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REVIEW

Magnetic Nanocomposite Hydrogels in Orthopedics: Applications and Perspectives

Sifeng Shi[1], Siyuan He[2], Qiang Lin[1], Shaosong Sun[1]

[1]Department of Orthopedic Surgery, The Affiliated Hospital of Xuzhou Medical University, Xuzhou, People's Republic of China; [2]School of Clinical Medicine, Xuzhou Medical University, Xuzhou, People's Republic of China

Correspondence: Shaosong Sun; Sifeng Shi, Department of Orthopedics, The Affiliated Hospital of Xuzhou Medical University, Xuzhou, People's Republic of China, Email sunshaosong2025@163.com; shisifeng20071@163.com

Abstract: Orthopedic regenerative medicine faces significant challenges in treating critical-sized bone defects, infections, and achieving spatiotemporal therapeutic control. Traditional hydrogels, while providing a biocompatible three-dimensional (3D) environment, often lack the dynamic responsiveness and mechanical strength required for effective bone repair. The integration of magnetic nanoparticles (MNPs), particularly iron oxides (Fe_3O_4, γ-Fe_2O_3), into hydrogel matrices has emerged as a transformative strategy to overcome these limitations. These magnetic nanocomposite hydrogels (MNHs) leverage the unique superparamagnetic properties of MNPs to enable remote and non-invasive control over their structure and function via external magnetic fields. This review comprehensively explores the design principles, synthesis methodologies, and multifaceted applications of MNHs in orthopedics. Key advancements discussed include their role in enhancing targeted drug delivery (eg, on-demand antibiotic or growth factor release), facilitating cell-based therapies through magnetic retention and mechanostimulation of mesenchymal stem cells (MSCs), and serving as dynamic scaffolds for bone tissue engineering with improved osteogenic commitment. Furthermore, MNHs exhibit great promise in anti-infective therapies by leveraging magnetic hyperthermia to eradicate biofilms and in diagnostic monitoring as contrast agents for MR. Despite their immense potential, clinical translation is contingent upon addressing critical challenges such as long-term biocompatibility of MNPs, scalability of fabrication, and achieving precise in vivo control of magnetic fields. Future perspectives highlight the convergence of MNHs with 4D bioprinting and artificial intelligence (AI) for designing patient-specific, intelligent systems. This review concludes that MNHs represent a paradigm shift towards personalized and adaptive regenerative solutions, poised to redefine treatment strategies in orthopedics and beyond.

Keywords: magnetic nanoparticles, hydrogels, bone regeneration, drug delivery, orthopedic infection

Introduction

Background of Orthopedic Challenges

Orthopedic injuries and degenerative bone diseases (eg, fractures, osteoporosis, osteoarthritis) represent a significant global health burden (Figure 1). According to the World Health Organization (WHO), over 20 million patients worldwide require surgical interventions for bone defects annually,[1] with aging populations and trauma cases further exacerbating this demand.[2] Despite advances in medical technologies, current strategies for bone repair face persistent limitations.[3] Slow healing and poor regeneration: Critical-sized bone defects (>2 cm) often fail to heal spontaneously due to inadequate vascularization and insufficient osteogenic activity.[4] For instance, non-union rates in tibial fractures remain as high as 5–14% even with surgical stabilization.[5] Infection risks: Orthopedic implants (eg, plates, screws) carry a 1–2% risk of infection for closed fractures, and can be as high as 25% to 30% for severe open injuries fractures.[6] Bacterial biofilm formation (eg, Staphylococcus aureus) lead to implant failure and systemic sepsis.[7] Mechanical mismatch: Conventional synthetic materials (eg, titanium alloys, PMMA bone cement) exhibit stiffness exceeding natural bone, causing stress shielding and secondary fractures.[8]

Traditional therapies, including autografts (gold standard) and allografts, are constrained by donor site morbidity, immune rejection, and limited availability.[9] Meanwhile, existing biomaterials often lack dynamic responsiveness to

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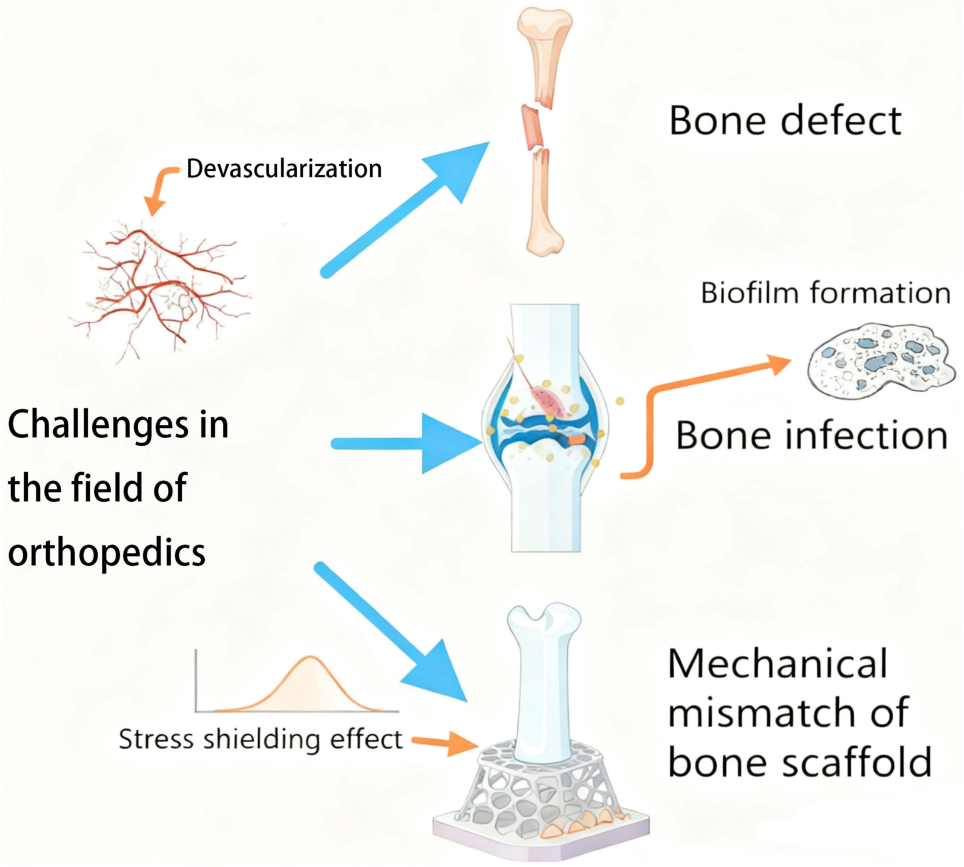

