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Review Article

Harnessing the potential of hyaluronic acid methacrylate (HAMA) hydrogel for clinical applications in orthopaedic diseases

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ABSTRACT

The treatment of orthopaedic diseases, such as fractures and osteoarthritis, remains a significant challenge due to the complex requirements for mechanical strength and tissue repair. Hydrogels based on hyaluronic acid methacrylate (HAMA) show promise as tissue engineering materials for these conditions. Hyaluronic acid (HA) is a natural component of the extracellular matrix, known for its good compatibility. The mechanical strength of HAMA-based hydrogels can be adjusted through crosslinking and by combining them with other materials. This review provides an overview of recent research on HAMA-based hydrogels for tissue engineering applications in orthopaedic diseases. First, we summarize the techniques for the preparation and characterization of HAMA hydrogels. Next, we offer a detailed review of the use of HAMA-based hydrogels in treating conditions such as cartilage injuries, bone defects, and meniscus injuries. Additionally, we discuss the applications of HAMA-based hydrogels in other diseases related to orthopaedics. Finally, we point out the challenges and propose future directions for the clinical translation of HAMA-based hydrogels.

Translational potential statement: HAMA-based hydrogels show strong translational potential in orthopaedics due to their biocompatibility, adjustable mechanical properties, and regenerative capabilities. With ongoing research, these hydrogels are well-positioned for clinical applications, particularly in cartilage repair, meniscus injuries, and osteoarthritis treatment.

1. Introduction

Orthopaedic diseases encompass a range of conditions and injuries affecting bone, cartilage, muscle, and related structures. These diseases, including fractures, osteoporosis, osteoarthritis (OA), etc., result in significant pain and impairment of musculoskeletal function [1]. With a high prevalence worldwide, orthopaedic diseases seriously impact daily activities and quality of life of patients [2,3]. Traditional treatments typically involve conservative or surgical approaches, yet they may not always be effective and carries inherent risks [4,5]. In recent years, tissue engineering utilizing biomaterials has emerged as a promising alternative for managing orthopaedic diseases, offering advantages over traditional approaches [6–9]. Among the various materials used in tissue engineering, hydrogels have garnered increasing attention due to their hydrophilicity, excellent biocompatibility, and similarity to the extracellular matrix (ECM) [10]. Hydrogels, classified as natural materials (e.g., chitosan, hyaluronic acid, and alginate) or synthetic materials (e.g., polyethylene glycol, polyvinyl alcohol, and poly-N-isopropylacrylamide), have been rapid developed since the pioneering work of Wichterle and Lim et al., in 1954 [11,12]. Although hydrogels show efficacy in tissue repair, their mechanical properties pose challenges to their applications in orthopaedic diseases [13–16]. For example, several distinct hydrogels have been extensively investigated and employed in the management of orthopaedic conditions,

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including gelatin, chitosan, and polyethylene glycol diacrylate (PEGDA). Gelatin has been widely utilized in various tissue engineering applications due to its excellent biocompatibility. However, its insufficient mechanical strength limits its application in weight-bearing bone repair [17]. Chitosan, owing to its natural origin and antimicrobial properties, has shown promise for bone repair. However, its mechanical properties are relatively weak, making it difficult to provide adequate support, especially in weight-bearing areas [18,19]. PEGDA, a synthetic polymer, offers good modifiability and mechanical strength. However, its biocompatibility is inferior to that of natural polymers, and its degradation products may elicit inflammatory responses [20].

Hyaluronic acid (HA), a natural component in synovial fluid and articular cartilage, has been utilized in the treatment of OA due to its biocompatibility and its ability to support cell growth and chondrogenic differentiation of chondrocytes [21,22]. However, HA exhibits relatively low mechanical property, and thus is unsuitable for handling orthopaedic conditions required higher mechanical loads [23]. Therefore, physical and chemical methods are used to enhance the mechanical property of HA. One effective strategy for enhancing the mechanical properties of hydrogels is through chemical grafting of specific functional groups onto them. For example, methacrylic anhydride is used to modify HA by substituting methacryloyl substitution groups onto the reactive amine [24]. This modification preserves biocompatibility, hydration, and biodegradability of HA while significantly enhancing its mechanical properties and adjustability, such as void structure, bioactivity, and rheological properties [25]. The resultant hyaluronic acid methacrylate (HAMA) hydrogels, formed through crosslinking, exhibit favorable biocompatibility and mechanical characteristics. By adjusting the degree of methacrylation and photocrosslinking conditions, it is possible to control the mechanical strength and degradation rate of HAMA hydrogels, making them suitable for various applications including drug delivery, tissue regeneration, immune response modulation, and self-repair capabilities. To further improve the biological performance, HAMA hydrogels are combined with other materials and biofactors to create HAMA hydrogel composites [26,27]. Moreover, the injectable nature of HAMA hydrogels makes them particularly advantageous for the use in minimally invasive procedures, showing promise in addressing orthopaedic diseases.

In this review, an overview of recent advances in HAMA-based hydrogels used for orthopaedic diseases is presented. First, the synthesis and characterization of HAMA and its derivates is introduced. Second, we focus on the current research progress of HAMA-based hydrogels in orthopaedic diseases and associated disorders. Challenges encountered during the applications of HAMA hydrogel are also discussed. Finaly, we describe the clinical translation and future opportunities for the applications of HAMA-based hydrogels in treating orthopaedic diseases.

2. Synthesis and characterization of HAMA hydrogels

HA, the precursor to HAMA, is a naturally occurring polysaccharide known for its exceptional biocompatibility and biofunction to promote cell proliferation and differentiation, favoring bone and cartilage repair. HA can form a stable gel-like substance with water molecules to ensure good moisture retention. The solubility and viscosity of HA can be modulated by changes in temperature and pH, namely, temperature- and pH-sensitive. More importantly, HA has been already approved in the treatment of orthopaedic diseases. One common application of HA is intra-articular injection for OA therapy. HA mimics the function of normal joint fluid, which improvs joint lubrication, reduces pain, and enhances joint function in OA patients [28]. Moreover, HA finds applications in cosmetology [29] and wound repair [30], highlighting its versatility and wide-ranging utility in various fields. Hence, HA-based hydrogels hold great promise for clinical translation in orthopaedic diseases.

However, the drawback of utilizing HA as a material for hard tissue engineering due to its relatively low physical and chemical stability. MA is a monomer featuring active double bonds capable of forming a crosslinked network through free radical polymerization reactions. This conjugation of MA with natural polymers allows for the preparation of hydrogels with varied properties, where the physicochemical characteristics such as elasticity, hydrophilicity, biodegradability, and biocompatibility can be finely tuned by adjusting the MA content, the copolymerization ratio with other monomers, and the degree of crosslinking. Hence, hydrogels containing MA groups are garnering attention, including HAMA, gelatin methacrylate (GelMA) [31], chondroitin sulfate methacrylate (CSMA) [32], serine protein glycidyl methacrylate (SilMA) [33], etc. The derivatization of polymers on the backbone should be indicated following the name of the main polymer, as recommended by the International Union of Pure and Applied Chemistry (IUPAC) in its Compendium of Polymer Terminology and Nomenclature [34]. Naming the group attached to the backbone polymer implies derivatization of the end groups of the polymerization. Since methacrylate groups are attached to the backbone, the term HAMA aligns more closely with the prescribed terminology. Therefore, terms such as MeHA, mHA, etc., mentioned in this paper are equivalent to HAMA.

Methods for synthesizing HAMA involve the reaction of glycerol methacrylate [35] or methacrylic anhydride [36] with HA to introduce methacrylic acid groups onto the molecule. Subsequently, a photosensitizer (e.g., lithium phenyl-2,4,6-trimethylbenzoylphosphinate, LAP) is added and the solution is exposed to ultraviolet (UV) or visible light to initiate crosslinking. The physicochemical properties of the resultant hydrogels are influenced by factors such as the duration and intensity of light exposure, as well as the concentration of the photoinitiator, all of which impact the degree of crosslinking. The pore size of HAMA hydrogels can be controlled by controlling the degree of crosslinking, thereby affecting its water absorption and nutrient diffusion capabilities. The mechanical properties of the hydrogel, including hardness, elasticity, and compressive strength, can be modulated by adjusting the amount of MA and the degree of crosslinking (Fig. 1A) [35]. The MA crosslinked networks also enable control over drug loading and release, rendering them suitable for targeted and sustained drug delivery [37]. Alternative synthesis methods for HAMA hydrogels have also been reported. A green synthesis method involves the preparation of methacryloyl hyaluronate with a tunable degree of substitution (SD) using methacryloylhydrazide as the reactive reagent and water as the sole solvent [38]. This approach offers the following advantages. First, it reduces the amount of functionalization reagents and eliminates the need for organic solvents. Second, it allows for easy control and enhancement of the degree of substitution (Fig. 1B). In another study, Bobula et al. [39] developed a novel photopolymerized HA derivative through a carbodiimide chemistry mothed involved conjugating the hydrazide group with the glucuronic acid moiety of HA. This approach not only enhances the hydrolytic stability of methacryloylhydrazide-based HA, but also circumvents the introduction of spacer substances. Subsequently, the conversion of HAMA into hydrogels via photocrosslinking was investigated. A novel photoinitiator (THX-Na) and co-initiator (TEOA) were employed. The degree of crosslinking of the hydrogel can be controlled by adjusting the reaction time and the amount of methacrylhydrazide group (Fig. 1C).

Moreover, the incorporation of MA groups not only preserves the biocompatibility of HA but also reduces the risk of allergic reactions. Kesti et al. [40] enhanced the long-term stability and functionality of implants by blending HA with the thermostable polymer poly (N-isopropyl acrylamide) (pNIPAAM) to fabricate high-resolution scaffolds with robust viability. Their study evaluated the rheological properties, swelling behavior, printability, and biocompatibility of this bio-ink for encapsulating bovine chondrocytes. They concluded that the ink demonstrated biocompatibility and facilitated the extrusion of various biopolymers. Additionally, these polymers, undergoing tandem gelation, could be laden with stratified chondrocytes to produce cell-loaded stratified cartilage structures, potentially serving as replacements for

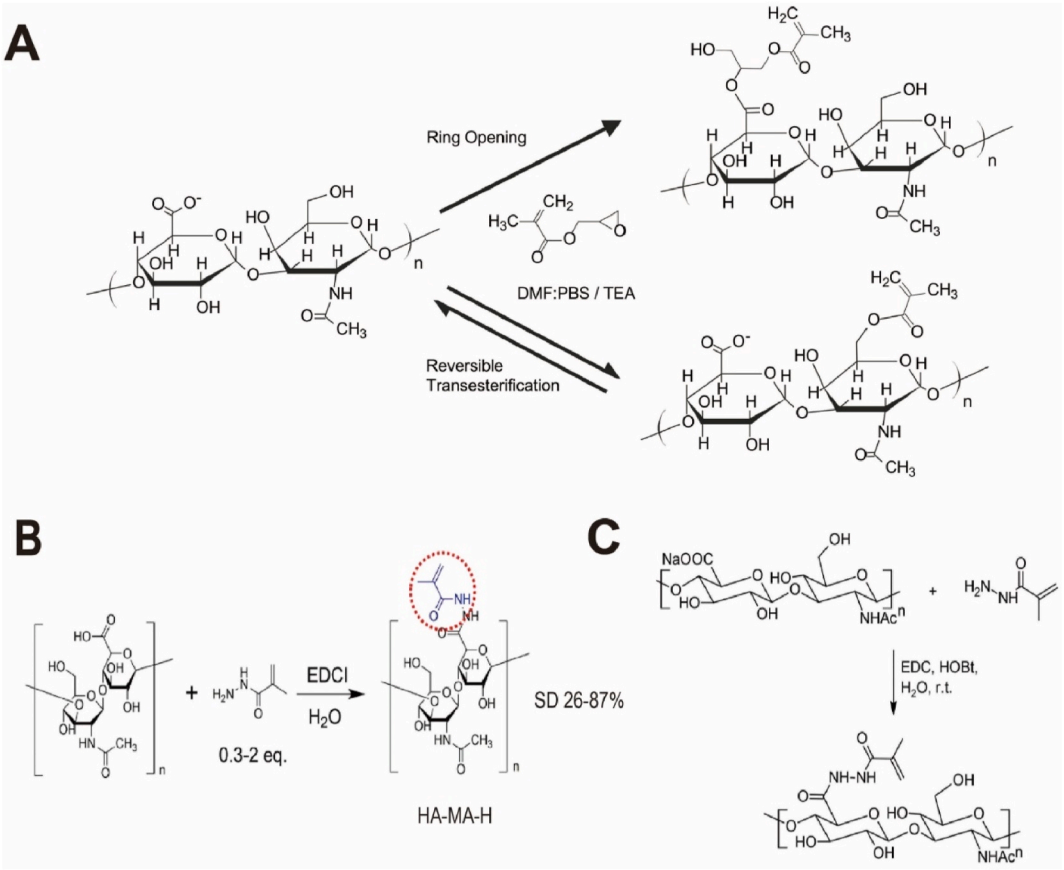

Fig. 1. Synthesis of HAMA (A) Conventional synthesis method of HAMA. Reproduced and adapted with permission from Ref. [35]. Copyright 2008 Elsevier (B) Synthesis approach of HAMA using methacryloyl hydrazide. Reproduced and adapted with permission from Ref. [38]. Copyright 2020 American Chemical Society (C) Synthesis of methacrylhydrazide-HA via a carbodiimide chemistry method. Reproduced and adapted with permission from Ref. [39]. Copyright 2017 Elsevier.

articular cartilage.

The physicochemical properties of HAMA hydrogels are significantly influenced by factors such as the choice of photoinitiator, HA concentration, and light intensity and duration during photocrosslinking. Irgacure 2959, a water-soluble photoinitiator, is widely used in the photocrosslinking of HAMA hydrogels. Under 365 nm UV light, it generates free radicals that initiate the crosslinking of methacrylate groups to form a three-dimensional hydrogel network. With low cytotoxicity and high initiation efficiency, Irgacure 2959 is suitable for cell encapsulation applications in tissue engineering. A typical concentration of 0.05 % (w/v) allows for a high degree of crosslinking in a relatively short time, ensuring the hydrogel is mechanically strong and biocompatible [41]. Another commonly used cross-linking agent is 1,4-Butanediol Diglycidyl Ether (BDDE), which reacts with the hydroxyl groups of hyaluronic acid to form stable ether bonds. BDDE-crosslinked HAMA hydrogels exhibit greater mechanical strength and longer degradation times compared to those formed by physical crosslinking, enhancing hydrogel stability for medical and cosmetic applications such as long-lasting tissue fillers and soft tissue repair materials. However, strict residue control of BDDE is necessary to ensure the biocompatibility of the final product [34]. HA concentration also significantly affects the mechanical and physicochemical properties of HAMA hydrogels. Higher HA concentrations lead to denser hydrogels with stronger crosslinked networks, resulting in increased mechanical properties like elastic modulus and shear modulus. This higher network density limits water uptake, decreasing the swelling capacity, which can affect applications like cell scaffolds in bioengineering. Conversely, lower HA concentrations produce hydrogels with sparser networks, reduced cross-linking density, and higher swelling capacity, accommodating more water molecules. These hydrogels typically have weaker mechanical strength and are suitable for applications requiring high permeability but lower mechanical demands, such as drug delivery systems. Therefore, higher HA concentrations are suitable in the preparation of HAMA hydrogels for cartilage or bone tissue engineering, and lower HA concentrations are more appropriate for skin or nerve tissue repair [41]. Although specific studies on the effects of light intensity and duration on the synthesis of HAMA hydrogel are limited, these parameters significantly impact hydrogel formation and properties in common photocrosslinking systems. Light intensity and duration determine the rate and total amount of free radicals produced by the photoinitiator, affecting the polymerization reaction and crosslink density. Higher light intensities and longer durations generally increase free radical generation and promote more complete cross-linking, leading to higher crosslinking densities and enhanced mechanical properties. However, excessive light intensity or duration may cause over-crosslinking and reduce hydrogel elasticity. It may also result in the accumulation of photoinitiator degradation products and increase cytotoxicity. Therefore, optimizing light intensity and duration during hydrogel synthesis is crucial for obtaining ideal material properties, requiring a balance among cross-linking efficiency, mechanical properties, and biosafety. By precisely controlling light parameters, the physicochemical properties of HAMA hydrogels can be modulated to meet specific biomedical application needs [42].

3. Applications of HAMA hydrogels in orthopaedic diseases

The enhanced mechanical characteristics of HAMA hydrogels enable its potential applications in healthcare. HAMA hydrogels have been extensively studied in tissue engineering of various fields, including but not limited to cartilage repair, bone repair, meniscus repair, wound

healing, etc. We specifically focused on the recent advances of HAMA hydrogels in the research of orthopaedic diseases (Fig. 2).

