelMA hydrogels M2-exos have the natural ability to target inflammatory sites and induce macrophages to polarize from pro-inflammatory M1 type to anti-inflammatory M2 type, reducing local inflammation; Meanwhile, melatonin released by exosomes alleviates excessive endoplasmic reticulum stress in PDLSCs in an inflammatory environment, inhibits apoptosis, and restores their osteogenic, odontogenic, and odontogenic differentiation potential.<sup>125</sup> Haiwei Zhuo's team designed GelMA@MP196/Exos hydrogel, which induces neutrophil apoptosis, enhances macrophage phagocytosis, and effectively inhibits periodontal bone loss.<sup>126</sup> Exosomes derived from dental pulp stem cells (DPSCs) can enhance alveolar bone regeneration efficiency. Yike Gao's team used magnesium ions to activate DPSCs, thereby inducing the production of small extracellular vesicles (sEVs) enriched in miR-451a, which promote vascularized bone regeneration via the AKT/eNOS/NO signalling axis.<sup>127</sup> The sustained release of sEVs was achieved through GelMA hydrogel, which significantly enhanced in vivo bone defect repair and effectively overcame the limited angiogenic ability of natural MSC-sEVs.

Infection is the primary driver of periodontitis progression and treatment failure, and the GelMA complex system can achieve synchronous regulation of antibacterial and bone-regenerative functions via slow degradation and controlled release. The Yuqi Ma team prepared nanoscale bismuth-doped GelMA electrospun fibre membranes that sustainably release bismuth nanoparticles (BiNPs), achieving a 100% killing rate against the key periodontitis pathogenic bacterium *Porphyromonas gingivalis* (*P. gingivalis*) and showing no significant cytotoxicity toward PDLSCs.<sup>128</sup> By combining antioxidant and anti-inflammatory effects, it can improve the periodontal repair microenvironment and promote bone tissue repair and regeneration. The multifunctional injectable microspheres (GM@Fe-Cur/PDA/MH) developed by the Ziliang Xiu team encapsulate iron-curcumin nanoparticles (Fe-Cur NPs) in a GelMA matrix using microfluidic technology, with the surface modified by polydopamine (PDA) and loaded with minocycline hydrochloride (MH).<sup>129</sup> The microspheres exhibit excellent retention capacity in the periodontal pocket, combining the photothermal effect of PDA with the antibacterial properties of MH to

effectively kill pathogenic bacteria, induce macrophage polarization from pro-inflammatory M1 to anti-inflammatory M2, inhibit the release of inflammatory factors, and promote the expression of the osteogenic protein BMP-2. In the rat periodontitis model, the microsphere significantly inhibited inflammation and reduced alveolar bone resorption. In addition, the GelMA hydrogel complex loaded with RvD1 developed by the Zhe team can achieve sustained RvD1 release, significantly promote PDLSC proliferation, reduce inflammatory cell infiltration, lower TNF- $\alpha$  and RANKL expression, and inhibit osteoclast generation.<sup>130</sup> It also upregulates the expression of anti-inflammatory and tissue regeneration-related genes, effectively improving the periodontal repair microenvironment (Table 4).

With tunable mechanical properties, excellent biocompatibility, and multifunctional carrier characteristics, GelMA hydrogel offers key advantages in the “inflammation regulation-antibacterial treatment-tissue regeneration” process for