Figure 1 Challenges in the field of orthopedics.

physiological changes (eg, pH, mechanical loading), hindering their ability to adapt to complex healing microenvironments. This unmet clinical need has driven the exploration of smart biomaterials capable of integrating structural support, bioactive signaling, and real-time therapeutic modulation.[10]

Overview of Hydrogels in Orthopedics

Hydrogels, three-dimensional hydrophilic polymer networks capable of absorbing large amounts of water, have emerged as a cornerstone material in modern orthopedics. Their unique physicochemical properties and biomimetic extracellular matrix (ECM) architecture make them ideal candidates for addressing complex bone and cartilage repair challenges (Figure 2).

Hydrogels have numerous properties driving orthopedic applications (Table 1). Biocompatibility and Bioactivity: Natural polymer-based hydrogels (eg, hyaluronic acid, collagen) exhibit intrinsic cell-adhesive motifs (eg, arginine-glycine-aspartic acid sequences), promoting osteoblast adhesion and mineralization.[11] Synthetic variants (eg, PEG-based hydrogels) can be functionalized with bioactive peptides (eg, BMP-2) to enhance osteogenesis.[12] Injectable and Minimally Invasive Delivery: Thermo-responsive hydrogels (eg, chitosan/β-glycerophosphate systems) undergo sol-gel transitions at body temperature, enabling precise filling of irregular bone defects through syringe injection.[13] Tunable Drug Delivery: Hydrogel porosity and degradation kinetics allow sustained release of therapeutics. For example, Vancomycin/MP-2-loaded gelatin hydrogels can continuously release Vancomycin and BMP-2 for 6 weeks, and the result showed an effective anti-bacterial activity with no significant cytotoxicity. While almost all vancomycin in Pluronic F127 solution was rapidly released within 10 h, the release of vancomycin in ALG solution was significantly delayed (~ 27% after 36 h), exhibiting an initial burst release within the first 5 hours, followed by a linear release profile from hours 5 to 36.[14]

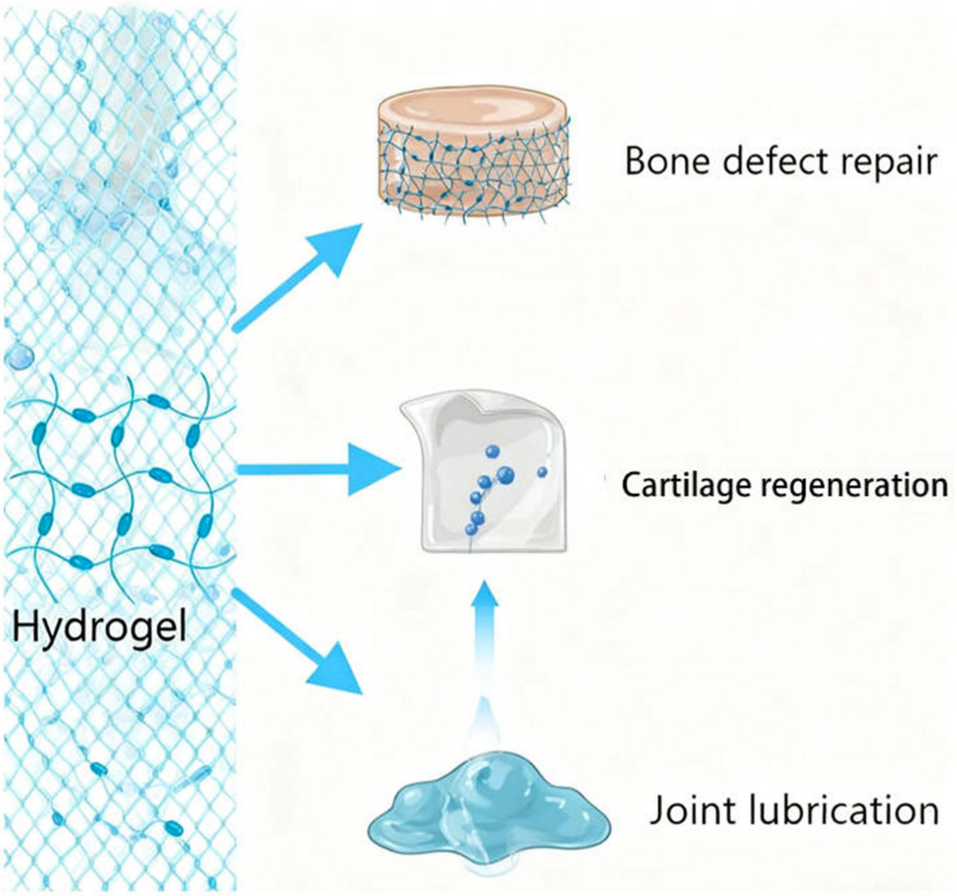

Figure 2 Applications of hydrogel in Orthopedics.