3.1. HAMA hydrogels for articular cartilage injuries

Cartilage is composed of chondrocytes and ECM, and it can be categorized into three types based on the composition of the ECM: hyaline cartilage, fibrocartilage, and elastic cartilage [43]. Articular cartilage, a type of hyaline cartilage, is characterized by a matrix rich in glycosaminoglycans (GAGs) and type II collagen (Col II) [44]. The recovery from injury to articular cartilage poses a challenge due to its avascularity, reliance on surrounding tissues for nutrition, and low cell density [45]. Current clinical approaches for treating articular cartilage injuries primarily involve surgical interventions, such as joint debridement, allogeneic cartilage transplantation, autologous chondrocyte implantation (ACI), and osteochondral transplantation [46–49]. While these methods can effectively repair cartilage damage, they are associated with certain limitations, including the need for advanced surgical techniques and potential mismatches between the transplanted cartilage and healthy cartilage [50,51]. In recent years, tissue engineering has emerged as a rapidly evolving approach for treating cartilage damage. It offers the potential to address cartilage injuries directly or indirectly, thereby reducing surgical trauma, shortening treatment cycles, improving therapeutic outcomes, and minimizing postoperative complications [52,53]. Hydrogels have emerged as promising materials for tissue repair and replacement due to their resemblance to ECM, featuring a three-dimensional network structure and high-water content [54]. HAMA hydrogels are regarded as promising materials for cartilage tissue repair. The advantages of HAMA hydrogels in cartilage repair involves (Table 1): (1) Promoting cell proliferation and aggregation to accelerate cartilage repair; (2) Direct application to the site of cartilage injury, such as using it as a bioink for 3D printing; (3) Serving as a carrier to transport drugs or cells to promote cartilage repair; (4) Integrating with other materials for cartilage repair. HAMA hydrogels have demonstrated efficacy in enhancing cartilage repair by fostering cell proliferation and aggregation. In a study by Chen et al. [55], AHAMA hydrogels were synthesized through the modification of HA hydrogels with aldehyde groups and methacrylate. These AHAMA hydrogels exhibited exceptional durability, stability, and adhesion in vitro, along with superior biocompatibility. Moreover, they significantly enhanced the proliferation and migration of bone marrow stem cells (BMSCs). In a rat osteochondral defect model, the implantation of AHAMA hydrogels notably facilitated integration between new cartilage and host tissue, leading to substantial improvements in cartilage regeneration (Fig. 3A). In another investigation by Liu et al. [56], photocurable HA hydrogels modified with 3-aminophenylboronic acid, sodium periodate, and methacrylic anhydride (AHAMA-PBA) were constructed. Results from in vivo and in vitro experiments indicated that AHAMA-PBA hydrogel could induce chondrocyte aggregate formation and promote the maintenance of chondrocyte phenotype (Fig. 3B).

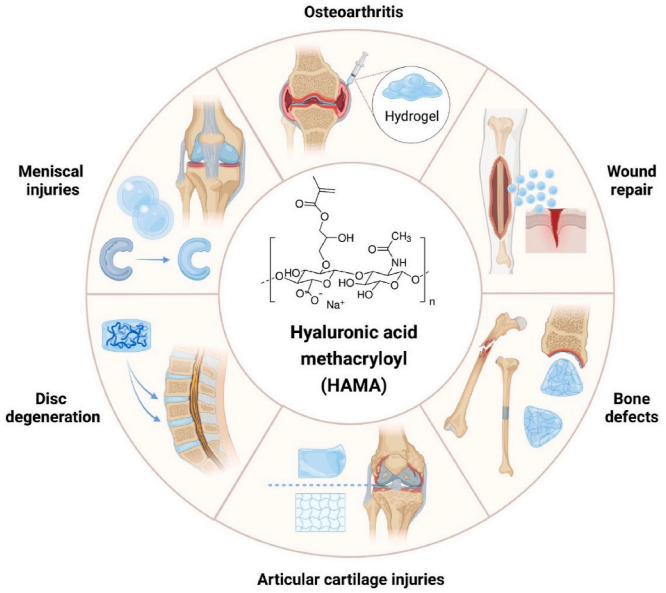

Fig. 2. Overview of HAMA hydrogels for orthopaedic diseases.

HAMA hydrogels, akin to the extracellular matrix (ECM), possess robust mechanical strength to serve as scaffolds for cartilage regeneration. In a study by Donagh GO'Shea et al. [57], two types of MeHA (MeHA-Col I/II and MeHA-Col II) were successfully configured in combination with Col I and Col II to address cartilage defects. The results revealed that MeHA-Col I/II, characterized by favorable mechanical properties, could serve as the preferred bioink. Conversely, MeHA-Col II demonstrated suitability for hydrogel injection due to enhanced formation of hydrogel-embedded MSC cartilage facilitated by the Col II inclusion complex. This investigation underscores the versatility of HA and Col II hydrogels in delivering autologous cells and matrix components in a minimally invasive manner at the arthroscopic level, facilitating precise fabrication of three-dimensional bioprinted scaffolds tailored to the size of the defect, thereby promoting cartilage repair. In a study by Vishal Saxena et al. [58], the effect of hydrogels on cartilage injury repair was explored through chemical crosslinking using ammonium persulfate (APS) and N, N, N′, N′-tetramethyl ethylenediamine (TEMED) in a cell-compatible manner (APS/TEMED). The resultant HAMA hydrogel exhibited superior cell biocompatibility and biomechanical properties compared to conventional UV-crosslinked constructs. This HAMA hydrogel can be employed to prepare constructs with complex structures suitable for use as anatomically shaped artificial articular cartilage, offering novel prospects for the clinical application of hydrogel materials in extensive cartilage degradation. Anna Abbadessa et al. [59] utilized a partially methacrylated poly (HPMA--lac-PEG) triblock copolymer (M10P10) as a base material for hydrogel formation via chemical crosslinking. This hydrogel, when combined with HAMA hydrogel, exhibited a temperature-sensitive property, transitioning from an injectable liquid state in vitro to a solid gel in vivo. The results demonstrated the hydrogel could support chondrocyte growth and differentiation with excellent biocompatibility.

HAMA hydrogels can also serve as carriers for drugs or cells to augment its efficacy in cartilage repair. Kartogenin (KGN), a small non-protein compound, facilitates MSC homing and chondrocyte formation. However, KGN metabolizes quickly after injected into the articular cavity. Thus, Chen et al. [60] developed an injectable cellulose gelatin (CNC)/GelMA/HAMA hybrid hydrogel loaded with KGN/synthetic melanin nanoparticles (SMNPs). They demonstrated sustained KGN release from this system, promoting bone marrow MSC homing and chondrocyte differentiation, thereby fostering cartilage regeneration (Fig. 3C). In another study by Tsanaktsidou et al. [61], human mesenchymal stem cells (hMSCs) were implanted into MeHA hydrogel. It was observed that hMSCs could proliferate within the MeHA hydrogel, with an increase in DNA content and gene expression over the culture period, thus facilitating cartilage repair.

HAMA hydrogel holds promise as a material for cartilage repair when combined with other substances to form composite structures. In a study conducted by Lin et al. [62], mHA (HAMA) was integrated into mGL (GelMA) scaffolds, which were found to promote cartilage formation by activating crucial cell signaling pathways. Lin and colleagues concluded that incorporating an optimal ratio of mHA could enhance the biological properties of mGL scaffolds, fostering cartilage formation from hBMSCs. They determined that at a mGL/mHA ratio of 9:1 (%, w/v), hBMSC hypertrophy was minimized, glycosaminoglycan production was maximized, and the total volume slightly increased. To assess the repair efficacy, a cartilage defect model was established in the rabbit femoral groove and treated with mGL/mHA scaffolds. The implantation

Table 1
Application of HAMA hydrogels in cartilage repair.

Hydrogels	Fabrication methods	Cell types	Research stages	Biological functions	Reference
HAMA/GelMA	3D bioprinting	hMSCs	In vitro	Promoting chondrogenic differentiation.	[63]
Fibrous protein/HAMA/ BMAC	Photocrosslinking	MSCs/ HPCS	In vitro	Inducing the differentiation of MSCs into chondrocytes and promoted cartilage repair.	[64]
HAMA	Physical crosslinking	hMSCs/ EVs	In vitro/in vivo (rat)	Co-encapsulation of hMSCs and EVs in HAMA hydrogels to promote cartilage regeneration.	[65]
HAMA/pHPMA-lac/PEG	3D bioprinting	—	In vitro	Excellent mechanical properties and cytocompatibility.	[66]
25 % sulfated HAMA/GF	Photocrosslinking	hMSCs	In vitro	Promoting the migration of chondrocytes and generation of new ECM.	[67]
HAMA/N-Calmodulin mimetic peptide	Chemical crosslinking	hMSCs	In vitro/in vivo (nude mice)	Promoting chondrogenesis and cartilage formation.	[68]
HAMA (DL/FL pre-processing)	Photocrosslinking	MSCs	In vitro/in vivo (nude mice)	Chondroinductivity and mechanical stimulation showing a synergistic effect on cartilage regeneration.	[69]

BMAC: bone marrow concentrate; HPCS: human progenitor cells; EVs: Extracellular vesicles GF: growth factor; DL: Dynamic compression load; FL: free load.

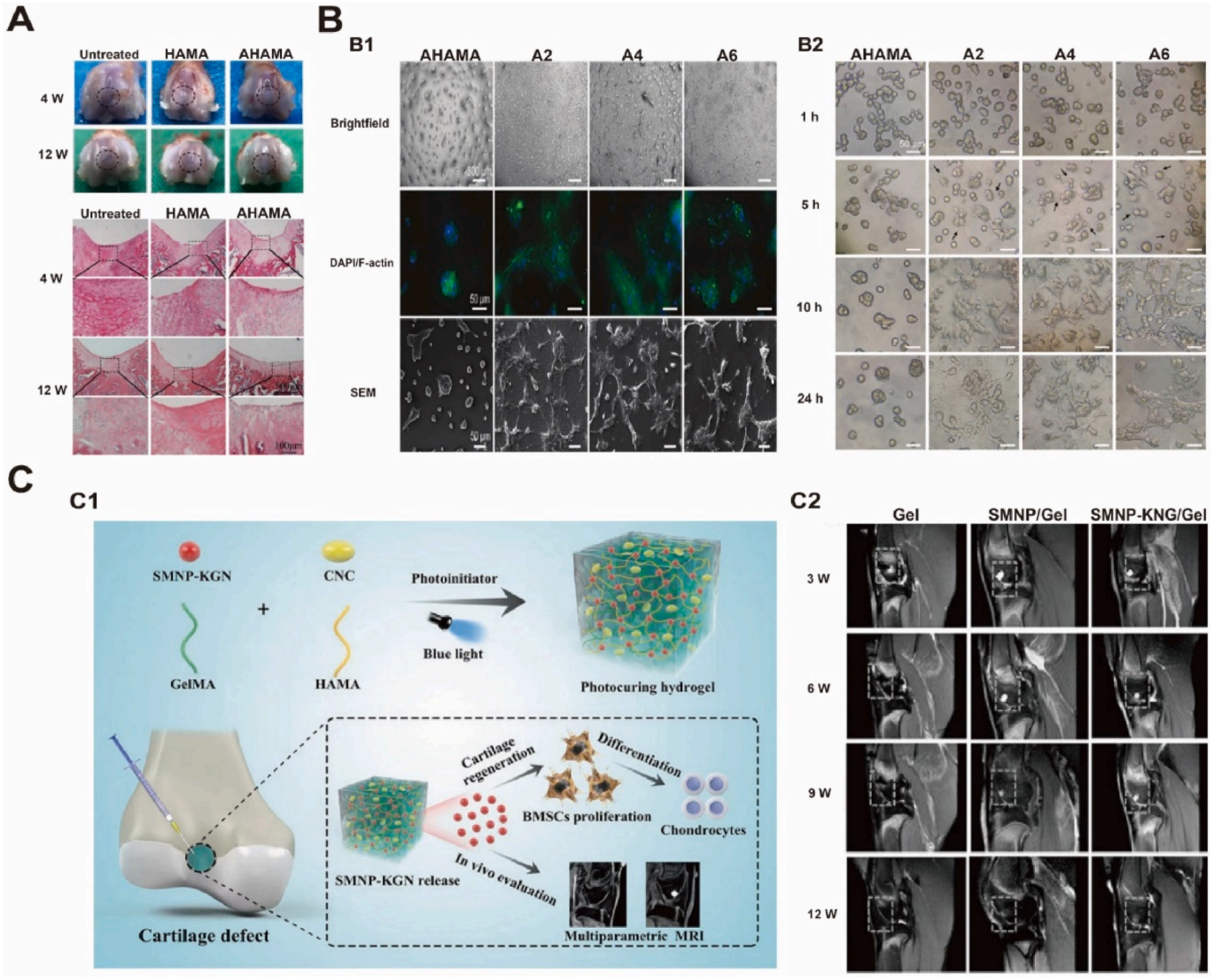

Fig. 3. HAMA hydrogels for articular cartilage injuries (A) Photos and H&E staining of cartilage after 4 and 12 weeks of AHMA hydrogel treatment in a rat osteochondral defect model. Reproduced and adapted with permission from Ref. [55]. Copyright 2021 Elsevier (B) Chondrocyte morphology in 2D culture from 1 h to 24 h. Optical microscopy images suggesting the formation of filopodia and cell aggregation at 1, 5, 10, and 24 h after cell seeding on AHAMA, A2, A4, and A6 hydrogels (the AHAMA-PBA was dissolved in PBS containing 0.2 % w/v I2959 with different concentrations of 2 %, 4 %, and 6 % w/v after UV curing, hydrogels were prepared via radical polymerization. The obtained hydrogels were designated as A2, A4, and A6, correspondingly; B1). Cell morphology of chondrocytes seeded on AHAMA-PBA hydrogels for 24 h (B2). Reproduced and adapted with permission from Ref. [56]. Copyright 2023 Wiley (C) Schematic illustration of preparation and functionalization of KGN loaded and SMNPs labeled multifunctional hydrogels for cartilage regeneration (C1). MR proton-density-weighted imaging (PDWI) for cartilage evaluation at 3, 6, 9, and 12 weeks after surgery (C2). Reproduced and adapted with permission from Ref. [60]. Copyright 2022 Wiley.

of mGL/mHA (9:1) structures successfully repaired the defect, indicating their potential for cartilage repair applications. Thus, HAMA hydrogels exhibit considerable potential in the realm of cartilage repair.

3.2. HAMA hydrogels for bone defects

Bone tissue, crucial for mobility and structural support, comprises cells, fibers, and a matrix [70]. Bone defects commonly arise from trauma, infection, and tumors, posing significant challenges to healing [71]. While small defects may self-heal, those surpassing a critical size present substantial hurdle [70]. Bone grafting, encompassing autologous and allogeneic approaches, is the prevailing treatment for substantial defects. Autologous grafting necessitates larger incisions, increasing the risk of infection, while allografting may face healing failure, low bioactivity, and immune rejection [72]. Traditional materials like ceramics and metals have limitations such as poor biocompatibility and low osteoinductivity [73,74].

The potential of HAMA hydrogels in bone repair has drawn growing attention (Table 2). HAMA hydrogels are often utilized in conjunction with other substances for bone defect repair. In a study by Wenz et al. [75], GelMA and HAMA-based hydrogels incorporated with hydroxyapatite (HAp) particles were utilized to encapsulate adipose-derived stem cells (ADSCs), yielding a novel bioink. The commendable mechanical properties of this bioink facilitate bone matrix formation, thereby promoting effective repair of bone defects. Arginine (Arg), known for its osteogenic activity and inhibition of osteoclast proliferation and activation, can be incorporated into hydrogels during bone defect repair. Zhou et al. [76] fabricated an arginine-based polyesteramide (Arg-PEA)/HAMA hybrid hydrogel via photocrosslinking of unsaturated Arg-PEA and HAMA. In both in vitro and in vivo assays, Col I, osteopontin (OPN), and bone morphogenetic protein 2 (BMP-2), crucial indicators of osteoblast genesis, exhibited significant intergroup differences across all three samples. Moreover, vascular organization observed in the Arg-PEA/HAMA group suggested its potential for bone repair (Fig. 4A). Ferrroni et al. [77] devised a composite scaffold by incorporating a MeHA-Hap bioactive layer into the pores of 3D-printed polyether ether ketone (PEEK) structures. UV crosslinking enhanced scaffold stability and retention time. This composite scaffold mimicked the nanocomposite structure of bone, with PEEK providing mechanical support, MeHA regulating tissue response as the ECM component, and HAp serving as the mineral component. The presence of the MeHA-HAp coating did not affect mechanical properties of PEEK. It notably improved surface hydrophilicity and biological behavior, facilitating cell adhesion, proliferation, and osteogenic differentiation.

Vascular restoration holds paramount importance in bone repair. Liu et al. [78] engineered a double crosslinked network utilizing HAMA and phenylbisabolylboronic acid. They integrated phosphatidylserine (PS) as a bridge to interact with copper-doped bioactive glass (CuBG), and further prepared the CuBG/PS/HAMA-PBA hydrogels. This hydrogel enhanced the expression of osteogenesis-related genes, promoted alkaline phosphatase (ALP) activity. Moreover, it could stimulate migration and proliferation of human umbilical vein endothelial cells (hUVECs), favoring angiogenesis. These findings indicated the promising osteogenic and angiogenic properties of the CuBG/PS/HAMA-PBA hydrogels, as validated in a rat cravarial defect model (Fig. 4B).