**Table 4** GelMA Studies for Periodontitis Treatment

Authors	Year	Keywords	Summary of Key Findings	Approach	Relevance to Periodontitis
Yuqi Ma et al <sup>128</sup>	2025	Bismuth nanoparticles, GelMA, Bioadhesive, Antibiofilm	BiNP-infused GelMA electrospun mats exhibit strong antibacterial/antibiofilm activity against periodontal pathogens and good compatibility with PDLSCs.	Electrospinning, BiNP loading, cell viability, antibacterial and biofilm assays.	Localized antimicrobial/antibiofilm dressing for periodontitis.
Ziliang Xiu et al <sup>129</sup>	2025	GelMA; iron-curcumin nanoparticles; polydopamine; ROS scavenging; immunomodulation; photo-antibacterial	GelMA-Fe-Cur/PDA microspheres enable NIR photothermal killing plus ROS scavenging/anti-inflammation, reducing oxidative stress and promoting bone regeneration.	Fe-Cur NP synthesis, GelMA encapsulation, PDA coating, NIR response, antibacterial, macrophage polarization, osteogenesis (in vitro/in vivo).	Injectable multifunctional system for disinfection, oxidative-stress control, and periodontal bone repair.
Xing Z et al <sup>130</sup>	2025	Periodontitis; RvD1; GelMA; inflammation; bone regeneration	RvD1-GelMA provides sustained pro-resolving release, lowers TNF- $\alpha$ /RANKL, inhibits osteoclasts, and enhances bone formation in rat periodontitis.	Cytocompatibility, rat periodontitis model, qPCR, histology, micro-CT.	Anti-inflammatory, pro-regenerative hydrogel for periodontal therapy.
Ya Cui et al <sup>125</sup>	2023	Melatonin; macrophage exosomes; ER stress; immune modulation	Mel@M2-exos reprogram macrophages, suppress ER stress, and enhance alveolar bone regeneration in rats (GelMA delivery).	Mel-loaded M2-exos, hPDLSC assays, rat ligature periodontitis, GelMA-based delivery.	Immune-targeted exosome therapy to resolve inflammation and promote periodontal bone regeneration.
Haiwei Zhuo et al <sup>126</sup>	2025	Neutrophil, Exosomes, Apoptosis, M2 polarization, Periodontitis	GelMA@MPI96/exos induces neutrophil apoptosis and macrophage M2 polarization, reducing alveolar bone loss in periodontitis models.	TEM, NTA, WB, in vivo rat periodontitis.	Immunomodulatory hydrogel to mitigate inflammation-driven bone loss in periodontitis.
Yike Gao et al <sup>127</sup>	2025	Small extracellular vesicles, Magnesium cation, Bone regeneration, AKT/eNOS/NO pathway	miR-451a-enriched sEVs from Mg <sup>2+</sup> -activated DPSCs enhance vascularized bone regeneration, improving periodontal tissue repair.	sEV isolation, in vivo bone regeneration model, qPCR, WB.	Stem cell-derived EV strategy for angiogenesis-coupled bone regeneration in periodontitis.
Yaru Zhu et al <sup>117</sup>	2023	PDLSCs; bioprinting; GelMA; osteogenesis	High-density (10%) GelMA promotes PDLSC osteogenesis via ephrinB2/EphB4 signaling and improves in vivo bone formation.	3D bioprinting (3/5/10% GelMA), in vitro osteogenesis assays, and mouse cranial defect.	Supports bioprinted PDLSC-laden high-density GelMA for alveolar bone regeneration.

(Continued)

**Table 4** (Continued).

Authors	Year	Keywords	Summary of Key Findings	Approach	Relevance to Periodontitis
Shiyang Wu et al <sup>131</sup>	2025	Matrix stiffness, Osteogenic differentiation, Human periodontal ligament stem cells, YAP activation	Matrix stiffness regulates hPDLSC osteogenesis via YAP activation, supporting stiffness-guided periodontal bone regeneration.	3D culture model, qRT-PCR, immunofluorescence, and in vivo rat model.	Mechanistic basis for stiffness-tuned cell therapy/scaffold design in periodontal regeneration.
Yufei Ma et al <sup>121</sup>	2017	3D bioprinting; PDLSCs; ECM screening; GelMA; PEGDA; injectable hydrogel; alveolar bone repair	PDLSC-laden injectable GelMA/PEGDA; 4:1 ratio maximized osteogenesis and rat alveolar bone formation.	3D bioprinting; physico-mechanics; ALP/osteogenic markers; rat defect; micro-CT /histology.	Optimized 4:1 GelMA/PEGDA injectable scaffold for periodontal bone regeneration.

the treatment of periodontitis. From regulating the mechanical strength of PDLSCs' function to precise immune regulation via exosomes to loading multiple active ingredients as a drug-delivery platform, GelMA can achieve synergistic enhancement of therapeutic effects by combining with materials or technologies. In the future, as material modification technology continues to advance, the precision of 3D bioprinting and the mechanisms of stem cell and exosome regulation are expected to further enhance the role of GelMA hydrogels in personalized treatment of periodontitis, particularly for complex periodontal defect repair and clinical translational applications, where there remains substantial scope for exploration.