Despite their promise, traditional hydrogels face critical barriers including Mechanical Weakness, Passive Therapeutic Action and Limited Responsiveness. Most hydrogels (elastic modulus <1 MPa) cannot withstand physiological loads in weight-bearing bones (eg, femur requires >100 MPa).[18] Drug release relies on diffusion/degradation, lacking spatiotemporal control over dosage[19] and Inability to dynamically adapt to microenvironmental changes (eg, pH shifts in infected wounds, mechanical loading cycles).[20] To address these inherent limitations, research has shifted toward stimuli-responsive "smart" hydrogels. These advanced materials can dynamically alter their properties or functions in response to external triggers—such as temperature, light, or magnetic fields—enabling spatiotemporal control that is crucial for advanced therapies. This paradigm shift paves the way for incorporating functional nanomaterials like

Table 1 Current Applications of Hydrogels in Orthopedics

Application	Hydrogel Type	Clinical Outcomes (Preclinical/Clinical)
Bone Defect Repair	Calcium/Silicon hydrogels	At the 12-week post-operative interval, the femoral condyle in the rabbit distal femoral defect model exhibits complete healing of the bone defect, with minimal callus formation observed around the external aperture[15]
Cartilage Regeneration	Chondroitin Sulfate-Tyramine-Based Hydrogels	During the 21-day chondrogenic culture period, the composite Significantly inhibited the release of ECM components from osteoarthritic cartilage explants: COMP release was reduced by approximately 42%[16]
Joint Lubrication	CLX/Lipo/HA Hydrogels	Significant increase in joint space width compared to the PBS group (anteroposterior view: 0.89 ± 0.07-fold vs 0.68 ± 0.05-fold; lateral view: 0.87 ± 0.17-fold vs 0.26 ± 0.12-fold)[17]

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magnetic nanoparticles (MNPs) to create actively controlled systems.[21] The integration of functional nanomaterials—particularly magnetic nanoparticles (MNPs)—into hydrogel matrices has opened new frontiers. MNPs empower hydrogels with remote controllability, mechanical reinforcement, and on-demand therapeutic activation.

Emergence of Magnetic Nanoparticles (MNPs)

The advent of magnetic nanoparticles (MNPs), typically iron oxide-based (eg, Fe_3O_4, γ-Fe_2O_3) with diameters ranging from 10–100 nm, has revolutionized therapeutic strategies in orthopedics (Figure 3). MNPs uniquely combine superparamagnetism, high surface-to-volume ratio, and biocompatibility, enabling remote control and dynamic modulation of biological processes through external magnetic fields.[22]

There are three key Properties of MNPs for Orthopedic Applications (Table 2), including Remote Controllability Flexibility, Biofunctionalization and Real-Time Imaging. Superparamagnetic MNPs generate heat (magnetic hyperthermia) or mechanical forces (magnetomechanical actuation) under alternating magnetic fields (AMF),[23] allowing spatiotemporal control over drug release or cell behavior.[24] MNPs can be coated with polymers (eg, PEG, dextran) or conjugated with targeting ligands (eg, RGD peptides) to enhance bone-specific accumulation and reduce off-target

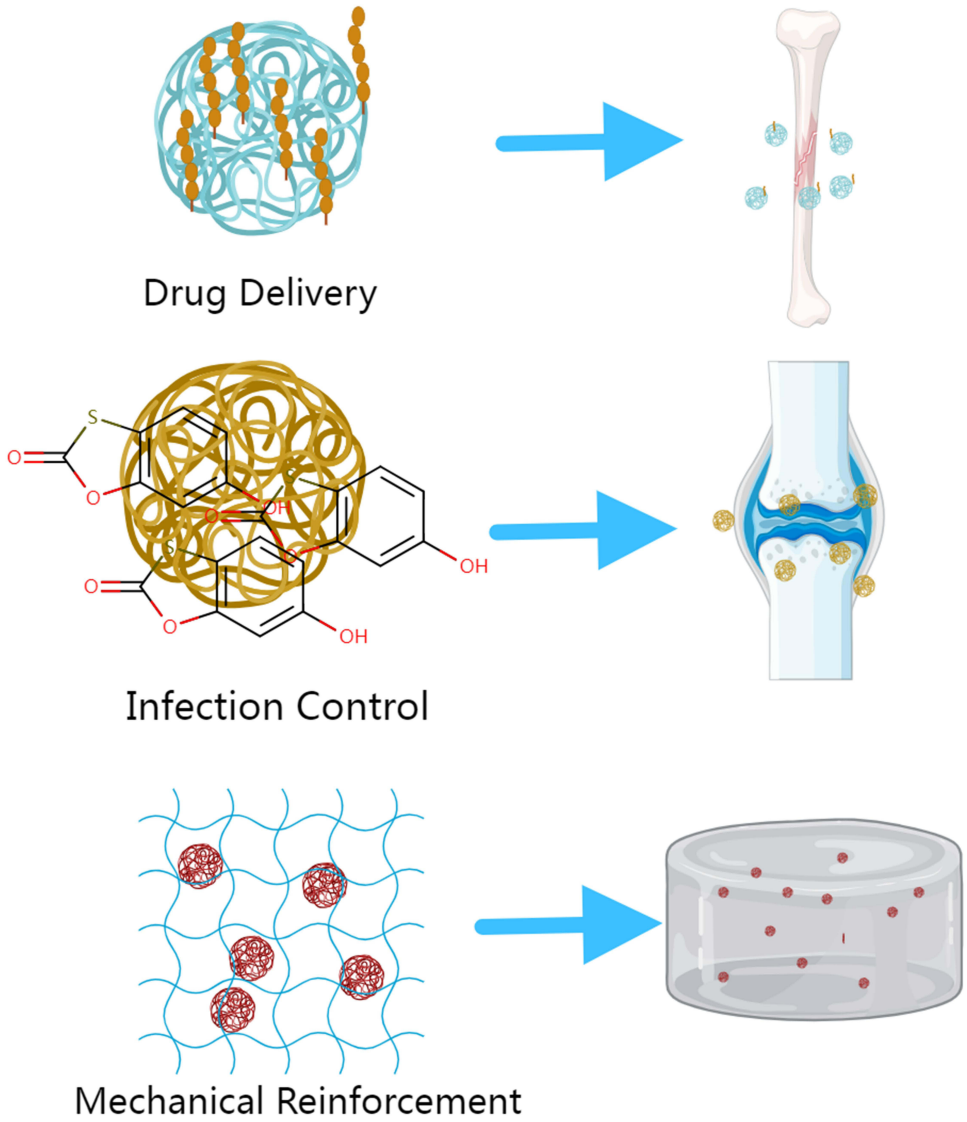

Figure 3 Applications of Magnetic Nanoparticles (MNPs) in orthopedics.