HAMA hydrogels are versatile scaffolds for loading drugs, cells, or proteins to address bone defects. Lu et al. [79] devised a novel hybrid hydrogel by blending GelMA, HAMA, and nanohydroxyapatite (nHap). They incorporated human neurogenic stem cell exosomes (USCEXOs) within the hydrogel for gradual release. This delivery system effectively transported USCEXOs to the bone defect and expedited bone regeneration. In vitro experiments demonstrated the composite hydrogel' could enhance osteogenic differentiation of hBMSCs and angiogenic capacity of endothelial precursor cells (EPCs). Subsequent in vivo trials revealed significantly increased expression of bone regeneration-associated proteins (e.g., RUNX-2 and OCN) and angiogenesis-related proteins (e.g., CD31 and EMCN). Thus, this hydrogel presents a promising approach for bone repair and angiogenesis in treating bone damage. Ma et al. [80] developed injectable hydrogels with stable mechanical properties (HA/γ-PGA hydrogels) through photopolymerization using HAMA and poly (γ-glutamic acid) (γ-PGA). HA/γ-PGA hydrogels exhibited excellent compression resistance and rapid shape recovery along with slow–release properties for loaded drugs. These results highlight the potential of HAMA hydrogels as an injectable drug delivery system for weight-bearing tissues, particularly in bone repair. Furthermore, Zhang et al. [81] fabricated a BMSCs-encapsulated hydrogel by photocrosslinking modified collagen, HAMA hydrogel, and BMSCs. This hydrogel system exhibited good injectability and precise control of cell distribution. Moreover, it promoted osteogenic differentiation of BMSCs without exogenous BMP-2 supplementation, offering a new strategy for bone repair.

The inherent low mechanical properties of hydrosols alone are not sufficed for effective bone repair. To address this limitation, researchers have explored the incorporation of materials such as nanohydroxyapatite (nHap) or polycaprolactone nanofibers (PCL NE) to bolster the mechanical strength of hydrogels. Zheng et al. [82] devised GelMA/HAMA/nHap hydrogels by uniformly dispersing nHap within a GelMA/HAMA network and employing photocrosslinking. The combination of this dual-network strategy with nHap integration significantly augmented the mechanical strength of the composite hydrogel. Its compressive elastic modulus was 20 times higher than that of the HAMA single-network hydrogel, with a compressive rupture strength of nearly 1 MPa. Moreover, the composite hydrogel maintained a high swelling ratio and water content (>88 %). Similarly, Patel and Koh [83] prepared a composite hydrogel by blending HAMA with PCL NE and embedding ADSCs within the hydrogel. Storage modulus measurements revealed an increase in modulus with the incorporation of nanofibers. Their study suggests that the resulting composite hydrogel, endowed with robust mechanical strength.

HAMA hydrogels can be enhanced by modulating certain signaling pathway in bone repair. Li et al. [84] engineered a 3D porous peptide-functionalized hyaluronic acid hydrogel by integrating a Wnt 5a mimetic ligand (Foxy 5 peptide) with MeHA hydrogel to augment mechanotransduction and osteogenesis of stem cells. They synthesized various MeHA hydrogels with distinct peptide sequences, including Foxy 5 peptide, RGD peptide, and Foxy 5 peptide with random

Table 2
Examples of HAMA hydrogels used for bone repair.

Hydrogels	Fabrication methods	Cell types	Research stages	Biological functions	Reference
HAMA/GelMA/HAp	Photocrosslinking	hASCs/ HDMECs	In vitro	Promoting bone matrix formation and angiogenesis.	[75]
HAMA/BMP-2	Photocrosslinking/3D bioprinting	MSCs	In vitro	Supporting the growth and differentiation of osteoblasts.	[86]
HAMA/N-calmodulin/ RGD peptide	Chemical crosslinking	hMSCs	In vitro/in vivo (nude mice)	Enhancing the osteogenic capacity of hMSCs to mimic the osteogenic microenvironment.	[87]
HAMA/GelMA/HAp	Physical crosslinking	ASCs	In vitro	Promoting the osteogenic differentiation and matrix mineralization of ASCs.	[88]

HDMECs:human dermal microvascular endo-thelial cells.

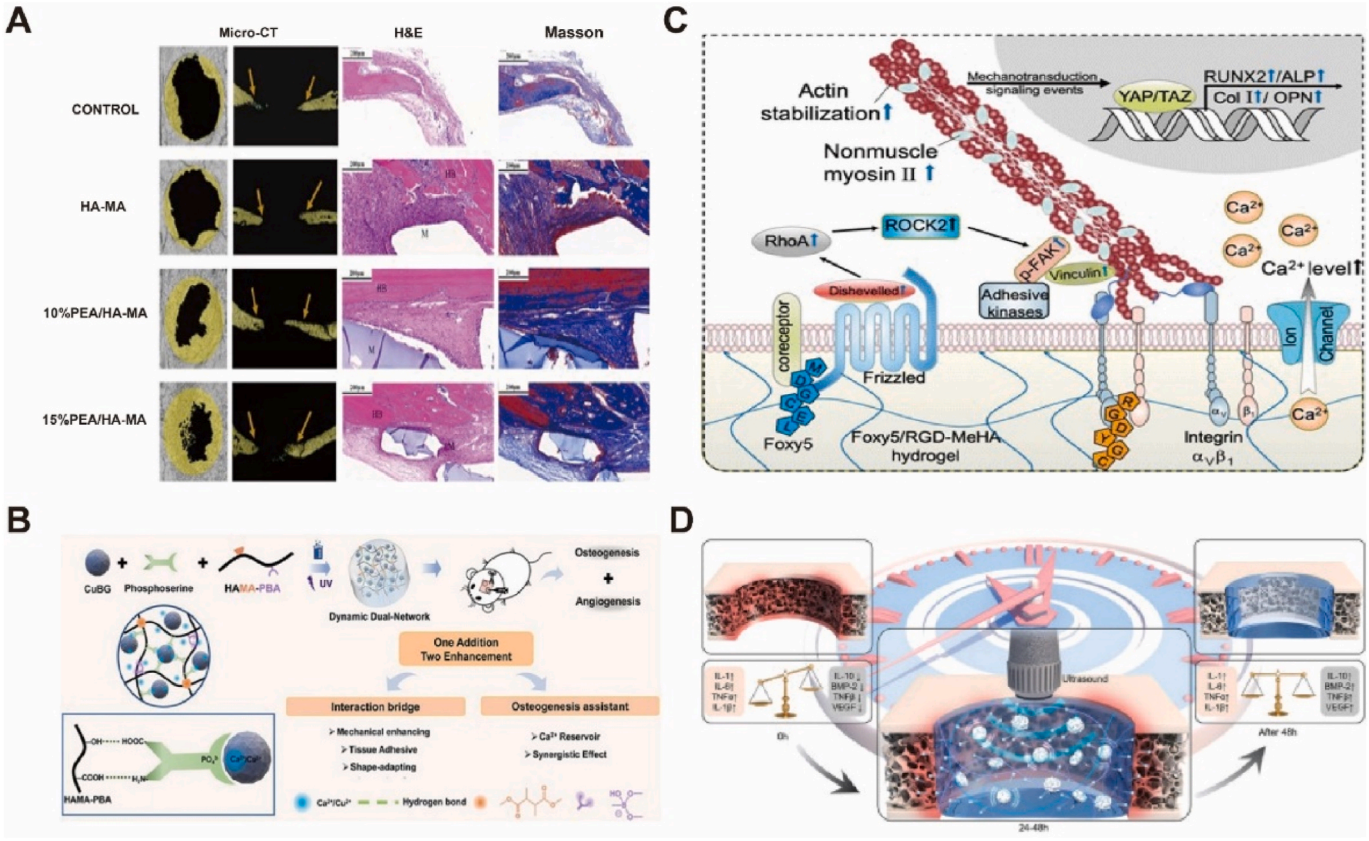

Fig. 4. HAMA hydrogels for bone defects (A) Bone repair using PEA/HA-MA or pure HA-MA hydrogels for one month in a rat calvarial defect model. Reproduced and adapted with permission from Ref. [76]. Copyright 2020 Elsevier (B) Schematic illustration of the preparation and application of CuBG/PS/HAMA-PBA hydrogels in bone regeneration. Reproduced and adapted with permission from Ref. [78]. Copyright 2023 Oxford University Press (C) Schematic illustration of the mechanism of Foxy5/RGD-MeHA hydrogels in bone repair. The hydrogels can activate RhoA signaling pathway and promote osteogenesis. Reproduced and adapted with permission from Ref. [84]. Copyright 2019 American Association for the Advancement of Science (D) UCE hydrogels (US@RES@GAHA) regulate the process of spatiotemporal disturbance of bone immunity. Reproduced and adapted with permission from Ref. [85]. Copyright 2023 Elsevier.

sequences, and assessed the expression levels of mechanotransduction-associated molecules in hMSCs cultured in Foxy 5 peptide-functionalized hydrogels via immunofluorescence staining. Experimental findings revealed that hMSCs in the Foxy 5 peptide-functionalized hydrogel group exhibited heightened expression of integrin αV, integrin β1, phosphorylated focal adhesion kinase (p-FAK), and ROCK2, pivotal factors in mechanotransduction mediation and stem cell osteogenesis promotion. Moreover, the Foxy 5 peptide-functionalized hydrogel group demonstrated a distinct advantage in a rat cranial defect model. HAMA hydrogel combined with immobilized Wnt 5a mimetic ligand activated nonclassical Wnt signaling, resulting in upregulation of Disheveled 2 and downstream RhoA-ROCK signaling. This cascade led to increased intracellular calcium levels, F-actin stability, actinomyosin contractility, and cellular adhesion development, promoting bone healing in vivo (Fig. 4C).

When evaluating the potential applications of HAMA hydrogel in bone repair, it is also essential to consider its role in modulating inflammation. Excessive inflammation leads to bone destruction and delays bone healing, whereas a moderate inflammatory response can promote tissue regeneration. Therefore, adjusting the anti-inflammatory properties of HAMA hydrogel to optimize the local microenvironment introduces a novel therapeutic strategy for promoting bone repair. Han et al. [85] engineered resveratrol@poly (lactic-co-glycolic acid) nanobubbles via double emulsification, integrating them with GelMA-HAMA hydrogels to form ultrasound-controlled explosive (UCE) hydrogels. Triggered by ultrasonic waves, these hydrogels released resveratrol to inhibit localized hyper-inflammatory responses. This precise modulation of temporal and spatial skeletal immunity disorders fosters bone defect repair (Fig. 4D).

Although HAMA hydrogel has been extensively studied in the fields of bone repair, its potential applications in various types of refractory bone defects remain a topic of significant interest for further investigation. For example, in cases of infected bone defect, HAMA hydrogel can be used as a drug carrier to enhance the local concentration of antibiotics, reduce infection rates, and facilitate tissue repair. In bone defects following tumor resection, HAMA hydrogel should be designed to not only promote bone repair, but also have anti-tumor ability to prevent tumor recurrence. Therefore, future research should explore the specific mechanisms and application strategies of HAMA hydrogel in different types of bone defects to fully realize its potential in bone tissue engineering.

3.3. *HAMA hydrogels for OA therapy*

Osteoarthritis (OA) is a chronic progressive joint disorder that leads to cartilage destruction, subchondral sclerosis, and formation of osteophyte. These changes result in joint pain, swelling, deformation, and dysfunction. Current non-surgical treatments include oral medications, physical therapy, and intra-articular injection of HA, while surgical procedures include arthroscopy and joint replacement [89]. However, non-surgical treatments only relief symptoms and cannot halt the progression of OA. Surgical treatments also have drawbacks. In addition to common surgical complications and postoperative rehabilitation, the long-term use of artificial joints faces challenges of loosening and wear [90]. Hence, tissue engineering is promising for OA treatment [91–93]. Since intra-articular injection of HA is already a clinical routine, its

derivative HAMA hydrogel has garnered attention in OA treatment.

Modulating macrophage activation is crucial for treating chronic inflammation in OA. Inspired by innate immunity, Xiao et al. [94] constructed immune cell-mobilized hydrogel microspheres using a microfluidic approach. These microspheres were loaded with chemokines, macrophage antibodies, and engineered cell membrane vesicles (sEVs) via covalent and non-covalent binding. The hydrogel microspheres, based on a mixture of streptavidin-grafted hyaluronic acid methacrylate (HAMA-SA) and chondroitin methacrylate sulfate (ChSMA), were designed to recruit, capture, and reprogram pro-inflammatory macrophages within the articular cavity, thereby ameliorating the inflammatory microenvironment of the joint (Fig. 5). In vitro experiments evaluated the macrophage reprogramming effect of the hydrogel microspheres. The results demonstrated that these microspheres exhibited excellent macrophage recruitment, capture, and reconditioning capabilities. Notably, the inflammatory M1 type macrophages were converted into anti-inflammatory M2 type macrophages with an efficiency of 88.5 %. In a rat OA model, the hydrogel microspheres were injected into the joints and demonstrated significant therapeutic effects, including a marked reduction in synovitis and cartilage matrix degradation. This study introduces new approaches for OA treatment.

It has been suggested that subcellular mitochondria significantly influence the fate of eukaryotic cells, thereby affecting the progression of OA. However, the dynamic regulation of mitochondrial biogenesis and degradation in impaired chondrocytes, as well as the specific role of mitochondrial metronome sirtuins 3 (SIRT3), remains unclear. Xia et al. [95] developed a dual-responsive hydrogel microsphere loaded with dihydromyricetin (DMY), a natural SIRT3 agonist, using microfluidics. This was achieved by utilizing the high levels of matrix protease and reactive oxygen species (ROS) present in the OA environment, enabling the microsphere to respond to both stimuli. They anchored GelMA and phenylenediboronic acid (PBA) onto HAMA to obtain DMY@HAMA-GelMA-PBA (termed DMY@HGP). Intra-articular

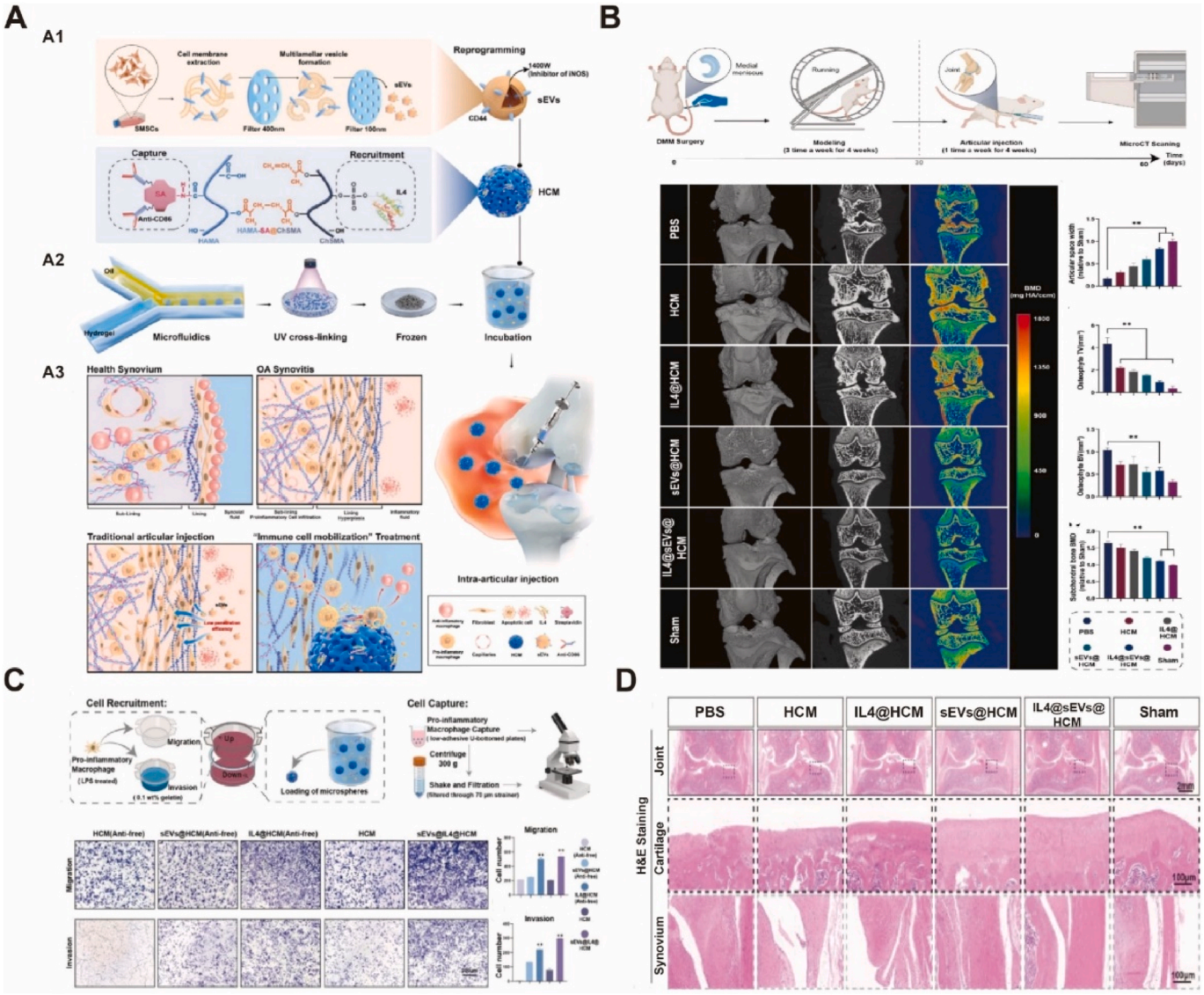

Fig. 5. HAMA hydrogels for OA therapy (A) Schematic diagram of the preparation of immune cell mobilized hydrogel microspheres. The extrusion method to prepare engineered sEVs derived from SMSCs (A1); The microfluidic method to construct streptavidin grafted HAMA-SA and ChSMA microspheres (A2); Intra-articular injection of the sEVs@IL4@HCM hydrogels for OA therapy (A3) (B) Micro-CT scanning indicated that sEVs@IL4@HCM hydrogel microspheres protected bone structure of OA rat models (C) The sEVs@IL4@HCM hydrogel microspheres enhanced the migration ability of macrophages, and then captured and reprogramed them (D) The sEVs@IL4@HCM hydrogels promoted cartilage repair of rat OA models. Reproduced and adapted with permission from Ref. [94]. Copyright 2024 Elsevier.