## Applications of GelMA in Skeletal Organoids

Bone organoids leverage the self-organizing properties of stem cells to faithfully replicate the *in vivo* microenvironment and induce seed cells to form 3D organ microtissues that simulate bone tissue structure and physiological function.<sup>6,132</sup> With ongoing research on bone organoids, a variety of bone organoid models, including trabeculae, callus, cartilage, and bone marrow, have been successfully constructed and play an essential role in the study of bone-defect-related diseases. Bone organoids are formed by the proliferation and differentiation of seed cells *in vitro*; seed cells include, but are not limited to, induced pluripotent stem cells, bone marrow mesenchymal stem cells, and periosteal cells.<sup>133–135</sup> At present, researchers often induce the differentiation of seed cells into osteoblasts and osteoclasts and inoculate them into culture matrices to replicate bone formation and bone resorption units, thereby simulating the equilibrium state of bone remodelling at the organoid level. Seed cells can retain the donor's genotype and exhibit high self-renewal and pluripotency, making them a powerful tool for studying and simulating bone defect-related diseases.<sup>136,137</sup> The construction of bone organoids can be classified into scaffold- and non-scaffold-based methods depending on the quality of the medium. Scaffolds are organoid culture methods that use matrix gels, hydrogels, or other polymers to support cell growth and provide rich nutrient and cytokine environments for seed cells.<sup>138</sup> Scaffolds are methods used to prevent cell adhesion and self-organization and to facilitate the formation of organoids. Standard methods include suspension culture, microarray, 3D printing, dynamic rotation culture, and microfluidic chips. Microfluidic chips enable continuous perfusion and spatiotemporal control of soluble cues, helping to overcome diffusion limitations and supporting more stable maturation of bone organoids. Given GelMA's rapid photo-crosslinking and patternability, it is well-suited for forming perfusable microchannels and spatially defined niches within microfluidic devices. Studies have shown that GelMA can effectively support the growth and differentiation of bone organoid-associated cells and promote cell-matrix interactions.

GelMA can form porous networks through photocrosslinking, serving as the structural skeleton of bone organoids and providing space for BMSCs to attach, proliferate, and self-organize. Peng Luo et al found that the porous structure of a 10% concentration of GelMA hydrogel (HG-2) supported the complete extension of BMSCs to form intercellular connections and constructed HG-2/3D-BMSC organoids within 14 days.<sup>139</sup> The elastic modulus of 10% GelMA

precisely covered the optimal stiffness range for osteogenesis and chondrogenesis.<sup>117</sup> It simultaneously promoted the differentiation of BMSCs into bone organoids, with differentiation toward osteoblasts and chondrocytes. Jian Wang et al used the porous structure of the GelMA/AlgMA/HAP composite scaffold, in which HAP released  $\text{Ca}^{2+}/\text{PO}_4^{3-}$  ions to promote BMSC mineralization. After 40 days of culture, the bone volume fraction of the organoids was significantly increased compared to pure GelMA, and the mechanical strength was close to that of loose bone.<sup>6</sup> Successfully guided BMSCs to self-organize into trabecular bone structures. The maturation of bone organoids depends on the directed differentiation of BMSCs into osteogenesis or chondrogenesis. GelMA can guide cell fate through both mechanical property regulation and biochemical signal loading pathways to construct bone organoids.<sup>6</sup> Guangyin Zhou et al constructed GelMA/DNA double network hydrogels (CGDE) with enhanced viscoelasticity through hydrogen bonding, increased storage modulus  $G'$ , increased stress relaxation rate, promoting BMSCs to self-organize into braided bone organoids, forming mineralized collagen networks after 21 days of culture, similar to the natural braided bone structure.<sup>23</sup>

