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REVIEW ARTICLE

Hydrogel-based materials for mandibular reconstruction

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Abstract

Mandibular reconstruction remains a significant clinical challenge due to irregular defect geometries, high functional restoration requirements, and complex oral environments. Traditional vascularized bone grafts, while effective, are limited by donor site complications and poor osseointegration. Hydrogel-based materials have emerged as promising alternatives due to their biocompatibility, tunable mechanical properties, and capacity to mimic the extracellular matrix for osteogenesis and angiogenesis. This review highlights recent advances in hydrogel design strategies tailored for mandibular regeneration. Key considerations include mechanical reinforcement through nanocomposites and dual-network architectures, which enhance compressive strength and toughness to withstand masticatory loads. Injectable hydrogels demonstrate minimally invasive delivery and shape adaptability for irregular defects, while biomimetic wet adhesives achieve robust tissue integration through covalent and coordination bonding mechanisms. Functionalization with bioactive factors and stem cells promotes spatiotemporal regulation of osteogenesis and angiogenesis, as evidenced by successful mandibular regeneration in preclinical models. Antibacterial strategies integrating metal ions, antibacterial agents, or peptides can contribute to addressing oral microbial challenges. This review underscores the potential of multifunctional hydrogels to bridge structural and functional regeneration in craniofacial reconstruction while identifying critical research gaps for future innovation.

Keywords: Polymer materials; Hydrogel biomaterials; Mandibular reconstruction; Nanocomposite reinforcement; Injectable hydrogel systems; Bioinspired wet-adhesive interfaces; Oral antibacterial strategies; 3D Printing

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1. Introduction

The mandible, as a crucial load-bearing structure in the craniofacial complex, not only maintains facial contours but also supports vital physiological functions such as mastication, swallowing, and speech. Clinically, mandibular defects primarily arise from pathological processes including head and neck tumor resection, traumatic fractures, osteoradionecrosis, and medication-related osteonecrosis of the jaw,[1,2] often resulting in maxillofacial deformities and functional impairments of mastication and swallowing. However, mandibular regeneration remains challenging due to irregular defect geometry, high functional restoration requirements, and complex healing environments. While small-sized bone defects demonstrate self-healing capacity, critical-sized defects necessitate clinical intervention. Ideal mandibular reconstruction requires both morphological continuity and functional rehabilitation. At present, vascularized bone grafts remain one of the optimal approaches for mandibular defect repair and quality-of-life improvement. Vascularized fibula flaps with over 95% success rates are considered the gold standard for jaw reconstruction.[3] Nevertheless, complications such as donor site infections, chronic pain, and poor osseointegration continue to constrain clinical outcomes. Thus, there is a pressing clinical demand for the innovative development of bioactive materials as alternatives that can precisely fill bone defects, as well as enhance bone regeneration and functional recovery,[4] to achieve integrated structural and functional regeneration.

Recent years have witnessed remarkable progress in bioactive materials. Hydrogels have garnered particular attention due to their exceptional biocompatibility, tunable properties, and potential to mimic the natural extracellular matrix (ECM) of mandibular bone. Through incorporation of bioactive factors (bone morphogenetic protein 2 [BMP-^{2}, vascular endothelial growth factor [VEGF]) and mesenchymal stem cells, hydrogels can create biomimetic microenvironments conducive to osteoblast migration and ordered differentiation of bone progenitor cells.[5,6] Compared to traditional implants, their minimally invasive injectability effectively avoids secondary surgery risks, while adjustable crosslinking density enables spatiotemporal control of degradation kinetics aligned with bone regeneration processes. This adaptability ensures seamless integration with existing bone while providing stable mechanical support.[7] Furthermore, their tunable mechanical properties allow customization of stiffness and degradation rates to meet mandibular reconstruction requirements. Taking gelatin methacryloyl (GelMA) hydrogel as an example, due to its excellent biocompatibility, tunable mechanical properties, and potential for functionalization, it has shown great applications in the repair of different types of bone defects. When combined with other bioactive materials, they offer highly customized and effective treatment strategies for bone tissue regeneration, meeting the needs for treating various bone defects (Figure 1). Given the oral cavity's dynamic environment characterized by high mobility,

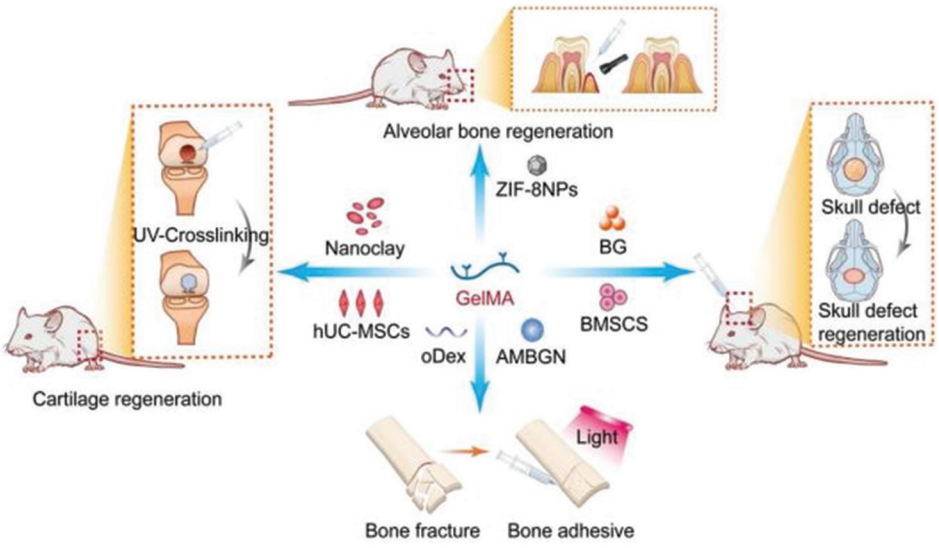

Figure 1. Schematic diagram of the application of GelMA-based hydrogels in repairing different bone defects. Created with BioRender.com
Abbreviations: AMBGN: Amino-modified mesoporous bioactive glass nanoparticles; BG: Bioactive glass; BMSCS: Bone marrow mesenchymal stem cells; GelMA: Gelatin methacryloyl; hUC-MSCs: Human umbilical cord mesenchymal stem cells; oDex: Oxidized dextran; UV: Ultraviolet; ZIF-8NPs: Zinc imidazole framework-8 nanoparticles

humidity, microbial diversity, and complex mandibular stress patterns (including axial and cantilever loads),[3,8] hydrogel design considerations for mandibular repair typically include: (1) superior biocompatibility and biodegradability for seamless tissue integration without foreign body reactions; (2) adequate mechanical strength matching mandibular stress characteristics to withstand masticatory loads; (3) excellent injectability to adapt to irregular defects; and (4) antibacterial properties against oral bacterial infections.

Considering the complexity of mandibular reconstruction, this review focuses on hydrogel design strategies and their applications in mandibular regeneration. In addition, we discuss common pathways by which hydrogel materials promote osteogenesis. Figure 2 illustrates hydrogel applications in bone defect repair, highlighting functions such as osteoconduction, angiogenesis, and osteoinduction.

2. Hydrogels-based scaffolds

Hydrogels have gained significant attention as a leading candidate for scaffold-driven mandibular repair, due to their biocompatibility and structural similarity to the body's natural ECM. These characteristics make hydrogels suitable for promoting cell adhesion, proliferation, and differentiation, which are essential for effective tissue regeneration in mandibular defects. Hydrogel-based scaffolds can be designed to deliver growth factors, stem cells, or bioactive molecules, thereby enhancing bone regeneration and functional recovery. Furthermore, their adaptable mechanical properties allow for the adjustment of stiffness and degradation rates to align with the specific needs of mandibular reconstruction. Advances in 3D printing technology allow for precise control over the shape and internal structure of hydrogel scaffolds, facilitating the creation of scaffolds that accurately mimic