injection of DMY@HGP efficiently reduced cartilage erosion and subchondral bone sclerosis in a post-traumatic OA model. DMY@HGP promoted motor function recovery by restoring endogenous mitochondrial apoptosis and mitochondrial autophagy homeostasis. In a related study, Xia et al. [96] prepared chitosan microspheres embedded with cordycepin (CM-cordycepin). Cordycepin is the main active ingredient in *Cordyceps militaris*, a new nucleoside drug, and the first nucleoside antibiotic isolated from fungi. Recent studies found that cordycepin inhibited the expression levels of a disintegrin and metalloproteinase with thrombospondin motifs 5 (ADAMTS-5) and matrix metallopeptidase 13 (MMP13) in IL-1β-induced OA chondrocytes [97,98]. These microspheres were combined with HAMA hydrogels, enabling controlled release of cordycepin into the joint for OA treatment. The results indicated that cordycepin inhibited cartilage degradation, partly by activating autophagy of IL-1β-induced chondrocytes. The combination of CM-cordycepin microspheres with HAMA hydrogel delayed the progression of OA mice. Overall, HAMA-based hydrogels show potential as efficient tissue engineering materials for OA treatment.

3.4. HAMA hydrogels for meniscal injury

Meniscus is a fibrous cartilage nestled between the femoral condyles and tibia within the knee joint. It is pivotal for maintaining normal knee function though ensuring knee stability, absorbing shock, providing joint nutrition and lubrication, and contributing to proprioception [99]. Meniscal injuries, often stemming from knee sprains in young individuals or degeneration in older individuals, leading to OA [100,101]. The location of injury determines its severity, with menisci classified into three zones based on blood supply: the red zone (well-supplied externally), red-white zone (less centrally supplied), and white zone (minimal internal blood supply) [102]. While lateral meniscal injuries in the red zone may self-repair, medial injuries in the white zone pose significant challenges [102]. Degenerative meniscal injuries are often managed nonsurgically, involving non-steroidal anti-inflammatory drugs (NSAIDs) or rehabilitation [103]. Surgical interventions, such as meniscectomy (partial or total resection) or meniscal repair, are typically required for most meniscal injuries. However, meniscectomy risks compromising joint integrity, destabilizing the joint, and exacerbating long-term knee issues [104,105].

Bahceioglu et al. [106] conducted an in vitro study to assess the supportive properties of various materials, including agarose inoculated with porcine fibrochondrocytes, GelMA, MeHA, GelMA-MeHA hybrid hydrogels, and 3D-printed polycaprolactone (PCL) scaffolds, for potential nerve regeneration in meniscal repair. Their investigation compared physical properties, compressive mechanical properties, scaffold microstructure, DNA content, and cell survival. The results indicated that agarose, GelMA, and MeHA exhibited superior support for meniscal regeneration in vitro compared to 3D-printed PCL scaffolds. Specifically, agarose and MeHA were deemed suitable for inner meniscus repair, while GelMA was more appropriate for outer meniscus repair (Fig. 6). Furthermore, Li et al. [107] optimized poly (ethylene glycol)-hydroxyapatite composites (PGHE) using PCL, HAMA, GelMA, and MECM to synthesize scaffolds. They encapsulated platelet-derived growth factor (PDGF-BB) and KGN within the PGHE scaffold and assessed its efficacy through in vitro experiments focusing on cell survival, value-added rate, cell adhesion, and morphology. Their dual drug-loaded artificial meniscal scaffold effectively promoted rabbit knee meniscus regeneration. Additionally, HAMA was observed to enhance the thermal stability of the constructs. In another study by Zihna et al. [108], GelMA and poly (ethylene glycol dimethacrylate) (PEGDMA) were crosslinked with decellularized meniscus tissues via an in-situ polymerization reaction. Subsequently, HAMA was introduced to create a novel GelMA/PEGDMA/HAMA hybrid (PGH-Hybrid). This hybrid hydrogel exhibited favorable mechanical properties and thermal stability, addressing concerns related to cellularization of meniscus tissue and enhancing its repair potential. These findings underscore the excellent prospects of HAMA-based composite hydrogels in meniscus repair.

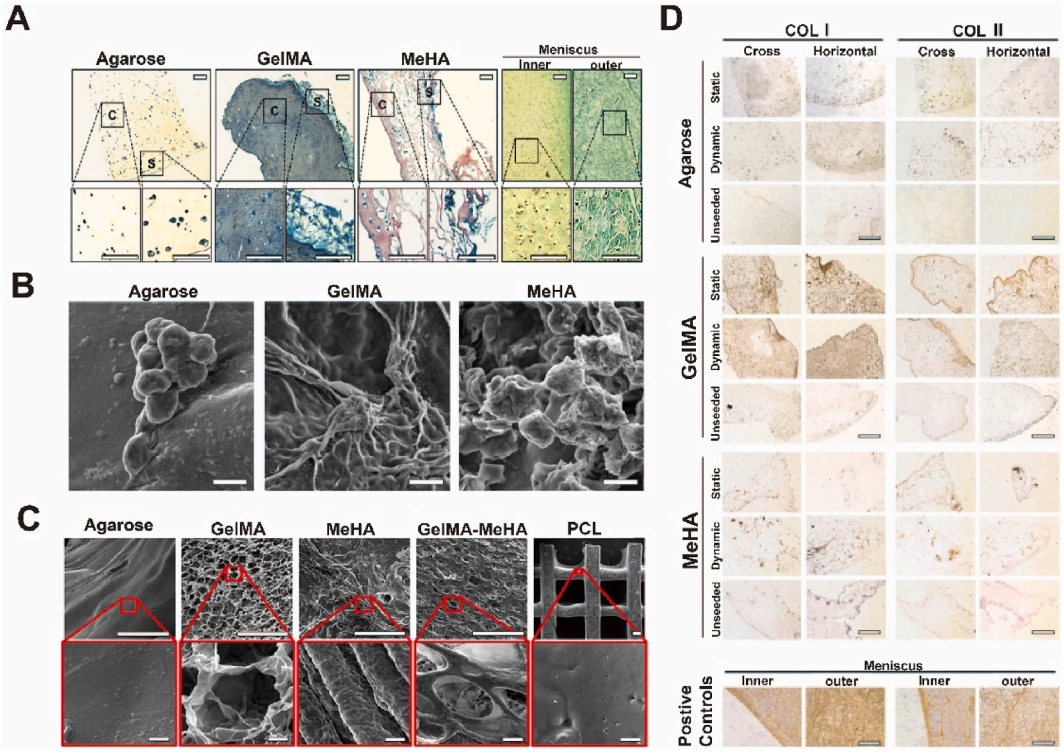

Fig. 6. Example of HAMA hydrogels used in meniscus repair (A) Regional differences in cell morphologies in the hydrogels (B) SEM images of the cells on the surface of hydrogels (C) Microarchitecture of the cell-free constructs after 35 days of culture (D) Immunohistochemistry staining of COL I and COL II expression in the hydrogels. Reproduced and adapted with permission from Ref. [106]. Copyright 2019 Elsevier.

3.5. HAMA hydrogels for intervertebral disc degeneration

Lower back pain (LBP) is a prevalent condition affecting individuals worldwide [109], with intervertebral disc degeneration (IVDD) being a primary cause [110]. The IVDD can arise from various factors such as genetics, injury, chronic diseases, obesity, and cellular necrosis [111, 112]. However, IVD is devoid of blood vessels and lacks self-healing ability. Current treatments for IVDD depend on the severity of the condition and pain [113]. Conservative approaches encompass oral pain medication, localized pain relief, physical therapy, and back muscle strengthening, which often provide relief but are prone to recurrence. Surgical interventions, like lumbar fusion, fuse adjacent vertebrae,

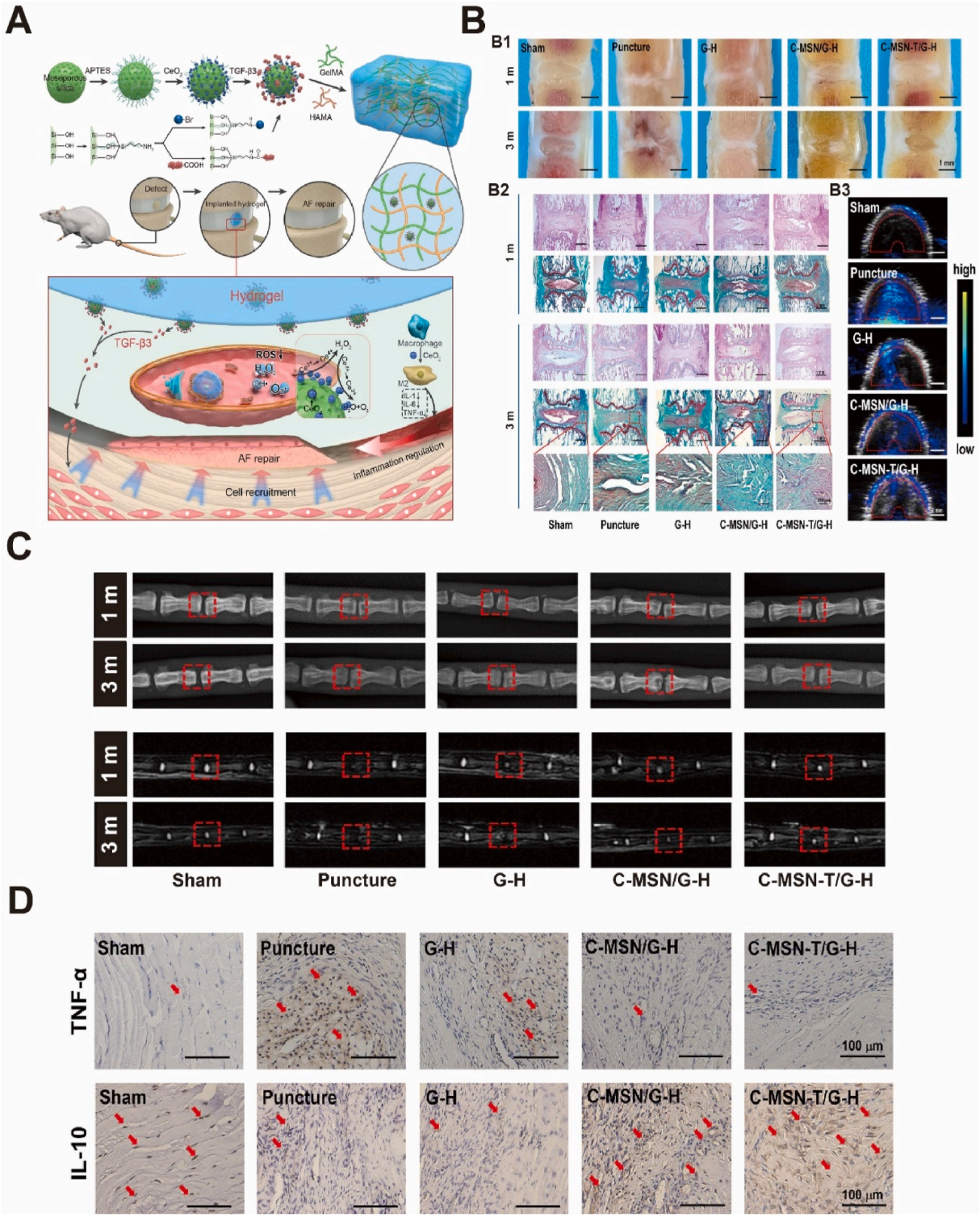

Fig. 7. HAMA hydrogels for disc degeneration (A) Schematic illustration of the composite C-MSN-T/G-H hydrogels for IVDD (B) Photos, H&E staining, SO/FG staining, and PA images of IVD after hydrogel treatment (C) X-ray and MRI images of the rat tail disc (marked by red wireframe) (D) Immunohistochemistry staining of TNF-α and IL-10 after different treatments. Reproduced and adapted with permission from Ref. [123]. Copyright 2023 American Chemical Society. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

yielding effective outcomes but with the risk of recurrence [114,115]. While both conservative and surgical treatments are essential, innovative approaches are warranted, including restorative methods utilizing natural or eco-friendly synthetic materials, biological therapies, gene therapy, etc [116–119]. The dysfunction of the annulus fibrosus (AF) stands as a crucial pathological change in IVDD, directly leading to nucleus pulposus (NP) protrusion. This event triggers the release of inflammatory factors and nerve root and spinal cord compression. Despite its significance, reconstructing the AF faces limitations due to an incomplete understanding of AF biology [120,121].

Wang et al. [122] identified a novel cell population, fibrocartilaginous-like fibrocyclic cells, capable of collagen I and collagen II synthesis, potentially serving in AF reconstruction. The authors developed a composite hydrogel comprising sericin methyl (SFMA) and HAMA, leveraging the dual nature of the fibrocyclic ring extracellular matrix. They supplemented the composite hydrogel with a fibrochondrocyte-like cell induction factor (FCI) to facilitate differentiation. Subsequently, annulus fibrosus stem cells were loaded into the novel composite hydrogel to address AF defects. The results revealed a 31.7 % restoration of chondrocyte-like matrix in the AF region, underscoring the potential of the composite hydrogel in AF repair and offering insights for IVDD treatment. AF injuries precipitate heightened levels of reactive oxygen species (ROS), inflammation, and impaired tissue regeneration, creating an unfavorable microenvironment for AF repair. Han et al. [123] developed a nanoparticle-loaded GelMA/HAMA composite hydrogel integrating antioxidant, anti-inflammatory, and AF cell recruitment functionalities by incorporating mesoporous silica nanoparticles (MSNs) modified with cerium dioxide (CeO_2) and transforming growth factor β3 (TGF-β3) into the hydrogel (C-MSN-T/G-H). This approach aimed at modulating the microenvironment rather than pathologically repairing scar tissue. As anticipated, the composite hydrogel effectively mitigated ROS and induced anti-inflammatory M2-type macrophage polarization. Furthermore, the released TGF-β3 served as an AF cell recruiter, promoting extracellular matrix (Fig. 7). MSC therapy is currently undergoing clinical trials for IVDD treatment [124]. Chen et al. [125] utilized GelHA, derived from HAMA and GelMA through photocrosslinking, combined with ADSCs to reconstruct the intervertebral disc. In vitro experiments demonstrated the hydrogel's efficacy in modulating the integrin αvβ6-TGF-β1 pathway, prompting ADSCs toward NP-like differentiation. Evaluation in a rat model showcased the efficacy of GelHA hydrogel combined with ADSCs in promoting stem cell proliferation and differentiation, thereby facilitating IVDD repair.

4. Applications of HAMA hydrogels in other diseases related to orthopaedics

4.1. HAMA hydrogels for other diseases

HAMA hydrogels show promising potential in the treatments of various orthopaedic injures such as nerve, muscle, and soft tissue. Among these, spinal cord injury stands out as a significant neurological condition lacking effective treatment options. Xin et al. [126] devised imine-crosslinked aldehyde hyaluronic acid methacrylate-hyaluronic acid/collagen hybrid hydrogel microfibers for encapsulating interleukin 4 (IL-4) loaded ZIF-8 nanoparticles (IL4@ZIF-8 NPs). Both in vitro and in vivo studies corroborated that the hydrogels achieved synergistic effects of neural induction and neuroprotection, thereby accelerating spinal cord injury repair. The nanostructured and viscoelastic characteristics of the hydrogel fibers hold promise in promoting nerve regeneration, suppressing inflammation and glial scarring, and augmenting endogenous neuronal differentiation, axonal regeneration, synaptic regeneration, and myelin sheath regeneration.