Table 2 Current Applications of MNPs in Orthopedics

Application	MNP Type/Modification	Mechanism & Outcomes
Targeted Drug Delivery	Fe_3O_4@MTX	The Methotrexate-loaded nanoparticles significantly enhanced the antitumor activity reducing the half-maximal inhibitory concentration by 2.7-fold less compared to the free chemotherapeutic[27]
Infection Control	Fe_3O_4 loaded with tobramycin	In liquid culture assays, iron oxide nanoparticles achieved complete biofilm inhibition against PAO1 at 17.5 mg/mL, with a remarkably low minimum inhibitory concentration of 8 ng/mL, demonstrating significant antibacterial effects comparable to zero-valent iron nanoparticles.[28]
Mechanical Reinforcement	Fe_3O_4-PCL	The bio-nanocomposite scaffold with a 0.1:0.9 Fe_3O_4-to-PCL weight ratio exhibited optimal mechanical properties, achieving a Young's modulus of 1 MPa and a stiffness of 13 N/mm, while maintaining non-cytotoxicity.[29]

effects.[25] MNPs also serve as contrast agents for MRI, enabling non-invasive tracking of hydrogel degradation and bone regeneration progress.[26]

Advantages Over Conventional Nanomaterials

Magnetic nanoparticles (MNPs) exhibit dynamic responsiveness by enabling on-demand activation mechanisms such as drug release triggered by alternating magnetic field (AMF) pulses. This capability overcomes the reliance on passive diffusion that limits traditional hydrogel-based systems.[30] A key strength of MNPs lies in their multifunctionality, allowing them to perform simultaneous roles in therapy as drug carriers, in diagnostics as MRI contrast agents, and in tissue engineering as mechanical reinforcement elements.[31] Furthermore, MNPs offer the advantage of deep tissue penetration. Since magnetic fields can penetrate bone tissue without significant attenuation, they enable non-invasive, remote control of implanted MNP-laden constructs.[32]

> While MNPs alone exhibit remarkable capabilities, their integration into hydrogels creates synergistic systems that address both mechanical and biofunctional limitations. Overview of Hydrogels in Orthopedics explores how MNP-hydrogel hybrids achieve programmable mechanics, smart drug delivery, and magnetically guided tissue regeneration.

Design and Synthesis of Magnetic Nanocomposite Hydrogels

While traditional hydrogels have served as invaluable static scaffolds by providing a biocompatible, three-dimensional environment for cell growth, their inability to dynamically interact with surrounding tissues limits their regenerative potential. In contrast, stimuli-responsive or "smart" hydrogels represent a significant evolution, capable of altering their physical or chemical properties—such as swelling, stiffness, or shape—in response to specific external cues like temperature, light, or magnetic fields. This dynamic functionality enables precise, spatiotemporal control over biological processes, bridging the gap between passive support and active tissue regeneration.[21] Among these advanced systems, magnetic nanocomposite hydrogels (MNHs), particularly those incorporating magnetic nanoparticles, have garnered significant attention. Their unique capacity to be remotely and non-invasively controlled by external magnetic fields offers unparalleled opportunities for targeted drug delivery, mechanical stimulation of cells, and the guidance of complex tissue morphogenesis, positioning them at the forefront of next-generation regenerative strategies.

Design Principles

The design of magnetic nanocomposite hydrogels follows several key principles to ensure optimal functionality. Iron oxide nanoparticles (Fe_3O_4, γ-Fe_2O_3) serve as the primary magnetic component due to their inherent biocompatibility and superparamagnetic properties.[33] These nanoparticles are typically engineered with a size range of 10–50 nm and surface modifications such as citrate coating to enhance colloidal stability and promote uniform dispersion within the hydrogel matrix.[34] The hydrogel matrix can be formulated using either natural polymers including collagen and hyaluronic acid, or synthetic polymers such as PEG and PLGA, with selection criteria based on required degradation kinetics, mechanical strength, and biological activity.[35] Crosslinking strategies employ either physical interactions like hydrogen bonding or chemical methods including photo-crosslinking to achieve an optimal balance between structural

Table 3 Synthesis Strategies of Magnetic Nanocomposite Hydrogels

Method	Description	Advantages and Limitations
Physical Blending	MNPs dispersed into pre-formed hydrogel via sonication or stirring.	Pros: Simple, scalable. Cons: Risk of MNP sedimentation.[38]
In Situ Synthesis	MNPs chemically synthesized within hydrogel (eg, co-precipitation of Fe^{3+}/Fe^{2+} in polymer solution).	Pros: Homogeneous distribution. Cons: Limited control over MNP crystallinity.[38]
3D Bioprinting	MNPs mixed with bioinks (eg, GelMA) for layer-by-layer magnetic patterning.	Pros: Spatial control of MNP alignment. Cons: Requires specialized equipment.[39]

integrity and nanoparticle mobility, as detailed in Table 3.[36] A critical consideration is interfacial engineering between the nanoparticles and polymer network. This can be accomplished through covalent bonding using amine-carbodiimide chemistry or physical adsorption via electrostatic interactions, both serving to enhance composite stability and prevent nanoparticle aggregation under magnetic stimulation.[37]

Key Parameters for Performance Optimization (Table 4)

The performance of magnetic nanocomposite hydrogels is governed by several key parameters that require careful optimization. The concentration of magnetic nanoparticle (MNP) loading plays a critical role, as higher loading generally enhances magnetic responsiveness but may concurrently compromise hydrogel elasticity and biocompatibility.[43] Surface functionalization strategies are essential for improving MNP stability and bioactivity. Approaches such as PEGylation or silica coating effectively reduce nanoparticle aggregation, while the conjugation of specific ligands like RGD peptides actively promotes cell adhesion and integration.[44] Furthermore, the parameters of the applied magnetic field significantly influence system performance. The frequency (typically 50–500 kHz) and strength (usually 5–20 mT) of an alternating magnetic field (AMF) must be precisely tuned to effectively trigger targeted drug release or hyperthermia effects while ensuring no damage occurs to surrounding tissues.[45]

The tailored design of magnetic nanocomposite hydrogels lays the foundation for their application in dynamic bone regeneration. Section III will delve into how these systems enable spatiotemporally controlled drug delivery, mechanostimulation, and real-time monitoring of healing processes.