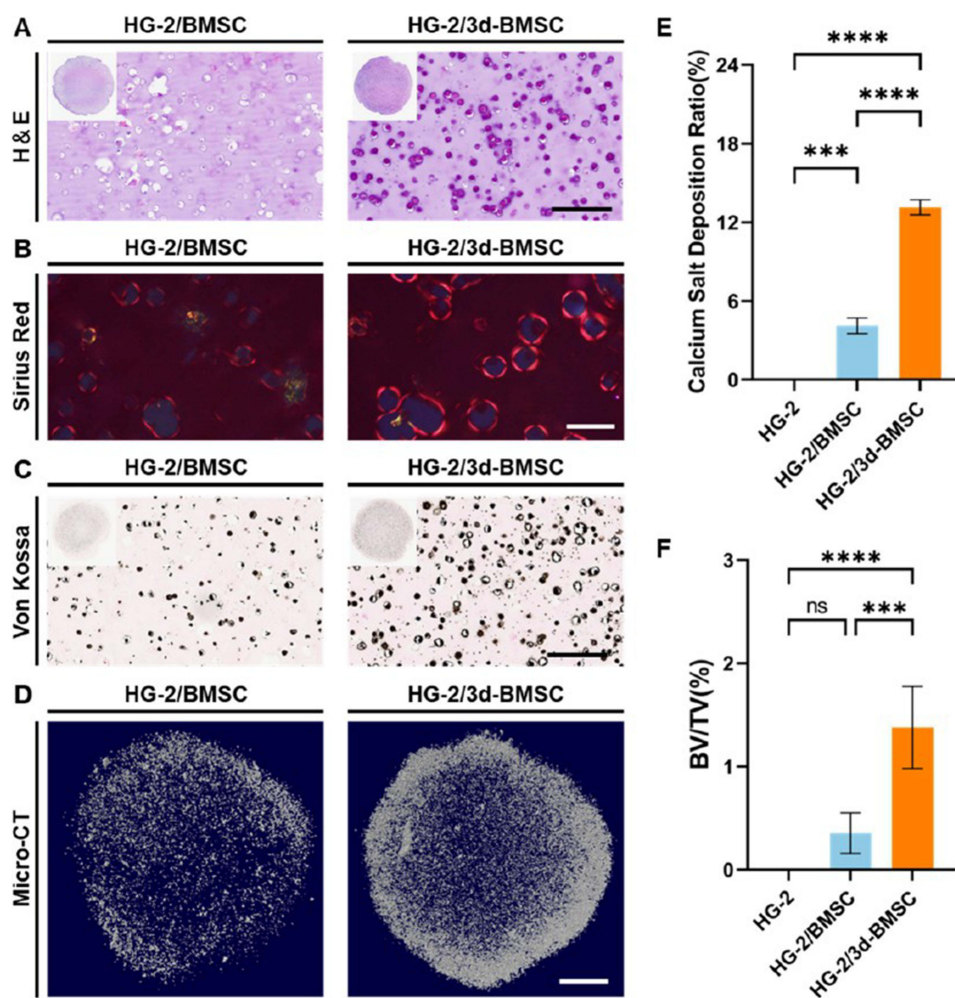
GelMA has a unique advantage in loading and releasing biochemical signals. Because of its slow degradation, GelMA enables long-term, stable release of biochemical signals. This enables GelMA to provide a more persistent environment than traditional signal-release systems, thereby promoting long-term cell differentiation and tissue repair. In tissue engineering, GelMA, as a sustained-release carrier, can be loaded with cytokines, nanoparticles, or bioactive molecules to provide sustained biochemical signalling for skeletal organoids, demonstrating significant advantages for application.<sup>113</sup> GelMA-loaded stem cell regulatory molecules induce cytoskeleton assembly through cell adhesion, activate the Yap/Tea4 mechanical conduction pathway, down-regulate Kat7, unlock the multi-directional differentiation potential of BMSCs, and enable the organoids to express osteogenic, chondrogenic, and other genes simultaneously. Promote the formation of bone organoids (Figure 6).<sup>139</sup>

With ongoing advances in bone tissue engineering and regenerative medicine, GelMA has demonstrated distinct advantages for the construction of bone organoids. Its excellent biocompatibility and controllable mechanical properties enable GelMA to effectively promote the attachment, proliferation, and differentiation of bone cells, thereby simulating the complex structure and function of bone tissue. This property not only provides an ideal *in vitro* model for basic research but also lays a solid foundation for analyzing the mechanisms of bone diseases and developing new therapeutic strategies. When combined with bioprinting technology, GelMA is expected to enable greater precision and complexity in the fabrication of bone organoids to meet personalized medical needs. The introduction of innovative materials, such as responsive hydrogels or drug-delivery systems, will further enable GelMA to dynamically regulate the microenvironment, thereby enhancing the efficiency of bone tissue regeneration and therapeutic outcomes.