Following major surgeries like laminectomy, scarring between the dura mater and adjacent tissues is unavoidable. Extensive epidural fibrosis emerges as the primary culprit behind postoperative failed surgery syndrome, leading to compromised nerve root mobility and severe pain. Ji et al. [127] screened the appropriate doses of pirfenidone (PFD), known for its antifibrotic properties attributed to the inhibition of collagen formation, and prepared PFD-loaded HAMA hydrogels. The preventive efficacy of the HAMA hydrogel against epidural fibrosis was investigated utilizing a spinal cord surgery model. The results unveiled the PFD loaded HAMA hydrogel significantly mitigate epidural fibrosis while ensuring sustained drug release. Histological analyses confirmed the impact of the hydrogels on epidural fibrosis and collagen synthesis. Remarkably, the results demonstrated a notable reduction in epidural fibrosis and collagen regeneration. This formulation effectively curbed cell infiltration, suppressed the expression of type Col I/Col III, and impeded adhesion formation. Moreover, the PFD loaded HAMA hydrogels exhibited both pharmacological and physical barrier effects.

Tendon repair poses a significant clinical challenge, primarily due to the unique characteristics of tendon tissue. Tendons exhibit poor vascularization and limited self-repair capacity, leading to slow and incomplete healing after injury [128]. Additionally, the complex histological structure of tendons requires that any repair material offers adequate mechanical support without compromising the tissue's biological function. However, current repair techniques, such as surgical suturing or grafting, often fail to fully restore the tendon's original strength and function. Postoperative complications, including scarring, fibrosis, and re-injury, are common and often lead to impaired function or incomplete recovery [129]. Ji et al. [130] addressed this issue by developing a hydrogel comprising light-cured gelatin/hyaluronic acid (GelMA/HAMA) bi-network gel (GH) incorporated with nano clay (NC) and loaded with BMSCs. This bioimplant was found to promote the deposition of fibrocartilaginous proteins and bone morphogenetic protein 2, enhancing the mechanical strength of the tendon–bone interface. Moreover, the gradient change of NC within GH effectively mimicked the structure of natural attachment points, facilitating long-term culture and embedding of BMSCs while providing biological signals to promote the gradient osteogenic differentiation of cells. Consequently, the combination of BMSCs and gNC@GH proved effective in promoting the regeneration of the fibrocartilage layer at the tendon–bone interface and inhibiting fat infiltration. Huang et al. [131] developed a double-crosslinked injectable hydrogel comprising methacrylamide-amidated oxidized hyaluronic acid (MOHA) and muscle decellularized matrix (MDM). Their findings demonstrated that the MOHA/MDM hydrogel enhanced the proliferation of mouse myoblasts (C2C12 cells) and facilitated muscle differentiation. In a rat muscle injure model, it exhibited favorable biomechanical properties and facilitated muscle regeneration. Under ischemic conditions, local lactate accumulation significantly impedes tissue repair and regeneration. To address this challenge, Shen et al. [132] devised injectable lactate-depleted microspheres (MS@MCL) by chemically grafting manganese dioxide (MnO_2)-lactate oxidase (LOX) composite nanoenzymes onto HAMA microspheres. This approach achieved the prolonged pro-oxidative lactate depletion effects and an extended in vivo half-life. Functionalized with nanoenzymes, the injectable MS@MCL significantly enhanced the regeneration and repair of ischemic tissues by effectively processing the enriched lactate in the local microenvironment (Table 3).

4.2. HAMA hydrogels for wound healing

The incidence of high-energy injuries and related open fractures continues to rise in orthopaedic diseases. Open fractures not only damage the bone but also cause severe soft tissue injury, exposing the wound to the external environment and significantly increasing the risk of infection [139,140]. Infection can delay bone healing and lead to serious complications, such as osteomyelitis, which can impede overall patient recovery. Moreover, incision healing following orthopaedic surgery cannot be overlooked. Effective wound care can reduce the incidence of postoperative infections, promote tissue regeneration, and accelerate patient recovery [141,142]. Therefore, incorporating

Table 3
HAMA hydrogels in the applications of other diseases related to orthopaedics.

Hydrogels	Diseases	Fabrication methods	Research stages	Biological functions	reference
HAMA/EGCG/PBA	Oxidative stress and inflammation	Chemical crosslinking	In vitro	Scavenging free radicals and relieving oxidative stress.	[133]
HAMA/CMCMA	Meningeal adhesion	Photocrosslinking	In vitro/in vivo (rabbit)	Good biocompatibility, degradability, and mechanical strength. Reducing cell adhesion and penetration to inhibit meningeal adhesion.	[134]
HAMA/CCNP/SF	Osteosarcoma	Photocrosslinking/Physical crosslinking	In vitro	Dual function for osteosarcoma treatment and bone repair.	[135]
PDA NPs/HAMA	Adhesions occur after nerve injury and surgery	Photocrosslinking	In vitro/in vivo (rat)	Reducing nerve adhesions, promoting nerve regeneration, and restoring nerve function.	[136]
HAMA/SF	Musculoskeletal system	Photocrosslinking	In vitro	Excellent mechanical strength and biocompatibility for 3D printing of customized functional scaffolds.	[137]
lleganHAMA/Col I/Col I	Neurological damage	Physical crosslinking/photocrosslinking/3D bioprinting	In vitro	Creating in vitro test beds that incorporate regeneration-promoting growth factors in neural repair processes.	[138]

EGCG: Epigallocatechin-3-gallate; CMCMA: carboxymethyl cellulose methacry-late; SF: Filipin protein; CCNP: Curcumin chitosan nanoparticles; PDA: polydopamine nanoparticles.

innovative wound repair strategy into orthopaedic treatment will improve the overall healthcare. Current conventional wound treatment options encompass cleansing, disinfection, wound patches, dressings, suturing and closure, antibiotic therapy, healing enhancers, physiotherapy, and surgical intervention [143,144]. However, these methods often fail to maintain a moist wound environment, contrary to the recommended wet healing approach. Wet healing entails utilizing specialized dressings or medications to sustain a moist wound environment, safeguard the wound, foster cellular regeneration, and manage wound secretions [145,146]. Hydrogels, with their hydrophilic three-dimensional crosslinked network, closely resemble the structure and composition of the natural extracellular matrix, boasting a water content of 70–90 %. Consequently, they stand as a promising material for wound repair, offering a moist environment for wounds and adeptly absorbing tissue exudates. Moreover, hydrogels can serve as carriers for drugs and other wound-healing factors [147–149].

In recent studies, scientists have explored the potential of HAMA hydrogels for treating skin injuries. HAMA hydrogels promote wound healing through various pathways: (1) serving as 3D-printed bioink at the injury site; (2) fostering skin vascular regeneration at the injury site; (3) suppressing inflammatory responses at the wound site; and (4) synergizing with other factors to enhance wound healing. Hao et al. [150]employed a novel approach to cross-link thermosensitive thiolated Pluronic F127 (PF127-SH) with HAMA. They pre-crosslinked the two at low temperatures, followed by high-temperature suspension for self-assembly, and finally photo-crosslinked for 3D embedded bioprinting. This temperature-sensitive bio-ink boasts a unique step-by-step crosslinking mechanism, maintaining suitable viscosity during various printing steps. This enables the printing of complex structures with excellent shape fidelity while preserving cellular bioactivity and harnessing the properties of PF127-SH and HAMA. In vivo experiments revealed that the cell-bearing printed hydrogel significantly accelerated wound healing and re-epithelialization by modulating the inflammatory response as well as promoting collagen deposition and angiogenesis. In another study, Zhang et al. [151] isolated human adipose tissue-derived microvascular fragments (HaMVFs) and encapsulated them in a hybrid hydrogel composed of GelMA, HAMA, and fibrinogen for 3D bioprinting. The resultant hydrogel exhibited a high capacity for vessel formation and acceptable biocompatibility to support the growth of vascular fragments while possessing suitable mechanical properties. The efficacy of 3D bioprinted skin for wound healing was verified through transplantation of HaMVFs in vivo.

To promote angiogenesis in wound healing, Peng et al. [152] synthesized HAMA/poly (N-hydroxyethyl acrylamide) (PHEAA) hydrogels by UV initiation. The tissue adhesion ability of the hydrogels was assessed through adhesion experiments with animal tissues (such as the heart, liver, spleen, etc.) or pig skin. Both in vitro and in vivo experiment results indicated that the hydrogels facilitated wound healing processes, encompassing epithelialization, angiogenesis, and collagen deposition, while also exhibiting commendable tissue adhesion ability (Fig. 8A–B). Studies have demonstrated that incorporating metal ions, including Mg, Cu, and Zn [153–155], into the synthesis process of wound dressings can compromise bacterial integrity, disrupting the bacterial periplasm and leading to the production of oxygen radicals from oxygen, resulting in bacterial death. Ju et al. [156] developed double crosslinked gas-assisted microfluidic sodium alginate (ALG) and HAMA-based polysaccharide hydrogel microspheres for wound healing. These hydrogel microspheres were fabricated using a composite polysaccharide, with Zn^{2+} employed in the synthesis process to crosslink ALG and histidine-labeled vascular endothelial growth factor (His--VEGF). They assessed the capacity of dual crosslinked microspheres to release growth factors and enhance wound healing in a mouse model. The results indicated that upon loading with His-VEGF, the novel Zn^{2+}-induced composite polysaccharide hydrogel microspheres exhibited synergistic antimicrobial and angiogenic effects, effectively promoting wound healing (Fig. 8C–E).

During the initial phases of wound healing, inflammation represents a necessary and innate response of the immune system aimed at clearing infected and damaged cells, as well as foreign material from the wound site. This physiological process often induces local manifestations such as redness, swelling, warmth, pain, and partial loss of function, all of which are typical reactions to injury. However, prolonged or excessive inflammation can impede the healing process, resulting in delayed recovery, heightened scarring, and an elevated risk of infection [157,158]. Hence, the utilization of antimicrobials becomes imperative in facilitating effective wound repair. Microneedling (MN) stands as a cutting-edge medical technology enabling painless transdermal drug delivery through minimally invasive methods. Researchers have amalgamated MN with hydrogels to capitalize on their synergistic benefits [159]. For instance, Yao et al. [160] devised ZIF-8@MeHA-MNs by encapsulating the antimicrobial and biodegradable metal–organic-framework material ZIF-8 within MeHA hydrogels. This ensures the sustained release of Zn^{2+}, thereby enhancing the antimicrobial effect during wound healing. Moreover, the application of the MeHA hydrogel obviates the necessity for secondary surgery to remove the MN. Both in vivo and in vitro experiments have demonstrated that ZIF-8 encapsulated degradable MN arrays significantly accelerate epithelial regeneration, foster neovascularization, and promote wound healing. Ming et al. [161] encapsulated active lactic acid bacteria (*Lactobacillus reuteri*) within GelMA microspheres, followed by the synthesis of a hydrogel dressing (LRHA) through the covalent crosslinking of HAMA. This dressing effectively shields the bacteria from potential threats by

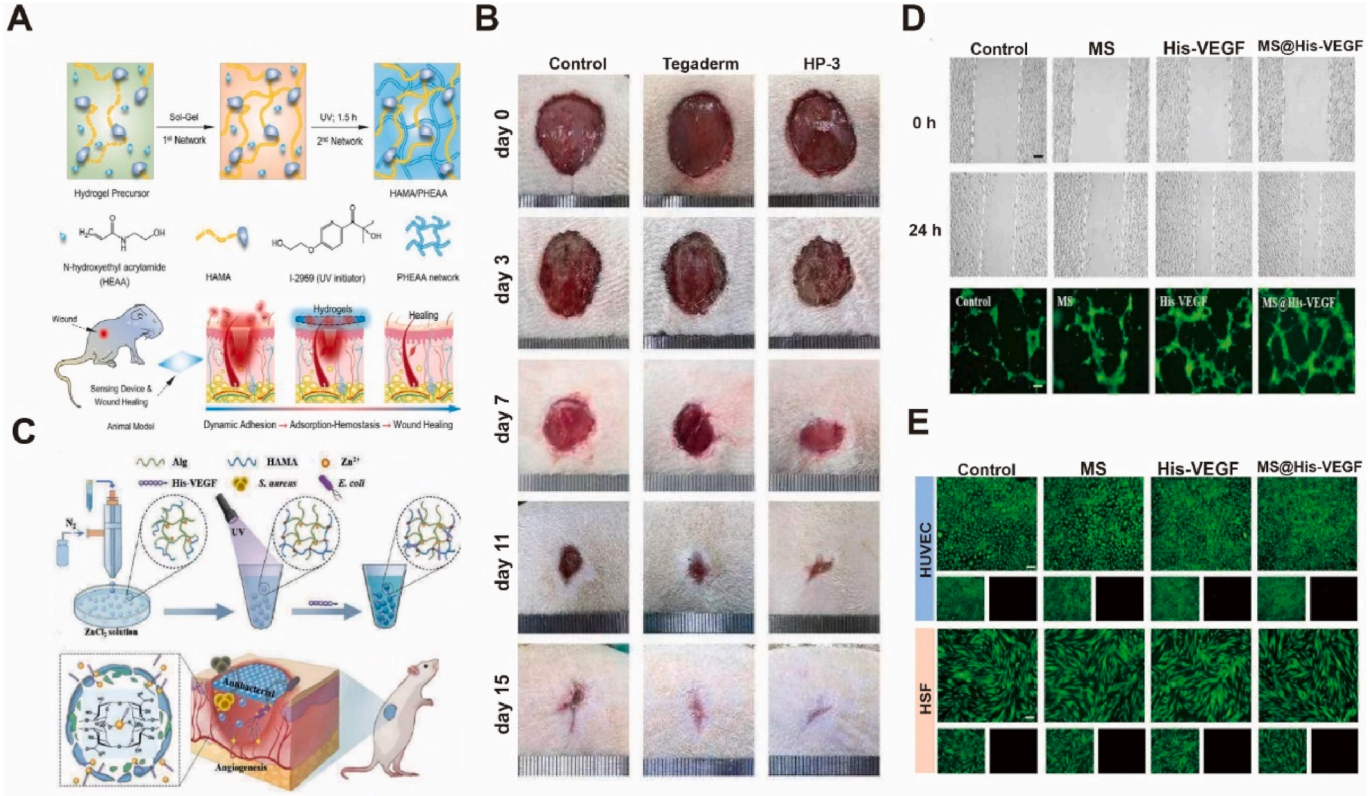

Fig. 8. HAMA hydrogels promote angiogenesis and accelerate wound healing (A) Schematic illustration of the synthesis for HAMA/PHEAA hydrogels as wound dressings (B) Healing of wounds after treated with hydrogels. Reproduced and adapted with permission from Ref. [152]. Copyright 2023 Frontiers (C) Zn^{2+} incorporated composite polysaccharide microspheres for sustained growth factor release and wound healing (D) Live/dead fluorescent images of HUVECs and HSF cells after culturing with different hydrogels for 3 days (E). HUVEC migration and tube formation in different hydrogel groups. Reproduced and adapted with permission from Ref. [156]. Copyright 2023 Elsevier.

insulating them from the immune system and preventing their release into the local environment. In vitro experiments indicated LRHA had antimicrobial activity against various bacteria. In vivo experiments demonstrated LRHA could diminish inflammatory cell infiltration, foster collagen deposition, and expedite wound healing. Silver is widely acknowledged for its robust antimicrobial properties. Massironi et al. [162] engineered a stable hydrogel by photocrosslinking silver nanoparticles (AgNPs) within HAMA. To fortify the silver hydrogel, cellulose nanocrystals (CNCs) and Ulva polysaccharides were incorporated. Huang et al. [163] developed a multifunctional hydrogel dressing, designated as HAMA-TPP-DMA, through redox-initiated crosslinking of HAMA with 5,10,15,20-tetrakis (4-methylphenyl methacrylate), porphyrin (TPP), and dopamine methacrylamide (DMA). This biodegradable hydrogel exhibited a broad-spectrum photodynamic antimicrobial activity. In vivo assays confirmed the efficacy of the HAMA-TPP-DMA hydrogel in resisting bacterial infection and expediting wound healing in a mouse model.

Stem cell therapy stands at the forefront of treatments aimed at accelerating skin regeneration. However, the challenge lies in the low survival rate of transplanted cells, attributed to inadequate protection during and after transplantation, resulting in diminished efficacy. To address this issue, Gong et al. [164] synthesized DA-MeHA hydrogels by crosslinking dopamine chloride with methacrylic anhydride HA. These hydrogels could tightly adhere to skin wound defects and enhance the viability of stem cells in skin regeneration therapies, facilitating skin regeneration in vivo. Wang et al. [165] introduced a flexible patch for wound healing involving self-conjugated anti-proteolytic hydrogel particles. The patch was fabricated by combining drug-loaded gelatin (GT) and carrageenan (CG) pre-gel, injected into an anti-opal scaffold comprising biocompatible HAMA and GelMA doped with graphene oxide quantum dots (GO QDs). Encapsulated antibiotics (amoxicillin) and vascular endothelial growth factors (VEGFs) were released from the hydrogel particles under near-infrared laser (NIR) irradiation. In vivo and in vitro experiments affirmed the biocompatibility, antimicrobial, and proangiogenic properties of the self-conjugated hydrogel particles. In a rat model of acute traumatic infection, the patch exhibited remarkable efficacy in promoting wound healing. These findings reveal the potential of HAMA hydrogels in wound repair.