Applications in Orthopedics

Drug Delivery and Controlled Release

Magnetic nano-hydrogels (MNHs) exhibit revolutionary potential in orthopedic drug delivery due to their spatiotemporal controllability and targeted release capabilities.[46] By embedding magnetic nanoparticles (MNPs) like Fe_3O_4 into hydrogel matrices, therapeutic agents such as bone morphogenetic protein-2 (BMP-2) and doxorubicin can be loaded and delivered with precision.[47] For instance, a study introduced a multifunctional supramolecular hydrogel system based

Table 4 Current Research Advances in Magnetic Nanocomposite Hydrogels

Nanocomposite System	Synthesis Method	Key Findings
Fe_2O_3chitosan/polyethylene glycol (PEG) hydrogel	Physical blending	Easily achieve increasing temperatures under an alternative magnetic field. The composite hydrogel resulted in high viability of mesenchymal stem cells (MSCs).[40]
Iron oxide composite particle/ Agarose Hydrogel	In Situ Synthesis	When bovine chondrocytes were seeded into the ferrogels and cultured for up to 14 days, there was good cell viability.[41]
Streptavidin-coated iron nanoparticles/agarose Hydrogel	3D bioprinting	After 21 days of culture, cell-loaded constructs with random fibers express markedly more collagen II in comparison to solely randomly oriented fiber constructs.[42]

on dehydropeptide gels, incorporating phenylalanine-coated magnetic nanoparticles and PEGylated liposomes co-assembled with doxorubicin to achieve dual-responsive drug release (thermal and low-frequency alternating magnetic field triggers), while enhancing gelation kinetics and cytocompatibility, thereby providing a novel strategy for smart drug delivery systems.[48]

External magnetic fields enable triggered release mechanisms, allowing localized drug activation. The application of an external magnetic field causes the hybrid hydrogel to quickly transition from gel to sol.[49] This dual functionality of MNPs—acting as both drug carriers and magnetic actuators—ensures minimal systemic toxicity and enhanced therapeutic efficacy.

Bone Tissue Engineering

MNHs can serve as dynamic scaffolds for osteoblast proliferation and differentiation.[50] Their 3D porous structure mimics the natural extracellular matrix (ECM), providing mechanical support and bioactive cues.[51] For example, Cetin et al investigated the bone-forming potential of a super porous hydrogel made from PHEMA and Gel, which was seeded with preosteoblastic MC3T3-E1 cells.[52]

The synergistic integration of additive manufacturing (3D printing) and advanced hydrogel science has emerged as a transformative paradigm in biomedical engineering, enabling the precise fabrication of intricate, hydrous constructs that closely mimic the native extracellular matrix (Figure 4).[53] This powerful combination is propelling groundbreaking advancements across a spectrum of applications, from regenerative medicine and personalized drug delivery to the

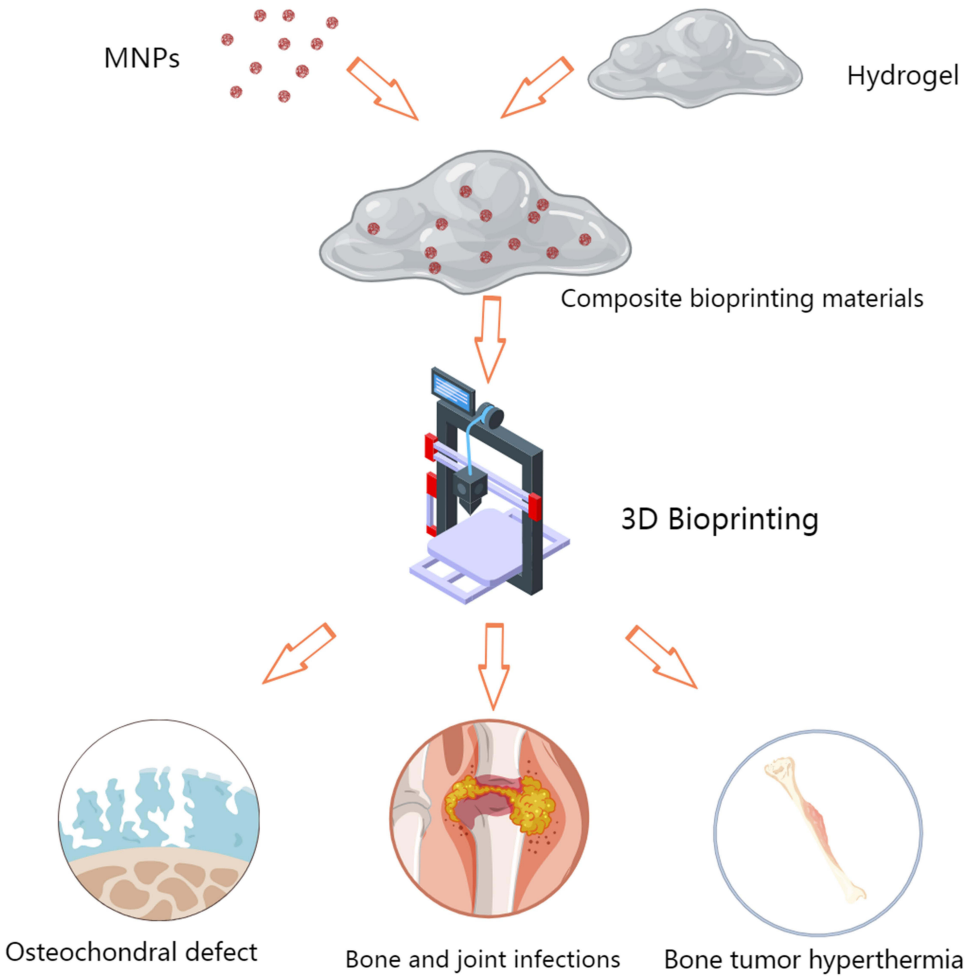

Figure 4 3D biological printing Magnetic Nanocomposite Hydrogels and its application in orthopedics.