## Clinical Translation Considerations and Challenges

Despite substantial progress in preclinical studies, clinical translation of GelMA-based nanocomposites for bone defect repair remains at an early stage. Most existing evidence is derived from *in vitro* experiments and small-animal models, whereas large-animal studies and well-designed clinical trials remain limited. This translational gap highlights the need for cautious interpretation of current outcomes and realistic assessment of clinical feasibility. Several key challenges must be addressed before GelMA-based systems can advance toward routine clinical use. First, although tunable, the mechanical strength of GelMA hydrogels remains insufficient for many load-bearing bone applications without reinforcement, raising concerns about long-term structural stability *in vivo*. Second, the photocrosslinking process, particularly when ultraviolet light is employed, may induce oxidative stress or DNA damage in encapsulated cells, necessitating optimization of crosslinking strategies, photoinitiator selection, and exposure parameters. From a translational perspective, issues related to large-scale manufacturing, batch-to-batch reproducibility, sterilization, and regulatory compliance under good manufacturing practice (GMP) standards also represent significant barriers. Furthermore, the degradation kinetics of GelMA scaffolds must be precisely matched with the rate of new bone formation to ensure sustained mechanical support while avoiding premature scaffold failure. Addressing these challenges through material optimization, advanced fabrication strategies, and rigorous *in vivo* validation could be critical for bridging the gap between experimental success and clinical application.

To bridge the gap between promising preclinical outcomes and clinical implementation, a stepwise and clinically oriented validation strategy is required. To strengthen translational readiness, future studies should move beyond proof-of-



**Figure 6** In vivo multidirectional differentiation ability of obtained grafts after osteogenic differentiation induction for 14 days. (A) H&E staining showing new tissue generation of different groups after 6 weeks. Scale bar = 200  $\mu$ m. (B) Sirius red staining showing collagen fibre formation of different groups after 6 weeks. (C and E) Von Kossa staining and quantitative analysis results showing calcium salt deposition across different groups after 6 weeks; one-way analysis of variance, one-tailed. (D and F) Micro-CT scan reconstruction and quantitative analysis results providing the mineralization degrees of different groups after 6 weeks, one-way analysis of variance, one-tailed. Scale bar = 200  $\mu$ m. All data are expressed as mean  $\pm$  SD ( $n = 3$ ; \*\*\* $p < 0.001$ ; \*\*\*\* $p < 0.0001$ ; ns means no significance). Reprinted from Luo P, Cheng Y, Luo Y et al Hydrogel enhanced organoid multidirectional differentiation via Yap/Tea4 mechanotransduction for accelerated tissue regeneration. ACS Appl Mater Interfaces. Jul 2 2025;17(26):37, 601–37616. doi:10.1021/acsami.5c06161.<sup>139</sup>

-concept demonstrations and adopt clinically oriented validation pathways. In particular, a stepwise evidence hierarchy (in vitro  $\rightarrow$  small-animal  $\rightarrow$  large-animal) is needed, with careful selection of defect models that better approximate human biomechanics and healing timelines. From a practical standpoint, early clinical positioning may be more feasible in non-load-bearing or lower-load indications before expanding to high-load long-bone reconstruction, where mechanical demands and regulatory scrutiny are typically higher. In parallel, scalable and reproducible manufacturing must be prioritized, including defined quality attributes (eg, degree of methacrylation, rheological properties, crosslinking kinetics, and nanoparticle dispersion), sterilization compatibility, and batch-to-batch consistency under GMP-aligned workflows. Finally, translational studies should incorporate clinically meaningful endpoints—such as longitudinal imaging, quantitative biomechanical testing, safety/toxicity evaluation, and degradation–bone formation matching—to support a realistic pathway toward human application.

## Conclusions and Future Perspectives

GelMA-based nanocomposites have emerged as a versatile and highly adaptable platform for bone defect regeneration, owing to their favourable biocompatibility, tunable mechanical properties, and the ability to integrate multifunctionally.

Rather than serving as a single-purpose biomaterial, GelMA enables the coordinated regulation of cellular behaviour, immune responses, and angiogenic–osteogenic coupling, all of which are essential for effective bone repair.

Nevertheless, current advances remain predominantly at the preclinical stage, and significant challenges related to mechanical robustness, biosafety, degradation control, and translational scalability must be overcome. Importantly, the clinical potential of GelMA-based systems should be evaluated not only on the basis of biological performance but also with respect to regulatory feasibility, manufacturing reproducibility, and long-term in vivo safety.

Future research should prioritize large-animal validation, standardized fabrication protocols, and the development of clinically compatible crosslinking strategies. By integrating materials science, mechanobiology, immunology, and translational medicine, GelMA-based platforms may ultimately evolve from experimental constructs into clinically viable solutions for repairing complex bone defects.

## Funding

This study was supported by Tianjin Education Commission Scientific Research Program (2024ZXZD001).

## Disclosure

The authors report no conflicts of interest in this work.

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