5. Challenges and perspectives

The above-mentioned studies underscore the potential of HAMA hydrogel for treating orthopaedic diseases. However, several unresolved issues impede its clinical utilization. While HAMA is generally biocompatible, it may elicit mild immune reactions or inflammation in specific systems, emphasizing the imperative to enhance its biocompatibility. Moreover, despite exhibiting higher mechanical strength compared to other hydrogel materials, HAMA hydrogel may still prove inadequate in withstanding highly stressed biological environments, particularly in hard tissue repair scenarios involving complex and dynamic mechanical loads. Another challenge lies in regulating the degradation rate of HAMA hydrogels in vivo to maintain adequate structural support while ensuring timely degradation. The degradation of HAMA hydrogels degradation rate of HAMA hydrogels is strongly influenced by the degree of methacrylate esterification and the crosslink density [41]. The formation of a denser network structure, due to higher degrees of methacrylate substitution and cross-linking density, results in slower hydrogel degradation in vivo. Although this provides sufficient initial mechanical strength, a degradation rate that is too slow may cause the material to persist in the body for an extended period,

potentially interfering with normal tissue regeneration. The prolonged presence of foreign material may trigger a chronic inflammatory response, adversely affecting tissue integration and functional recovery. On the contrary, reducing the degree of methacrylation and cross-linking density accelerates HAMA hydrogel degradation [166]. However, if degradation occurs too quickly, it may lead to a rapid loss of mechanical strength and the essential support during critical phases of tissue repair. The lack of necessary mechanical support can result in incomplete bone regeneration and even pathological fracture. Additionally, the production of low molecular weight degradation products during the hydrogel breakdown process poses a significant concern. The small molecular fragments of methacrylated hyaluronic acid are released during the in vivo degradation of HAMA hydrogels. These degradation products may interact with surrounding cells and tissues, potentially inducing localized inflammatory or immune responses. The degradation products may activate macrophages and other immune cells, which are key mediators of foreign body reactions to implants. Activated macrophages release inflammatory mediators, such as tumor necrosis factor-alpha (TNF-α) and interleukin-1beta (IL-1β), which can disrupt normal tissue healing [167]. Furthermore, unreacted methacrylate groups or residual photoinitiators left in the hydrogel could provoke cytotoxic or inflammatory responses. If these compounds are not entirely removed during hydrogel synthesis and cross-linking, they may gradually release post-implantation, exacerbating adverse effects on the tissue. This may lead to apoptosis, cellular dysfunction, or negatively impact the quality and functionality of newly formed tissue [42].

To mitigate these challenges, optimizing the design and preparation of HAMA hydrogels is essential. Key considerations include: (1) Precise control of cross-linking density and methacrylation degree: By optimizing synthesis parameters, a balance between mechanical strength and degradation rate can be achieved, ensuring sufficient initial support while allowing the hydrogel to degrade within an appropriate timeframe to avoid long-term retention. (2) Purification processes: Effective purification techniques, such as dialysis or ultrafiltration, should be employed after hydrogel preparation to remove residual unreacted monomers and photoinitiators, reducing the toxicity and immunogenicity of the materials. (3) Modification of chemical structure: Introducing biodegradable cross-linking agents or hydrolyzable chemical bonds can control the nature and size of degradation products, reducing irritation to surrounding tissues. Additionally, incorporating natural enzyme-degradable linkages may ensure that the degradation products resemble physiological molecules. (4) Incorporation of anti-inflammatory components: Integrating anti-inflammatory agents or bioactive molecules, such as antioxidants or anti-inflammatory peptides, into the hydrogels can mitigate inflammatory responses triggered by the degradation process and facilitate tissue regeneration. (5) In vitro and in vivo evaluation: Enhancing systematic studies on the degradation behavior of HAMA hydrogels will allow for the evaluation of the biological effects of degradation products, including cytotoxicity, immunogenicity, and their impact on tissue healing. Such studies will guide material optimization and provide crucial information for assessing the safety of their clinical use.

Most importantly, HAMA hydrogels face significant challenges in moving from the laboratory to the clinic. First, the challenges of regulatory review. As a novel biomaterial, HAMA hydrogel must undergo a rigorous regulatory approval process before its clinical application. Comprehensive preclinical studies are required to obtain approval from regulatory agencies, including the National Medical Products Administration (NMPA) in China, the Food and Drug Administration (FDA) in the United States, and the European Medicines Agency (EMA). These studies encompass biocompatibility testing, toxicological evaluations, and functionality experiments, all aimed at demonstrating the material's safety and efficacy. Upon the completion of these studies, HAMA hydrogels must undergo a series of human clinical trials, typically in phases I, II, and III, to systematically validate their safety and efficacy in humans. This process is time-consuming, costly, and demands a high level of study design and data quality. Several key criteria must be met to gain regulatory approval. The first is the safety of the material's degradation products. Regulators must fully understand the chemical nature, biological effects, and metabolic and excretory pathways of these degradation products to ensure they do not cause toxic side effects in patients. Secondly, sterility and quality control are critical. As an implantable material, HAMA hydrogel must be manufactured using aseptic techniques and in compliance with Good Manufacturing Practices (GMP). Additionally, a rigorous quality control system must be in place to ensure product consistency and traceability between batches. These requirements impose stringent standards on the production process and quality management, further complicating the product's path to market. In China, the NMPA has established stringent regulatory standards for the approval of medical devices and biological materials. Applicants must submit detailed technical documentation and clinical trial data in accordance with the Regulations for the Supervision and Administration of Medical Devices and relevant technical guidelines. Moreover, applicants are required to demonstrate that their products meet national and industry standards by successfully completing registration tests. The regulatory process is complex and stringent, ensuring the safety of patients and the efficacy of the approved products.

Second, the challenges of large-scale production. Scaling up the production of HAMA hydrogels from laboratory to industrial scale presents a series of complex challenges. First and foremost is maintaining the purity of the product. In laboratory settings, reaction conditions can be precisely controlled to yield a highly pure product. However, in large-scale production, variations in raw materials and minor fluctuations in reaction conditions can impact the purity and performance of the final product. Additionally, ensuring consistent mechanical properties is crucial. The mechanical strength of hydrogels directly influences their clinical functionality, making it essential to maintain stable mechanical properties across batches. This requires precise control over parameters such as cross-linking degree, gelation time, and drying conditions during production. Moreover, large-scale production involves addressing issues such as equipment scaling, process optimization, and cost control to ensure an efficient and stable production process.

Third, the challenge of cost-effectiveness. Cost-effectiveness is a critical factor in the clinical adoption of HAMA hydrogels. While their synthesis is relatively straightforward and affordable in laboratory settings, the same cannot be said for large-scale industrial production. The specific chemical cross-linking agents (e.g., photoinitiators) and high-purity raw materials required for production are expensive and consumed in large quantities. The production process must comply with GMP standards, which involves the construction of clean rooms, significant investments in equipment, and rigorous quality control, all of which contribute to higher production costs. To make HAMA hydrogels economically viable for clinical use, strategies to reduce production costs or optimize the manufacturing process must be implemented. These strategies may include exploring alternative, more affordable cross-linking agents or raw materials, simplifying production steps, and improving process efficiency. Additionally, the cost per unit can be reduced by scaling up production, thus diluting fixed costs. If HAMA hydrogels can demonstrate significant advantages over existing treatments in terms of efficacy, reduced complications, and shorter recovery times, they could ultimately prove more cost-effective despite a higher initial price. This, however, would need to be substantiated through economic evaluations and clinical cost-benefit analyses.

The future of HAMA hydrogels in orthopaedic clinical applications appears highly promising. Future research should prioritize several key directions. For instance, the integration of 3D bioprinting technology presents new opportunities for the development of customized HAMA hydrogel implants. These implants can be precisely designed to meet specific anatomical structures and functional requirements based on individual patient needs and pathological conditions. Such highly personalized implants may improve repair outcomes and reduce rejection risks. Moreover, nanomaterials offer significant potential in bone

tissue regeneration, drug delivery, and controlled release. When incorporated into HAMA hydrogels, nanomaterials can enhance the material's mechanical strength and bioactivity, promoting osteoblast adherence, proliferation, and differentiation, while simultaneously enabling controlled drug release. Last but not least, the combination of smart materials can imbue HAMA hydrogels with dynamic response capabilities. By incorporating functional groups that respond to external stimuli such as temperature, pH, or mechanical stress, HAMA hydrogels can adjust their properties in real time, facilitating the controlled release of therapeutic agents or adapting their physical characteristics as needed. This adaptability is particularly valuable in complex in vivo environments, providing optimal support during various phases of tissue regeneration and environmental changes. Achieving these goals will require interdisciplinary collaboration, involving the integration of cutting-edge technologies and expertise from materials science, engineering, and biomedicine. Future research should focus on combining advanced technologies with HAMA hydrogels to ensure their continuous optimization in terms of performance and functionality, thereby meeting clinical demands.

6. Conclusions

This review presents an overview of the synthesis and applications of HAMA hydrogels. Specifically, recent research progress of HAMA hydrogels in orthopaedic diseases was highlighted. Currently, the use of HAMA hydrogels in orthopaedic diseases primarily involves three avenues: 3D scaffolds, drug carriers, and modulation of cell behavior. These approaches suggest the versatility and promising potential of HAMA hydrogels in addressing various challenges in orthopaedic healthcare. First, in tissue engineering, HAMA hydrogels serve as scaffolds to facilitate the regeneration of damaged tissue. These hydrogels enable the growth of specific cell types within them, which are then implanted at the site of tissue repair. Second, HAMA hydrogels function as a drug delivery system capable of controlling the release of therapeutic agents for treating various diseases. They can effectively load and deliver growth factors, cytokines, and other biologically active molecules that promote cell growth, differentiation, and tissue regeneration. Third, HAMA hydrogels provide a three-dimensional microenvironment that supports cell adhesion, growth, and differentiation. The structure of these hydrogels closely mimics the natural ECM, thus maintaining normal cell function and structure. Moreover, their chemical composition and physical properties can be modified to modulate cellular behaviors such as adhesion, migration, and differentiation, thereby promoting tissue repair. Last, a significant advantage of HAMA hydrogels lies in their tunable mechanical properties, which can be adjusted to suit the specific requirements of clinical applications, enabling the appropriate support and elasticity. The biodegradable nature of HAMA hydrogels ensures gradual uptake and replacement in vivo, which is essential for maintaining tissue integrity and promoting new tissue formation. With continued scientific and technological progress, HAMA hydrogels are expected to become an increasingly important treatment option for orthopaedic diseases.

Declaration of competing interest

None.

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References

[1] Stephenson MK, Farris AL, Grayson WL. Recent advances in tissue engineering strategies for the treatment of joint damage. Curr Rheumatol Rep 2017 Aug;19(8):44.
[2] World Health Organizaztion. Musculoskeletal health [internet] [cited 2022 Jul 14]. Available from: https://www.who.int/zh/news-room/fact-sheets/detail/musculoskeletal-conditions. [Accessed 15 December 2023].
[3] Dieleman JL, Baral R, Birger M, Bui AL, Bulchis A, Chapin A, et al. US spending on personal health care and public health, 1996-2013. JAMA 2016 Dec 27;316(24):2627–46.
[4] Perez S, Dauchy FA, Salvo F, Quéroué M, Durox H, Delobel P, et al. Severe adverse events during medical and surgical treatment of hip and knee prosthetic joint infections. Infect Dis Now 2021 Jun;51(4):346–50.
[5] Madry H. Surgical therapy in osteoarthritis. Osteoarthritis Cartilage 2022 Aug;30(8):1019–34.
[6] Dec P, Modrzejewski A, Pawlik A. Existing and novel biomaterials for bone tissue engineering. Int J Mol Sci 2022 Dec 28;24(1).
[7] Alvarez Echazú MI, Perna O, Olivetti CE, Antezana PE, Municoy S, Tuttolomondo MV, et al. Recent advances in synthetic and natural biomaterials-based therapy for bone defects. Macromol Biosci 2022 Apr;22(4):e2100383.
[8] Liu H, Su J. Organoid and organoid extracellular vesicles for osteoporotic fractures therapy: current status and future perspectives. Interdisciplinary Medicine 2023 Jul;1(3):e20230011.
[9] Li Y, Zhang H, Jiang Y, Yang J, Cai D, Bai X. The application of extracellular vesicles in orthopedic diseases. Interdisciplinary Medicine 2024 Jul;2(3):e20230055.
[10] Ho TC, Chang CC, Chan HP, Chung TW, Shu CW, Chuang KP, et al. Hydrogels: properties and applications in biomedicine. Molecules 2022 May 2;27(9):2902.
[11] Wichterle O, Lim D. Hydrophilic gels for biological use. Nature 1960 Jan;185:117–8.
[12] Varaprasad K, Raghavendra GM, Jayaramudu T, Yallapu MM, Sadiku R. A mini review on hydrogels classification and recent developments in miscellaneous applications. Mater Sci Eng C 2017 Oct 1;79:958–71.
[13] Manzini BM, Machado LMR, Noritomi PY, Da Silva JVL. Advances in Bone tissue engineering: a fundamental review. J Bio Sci 2021 Dec;46(1):17.
[14] Atesok K, Doral MN, Karlsson J, Egol KA, Jazrawi LM, Coelho PG, et al. Multilayer scaffolds in orthopedic tissue engineering. Knee Surg Sports Traumatol Arthrosc 2016 Jul;24(7):2365–73.
[15] Liu W, Madry H, Cucchiarini M. Application of alginate hydrogels for next-generation articular cartilage regeneration. IJMS 2022 Jan 20;23(3):1147.
[16] Chakraborty A, Alexander S, Luo W, Al-Salam N, Van Oirschot M, Ranganath SH, et al. Engineering multifunctional adhesive hydrogel patches for biomedical applications. Interdisciplinary Medicine 2023 Oct;1(4):e20230008.
[17] Lee BH, Lum N, Seow LY, Lim PQ, Tan LP. Synthesis and characterization of types A and B gelatin methacryloyl for bioink applications. Materials 2016 Sep 24;9(10):797.
[18] Muxika A, Etxabide A, Uranga J, Guerrero P, de la Caba K. Chitosan as a bioactive polymer: processing, properties and applications. Int J Biol Macromol 2017 Dec;105(Pt 2):1358–68.
[19] Yasmeen S, Lo MK, Bajracharya S, Roldo M. Injectable scaffolds for bone regeneration. Langmuir 2014 Nov 4;30(43):12977–85.
[20] Caliari SR, Burdick JA. A practical guide to hydrogels for cell culture. Nat Methods 2016 Apr 28;13(5):405–14.
[21] Zhang C, Cheng Z, Zhou Y, Yu Z, Mai H, Xu C, et al. The novel hyaluronic acid granular hydrogel attenuates osteoarthritis progression by inhibiting the TLR -2/NF-κB signaling pathway through suppressing cellular senescence. Bioengineering & Transla Med 2023 May;8(3):e10475.
[22] Bowman S, Awad ME, Hamrick MW, Hunter M, Fulzele S. Recent advances in hyaluronic acid based therapy for osteoarthritis. Clin Transl Med 2018 Dec;7(1):e6.
[23] Han C, Zhang H, Wu Y, He X, Chen X. Dual-crosslinked hyaluronan hydrogels with rapid gelation and high injectability for stem cell protection. Sci Rep 2020 Sep 14;10(1):14997.
[24] Spearman BS, Agrawal NK, Rubiano A, Simmons CS, Mobini S, Schmidt CE. Tunable methacrylated hyaluronic acid-based hydrogels as scaffolds for soft tissue engineering applications. J Biomed Mater Res 2020 Feb;108(2):279–91.
[25] Nejati S, Mongeau L. Injectable, pore-forming, self-healing, and adhesive hyaluronan hydrogels for soft tissue engineering applications. Sci Rep 2023 Aug 31;13(1):14303.
[26] Fan Y, Yue Z, Lucarelli E, Wallace GG. Hybrid printing using cellulose nanocrystals reinforced GelMA/HAMA hydrogels for improved structural integration. Adv Healthcare Mater 2020 Dec;9(24):e2001410.
[27] Ferroni L, Gardin C, D'Amora U, Calzà L, Ronca A, Tremoli E, et al. Exosomes of mesenchymal stem cells delivered from methacrylated hyaluronic acid patch improve the regenerative properties of endothelial and dermal cells. Biomater Adv 2022 Aug;139:213000.
[28] Kim YS, Guilak F. Engineering hyaluronic acid for the development of new treatment strategies for osteoarthritis. Int J Mol Sci 2022 Aug 4;23(15):8662.
[29] Bukhari SNA, Roswandi NL, Waqas M, Habib H, Hussain F, Khan S, et al. Hyaluronic acid, a promising skin rejuvenating biomedicine: a review of recent updates and pre-clinical and clinical investigations on cosmetic and nutricosmetic effects. Int J Biol Macromol 2018 Dec;120(Pt B):1682–95.
[30] Price RD, Myers S, Leigh IM, Navsaria HA. The role of hyaluronic acid in wound healing: assessment of clinical evidence. Am J Clin Dermatol 2005;6(6):393–402.