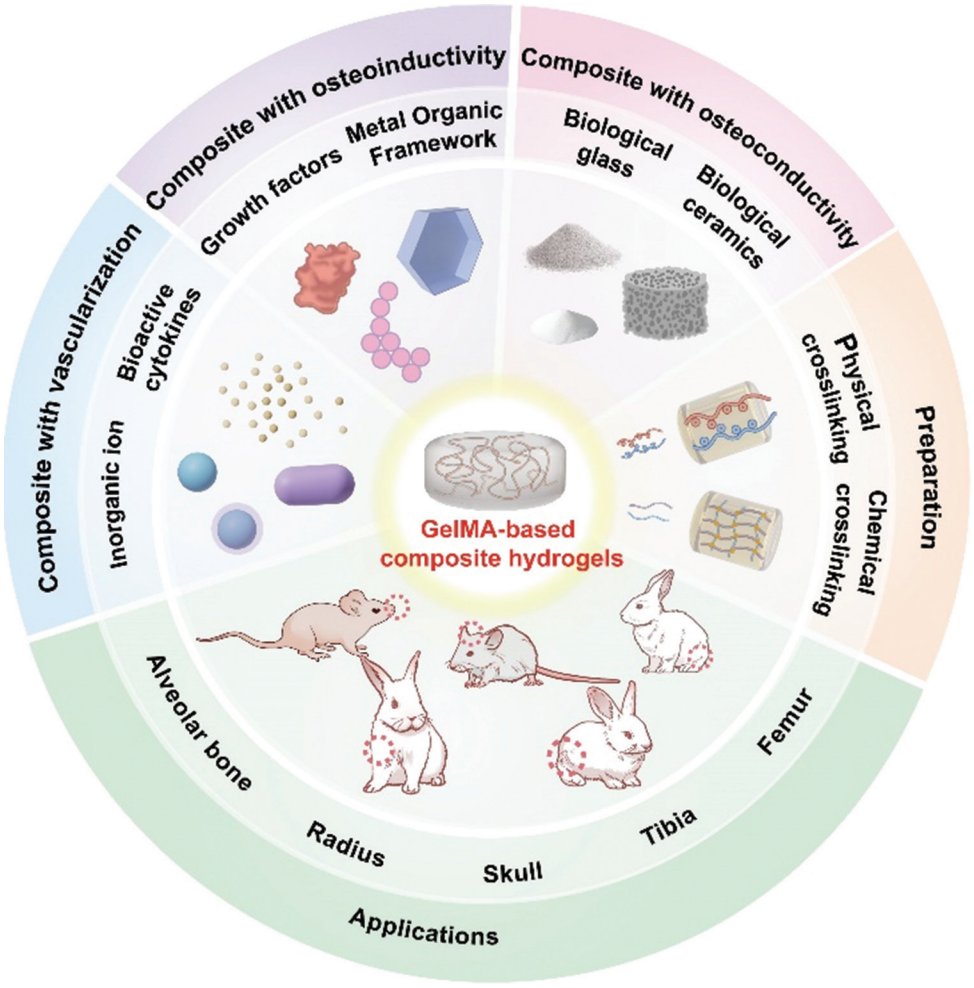

Figure 2. Illustration of hydrogel-based materials for bone regeneration, with a specific focus on three pivotal aspects: osteoconduction, angiogenesis, and osteoinduction. Some fabrication methods are shown as examples. Created with BioRender.com

the mandible's intricate anatomical structure. This high level of customization provides an effective treatment strategy for bone tissue regeneration, as the scaffolds can be designed for patient-specific defects with remarkable precision, offering a highly personalized and efficient solution for clinical applications.

2.1. Natural and synthetic hydrogels

Hydrogels can be categorized into natural and synthetic types based on polymer substrate origins.[7] Natural hydrogels include polysaccharides (chitosan, agarose, hyaluronic acid, alginate, cellulose, *etc.*) and polypeptides (gelatin, collagen, poly-L-glutamic acid, poly-L-lysine, *etc.*).[9] Their composition resembles the ECM, granting them superior biocompatibility and bioactivity. For instance, chitosan exhibits antibacterial properties, while collagen's RGD sequences enhance osteoblast adhesion. Their non-toxic degradation byproducts make them suitable for carrying stem cells or growth factors to promote localized regeneration. However, low mechanical strength and unpredictable degradation rates limit their use in large-scale defects (like post-tumor resection), often necessitating reinforcement with hydroxyapatite or crosslinking modifications.

Synthetic hydrogels (polyethylene glycol [PEG], polyacrylic acid, poly [lactic-co-glycolic acid], *etc.*) allow precise control over mechanical properties, pore structures, and degradation timelines through molecular design. Photocurable PEG hydrogels adapt to complex defect geometries, while thermosensitive poly(*N*-isopropylacrylamide) gels enable minimally invasive filling of irregular defect areas with robust enzymatic resistance for long-term support. Nevertheless, their inherent bioinertia requires modification with bioactive peptides to enhance cellular interaction, and residual monomers or acidic degradation products may trigger inflammation.

2.2. Physically, chemically, and multi-crosslinked hydrogels

The crosslinking mechanism of hydrogels is a pivotal factor in regulating their network structures and functional properties. Based on crosslinking mechanism, hydrogels can be categorized into physically crosslinked, chemically crosslinked, and multi-crosslinked systems (Figure 3A).[10,11]

Physically crosslinked hydrogels form reversible networks through dynamic non-covalent interactions such as ionic interactions, complementary base pairing, hydrogen bonding, or hydrophobic associations. These hydrogels exhibit environmental responsiveness, making them suitable for minimally invasive injection and controlled drug release. However, their inherent instability – due to reversible state changes under altered physical conditions – limits their application in high mechanical load scenarios.

In contrast, chemically crosslinked hydrogels rely on irreversible covalent bonds formed through mechanisms such as Schiff base crosslinking, Diels–Alder (DA) reactions, or radical polymerization.[12] These hydrogels achieve mechanical strength on the order of MPa, meeting the mechanical demands of bone tissue repair. Nevertheless, challenges such as residual crosslinking agents or overly dense networks may lead to cytotoxicity.

Hydrogels with greater complexity can be synthesized through the integration of multiple crosslinking techniques.[13] Even when composed of identical materials, hydrogels produced through distinct crosslinking approaches develop varied network architectures, ultimately leading to differences in their physical and chemical properties.[14-16] For instance, double-network hydrogels utilize covalent crosslinking to provide mechanical support, combined with physical crosslinking to enable self-healing capabilities. Alternatively, they may employ dynamic covalent bonds to balance reconfigurability and stability, significantly enhancing the material's strength and toughness. In addition, Chuang *et al.*[17] analyzed collagen hydrogels with comparable chemical compositions and physical attributes but prepared using distinct crosslinking techniques. Their study revealed that variations in crosslinking bonds between the two hydrogel types resulted in disparities in permeability, microstructure, and mechanical strength. Specifically, covalently bonded hydrogels exhibited lower permeability, higher density, and enhanced mechanical stability due to their tightly interconnected networks.

2.3. Stimulus-responsive hydrogel

Smart hydrogels are fabricated by incorporating specific chemical structures and additives during or after the polymerization process, enabling them to exhibit stimuli-responsive properties.[18] These hydrogels can dynamically respond to external triggers such as pH levels, magnet, temperature, light, or electricity (Figure 3B). By leveraging mechanisms like controlled drug release, they adapt to the unique microenvironments of diseased tissues, thereby enhancing therapeutic efficacy.

Bone tissue, as a mechanosensitive tissue, relies on mechanical stimulation to maintain its structure and function. This is particularly evident in the jawbone, which experiences frequent occlusal forces, resulting in a significantly higher metabolic rate and bone remodeling activity compared to other skeletal regions. To enhance bone regeneration, researchers have developed mechanically