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development of intelligent, responsive medical devices. The efficacy of this approach is critically dependent on the selection of appropriate printing modalities and tailored biomaterial inks, each offering distinct advantages and technical considerations. Regarding fabrication techniques, several key 3D printing technologies have been adapted to process hydrogel-based bioinks. Material extrusion, notably through direct ink writing (DIW), represents a cost-effective and widely accessible method that operates via the layer-by-layer deposition of viscous materials through a nozzle.[54] Its success is heavily contingent on the ink's rheological properties, which must exhibit shear-thinning behavior for extrudability and rapid shape fidelity post-deposition. In contrast, vat photopolymerization techniques, such as stereolithography (SLA) and digital light processing (DLP), utilize light energy to selectively crosslink liquid photopolymer resins. These methods are renowned for their superior printing speed and high resolution (typically 20–200 μm), but necessitate the use of photocrosslinkable polymers (eg, gelatin methacryloyl, GelMA).[55] Pushing the boundaries of precision, high-definition (HD) printing methods like two-photon polymerization (TPP) achieve remarkable sub-micron resolution, facilitating the creation of highly complex microarchitectures. Alternatively, material jetting operates by precisely depositing droplets of bioink to generate constructs with defined cellular heterogeneity. While it offers high resolution, it typically requires low-viscosity inks and the jetting process itself (thermal or piezoelectric) can introduce stressors that challenge cell viability. The material composition of the bioink is equally paramount, dictating the biological and mechanical functionality of the printed construct. Nature-derived polymers —such as alginate, collagen, chitosan, and hyaluronic acid—are extensively utilized for their innate biocompatibility, bioactivity, and inherent cell-interaction motifs.[56] Conversely, synthetic polymers like poly(ethylene glycol) (PEG) provide a platform with highly tunable mechanical and chemical properties.[57] A particularly innovative frontier is the advent of 4D printing using stimuli-responsive hydrogels (SRHs). These "intelligent" materials can undergo predictable changes in shape, volume, or functionality in response to external cues such as temperature (eg, poly(N-isopropylacrylamide), PNIPAM), pH, or magnetic fields. For instance, the strategic incorporation of magnetic nanoparticles (eg, Fe_3O_4) within the hydrogel matrix creates magneto-responsive scaffolds.[58] These composites can be non-invasively actuated or manipulated under an applied magnetic field, enabling advanced applications such as untethered soft robotic devices for targeted object manipulation, dynamic tissue scaffolds, and spatially controlled drug delivery systems.

Magnetic Nanoparticles for Enhanced Cell Delivery and Function The integration of magnetic nanoparticles (MNPs) into hydrogel scaffolds provides a powerful, remote-controlled strategy to enhance cell-based therapies in bone tissue engineering.[59] This approach, known as magnetic cell targeting, fundamentally improves upon passive cell delivery methods. When therapeutic cells (eg, mesenchymal stem cells - MSCs) are labeled with MNPs or encapsulated within MNP-laden hydrogels, the application of an external static magnetic field (SMF) can actively guide and retain these cells at the specific defect site. This significantly increases cell localization and engraftment efficiency, overcoming a major limitation of systemic or passive local delivery where cell dispersion leads to poor therapeutic outcomes.[60] Beyond targeted delivery, MNPs exert significant positive effects on cell viability and proliferation. The presence of MNPs, particularly under SMF exposure, has been shown to upregulate key integrins and enhance cell-scaffold interactions, leading to improved adhesion and spreading.[61] Furthermore, studies indicate that MNP-induced SMF conditions can stimulate mitochondrial activity and promote the secretion of autocrine and paracrine growth factors, creating a more favorable microenvironment that boosts metabolic activity and proliferation.[62] Crucially, MNPs can directly influence osteogenic commitment. The mechanical forces exerted by MNPs under a magnetic field activate critical mechanotransduction pathways, such as the RhoA/ROCK signaling cascade.[63] This mechanical stimulation can synergize with biochemical cues to promote the expression of osteogenic markers and enhance extracellular matrix mineralization. Therefore, MNPs act not merely as delivery vehicles but as active biophysical stimulators that enhance cell survival, proliferation, and differentiation, ultimately leading to more robust and accelerated bone regeneration.

Anti-Infective Therapies

Orthopedic infections, particularly biofilm-associated ones, pose significant challenges. MNHs integrate magnetic hyperthermia to eradicate biofilms. Under alternating magnetic fields (AMF), Fe_3O_4 nanoparticles generate localized heat (42–45°C), disrupting biofilm integrity and enhancing antibiotic penetration. Elena et al explored a novel combination therapy using magnetic-responsive nanocarriers for treating biofilm-associated infections, which involves antibiotic-

loaded mesoporous silica nanoparticles capped with a thermo-responsive polymer and decorated with superparamagnetic iron oxide nanoparticles. Upon application of an alternating magnetic field, the nanoparticles generate heat, triggering antibiotic release and significantly reducing bacterial viability in E. coli biofilms by 4 log10 units compared to controls.[64]

Lu et al designed poly (β-amino ester) (PBAE) hydrogel that combined antibacterial and osteogenic functions, dual release of vancomycin (VAN) and total flavonoids of Rhizoma Drynariae (TFRD), demonstrating effective antibacterial properties against S. aureus and E. coli, as well as enhanced osteogenic differentiation capabilities.[65]

This dual-action strategy—thermal ablation and sustained antimicrobial release—addresses both acute and chronic orthopedic infections.

Mechanical Reinforcement and Lubrication

Hydrogels usually have less mechanical strength even compared to normal cartilage.[66]

The inclusion of Fe3O4 nanoparticles in the Hydrogels provides magnetic responsive properties and also boosts the mechanical strength and toughness of the hydrogels, making them suitable for load-bearing applications. For instance, in Lee research, the Fe3O4 nanoparticles significantly enhance the mechanical properties of the magneto-responsive nanocomposite hydrogels (MR_NCHs) by contributing to the formation of a robust network structure through physical interactions with laponite nanoparticles and poly(DMAAm) (PDMAAm) chains. This network structure increases the crosslinking density, leading to improved toughness, elasticity, and overall mechanical strength of the hydrogels. Making the hydrogels suitable for biomedical applications.[67] Magnetic alignment techniques create anisotropic structures that mimic natural tissue mechanics. Hydrogel with magnetically oriented Fe_3O_4-MMT hybrids demonstrated a low friction coefficient, rivaling natural synovial fluid.[30] Such lubricious properties are critical for joint repair, reducing wear and preventing secondary inflammation.