[31] Lv B, Lu L, Hu L, Cheng P, Hu Y, Xie X, et al. Recent advances in GelMA hydrogel transplantation for musculoskeletal disorders and related disease treatment. Theranostics 2023 Mar 27;13(6):2015–39.
[32] Zhang Y, Li Z, Wang Z, Yan B, Shi A, Xu J, et al. Mechanically enhanced composite hydrogel scaffold for in situ bone repairs. Biomater Adv 2022 Mar;134:112700.
[33] Shen C, Wang J, Li G, Hao S, Wu Y, Song P, et al. Boosting cartilage repair with silk fibroin-DNA hydrogel-based cartilage organoid precursor. Bioact Mater 2024 Feb 16;35:429–44.
[34] Schuurmans CCL, Mihajlovic M, Hiemstra C, Ito K, Hennink WE, Vermonden T. Hyaluronic acid and chondroitin sulfate (meth)acrylate-based hydrogels for tissue engineering: synthesis, characteristics and pre-clinical evaluation. Biomaterials 2021 Jan;268:120602.
[35] Bencherif SA, Srinivasan A, Horkay F, Hollinger JO, Matyjaszewski K, Washburn NR. Influence of the degree of methacrylation on hyaluronic acid hydrogels properties. Biomaterials 2008 Apr;29(12):1739–49.
[36] Pitarresi G, Pierro P, Palumbo FS, Tripodo G, Giammona G. Photo-cross-linked hydrogels with polysaccharide-poly(amino acid) structure: new biomaterials for pharmaceutical applications. Biomacromolecules 2006 Apr;7(4):1302–10.
[37] Yao SY, Shen ML, Li SJ, Wu XD, Zhang MM, Ma LN, et al. Application of a mechanically responsive, inflammatory macrophage-targeted dual-sensitive hydrogel drug carrier for atherosclerosis. Colloids Surf B Biointerfaces 2020 Feb;186:110718.
[38] A S, Zeng M, Johnson M, Creagh-Flynn J, Xu Q, Tai H, et al. Green synthetic approach for photo-cross-linkable methacryloyl hyaluronic acid with a tailored substitution degree. Biomacromolecules 2020 Jun 8;21(6):2229–35.
[39] Bobula T, Buffa R, Hermannová M, Kohutová L, Procházková P, Vágnerová H, et al. A novel photopolymerizable derivative of hyaluronan for designed hydrogel formation. Carbohydr Polym 2017 Apr 1;161:277–85.
[40] Kesti M, Müller M, Becher J, Schnabelrauch M, D'Este M, Eglin D, et al. A versatile bioink for three-dimensional printing of cellular scaffolds based on thermally and photo-triggered tandem gelation. Acta Biomater 2015 Jan;11:162–72.
[41] Burdick JA, Chung C, Jia X, Randolph MA, Langer R. Controlled degradation and mechanical behavior of photopolymerized hyaluronic acid networks. Biomacromolecules 2005 Jan-Feb;6(1):386–91.
[42] Bryant SJ, Nuttelman CR, Anseth KS. Cytocompatibility of UV and visible light photoinitiating systems on cultured NIH/3T3 fibroblasts in vitro. J Biomater Sci Polym Ed 2000;11(5):439–57.
[43] Wu J, Chen Q, Deng C, Xu B, Zhang Z, Yang Y, et al. Exquisite design of injectable hydrogels in cartilage repair. Theranostics 2020;10(21):9843–64.
[44] Miguel F, Barbosa F, Ferreira FC, Silva JC. Electrically conductive hydrogels for articular cartilage tissue engineering. Gels 2022 Nov 3;8(11):710.
[45] Muthu S, Korpershoek JV, Novais EJ, Tawy GF, Hollander AP, Martin I. Failure of cartilage regeneration: emerging hypotheses and related therapeutic strategies. Nat Rev Rheumatol 2023 Jul;19(7):403–16.
[46] Cong B, Sun T, Zhao Y, Chen M. Current and novel therapeutics for articular cartilage repair and regeneration. TCRM 2023 Jun;19:485–502.
[47] Lee DH, Kim SJ, Kim SA, Ju GI. Past, present, and future of cartilage restoration: from localized defect to arthritis. Knee Surg Relat Res 2022 Jan 28;34(1):1.
[48] Borrelli JJ, Olson SA, Godbout C, Schemitsch EH, Stannard JP, Giannoudis PV. Understanding articular cartilage injury and potential treatments. J Orthop Trauma 2019 Jun;33(Suppl 6):S6–12.
[49] Madry H, Grün UW, Knutsen G. Cartilage repair and joint preservation: medical and surgical treatment options. Dtsch Arztebl Int 2011 Oct;108(40):669–77.
[50] Trengove A, Di Bella C, O'Connor AJ. The challenge of cartilage integration: understanding a major barrier to chondral repair. Tissue Eng Part B 2022 Feb;28(1):114–28.
[51] Sheng R, Chen J, Wang H, Luo Y, Liu J, Chen Z, et al. Nanosilicate-Reinforced silk fibroin hydrogel for endogenous regeneration of both cartilage and subchondral bone. Adv Healthcare Mater 2022 Sep;11(17):e2200602.
[52] Feng H, Ang K, Guan P, Li J, Meng H, Yang J, et al. Application of adhesives in the treatment of cartilage repair. Interdisciplinary Medicine 2024 Sep;9:e20240015.
[53] Zheng K, Ma Y, Chiu C, Xue M, Zhang C, Du D. Enhanced articular cartilage regeneration using costal chondrocyte-derived scaffold-free tissue engineered constructs with ascorbic acid treatment. J Orthop Translat 2024 Mar 22;45:140–54.
[54] Koh RH, Jin Y, Kim J, Hwang NS. Inflammation-modulating hydrogels for osteoarthritis cartilage tissue engineering. Cells 2020 Feb 12;9(2):419.
[55] Chen J, Yang J, Wang L, Zhang X, Heng BC, Wang DA, et al. Modified hyaluronic acid hydrogels with chemical groups that facilitate adhesion to host tissues enhance cartilage regeneration. Bioact Mater 2021 Jun;6(6):1689–98.
[56] Liu Y, Yuan Z, Liu S, Zhong X, Wang Y, Xie R, et al. Bioactive phenylboronic acid-functionalized hyaluronic acid hydrogels induce chondro-aggregates and promote chondrocyte phenotype. Macromol Biosci 2023 Nov;23(11):e2300153.
[57] O'Connell CD, Di Bella C, Thompson F, Augustine C, Beirne S, Cornock R, et al. Development of the Biopen: a handheld device for surgical printing of adipose stem cells at chondral wound site. Biofabrication 2016 Mar 23;8(1):015019.
[58] Saxena V, Kim M, Keah NM, Neuwirth AL, Stoeckl BD, Bickard K, et al. Anatomic mesenchymal stem cell-based engineered cartilage constructs for biologic total joint replacement. Tissue Eng 2016 Feb;22(3–4):386–95.
[59] Abbadessa A, Mouser VHM, Blokzijl MM, Gawlitta D, Dhert WJA, Hennink WE, et al. A synthetic thermosensitive hydrogel for cartilage bioprinting and its biofunctionalization with polysaccharides. Biomacromolecules 2016 Jun 13;17(6):2137–47.
[60] Chen C, Huang S, Chen Z, Liu Q, Cai Y, Mei Y, et al. Kartogenin (KGN)/synthetic melanin nanoparticles (SMNP) loaded theranostic hydrogel scaffold system for multiparametric magnetic resonance imaging guided cartilage regeneration. Bioeng Transl Med 2023 Jan;8(1):e10364.
[61] Tsanaktsidou E, Kammona O, Labude N, Neuss S, Krüger M, Kock L, et al. Biomimetic cell-laden MeHA hydrogels for the regeneration of cartilage tissue. Polymers 2020 Jul 18;12(7).
[62] Lin H, Beck AM, Shimomura K, Sohn J, Fritch MR, Deng Y, et al. Optimization of photocrosslinked gelatin/hyaluronic acid hybrid scaffold for the repair of cartilage defect. J Tissue Eng Regen Med 2019 Aug;13(8):1418–29.
[63] Posniak S, Chung JHY, Liu X, Mukherjee P, Gambhir S, Khansari A, et al. Bioprinting of chondrocyte stem cell Co-cultures for auricular cartilage regeneration. ACS Omega 2022 Feb 22;7(7):5908–20.
[64] Li Y, Wang J, Tao R, Zhang X. Bone marrow concentration in combination with hyaluronan and fibrin for the treatment of primary and non-primary in orthopedic cases of osteochondral defects of the ankle. Cell Mol Biol (Noisy-le-grand) 2023 Sep 30;69(9):24–30.
[65] Cho WJ, Ahn J, Lee M, Choi H, Park S, Cha KY, et al. Combinatorial effect of mesenchymal stem cells and extracellular vesicles in a hydrogel on cartilage regeneration. Tissue Eng Regen Med 2023 Feb;20(1):143–54.
[66] Mouser VHM, Abbadessa A, Levato R, Hennink WE, Vermonden T, Gawlitta D, et al. Development of a thermosensitive HAMA-containing bio-ink for the fabrication of composite cartilage repair constructs. Biofabrication 2017 Mar 23;9(1):015026.
[67] Puiggalí-Jou A, Asadikorayem M, Maniura-Weber K, Zenobi-Wong M. Growth factor-loaded sulfated microislands in granular hydrogels promote hMSCs migration and chondrogenic differentiation. Acta Biomater 2023 Aug;166:69–84.
[68] Bian L, Guvendiren M, Mauck RL, Burdick JA. Hydrogels that mimic developmentally relevant matrix and N-cadherin interactions enhance MSC chondrogenesis. Proc Natl Acad Sci USA 2013 Jun 18;110(25):10117–22.
[69] Lin S, Lee WYW, Feng Q, Xu L, Wang B, Man GCW, et al. Synergistic effects on mesenchymal stem cell-based cartilage regeneration by chondrogenic preconditioning and mechanical stimulation. Stem Cell Res Ther 2017 Oct 3;8(1):221.
[70] Manzini BM, Machado LMR, Noritomi PY, Da Silva JVL. Advances in Bone tissue engineering: a fundamental review. J Biosci. 2021;46:17.
[71] Rodan GA. Introduction to bone biology. Bone 1992;13(Suppl 1):S3–6.
[72] Xue N, Ding X, Huang R, Jiang R, Huang H, Pan X, et al. Bone tissue engineering in the treatment of bone defects. Pharmaceuticals 2022 Jul 17;15(7).
[73] Ding Q, Zhang S, Liu X, Zhao Y, Yang J, Chai G, et al. Hydrogel tissue bioengineered scaffolds in bone repair: a review. Molecules 2023 Oct 12;28(20).
[74] Al Maruf DSA, Ghosh YA, Xin H, Cheng K, Mukherjee P, Crook JM, et al. Hydrogel: a potential material for bone tissue engineering repairing the segmental mandibular defect. Polymers 2022 Oct 5;14(19).
[75] Wenz A, Tjoeng I, Schneider I, Kluger PJ, Borchers K. Improved vasculogenesis and bone matrix formation through coculture of endothelial cells and stem cells in tissue-specific methacryloyl gelatin-based hydrogels. Biotechnol Bioeng 2018 Oct;115(10):2643–53.
[76] Zhou Y, Gu Z, Liu J, Huang K, Liu G, Wu J. Arginine based poly (ester amide)/hyaluronic acid hybrid hydrogels for bone tissue Engineering. Carbohydr Polym 2020 Feb 15;230:115640.
[77] Ferroni L, D'Amora U, Leo S, Tremoli E, Raucci MG, Ronca A, et al. PEEK and hyaluronan-based 3D printed structures: promising combination to improve bone regeneration. Molecules 2022 Dec 9;27(24).
[78] Liu Y, Wang G, Luo H, Zhao B, Liao M, Dai Q, et al. Phosphoserine enhanced Cu-doped bioactive glass dynamic dual-network hydrogel for craniofacial bone defect repair. Regen Biomater 2023;10:rbad054.
[79] Lu W, Zeng M, Liu W, Ma T, Fan X, Li H, et al. Human urine-derived stem cell exosomes delivered via injectable GelMA templated hydrogel accelerate bone regeneration. Mater Today Bio 2023 Apr;19:100569.
[80] Ma X, Liu S, Tang H, Yang R, Chi B, Ye Z. In situ photocrosslinked hyaluronic acid and poly (γ-glutamic acid) hydrogels as injectable drug carriers for load-bearing tissue application. J Biomater Sci Polym Ed 2018 Dec;29(18):2252–66.
[81] Zhang T, Chen H, Zhang Y, Zan Y, Ni T, Liu M, et al. Photo-crosslinkable, bone marrow-derived mesenchymal stem cells-encapsulating hydrogel based on collagen for osteogenic differentiation. Colloids Surf B Biointerfaces 2019 Feb 1;174:528–35.
[82] Zheng J, Wang Y, Wang Y, Duan R, Liu L. Gelatin/hyaluronic acid photocrosslinked double network hydrogel with nano-hydroxyapatite composite for potential application in bone repair. Gels 2023 Sep 13;9(9).
[83] Patel M, Koh WG. Composite hydrogel of methacrylated hyaluronic acid and fragmented polycaprolactone nanofiber for osteogenic differentiation of adipose-derived stem cells. Pharmaceutics 2020 Sep 22;12(9).
[84] Li R, Lin S, Zhu M, Deng Y, Chen X, Wei K, et al. Synthetic presentation of noncanonical Wnt5a motif promotes mechanosensing-dependent differentiation of stem cells and regeneration. Sci Adv 2019 Oct;5(10):eaaw3896.
[85] Han X, Shen J, Chen S, Cai Z, Zhu Y, Yi W, et al. Ultrasonic-controlled "explosive" hydrogels to precisely regulate spatiotemporal osteoimmune disturbance. Biomaterials 2023 Apr;295:122057.
[86] Poldervaart MT, Goversen B, de Ruijter M, Abbadessa A, Melchels FPW, Öner FC, et al. 3D bioprinting of methacrylated hyaluronic acid (MeHA) hydrogel with intrinsic osteogenicity. PLoS One 2017;12(6):e0177628.
[87] Zhu M, Lin S, Sun Y, Feng Q, Li G, Bian L. Hydrogels functionalized with N-cadherin mimetic peptide enhance osteogenesis of hMSCs by emulating the osteogenic niche. Biomaterials 2016 Jan;77:44–52.