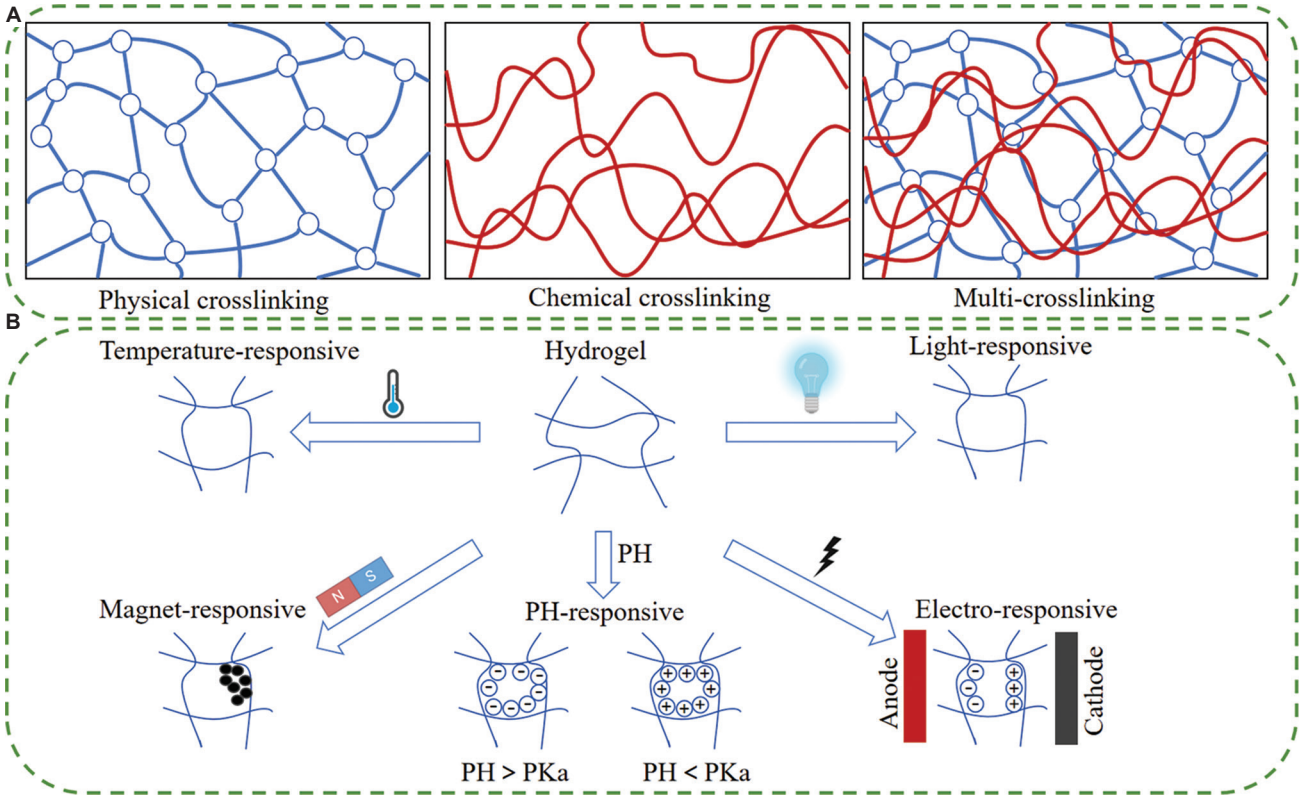

Figure 3. Hydrogel crosslinking strategies and stimuli-responsive mechanisms. (A) Crosslinked network structure in hydrogels. (B) Schematic diagram of stimulus-responsive hydrogel driving mechanism. Created with BioRender.com

tunable, high-strength hydrogels by incorporating nanoparticles or nanosheets into gel networks through multi-crosslinking strategies or hybridizing hydrogels with 3D-printed or electrospun scaffolds.[19] Rauner *et al.*[20] fabricated the ultra-robust hydrogels through enzyme-induced mineralization. Their dual-crosslinking system, centered on cage-like polyhedral oligomeric silsesquioxane (POSS), integrates high-strength hydrogen bonds and dynamic disulfide bonds to form a core/shell star-shaped architecture. Quadruple hydrogen bonds act as physical crosslinking points to optimize the network's local mechanical reinforcement, while reversible hydrogen bond breakage dissipates energy, markedly improving mechanical strength and toughness.[21]

Bone tissue functions not only as a mechanical load-bearing system but also exhibits piezoelectric properties that regulate bone metabolism and growth through electromagnetic signals. Piezoelectric biomaterials (polylactic acid, collagen, potassium sodium niobate, *etc.*) generate intrinsic electrical charges under mechanical deformation, mimicking the natural bioelectrical microenvironment of bone. This enables drug-free electrical stimulation strategies for bone defect repair. For example, Wu *et al.*[22] incorporated polydopamine-modified barium titanate and hydroxyapatite nanoparticles into a chitosan/gelatin hydrogel, constructing a piezoelectric scaffold with self-powered electrical activity, pro-angiogenic, and osteogenic capabilities. This scaffold accelerates cranial bone regeneration by activating cellular voltage-gated calcium channels and integrin-related signaling pathways through endogenous electrical signals, while promoting secretion of growth factors. Current studies suggest piezoelectric materials enhance osteogenesis through multiple pathways, including improved local blood flow and immunomodulation, though their precise molecular mechanisms remain unclear. Furthermore, balancing the mechanical strength and electrophysiological activity of hydrogels to match the dynamic electrical microenvironment of bone remains a core challenge in optimizing material design for clinical applications.

3. Considerations in hydrogel design for mandibular regeneration

Hydrogel-based mandibular regeneration strategies require careful optimization of multifunctional properties to meet complex anatomical and physiological needs (Figure 4). Mechanical properties must mimic natural bone to withstand chewing forces while promoting bone formation.

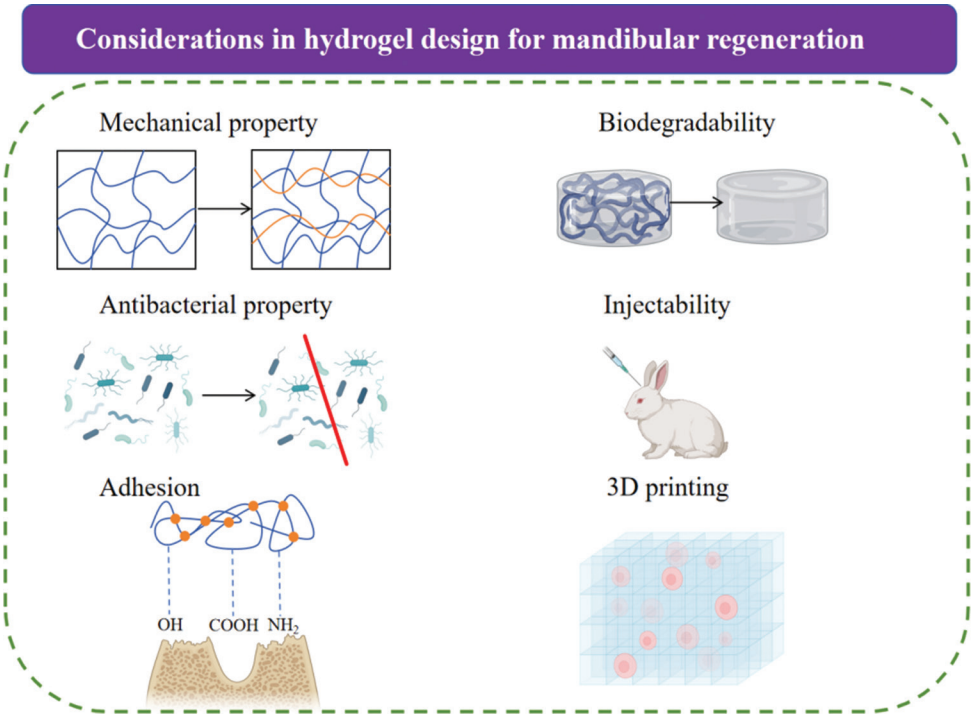

Figure 4. Considerations in hydrogel design for mandibular regeneration. Created with BioRender.com

Antimicrobial properties are key to preventing infection in the oral microenvironment, often achieved through ion/metal-polymer networks. Strong tissue adhesion ensures stable integration with irregularly defective surfaces. Controlled biodegradability balances the structural support that is gradually absorbed during the healing process to avoid secondary intervention. Injectability enables minimally invasive delivery, adapting to complex geometries, while 3D printing technology allows precise fabrication of patient-specific anatomical structures to achieve personalized mandibular regeneration.

3.1. Considerations in physical properties

3.1.1. Mechanical properties

Theoretically, hydrogels intended for bone repair should possess mechanical properties matching the implantation site tissues to ensure adequate support and functionality.[23] However, the mandible's complex anatomy, combined with high axial and non-axial (cantilever) stress loads, along with the humidity and warmth of the oral environment, compromises hydrogel mechanical strength, making it challenging to maintain structural and functional stability in bone defect regions. To address this technical bottleneck, researchers have significantly enhanced hydrogel mechanical performance through strategies such as nanocomposite (NC) modifications and network structural optimization.

NC hydrogels achieve tailored mechanical properties by incorporating nanoreinforcement phases (nanoparticles or nanostructures). Hydrogel matrices can incorporate various nanoparticles – including ceramic-based materials such as hydroxyapatite,[24,25] carbon-based structures such as graphene oxide,[26] and metallic nanoparticles (gold, silver)[27,28] – through methods like *in situ* polymerization or direct nanoparticle synthesis within the matrix. This approach produces NC with precisely engineered physical properties and functional capabilities.[29] The hydrogel network structure gains strength through hydrogen bonding or van der Waals forces between nanoparticles and polymer chains, enhancing its stability and structural integrity. For instance, hydrogels reinforced with nano-hydroxyapatite (nHAp) demonstrate tensile stress values between 0.21 and 0.86 MPa and compressive strengths reaching up to 35.8 MPa – well beyond the compressive strength range of human mandibular trabecular bone (0.22 – 10.44 MPa).[30] These mechanically enhanced hydrogels, while maintaining excellent bioactivity and injectability, have been successfully applied in minimally invasive mandibular augmentation in rats (Figure 5), demonstrating broad clinical potential in oral implantology. Guo *et al.*[31] developed a magnesium NC hydrogel where magnesium oxide nanoparticles modulated the gelation kinetics between *N*-hydroxysuccinimide-functionalized hyperbranched poly (ethylene glycol) and proteins. The optimized hydrogel not only showed markedly improved