Diagnostic and Monitoring Tools

Combining cutting-edge advancements in nanotechnology and biomedical imaging, magnetic nanoparticles (MNPs) have emerged as pivotal tools for non-invasive tracking of hydrogel degradation and tissue regeneration. MNPs serve as contrast agents in MRI, enabling non-invasive tracking of hydrogel degradation and tissue regeneration. For example, superparamagnetic Fe_3O_4 in scaffolds allowed real-time visualization of subchondral bone repair, correlating MRI signal attenuation with new bone formation.[68] Superparamagnetic iron oxide nanoparticles (SPIONs, eg, Fe_3O_4) with sizes of 10–50 nm exhibit high T2 relaxation enhancement due to their magnetic moment fluctuations, which disrupt local magnetic fields. This property is critical for visualizing hydrogel degradation and bone regeneration in scaffolds like GMHA (gelatin-methacryloyl/hyaluronic acid). MSC-recruiting hydrogels, and AI-enhanced systems are transforming MNPs from passive imaging tools into dynamic theranostic platforms. These theranostic systems provide feedback on scaffold integration and therapeutic efficacy, essential for personalized orthopedics. These advancements hold promise for personalized orthopedics, oncology, and regenerative medicine, bridging the gap between lab research and clinical translation.[69]

Challenges and Limitations

Despite the immense potential of magnetic nanocomposite hydrogels in biomedical and engineering applications, their practical implementation faces several critical challenges.

Biocompatibility and Long-Term Safety of MNPs

The clinical translation of magnetic nanoparticles (MNPs) is hindered by unresolved concerns about their biocompatibility and long-term biological effects.[70,71] Prolonged retention of MNPs (eg, Fe_3O_4) in vivo may lead to iron ion release, causing oxidative stress or inflammatory responses.[72] Poor interfacial bonding between MNPs and hydrogel matrices can also result in particle leakage, compromising stability.[73] While MNPs like Fe_3O_4 are generally considered safe, their accumulation in organs (eg, liver, lung) raises risks of localized toxicity and chronic inflammation.[74] For instance, Doxorubicin-Loaded Iron Oxide Nanoparticles in cancer chemotherapy may trigger unintended immune reactions or oxidative stress, potentially damaging healthy tissues.[75] Because doxorubicin itself is a cytotoxic drug,

being carried by nanoparticles may further exacerbate its damage to normal tissues. Research by Huang et al revealed that when iron oxide nanoparticles break down inside cells, they release ferric (Fe3+) ions, potentially causing cytotoxic effects.[76] Furthermore, the lack of long-term safety data in large animal models (eg, non-human primates) and human trials limits confidence in their clinical use.[77] Biodegradable MNP design and surface functionalization may help address this issue. Core-shell structures like Fe_3O_4@SiO_2 delay iron ion release and enable macrophage-mediated clearance.[78] Coating MNPs with Dextran reduces immunogenicity and improved biocompatibility of nanoparticles.[79] Recent studies also highlight the potential for MNPs to interfere with cellular processes, such as promoting carcinogenic clonal evolution by enhancing pinocytosis in cancer cells. Comprehensive toxicological profiling, including biodegradation kinetics and immunogenicity assessments, is urgently needed to address these gaps.

Scalability and Stability of Hydrogel-MNP Systems

The manufacturing scalability and structural stability of hydrogel-MNP composites remain critical bottlenecks.[80] Key challenges include: Batch-to-batch variability: Heterogeneity in MNP size, shape, and polymer coatings (eg, PEG, dextran) can alter hydrogel mechanical properties and drug-release profiles.[81,82] Aggregation of MNPs via physical mixing methods weakens magnetic responsiveness and mechanical integrity is another problem that needs to be solved. Directly synthesizing MNPs within hydrogel networks (eg, co-precipitation of Fe^{3+}/Fe^{2+} clusters) ensures monodispersity.[67] Magnetic field dependency: Hydrogel-MNP systems often require sustained external magnetic fields for targeted delivery, but field strength decays rapidly in vivo, especially in obese patients, leading to inconsistent MNP retention and dispersion.[83] Storage stability: Hydrogels loaded with MNPs may undergo phase separation or oxidation during long-term storage, compromising their therapeutic efficacy.[84] Advanced quality control protocols, such as microfluidic synthesis and lyophilization techniques, are being explored to improve reproducibility and shelf life.[85,86]

Precision Control of Magnetic Fields in vivo

Achieving spatiotemporal precision in magnetic field control under in vivo conditions presents a formidable challenge, primarily due to several key factors. A fundamental limitation arises from Earnshaw's theorem, which dictates that static magnetic fields cannot stably trap magnetic nanoparticles (MNPs) at deep tissue targets.[87] This necessitates the implementation of dynamic field adjustments and feedback-controlled systems for effective targeting.[88] Further complexity is introduced by the requirement for dynamic adaptability within complex tissue environments. Implanted constructs may face structural failure or functional inactivation when exposed to dynamic microenvironments, such as those involving wound contraction or bacterial infection.[89] Real-time imaging constraints also pose a significant hurdle, as current MRI-based tracking technologies lack the necessary resolution and speed for real-time MNP guidance, often leading to off-target accumulation.[90] Finally, inherent physiological variability presents a major challenge. Factors including blood flow, tissue density, and local metabolic activity can significantly disrupt intended MNP trajectories. Addressing this variability requires the development of adaptive control algorithms, such as PID control, to continuously optimize magnetic field parameters in response to the changing biological milieu.[91]

Emerging solutions include closed-loop systems combining magnetic particle imaging (MPI) and AI-driven predictive models to enhance targeting accuracy.[92] Addressing these challenges demands interdisciplinary innovation, from nanoparticle engineering to AI-enhanced control systems. While MNPs hold transformative potential in orthopedics, their safe and effective translation hinges on resolving biocompatibility concerns, optimizing scalable fabrication, refining magnetic targeting, and navigating regulatory complexities. Future research should prioritize large-scale human trials and degradable MNP designs to mitigate long-term risks.