[88] Wenz A, Borchers K, Tovar GEM, Kluger PJ. Bone matrix production in hydroxyapatite-modified hydrogels suitable for bone bioprinting. Biofabrication 2017 Nov 14;9(4):044103.
[89] Lv Z, Wang Z, Chen D, Shi D. Advances in osteoarthritis research: from diagnosis, treatment to mechanism studies. J Orthop Translat 2024 Feb 6;44:A4–6.
[90] Kolasinski SL, Neogi T, Hochberg MC, Oatis C, Guyatt G, Block J, et al. American college of rheumatology/arthritis foundation guideline for the management of osteoarthritis of the hand, hip, and knee. Arthritis Care Res 2019;72(2):149–62. 2020 Feb.
[91] Lu Y, Chen J, Li L, Cao Y, Zhao Y, Nie X, et al. Hierarchical functional nanoparticles boost osteoarthritis therapy by utilizing joint-resident mesenchymal stem cells. J Nanobiotechnol 2022 Feb 19;20(1):89.
[92] Cai Y, Wu C, Ou Q, Zeng M, Xue S, Chen J, et al. Enhanced osteoarthritis therapy by nanoengineered mesenchymal stem cells using biomimetic CuS nanoparticles loaded with plasmid DNA encoding TGF-β1. Bioact Mater 2023 Jan;19:444–57.
[93] Wang X, Cai Y, Wu C, Liang J, Tang K, Lin Z, et al. Conversion of senescent cartilage into a pro-chondrogenic microenvironment with antibody-functionalized copper sulfate nanoparticles for efficient osteoarthritis therapy. J Nanobiotechnol 2023 Aug 8;21(1):258.
[94] Xiao P, Han X, Huang Y, Yang J, Chen L, Cai Z, et al. Reprogramming macrophages via immune cell mobilized hydrogel microspheres for osteoarthritis treatments. Bioact Mater 2024 Feb;32:242–59.
[95] Xia X, Liu Y, Lu Y, Liu J, Deng Y, Wu Y, et al. Retuning mitochondrial apoptosis/mitophagy balance via SIRT3-energized and microenvironment-modulated hydrogel microspheres to impede osteoarthritis. Adv Healthcare Mater 2023 Sep;11:e2302475.
[96] Xia C, Chen P, Mei S, Ning L, Lei C, Wang J, et al. Photo-crosslinked HAMA hydrogel with cordycepin encapsulated chitosan microspheres for osteoarthritis treatment. Oncotarget 2017 Jan 10;8(2):2835–49.
[97] Ramesh T, Yoo SK, Kim SW, Hwang SY, Sohn SH, Kim IW, et al. Cordycepin (3'-deoxyadenosine) attenuates age-related oxidative stress and ameliorates antioxidant capacity in rats. Exp Gerontol 2012 Dec;47(12):979–87.
[98] Hu P, Chen W, Bao J, Jiang L, Wu L. Cordycepin modulates inflammatory and catabolic gene expression in interleukin-1beta-induced human chondrocytes from advanced-stage osteoarthritis: an in vitro study. Int J Clin Exp Pathol 2014 Sep 15;7(10):6575–84.
[99] Fox AJS, Wanivenhaus F, Burge AJ, Warren RF, Rodeo SA. The human meniscus: a review of anatomy, function, injury, and advances in treatment. Clin Anat 2015 Mar;28(2):269–87.
[100] Englund M, Guermazi A, Lohmander SL. The role of the meniscus in knee osteoarthritis:a cause or consequence? Radiol Clin 2009 Jul;47(4):703–12.
[101] Ozeki N, Koga H, Sekiya I. Degenerative meniscus in knee osteoarthritis: from pathology to treatment. Life 2022 Apr 18;12(4).
[102] Barber-Westin SD, Noyes FR. Clinical healing rates of meniscus repairs of tears in the central-third (red-white) zone. Arthroscopy 2014 Jan;30(1):134–46.
[103] Chirichella PS, Jow S, Iacono S, Wey HE, Malanga GA. Treatment of knee meniscus pathology: rehabilitation, surgery, and orthobiologics. Pharm Manag PM R 2019 Mar;11(3):292–308.
[104] Mordecai SC, Al-Hadithy N, Ware HE, Gupte CM. Treatment of meniscal tears: an evidence based approach. World J Orthoped 2014 Jul 18;5(3):233–41.
[105] Bansal S, Floyd ER, A Kowalski M, Aikman E, Elrod P, Burkey K, et al. Meniscal repair: the current state and recent advances in augmentation. J Orthop Res 2021 Jul;39(7):1368–82.
[106] Bahcecioglu G, Hasirci N, Bilgen B, Hasirci V. Hydrogels of agarose, and methacrylated gelatin and hyaluronic acid are more supportive for in vitro meniscus regeneration than three dimensional printed polycaprolactone scaffolds. Int J Biol Macromol 2019 Feb 1;122:1152–62.
[107] Hao L, Tianyuan Z, Zhen Y, Fuyang C, Jiang W, Zineng Y, et al. Corrigendum: biofabrication of cell-free dual drug-releasing biomimetic scaffolds for meniscal regeneration (2022Biofabrication14015001). Biofabrication 2021 Nov 30;14(1).
[108] Zihna G, Topuz B, Günal G, Aydin HM. Preparation of hybrid meniscal constructs using hydrogels and acellular matrices. J Biomater Sci Polym Ed 2023 Apr;34(5):587–611.
[109] Hong JY, Song KS, Cho JH, Lee JH, Kim NH. An updated overview of low back pain management. Asian Spine J 2022 Dec;16(6):968–82.
[110] Ying Y, Cai K, Cai X, Zhang K, Qiu R, Jiang G, et al. Recent advances in the repair of degenerative intervertebral disc for preclinical applications. Front Bioeng Biotechnol 2023 Sep 22;11:1259731.
[111] Ravichandran D, Pillai J, Krishnamurthy K. Genetics of intervertebral disc disease: a review. Clin Anat 2022 Jan;35(1):116–20.
[112] Guo W, Li BL, Zhao JY, Li XM, Wang LF. Causal associations between modifiable risk factors and intervertebral disc degeneration. Spine J 2024 Feb;24(2):195-209.
[113] Liu W, Ma Z, Wang Y, Yang J. Multiple nano-drug delivery systems for intervertebral disc degeneration: current status and future perspectives. Bioact Mater 2023 May;23:274–99.
[114] Verma R, Virk S, Qureshi S. Interbody fusions in the lumbar spine: a review. HSS J 2020 Jul;16(2):162–7.
[115] Harris IA, Traeger A, Stanford R, Maher CG, Buchbinder R. Lumbar spine fusion: what is the evidence? Intern Med J 2018 Dec;48(12):1430–4.
[116] Roh EJ, Darai A, Kyung JW, Choi H, Kwon SY, Bhujel B, et al. Genetic therapy for intervertebral disc degeneration. Int J Mol Sci 2021 Feb 4;22(4).
[117] Li QW, Guo RC, Wu ZM, Shen CL. Potential use of extracellular vesicles in the treatment of intervertebral disc degeneration. Tissue Eng C Methods 2024 Feb;30(2):73–84.
[118] Dou Y, Sun X, Ma X, Zhao X, Yang Q. Intervertebral disk degeneration: the microenvironment and tissue engineering strategies. Front Bioeng Biotechnol 2021;9:592118.
[119] Frauchiger DA, Tekari A, Wöltje M, Fortunato G, Benneker LM, Gantenbein B. A review of the application of reinforced hydrogels and silk as biomaterials for intervertebral disc repair. Eur Cell Mater 2017 Oct 24;34:271–90.
[120] Liu C, Gao X, Lou J, Li H, Chen Y, Chen M, et al. Aberrant mechanical loading induces annulus fibrosus cells apoptosis in intervertebral disc degeneration via mechanosensitive ion channel Piezo1. Arthritis Res Ther 2023 Jul 7;25(1):117.
[121] Ito K, Creemers L. Mechanisms of intervertebral disk degeneration/injury and pain: a review. Global Spine J 2013 Jun;3(3):145–52.
[122] Wang H, Wang D, Luo B, Wang D, Jia H, Peng P, et al. Decoding the annulus fibrosus cell atlas by scRNA-seq to develop an inducible composite hydrogel: a novel strategy for disc reconstruction. Bioact Mater 2022 Aug;14:350–63.
[123] Han F, Tu Z, Zhu Z, Liu D, Meng Q, Yu Q, et al. Targeting endogenous reactive oxygen species removal and regulating regenerative microenvironment at annulus fibrosus defects promote tissue repair. ACS Nano 2023 Apr 25;17(8):7645–61.
[124] Xin J, Wang Y, Zheng Z, Wang S, Na S, Zhang S. Treatment of intervertebral disc degeneration. Orthop Surg 2022 Jul;14(7):1271–80.
[125] Chen P, Ning L, Qiu P, Mo J, Mei S, Xia C, et al. Photo-crosslinked gelatin-hyaluronic acid methacrylate hydrogel-committed nucleus pulposus-like differentiation of adipose stromal cells for intervertebral disc repair. J Tissue Eng Regen Med 2019 Apr;13(4):682–93.
[126] Xin N, Liu X, Chen S, Zhang Y, Wei D, Sun J, et al. Neuroinduction and neuroprotection co-enhanced spinal cord injury repair based on IL-4@ZIF-8-loaded hyaluronan-collagen hydrogels with nano-aligned and viscoelastic cues. J Mater Chem B 2022 Aug 24;10(33):6315–27.
[127] Ji J, Cheng J, Chen C, Lu Y, Chen X, Zhang F. Pirfenidone-loaded hyaluronic acid methacryloyl hydrogel for preventing epidural adhesions after laminectomy. Drug Deliv Transl Res 2023 Mar;13(3):770–81.
[128] Voleti PB, Buckley MR, Soslowsky LJ. Tendon healing: repair and regeneration. Annu Rev Biomed Eng 2012;14:47–71.
[129] Thomopoulos S, Parks WC, Rifkin DB, Derwin KA. Mechanisms of tendon injury and repair. J Orthop Res 2015 Jun;33(6):832–9.
[130] Ji W, Han F, Feng X, Shi L, Ma H, Lu Y, et al. Cocktail-like gradient gelatin/hyaluronic acid bioimplant for enhancing tendon-bone healing in fatty-infiltrated rotator cuff injury models. Int J Biol Macromol 2023 Jul 31;244:125421.
[131] Huang Z, Cheng J, Su W. A double cross-linked injectable hydrogel derived from muscular decellularized matrix promotes myoblast proliferation and myogenic differentiation. Materials 2023 Jul 29;16(15).
[132] Shen J, Chen A, Cai Z, Chen Z, Cao R, Liu Z, et al. Exhausted local lactate accumulation via injectable nanozyme-functionalized hydrogel microsphere for inflammation relief and tissue regeneration. Bioact Mater 2022 Jun;12:153–68.
[133] He Z, Luo H, Wang Z, Chen D, Feng Q, Cao X. Injectable and tissue adhesive EGCG-laden hyaluronic acid hydrogel depot for treating oxidative stress and inflammation. Carbohydr Polym 2023 Jan 1;299:120180.
[134] Huang YC, Liu ZH, Kuo CY, Chen JP. Photo-crosslinked hyaluronic acid/carboxymethyl cellulose composite hydrogel as a dural substitute to prevent post-surgical adhesion. Int J Mol Sci 2022 May 31;23(11).
[135] Yu Q, Meng Z, Liu Y, Li Z, Sun X, Zhao Z. Photocuring hyaluronic acid/silk fibroin hydrogel containing Curcumin loaded CHITOSAN nanoparticles for the treatment of MG-63 cells and me3t3-E1 cells. Polymers 2021 Jul 14;13(14).
[136] Zhan Y, Zhou Z, Chen M, Gong X. Photothermal treatment of polydopamine Nanoparticles@Hyaluronic acid methacryloyl hydrogel against peripheral nerve adhesion in a rat model of sciatic nerve. Int J Nanomed 2023;18:2777–93.
[137] Sun M, Cheng J, Zhang J, Wu N, Zhao F, Li Z, et al. Stepwise cross-linking of fibroin and hyaluronic for 3D printing flexible scaffolds with tunable mechanical properties. ACS Biomater Sci Eng 2021 Mar 8;7(3):916–25.
[138] Ngo TB, Spearman BS, Hlavac N, Schmidt CE. Three-dimensional bioprinted hyaluronic acid hydrogel test beds for assessing neural cell responses to competitive growth stimuli. ACS Biomater Sci Eng 2020 Dec 14;6(12):6819–30.
[139] Sagi HC, Patzakis MJ. Evolution in the acute management of open fracture treatment? Part 1. J Orthop Trauma 2021 Sep 1;35(9):449–56.
[140] Rupp M, Popp D, Alt V. Prevention of infection in open fractures: where are the pendulums now? Injury 2020 May;51(Suppl 2):S57–63.
[141] Pugely AJ, Martin CT, Gao Y, Schweizer ML, Callaghan JJ. The incidence of and risk factors for 30-day surgical site infections following primary and revision total joint arthroplasty. J Arthroplasty 2015 Sep;30(9 Suppl):47–50.
[142] Marusic V, Markovic-Denic L, Djuric O, Cirkovic A, Nikolic V, Dubljanin-Raspopovic E, et al. Incidence and risk factors of 30-day surgical site infection after primary total joint arthroplasty in a middle-income country: a single-center experience. Int J Environ Res Publ Health 2021 Jan 20;18(3):863.
[143] Virador GM, de Marcos L, Virador VM. Skin wound healing: refractory wounds and novel solutions. Methods Mol Biol 2019;1879:221–41.
[144] Cho CY, Lo JS. Dressing the part. Dermatol Clin 1998 Jan;16(1):25–47.
[145] Ousey K, Cutting KF, Rogers AA, Rippon MG. The importance of hydration in wound healing: reinvigorating the clinical perspective. J Wound Care 2016 Mar;25(3):124–30. 122.
[146] Junker JPE, Kamel RA, Caterson EJ, Eriksson E. Clinical impact upon wound healing and inflammation in moist, wet, and dry environments. Adv Wound Care 2013 Sep;2(7):348–56.
[147] Nuutila K, Eriksson E. Moist wound healing with commonly available dressings. Adv Wound Care 2021 Dec;10(12):685–98.

[148] Op 'T Veld RC, Walboomers XF, Jansen JA, Wagener FADTG. Design considerations for hydrogel wound dressings: strategic and molecular advances. Tissue Eng B Rev 2020 Jun 1;26(3):230–48.
[149] Hu Y, Xiong Y, Tao R, Xue H, Chen L, Lin Z, et al. Advances and perspective on animal models and hydrogel biomaterials for diabetic wound healing. Biomater Transl 2022 Sep 28;3(3):188–200.
[150] Hao L, Tao X, Feng M, Zhou K, He Y, Yang J, et al. Stepwise multi-cross-linking bioink for 3D embedded bioprinting to promote full-thickness wound healing. ACS Appl Mater Interfaces 2023 May 24;15(20):24034–46.
[151] Zhang Z, Xu C, Xu L, Wan J, Cao G, Liu Z, et al. Bioprinted dermis with human adipose tissue-derived microvascular fragments promotes wound healing. Biotechnol Bioeng 2024 Apr;121(4):1407–21.
[152] Peng Z, Xue H, Liu X, Wang S, Liu G, Jia X, et al. Tough, adhesive biomimetic hyaluronic acid methacryloyl hydrogels for effective wound healing. Front Bioeng Biotechnol 2023;11:1222088.
[153] Lu Y, Li L, Zhu Y, Wang X, Li M, Lin Z, et al. Multifunctional copper-containing carboxymethyl chitosan/alginate scaffolds for eradicating clinical bacterial infection and promoting bone formation. ACS Appl Mater Interfaces 2018 Jan 10;10(1):127–38.
[154] Wang W, Cheng X, Liao J, Lin Z, Chen L, Liu D, et al. Synergistic photothermal and photodynamic therapy for effective implant-related bacterial infection elimination and biofilm disruption using Cu9S8 nanoparticles. ACS Biomater Sci Eng 2019 Nov 11;5(11):6243–53.
[155] Wang W, Li B, Yang H, Lin Z, Chen L, Li Z, et al. Efficient elimination of multidrug-resistant bacteria using copper sulfide nanozymes anchored to graphene oxide nanosheets. Nano Res 2020 Aug;13(8):2156–64.
[156] Ju Y, Zeng H, Ye X, Dai M, Fang B, Liu L. Zn(2+) incorporated composite polysaccharide microspheres for sustained growth factor release and wound healing. Mater Today Bio 2023 Oct;22:100739.
[157] Holzer-Geissler JCJ, Schwingenschuh S, Zacharias M, Einsiedler J, Kainz S, Reisenegger P, et al. The impact of prolonged inflammation on wound healing. Biomedicines 2022 Apr 6;10(4).
[158] Raziyeva K, Kim Y, Zharkinbekov Z, Kassymbek K, Jimi S, Saparov A. Immunology of acute and chronic wound healing. Biomolecules 2021 May 8;11(5).
[159] Tavafoghi M, Nasrollahi F, Karamikamkar S, Mahmoodi M, Nadine S, Mano JF, et al. Advances and challenges in developing smart, multifunctional microneedles for biomedical applications. Biotechnol Bioeng 2022 Oct;119(10):2715–30.
[160] Yao S, Chi J, Wang Y, Zhao Y, Luo Y, Wang Y. Zn-MOF encapsulated antibacterial and degradable microneedles array for promoting wound healing. Adv Healthcare Mater 2021 Jun;10(12):e2100056.
[161] Ming Z, Han L, Bao M, Zhu H, Qiang S, Xue S, et al. Living bacterial hydrogels for accelerated infected wound healing. Adv Sci 2021 Dec;8(24):e2102545.
[162] Massironi A, Franco AR, Babo PS, Puppi D, Chiellini F, Reis RL, et al. Development and characterization of highly stable silver NanoParticles as novel potential antimicrobial agents for wound healing hydrogels. Int J Mol Sci 2022 Feb 15;23(4).
[163] Huang B, Hu D, Dong A, Tian J, Zhang W. Highly antibacterial and adhesive hyaluronic acid hydrogel for wound repair. Biomacromolecules 2022 Nov 14;23(11):4766–77.
[164] Gong M, Yan F, Yu L, Li F. A dopamine-methacrylated hyaluronic acid hydrogel as an effective carrier for stem cells in skin regeneration therapy. Cell Death Dis 2022 Aug 27;13(8):738.
[165] Wang L, Sun L, Bian F, Wang Y, Zhao Y. Self-bonded hydrogel inverse opal particles as sprayed flexible patch for wound healing. ACS Nano 2022 Feb 22;16(2):2640–50.
[166] Sahoo S, Chung C, Khetan S, Burdick JA. Hydrolytically degradable hyaluronic acid hydrogels with controlled temporal structures. Biomacromolecules 2008 Apr;9(4):1088–92.
[167] Veiseh O, Doloff JC, Ma M, Vegas AJ, Tam HH, Bader AR, et al. Size- and shape-dependent foreign body immune response to materials implanted in rodents and non-human primates. Nat Mater 2015 Jun;14(6):643–51.