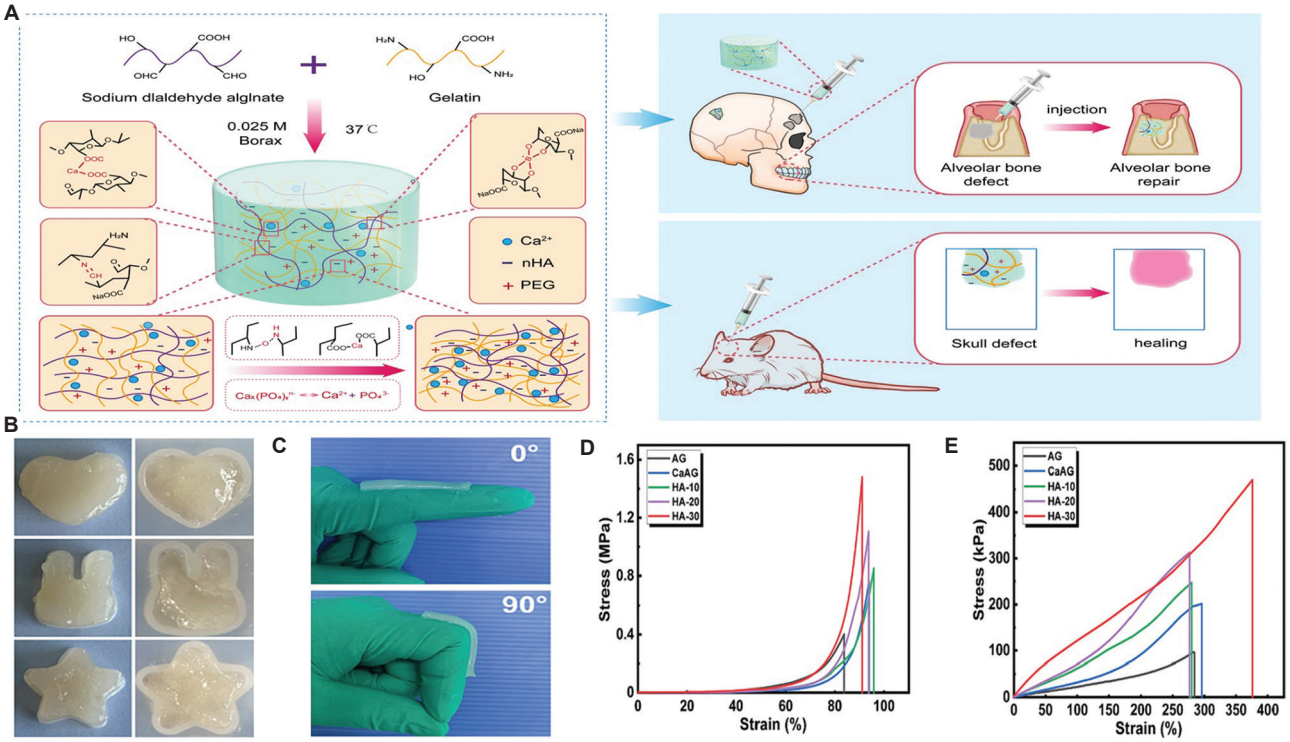

Figure 5. Multifunctional ADA-Gel/nHA composite hydrogels demonstrate moldable architectures, robust mechanical behavior, and flexibility suitable for biomedical bone regeneration applications. (A) Schematic diagram of chemical and ionic crosslinking (Ca^{2+}) of a composite ADA-Gel hydrogel modified with nHA, where dynamically dissociated PO_4^{3-} and Ca^{2+} interact with biopolymers to form tight and compact structures.[36] Created with BioRender.com. (B) Adaptability of composite hydrogels in molds with different shapes. (C) Flexibility of composite hydrogels adhered on knuckles. (D) Compressive stress-strain curves of composite hydrogels. (E) Tensile stress-strain curves of composite hydrogels. Panels B-E reprinted with permission from ref.[36]

Abbreviations: ADA: Alginate dialdehyde; nHA: Nano-sized hydroxyapatite

mechanical properties after instantaneous curing but also exhibited robust gel stability in simulated physiological environments (moisture and bleeding). It induced H-type angiogenesis, activated Osterix + osteoprogenitor cells, and created an anti-inflammatory microenvironment, achieving successful mandibular regeneration in an MRONJ rat model.

Dual-network (DN) hydrogels, formed by interpenetrating and independently crosslinked natural or synthetic polymers, combine the advantageous properties of both components.[32] Compared to traditional single-network hydrogels, DN hydrogels significantly enhance strength and toughness through an interpenetrating network of rigid polyelectrolytes and flexible neutral polymers, utilizing a "sacrificial bond" mechanism for stress dispersion. This makes them more suitable for maxillofacial tissue engineering under high mechanical loads. Zhang *et al.*[33] developed a DN hydrogel using polyvinyl alcohol (PVA) and sodium alginate (SA) through freeze-thaw cycling and ionic crosslinking, followed by enzymatic mineralization. The results revealed synergistic effects between the PVA-SA dual network and enzymatic mineralization in enhancing mechanical properties: Young's modulus reached 1.03 MPa (20408% higher than pure PVA), storage modulus 103 kPa (697% higher), and equilibrium swelling ratio 132% (47% higher). Notably, the mineralized PVA-SA hydrogel retained high toughness (1.86 MJ/m^3) and demonstrated osteogenic potential. Li *et al.*[34] designed a biomimetic DN composite hydrogel (GelMA/DNA/Apt19S/AptV, GDSV) mimicking the bone ECM. By integrating a covalent GelMA network with an aptamer-functionalized DNA physical network, the hydrogel achieved hierarchical regulation of vascularized bone regeneration. The GelMA network provided mechanical and biological stability, while the DNA network enabled dynamic capabilities like stress relaxation. Functionalized aptamers (Apt19S and AptV) mediated bone marrow stromal cell (BMSC) recruitment and VEGF-controlled release, establishing a dual bio-regulatory mechanism in a cell-free scaffold: The DNA network's dynamic mechanical microenvironment synergized with GelMA's rigid support and time-dependent VEGF release to accelerate bone repair. Traditional GelMA exhibits good biocompatibility, but its mechanical strength and

stability need to be improved. A double-network hydrogel containing magnesium ions was synthesized using *in situ* radical polymerization and crosslinking via magnesium ion coordination. The introduction of magnesium ions not only increased the crosslinking density of the hydrogel but also enhanced its mechanical strength and stability. The hydrogel, enhanced by integrating a double-network architecture and POSS-Mg composites, achieved a six-fold increase in peak compressive strength. This improvement highlights its suitability for applications such as bone regeneration and promoting blood vessel formation in rat cranial defect models.[35]

Furthermore, adjusting parameters such as hydrogel component concentrations or molecular weights can markedly improve mechanical properties such as elastic modulus and tensile strength. However, mechanical enhancement inevitably introduces challenges, including fabrication complexity, altered degradation kinetics, and potential component toxicity. Therefore, to meet the unique demands of mandibular defect repair, current research must focus on optimizing synthesis protocols, degradation parameters, and biosafety evaluation systems to synergistically enhance mechanical compatibility, tissue induction, and clinical translatability. Table 1 summarizes recent advances in mechanically reinforced hydrogels for mandibular defect repair.

3.1.2. Adhesion

An ideal hydrogel for maxillofacial repair must exhibit strong adhesiveness to resist washing by blood and tissue fluids, ensuring stable adhesion to physiological tissue surfaces. However, hydration barriers often hinder effective tissue-hydrogel integration.

In recent years, researchers have developed novel hydrogel systems integrating wet adhesion and mechanical reinforcement through biomimetic design and multi-scale composite strategies. Inspired by marine mussel adhesive proteins, chemical modifications based on L-DOPA or catechol groups can endow hydrogels with robust wet adhesion at tissue interfaces.[40] These systems overcome hydration barriers through covalent crosslinking between catechol groups and tissue surface amino/thiol groups, coupled with metal coordination. For example, Hu *et al.*[41] developed an L-DOPA-PVA-ZIF-8 hydrogel (L-DPZ) that integrates multiple functionalities through a biomimetic approach: a biocompatible PVA polymer matrix was covalently grafted with L-DOPA to provide catechol active groups, while ZIF-8 nanoparticles formed a metal-catecholamine coordination network. This system achieved a shear strength of 10 MPa through amino/thiol covalent bonds and metal coordination. In addition, the high porosity of ZIF-8 enabled controlled Zn^{2+} release, promoting osteogenic differentiation of rat BMSCs. Simultaneously, nano-scale bonding between ZIF-8 and catechol groups significantly enhanced mechanical strength, ensuring that hydrogel degradation kinetics matched new bone regeneration. This strategy demonstrates potential for resolving clinical challenges such as stabilizing comminuted fractures, reconstructing bone defects, and replanting teeth, offering promising solutions in complex medical scenarios.