Future Perspectives

Advanced Fabrication Techniques: 4D Printing and AI-Driven Design

The development of next-generation hydrogel systems increasingly leverages advanced fabrication technologies such as 4D printing and artificial intelligence (AI) to construct dynamic, adaptive architectures with unprecedented precision.[93] A prominent direction involves the creation of 4D-printed reconfigurable hydrogels. Emerging techniques, including

femtosecond laser bimodal processing that combines additive and removal modes, allow for the fabrication of intricate microchannels and anisotropic structures within hydrogels like GelMA at submicron resolution.[94–96] These engineered systems possess the capability to dynamically alter their shape or porosity in response to external stimuli such as pH or temperature changes, thereby mimicking natural tissue remodeling processes. For instance, the use of photocontrolled metallopolymer adhesives enables the reversible assembly of basic hydrogel units into complex, reconfigurable structures, showing great potential for applications in soft robotics or adaptive implants.[96–98] Concurrently, AI-driven optimization is being integrated into the hydrogel design pipeline. Machine learning algorithms are employed to predict key performance metrics, including mechanical properties, drug-release kinetics, and biodegradation rates, thereby accelerating the development of tailored hydrogel materials.[99,100]

Multifunctional Hydrogels: Synergistic Integration of MNPs and Nanomaterials

Future hydrogel systems are evolving towards multifunctional "all-in-one" platforms through the synergistic integration of magnetic nanoparticles (MNPs) with diverse nanomaterials such as carbon nanotubes and quantum dots.[101–104] These advanced composites demonstrate remarkable capabilities for biomedical applications. A prominent development involves self-healing conductive hydrogels created by integrating MNPs with conductive polymers like PEDOT: PSS or graphene oxide. These hybrid networks achieve dual functionality, combining magnetic targeting with real-time electrical signaling capabilities that show particular promise for neural and cardiac tissue repair applications.[105–107] Another significant advancement emerges in theranostic nanocomposites, where core-shell structured MNPs (eg, Fe_3O_4 @Au) embedded within hydrogel matrices can simultaneously function as MRI contrast agents, photothermal actuators, and controlled drug release carriers.[108–111] Further innovation includes pH-responsive hydrogel systems loaded with MNPs that enable localized chemo-photothermal therapy while effectively evading immune detection, representing a sophisticated approach to targeted cancer treatment.[112–114]

Integration with Wearable Devices for Personalized Medicine

Hydrogels are poised to revolutionize wearable health technologies by enabling seamless integration with the human body for real-time diagnostics and therapy.[115,116] This integration manifests through several key applications. Smart wound dressings represent a significant advancement, where 3D-printed hydrogel patches loaded with engineered extracellular vesicles (EVs) and magnetic nanoparticles (MNPs) can monitor wound parameters including pH, temperature, and bacterial load while releasing antimicrobial agents on demand.[117,118] These systems are further enhanced by AI algorithms that analyze data from embedded biosensors to dynamically adjust drug-release rates.[119,120] Closed-loop implantable systems constitute another promising direction. Hydrogel-based wearables interfacing with soft robotic micromachines, such as ECM-mimetic actuators, could autonomously regulate drug delivery or provide mechanical support.[121,122] A specific example includes glucose-responsive hydrogels combined with MNPs and insulin reservoirs, potentially forming self-regulating implants for diabetes management.[123,124] Remote patient monitoring applications are also emerging, where hydrogel sensors integrated into wearables like smart insoles or epidermal patches can transmit biomechanical data (eg, joint pressure) and biochemical data (eg, cytokine levels) to cloud platforms for AI-driven health predictions.[125] The convergence of advanced fabrication, multifunctional nanomaterials, and wearable integration is driving hydrogels toward intelligent, patient-specific solutions. While key challenges remain—including scaling AI-designed hydrogels for clinical use and ensuring long-term biocompatibility of hybrid systems—these are being addressed through interdisciplinary collaboration. With ongoing innovations in 4D-printed adaptive scaffolds and closed-loop theranostic wearables, hydrogels are positioned to redefine personalized orthopedics and regenerative medicine. Current research continues to advance AI-driven hydrogel design, multifunctional nanocomposites, and wearable health technologies.[126–128]

Conclusion

The integration of magnetic nanoparticles into hydrogel matrices represents a significant advancement in smart biomaterials for orthopedic applications. This review has detailed how magnetic nanocomposite hydrogels overcome the limitations of traditional systems by enabling remote spatiotemporal control over therapeutic actions through external

magnetic fields. These systems demonstrate multifunctional capabilities, serving as mechanically reinforced scaffolds that promote bone regeneration while simultaneously functioning as theranostic platforms for diagnosis and treatment. The convergence with additive manufacturing facilitates the fabrication of patient-specific constructs with predefined responsiveness. Clinical translation, however, depends on addressing several critical challenges. Long-term biocompatibility and biodegradation of MNPs require thorough investigation, while scalable fabrication processes must be developed to ensure consistency. Achieving precise magnetic field control in deep tissues remains an engineering hurdle that may require closed-loop systems with real-time feedback. Future research should focus on developing next-generation MNPs with biodegradable coatings and hybrid nanostructures to enhance functionality and safety. Intelligent system integration involving artificial intelligence and wearable devices could enable predictive design and adaptive therapy. Ultimately, high-quality clinical studies are essential to validate the efficacy and safety of these promising systems.

In summary, magnetic nanocomposite hydrogels represent a paradigm shift toward personalized orthopedic regeneration. By addressing existing translational barriers through interdisciplinary collaboration, these advanced systems are poised to redefine standards of care in bone repair and broader regenerative medicine applications.

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Disclosure

The authors declare no competing interests.

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