Table 1. Applications of mechanically enhanced hydrogels for the repair of mandibular defects

Composite hydrogels	Cell type	Animal model	Outcome achieved	References
nHA@ADA/Gel	MC3T3-E1, ATCC	SD rats critical-sized mandibular defects	• Increased mechanical strength • Antioxidant capacity • Promoted mandibular bone regeneration	36
BPDAH-GPEGD	BMSC, macrophage	SD rat cranial defect	• Excellent injectability, self-healing property and shape adaptability • Increased mechanical strength • Repaired critical-sized skull bone defect	37
SIM@ZIF-8/ PEGDA/SA	BMSC	SD rats cranial and premaxillary defect	• Excellent injectability and mechanical strength • Promoted osteogenesis and suppress adipogenesis	38
POSS-UPy	PDLSCs	Cranial bone defect	• Increased mechanical strength • Promoted osteogenesis	21
SF/MBG/SA	BMSC	Rabbit maxillary sinus elevation	• Great injectability and shapeability • Increased mechanical strength • Promoted osteogenesis	39

Abbreviations: ADA: Alginate dialdehyde; BMSC: Bone marrow stromal cell; BPDAH: BMP-2 loaded polydopamine/heparin nanoparticles; GPEGD: Gelatin/polyethylene glycol diacrylate/2-(dimethylamino) ethyl methacrylate; MBG: Bioactive mesoporous glass; nHA: Nano-sized hydroxyapatite; PDLSCs: Periodontal ligament stem cells; PEGDA: Polyethylene glycol diacrylate; POSS-UPy: Polyhedral oligomeric silsesquioxane 2-ureido-4[1H]-pyrimidinone; SA: Sodium alginate; SD: Sprague–Dawley; SF: Silk fibroin; SIM@ZIF-8: simvastatin-laden zeolitic imidazolate framework-8.

Inspired by the composition of natural bone hydroxyapatite (HAp) and collagen matrices, Yang *et al.*[42] fabricated an nHAp-reinforced degradable bone adhesive (O-BDSG) through *in situ* free radical ring-opening polymerization. nHAp acted as a non-covalent crosslinker between polymer chains and increased the molecular weight of the polymer matrix, significantly enhancing mechanical performance and bone adhesion for rapid fracture fixation. The adhesive exhibited a bending adhesion strength of 9.79 MPa on bone – 4.7 times higher than nHAp-free formulations and far surpassing commercial cyanoacrylate adhesives (0.64 MPa). Yang *et al.*[43] also developed an injectable dual-crosslinked hydrogel (A-O hydrogel) based on dynamic Schiff base covalent networks and multi-hydrogen bonding. The system utilized amino-rich polyhydroxy polymers and oxidized methylcellulose as core components. The former enhanced gel cohesion through a tertiary hydrogen-bond network, while hydroxyl-rich sites facilitated interfacial bonding, achieving exceptional underwater adhesion with a peek adhesion strength of 2.32 MPa. The natural origin of oxidized methylcellulose ensured biocompatibility and biosafety. Functioning as a porous interfacial layer, the hydrogel not only promoted cell proliferation and migration but also created pathways for nutrient transport and the infiltration of osteogenesis-related cells. In rat skull *in situ* bone fixation and onlay bone grafting models, this hydrogel outperformed commercial bioadhesives, ensuring graft survival and integration while maintaining stable retention. This offers a robust and effective strategy for clinical bone adhesion applications.

3.1.3. Injectability

Mandibular defects often involve complex and narrow anatomical regions, making it difficult to fabricate grafts that precisely adapt to small, irregular-shaped defects. Injectable hydrogels address this challenge by enabling minimally invasive delivery and conforming to intricate anatomical geometries through flexible shape adaptation, ensuring optimal defect filling.[44] Ideal injectable scaffolds should possess appropriate porosity and pore sizes to serve as effective carriers for osteogenic growth factors, coupled with tunable release kinetics to maximize osteoblast adhesion, proliferation, and differentiation. Post-injection, hydrogels must tightly integrate with surrounding tissues while maintaining sufficient mechanical strength to withstand frequent oral movements such as mastication and swallowing. Recent advances in mechanically reinforced injectable hydrogels have focused on enhancing mechanical properties without compromising injectability, primarily through DN hydrogels combining physical and chemical crosslinking, or incorporation of nanoparticles/nanofibers as reinforcing components.[45]

Bioactive functional nanomaterials have been integrated into injectable hydrogel scaffolds to enhance mechanical performance while adding multifunctionality.[46] Zhou *et al.*[47] developed a gelatin/oxidized chondroitin sulfate hydrogel loaded with mesoporous bioactive glass nanoparticles (MBGNs), which act as bioactive additives to enhance functionality. MBGNs accelerated hydrogel crosslinking and improved mechanical properties, especially in storage modulus and compressive strength, while retaining its injectable capability. Zhao *et al.*[48] designed a self-expanding dual-crosslinked gelatin-hyaluronic acid hydrogel (GH) with niobium-doped bioactive glass (NbBG), where NbBG dispersion enhanced mechanical performance while transforming the hydrogel's inherent expansion limitation into an advantage for bone augmentation. Bai *et al.*[49] created a self-reinforced injectable hydrogel combining non-covalent crosslinking and DA chemical dual-crosslinking, achieving 25 MPa mechanical strength while effectively promoting bone repair.

To maintain facial esthetics and carrying important physiological functions such as chewing and swallowing, jaw bone's irregular shape, adjacent neurovascular bundles, and dynamic load environment are considered reference factors for the reconstruction of mandibular regenerated materials. Hydrogel can accurately fill complex defect areas through minimally invasive injection, avoiding the damage to surrounding tissues caused by traditional open surgery, and its environmental responsiveness (such as temperature sensitivity, pH, or ion-triggered gelation) enables it to adapt to the defect shape after injection, achieving personalized shaping and reducing the risk of microleakage. In addition, hydrogels can support stem cells, growth factors and antibacterial components, promote bone-soft-tissue cooperative regeneration, and match jaw mechanical gradient through mechanical property regulation, taking into account functional reconstruction and esthetic repair.

3.2. Considerations in biological properties

3.2.1. Antibacterial property

The oral cavity is one of the most complex microbial ecosystems in the human body, hosting over 700 microbial species that form a dynamically balanced microenvironment.[50] During mandibular defect repair, the surgical site is exposed to a protein-rich, moist environment,[51] and food residues provide organic substrates,[52] creating ideal conditions for microbial proliferation. Notably, post-operative infection has emerged as a critical clinical challenge hindering bone defect repair, as persistent inflammatory responses not only impair osteoblast differentiation but also lead to osseointegration failure. Current clinical strategies

primarily focus on passive defense measures, including antimicrobial dressings,[53] localized growth factor release,[54] and hyperbaric oxygen therapy.[55] However, limitations imposed by the unique oral environment – continuous saliva washing, mechanical stress from mastication, and temperature/humidity fluctuations – result in short residence times and low bioavailability for conventional therapies. To address these challenges, functionalized hydrogel systems with environmental adaptability offer unique advantages. Their 3D network structures enable precise loading of diverse active components (antibacterial peptides, metal ions, and exosomes), enhancing drug delivery efficiency and stability, thereby providing more effective solutions for oral tissue repair and antimicrobial therapy.

Researchers have developed hydrogels crosslinked with antibiotics[56] or antibacterial peptides[57] to effectively inhibit bacterial growth. However, prolonged use of antibiotics and antimicrobial agents risks drug resistance and disrupts oral microbial homeostasis. To overcome this, Chen *et al.*[58] innovatively incorporated polyamidoamine dendrimers (PAMAM-G3) into polymer backbones to capture negatively charged microbial-associated molecular patterns, creating cationic hydrogels that alleviate bacterial-induced inflammation while preserving oral microbial balance. Furthermore, incorporating inorganic antibacterial components into hydrogels not only strengthens their antimicrobial performance and durability but also mitigates the likelihood of triggering bacterial resistance, offering a sustainable strategy for infection control. Leveraging synergistic crosslinking between SH-PEG and Ag^{+}, researchers embedded viscous liposomes into PEG hydrogels to construct an injectable, antibacterial, and self-healing drug delivery system,[59] offering innovative solutions for bone tissue engineering and anti-infection therapy. Antibiotic-loaded hydrogels are widely applied in mandibular reconstruction. Preclinical studies focus on local delivery of antibiotics (gentamicin and vancomycin) through hydrogels to enhance anti-infective capacity and promote bone regeneration.[60] In a rabbit mandibular osteomyelitis model, local injection of gentamicin-loaded collagen hydrogel significantly increased bone area in infected regions after 4 weeks, demonstrating superior antibacterial and osteogenic effects.[61] This strategy not only improves drug stability and delivery efficiency but also reduces systemic side effects, supporting optimization and clinical translation of mandibular substitutes. Xu *et al.*[62] designed a novel peptide-based polymer with excellent antibacterial properties, capable of killing bacteria, releasing growth factors, and promoting bone regeneration. This polymer carries BMP-2 and gentamicin-loaded microspheres, effectively inhibiting *Escherichia coli*, *Staphylococcus aureus*, and oral bacteria through sustained gentamicin release.

Beyond metal ions, antibacterial agents, and peptides, photothermal therapy is widely explored in antibacterial hydrogel research. When localized temperatures exceed 48°C, irreversible thermal ablation directly eliminates pathogens, while hydrogel carriers optimize heat distribution to minimize collateral tissue damage. In the 41 – 47°C range, hyperthermia synergizes with chemotherapy or photodynamic therapy by accelerating oxidative stress responses. Mild hyperthermia (<41°C) enhances antibacterial effects through physical microenvironment modulation. Miao *et al.*[63] integrated black phosphorus (BP) nanosheets into hydrogels to construct BP/Gel NC hydrogels, which exhibited excellent near-infrared (NIR) photothermal performance both *in vitro* and *in vivo*. When exposed to NIR irradiation, the hydrogel exhibited potent antibacterial properties. Furthermore, the BP nanosheet-hydrogel matrix promoted osteogenesis *in vitro* without exogenous osteoinductive factors and stimulated significant new bone formation in a rat cranial defect model.

3.2.2. Biodegradability

Hydrogels can provide essential support during bone healing while gradually degrading in sync with bone remodeling, thereby avoiding potential inflammation caused by long-term retention. The mandible exhibits faster remodeling rates compared to other bones,[64] particularly during alveolar bone formation, which necessitates that hydrogel degradation rates synchronize with rapid mandibular ingrowth while eliminating the trauma associated with secondary surgical removal of traditional materials. Excessively slow degradation may hinder timely replacement by nascent bone tissue during repair, delaying mandibular healing. Conversely, overly rapid degradation could compromise mechanical support and impair bone repair efficacy. Zheng *et al.*[39] innovatively incorporated inorganic mesoporous bioactive glass (MBG) nanoparticles as *in situ* sustained-release crosslinkers, overcoming the challenges in controlling gelation rates inherent to traditional divalent ion-alginate systems. This approach stimulated Ca^{2+}-release in weakly acidic microenvironments, accelerating MBG degradation and generating enhanced porous structures *in situ*. Concurrently, the increasing porosity from MBG degradation facilitates cellular infiltration into hydrogels, ensuring rapid tissue regeneration. However, excessively high degradation rates may cause wound collapse, preventing effective filling of defect areas by new tissue. To address this, Parsaee *et al.*[65] successfully developed a stable chitosan/collagen composite hydrogel system

through innovative incorporation of high-concentration β-tricalcium phosphate (β-TCP). Their research revealed that positive charges on β-TCP particles form dense electrostatic networks with negative charge groups in the chitosan/collagen matrix, significantly enhancing interpolymer chain cohesion and delaying hydrogel swelling/degradation.

Hydrogel degradation characteristics directly determine bone regeneration efficiency. Given the accelerated remodeling of mandible,[64] hydrogels require faster degradation rates to accommodate osteogenesis needs. Excessive degradation risks premature scaffold collapse and loss of structural support, while insufficient degradation impedes bone ingrowth and delays healing. Ideal degradable hydrogels achieve precise degradation rate control through optimized crosslinking density, natural/synthetic polymer composites, or responsiveness to external stimuli (enzymatic action, pH), thereby creating spatial accommodation for new bone formation during degradation.

3.3. Three-dimensional bioprinted hydrogels

The optimal scaffold mimics the structural and biochemical properties of natural bone, delivering nutrients to grafted cells, releasing bioactive signaling molecules, and allowing for vascularized tubular structures. These advantages can positively impact the success of bone grafts. However, constructing a vascularized structure that simulates natural tissue remains a major challenge. Thus, advanced micropatterning methods – such as 3D printing – have emerged, enabling the design of 3D frameworks that boost blood vessel formation while maintaining optimal porosity to support cellular integration and growth.[66,67] Through 3D bioprinting technology, it is possible to precisely construct hydrogel scaffolds that match the anatomical structure of a patient's mandible. These scaffolds can be loaded with osteogenic cells and growth factors, providing an ideal microenvironment for bone tissue regeneration (Figure 6A). When these 3D-bioprinted hydrogel scaffolds are implanted into mandibular defect sites, they can promote the regeneration and vascularization of bone tissue, effectively restoring the structure and function of the mandible. The porous structure and high water content of the hydrogel facilitate the exchange of nutrients and waste, further promoting cell growth and differentiation. In addition, 3D bioprinting technology allows for the personalized customization of hydrogel scaffolds tailored to the specific mandibular defect of each patient, based on their facial anatomical data, thereby achieving personalized treatment.

3D printing technologies used for various hydrogel applications include laser printing, inkjet printing, and extrusion printing[68] (Figure 6B-D). These three printing techniques can also effectively print hydrogels of desired shapes or structures using other mixed materials, including cells, growth factors, and more. A variety of hydrogel materials – such as gelatin, collagen, alginate, and PEG diacrylate – are commonly utilized in the development of laser-assisted 3D-printed scaffolds.[69,70] This printing technology allows for the precise production of complex 3D structures based on computer-aided design and computer-aided manufacturing models, printing the desired hydrogel scaffolds with micrometer-level resolution while effectively avoiding damage to the cells.[67,71] Gruene *et al.*[72] used alginate hydrogel-coated donor strips for the laser printing of mesenchymal stem cells and confirmed that the laser printing technology can effectively reduce cell damage during the printing process, which is crucial for cell viability and subsequent tissue regeneration. The printed bone grafts demonstrated good osteogenic and chondrogenic differentiation *in vivo*, which proves the effectiveness of this technology in bone and cartilage tissue engineering. Inkjet printing technology can precisely construct customized bone repair implants by layer-by-layer deposition of biomaterials. This technology is suitable for both on-demand and continuous jetting systems, where liquid biomaterials are jetted layer by layer onto a substrate for 3D-printing hydrogel-based scaffolds. Inkjet-based printing methods offer excellent precision and resolution (50 – 500 μm) for manufacturing complex 3D structures.[69] In thermosensitive inkjet printers, acrylated PEG can be combined with acrylated peptides[73] or GelMA,[74] enabling the fabrication of hydrogel-based scaffolds through *in situ* photopolymerization during the printing procedure. Human mesenchymal stem cells (hMSCs) have been encapsulated within these hydrogels and directly printed alongside them, resulting in enhanced capabilities for osteogenic (bone-forming) and chondrogenic (cartilage-forming) differentiation. Extrusion-driven 3D bioprinting is commonly employed in tissue engineering and regenerative medicine due to its adaptability with diverse biomaterials and crosslinking approaches. This technology is particularly suitable for shear-thinning materials, such as alginate, PEG-based hybrid hydrogels, and GelMA hybrids.[75,76] In bone and cartilage tissue engineering, alginate, polycaprolactone, and GelMA are the main materials for extrusion bioprinting.[77] Extrusion bioprinting is regarded as viable for fabricating hydrogels that incorporate alginate or Lutrol F127 (a poly(ethylene oxide)-poly(propylene oxide) copolymer) alongside BMSCs, maintaining compatibility and functionality in bioprinting applications. Cells printed through extrusion bioprinting not only remain viable throughout the process but also express osteogenic markers such as alkaline

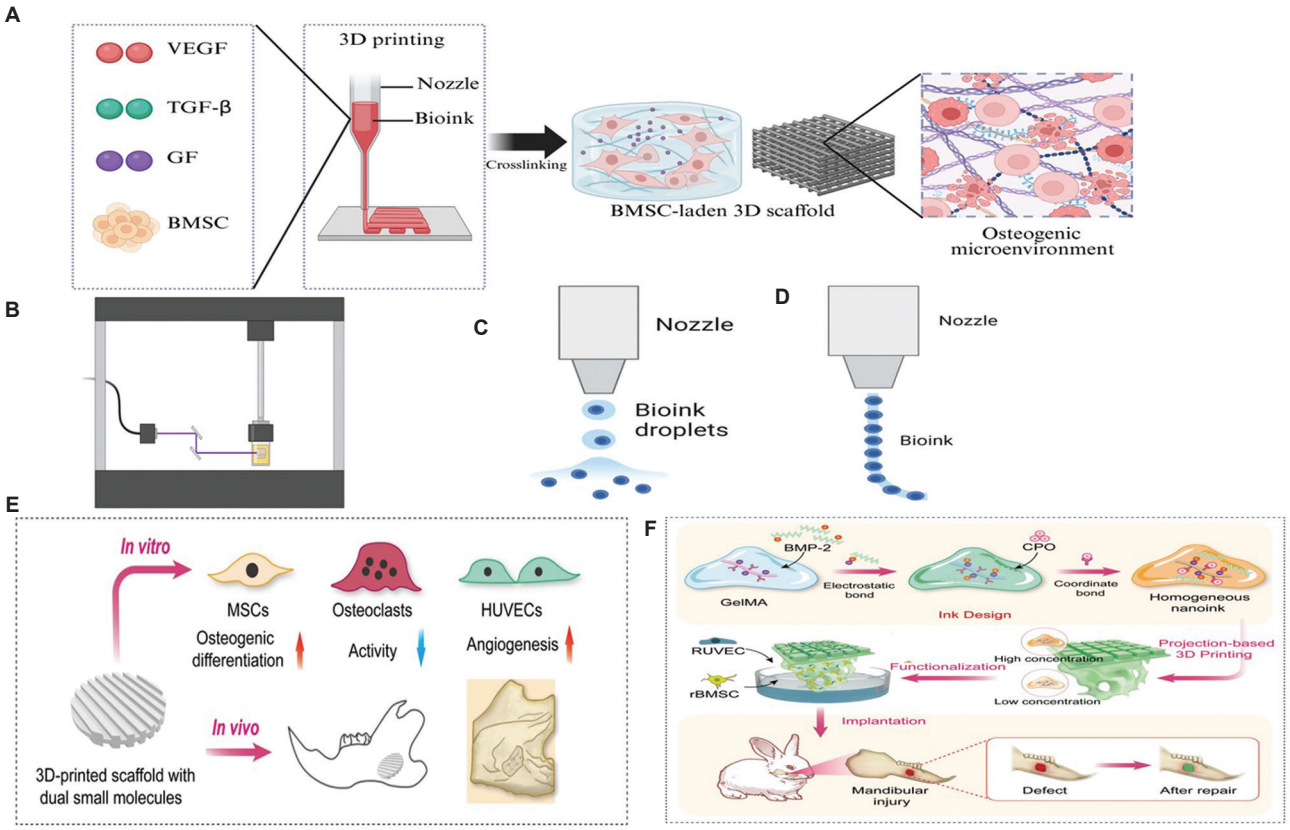

Figure 6. Application of 3D-bioprinted scaffolds integrating stem cells and growth factors in mandibular regeneration. (A) The 3D-printed scaffold is loaded with growth factors and osteoblasts, providing an ideal microenvironment for bone regeneration. (B-D) Schematic diagram of laser printing, inkjet printing, and extrusion printing. (E) Dual-molecules-loaded 3D-printed bone scaffolds offer benefits by enhancing angiogenesis while suppressing osteoclast activity, synergistically stimulating the osteogenic differentiation of MSCs. The scaffold also markedly enhanced *in vivo* bone regeneration after 8-week implantation.[81] (F) Bone morphogenetic protein-2 (BMP-2) and CPO were blended into a GelMA precursor to develop a biomimetic scaffold replicating the mandible's structural complexity. Fabricated through projection-based 3D printing, this scaffold facilitated accelerated vascular network formation and bone regeneration in rabbit models with mandibular defects, demonstrating its potential for clinical bone repair applications.[82] Created with BioRender.com

Abbreviations: BMP-2: Bone morphogenetic protein 2; BMSC: Bone marrow stromal cell; CPO: Calcium phosphate oligomers; GelMA: Gelatin methacryloyl; GF: Growth factors; HUVECs: Human umbilical vein endothelial cells; MSCs: Mesenchymal stem cells; rBMSC: Rat bone marrow stromal cell; RUVEC: Rat umbilical vein endothelial cell; TGF-β: Transforming growth factor beta; VEGF: Vascular endothelial growth factor

phosphatase, confirming their functional potential in bone-related applications.[78]

3D bioprinting technology enables the precise placement and intricate embedding of various cell types, allowing different cell types to be arranged as needed to mimic the complex structure of natural bone tissue, opening new possibilities for mandibular reconstruction.[79,80] This technology permits the application of bio-hydrogels in combination with different polymers and can also incorporate controlled release of small molecules, thereby providing multi-level biological activity support to meet complex biological and mechanical requirements. Small molecules such as resveratrol (RVS) and strontium ranelate play several roles in promoting bone regeneration. By integrating these small molecules with PCL/hydrogel composite materials through 3D printing technology, it is possible to achieve controlled dual-drug release, further enhancing bone regeneration effects. The scaffolds significantly promote the formation of mandible *in vivo* after 8 weeks of implantation[81] (Figure 6E). Inspired by the process of bone healing, Shi *et al.*[82] developed a hybrid organic-inorganic nano-ink by integrating nanoscale calcium phosphate oligomers and BMP-2 to enable spatially controlled guidance of bone regeneration. Utilizing projection-based 3D printing, they fabricated a biomimetic graft comprising a Haversian system-inspired cortical layer and a cancellous layer structured with a triply periodic minimal surface macro-architecture (Figure 6F).

3D bioprinting can accurately construct a 3D model of the mandibular defect based on the patient's facial computed

tomography (CT) or magnetic resonance imaging (MRI) data, so that the hydrogel scaffold perfectly matches the shape of the defect, achieving a highly personalized treatment plan. This technique overcomes the difficulty of accurately replicating complex anatomical structures with traditional restorative materials. The unique rheological properties of the hydrogel, especially the shear thinning behavior, make it easy to flow when printing and quickly recover the viscosity after deposition, ensuring high printing accuracy and structural stability of the scaffold. In addition, 3D bioprinting technology optimizes the porosity and microstructure of the scaffold by adjusting printing parameters such as layer thickness and printing path, helping to promote cell migration and angiogenesis, thus providing an ideal environment for bone tissue regeneration. Hydrogels can also be loaded with growth factors or stem cells to provide bioactive support and speed up the repair process of the mandible. In mandibular defect models in rats and New Zealand rabbits, 3D-printed scaffolds not only integrate well with host tissues but also stimulated the growth of new bone tissue and vascular networks and successfully restored both the structural integrity and functional capacity of the mandible. These results show the great potential of effluent gels in mandibular repair, representing a breakthrough in the field of oral and maxillofacial surgery. The research progress of 3D-bioprinted hydrogels used for the repair of mandibular defects is summarized in Table 2.

4. Mechanisms of hydrogels promoting bone defect repair

Bone defect repair is a complicated pathophysiological process that requires the dynamic balance between osteoblasts and osteoclasts. Its molecular mechanisms involve coordinated regulation of multiple signaling pathways including Hypoxia-inducible factor 1-alpha (HIF-α), Wnt/β-catenin, Mitogen-activated protein kinases (MAPK), and PI3K/AKT/mTOR. These pathways not only regulate the directional differentiation of osteoprogenitor cells and functional expression of mature bone cells but also promote the balance between bone matrix anabolism and mineralization through activation of transcription factors such as RunX2 and Osterix.

4.1. Hydrogels promote bone defect repair by regulating HIF-α signaling

HIF-α, a hypoxia-sensitive transcriptional regulator, exhibits significantly upregulated expression levels under hypoxic microenvironments. This pathway participates in bone development and remodeling through a dual regulatory mechanism. On the one hand, it transcriptionally activates pro-angiogenic factors such as VEGF, fibroblast growth factor 2, and platelet-derived growth factor to drive neovascular network formation (Figure 7A); on the other hand, it promotes osteogenic differentiation of MSCs and boosts bone matrix deposition.[86-89] The mechanism by which the HIF-α signaling pathway facilitates bone growth is illustrated in Figure 7A. The activity of HIF-α is tightly regulated by cellular oxygen concentrations. Hypoxic microenvironments created by specific hydrogel components such as deferoxamine (DFO) and dimethyloxallyl glycine can effectively stimulate HIF-α pathway activation. DFO, an iron-chelating compound and hypoxia-inducing agent, upregulates VEGF expression in hMSCs and human umbilical vein endothelial cells.

Table 2. Applications of 3D-bioprinted hydrogels for the repair of mandibular defects

Composite hydrogels	Cell type	Animal model	Outcome achieved	References
3D-printed PCL/hydrogel composite with RVS and SrRn sustained releasing	MSCs, HUVECs	Rat critical-sized mandibular defect	Promoted mandibular bone formation after 8-week implantation	81
3D organic-inorganic nanoink with BMP-2 and ultrasmall CPO incorporated into GelMA precursor	HUVECs	Rabbit mandibular defect	• Exceptional potential for osteogenesis and angiogenesis *in vitro* • Accelerated revascularization and reconstructed neo-bone *in vivo*	82
3D-bioprinted multicellular GelMA/PEGDA scaffold	Osteoblasts and endothelial cells	*In vitro*	Effective bioprinting of a mandibular structure	83
3D-printed bone frameworks of PCL/HA and SVF-derived cell (SVFC) loaded bioink	MSC, EC	*In vitro*	• Effective blood vessel generation *in vitro* and *in vivo* • Significant potential for craniofacial skeletal defects	84
Coaxial 3D printing of HSM@HSA scaffold	MC3T3-E1, BMSC	Rat/Rabbit mandibular defect	• Inhibited infection and inflammation • Promoted osteogenesis and angiogenesis	85

Abbreviations: BMP-2: Bone morphogenetic protein 2; BMSC: Bone marrow stromal cell; CPO: Calcium phosphate oligomers; GelMA: Gelatin methacryloyl; HA: Hydroxyapatite; HUVECs: Human umbilical vein endothelial cells; HSA: Hydroxyapatite-sodium alginate-antler powders (HA-SA-APs); HSM: Hydroxyapatite-sodium alginate-minocycline hydrochloride (HA-SA-MINO); MSCs: Mesenchymal stem cells; PCL: Polycaprolactone; PEGDA: Polyethylene glycol diacrylate; RVS: Resveratrol; SrRn: Strontium ranelate; SVF: Stromal vascular fraction.

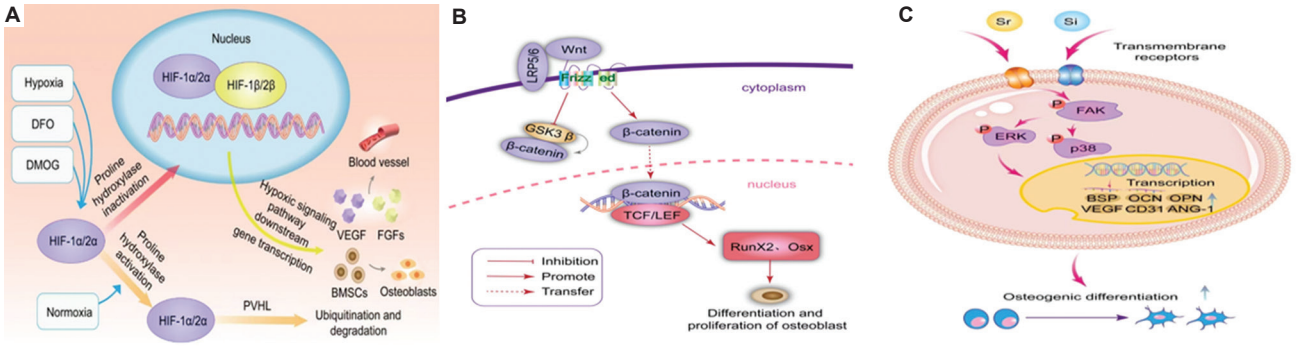

Figure 7. Schematic diagram of the hypoxia-inducible factor 1-alpha (A), Wnt/β-Catenin (B) and Mitogen-activated protein kinases (C) osteogenic signaling pathway. Created with BioRender.com

This activation of intrinsic hypoxia-driven angiogenesis enhances osteogenesis, fostering new bone formation.[90] In the BG-XLS/GelMA-DFO scaffold developed by Wang *et al.*,[91] DFO functioned as a hypoxia mimetic to activate HIF-α, significantly boosting VEGF expression. This approach accelerated bone defect repair through synergistic effects of hypoxia simulation and angiogenesis. Zhang *et al.*[92] demonstrated that DFO-loaded bone grafts effectively enhanced healing in rabbit radial defects. Stewart *et al.*[93] proved that DFO incorporation in biomaterials for rat femoral segmental defect repair improved vascularization and biomechanical properties during bone healing. HIF-α has been identified as a critical regulatory factor in bone defect repair, not only promoting angiogenesis and osteoblast differentiation but also enabling cellular adaptation to hypoxic environments, thereby facilitating bone regeneration. Consequently, research on the HIF-1α pathway may provide crucial molecular targets for developing novel bone repair strategies.

4.2. Hydrogels promote bone defect repair by regulating Wnt/β-catenin signaling

The Wnt/β-catenin signaling pathway, recognized as the primary pathway regulating BMSCs differentiation, has emerged as a critical therapeutic target for bone disorders such as osteoporosis. On Wnt pathway activation, Wnt ligands bind to lipoprotein receptor-related protein 5 (LRP5)/6 receptors, leading to inhibition of GSK-3β activity and subsequent β-catenin activation. Activated β-catenin migrates into the nucleus and binds to transcription factors, upregulating osteogenesis-related genes in BMSCs. Key targets include Runx2 and Osterix (Osx), a transcription factor critical for osteoblast differentiation, as depicted in Figure 7B. Ning *et al.*[94] developed a porous GelMA hydrogel-based delivery system for abaloparatide, which significantly upregulated key Wnt pathway-related genes such as low-density LRP5, β-catenin, and Runx2. These genetic upregulations are essential for osteocyte proliferation, differentiation, and mineralization. In this study, abaloparatide-treated cells exhibited markedly enhanced mineralization, indicating Wnt pathway-mediated promotion of bone matrix deposition and hardening. This suggests that abaloparatide may activate Wnt signaling-associated genes and facilitate bone anabolism.

4.3. Hydrogels promote bone defect repair by regulating MAPK signaling

The MAPK pathway is widely regarded as one of the most vital pathways in mammals. Studies have shown that MAPK activation is influenced by various stimuli, including neurotransmitters, inflammatory cytokines, and hormones. Activated MAPK participates in multiple physiological processes such as cell proliferation, differentiation, and apoptosis, particularly in osteoblast proliferation and differentiation.[95,96] Focal adhesion kinase (FAK), a tyrosine kinase, is involved in various signaling pathways in organisms, including the MAPK pathway.[97] The MAPK pathway primarily comprises three subfamilies: ERK, p38, and JNK.[98] Among these, ERK and p38 are recognized for their roles in regulating cell proliferation, differentiation,[99] and apoptosis.[100] Research has demonstrated that strontium ions (Sr^{2+}) stimulate the Ras/MAPK signaling cascade, thereby enhancing the osteogenic differentiation potential of MSCs and driving bone-forming cellular activity.[101] Wang *et al.*[102] developed a GelMA/Sr-CSH NC hydrogel for *in situ* bone regeneration. Through Western blot analysis, they demonstrated that this hydrogel stimulates FAK phosphorylation in BMSCs, activating ERK and p38 pathways to enhance osteogenic differentiation. Figure 7C provides a schematic illustration of the pathways involved.

5. Conclusion and future perspectives

The innovation in biomaterial fabrication and continuous advancements in regenerative medicine have driven the transition from simple wound healing to complex bone tissue regeneration. Hydrogels are undergoing a

transformative shift from fundamental research to clinical translation in mandibular defect repair. Addressing the unique anatomical complexity, dynamic mechanical loading, and functional integration requirements of the mandible, this review examines the design considerations and applications of hydrogels in mandibular regeneration. By synthesizing current achievements in this field, we aim to deepen understanding and motivate future research.

Regarding hydrogel design, ideal hydrogels for mandibular regeneration should combine exceptional physical properties – including adequate mechanical strength, adhesive properties, and injectability – with superior biological performance, encompassing antibacterial activity and controlled biodegradability. Although numerous studies demonstrate the therapeutic potential of hydrogels in mandibular defects, clinical translation remains hindered by limitations such as functional constraints, procedural complexities, and insufficient comprehensive safety evaluations. Therefore, intensified fundamental research and high-quality clinical trials are urgently needed to accelerate material development. Future research should prioritize the following directions: (1) developing hydrogel materials with enhanced biocompatibility and mechanical strength through advanced crosslinking strategies and composite formulations; (2) exploring novel antimicrobial mechanisms and components to optimize hydrogel performance in the complex oral microenvironment; (3) utilizing 4D bioprinting technology to enable printed structures to dynamically alter their contours, properties, and functionalities in response to external stimuli over time, achieving personalized mandibular reconstruction; and (4) establishing standardized animal models and clinical validation systems to rigorously assess hydrogel efficacy and biosafety. Through multidisciplinary collaboration and technological innovation, we anticipate overcoming current technical barriers and elevating mandibular repair to unprecedented levels of precision and clinical applicability.

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Conflicts of interest

The authors declare that they have no competing interests.

Authors' contributions

Conceptualization: All authors
Visualization: Yiwen Zhang, Yilan Sun
Writing–original draft: Yiwen Zhang, Yilan Sun
Writing–review and editing: All authors

Ethics approval and consent to participate

Not applicable.

Consent for publication

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Availability of data

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