International Journal of Nanomedicine

Dovepress
Taylor & Francis Group

Open Access Full Text Article

REVIEW

Nanotechnology in Orthopedic Care: Advances in Drug Delivery, Implants, and Biocompatibility Considerations

Linying Xia[1,*], Chao Zhou[2,*], Qingping Li[1], Lu Liu[1], Chanyi Jiang[3], Haidong Dai[4], Hengjian Zhang[4], Jiayi Zhao[4], Wenqing Liang[4]

[1]Medical Research Center, Zhoushan Hospital of Traditional Chinese Medicine Affiliated to Zhejiang Chinese Medical University, Zhoushan, Zhejiang, 316000, People's Republic of China; [2]Department of Orthopedics, Zhoushan Guanghua Hospital, Zhoushan, Zhejiang, 316000, People's Republic of China; [3]Department of Pharmacy, Zhoushan Hospital of Traditional Chinese Medicine Affiliated to Zhejiang Chinese Medical University, Zhoushan, Zhejiang, 316000, People's Republic of China; [4]Department of Orthopaedics, Zhoushan Hospital of Traditional Chinese Medicine Affiliated to Zhejiang Chinese Medical University, Zhoushan, Zhejiang, 316000, People's Republic of China

*These authors contributed equally to this work

Correspondence: Wenqing Liang; Jiayi Zhao, Department of Orthopaedics, Zhoushan Hospital of Traditional Chinese Medicine Affiliated to Zhejiang Chinese Medical University, 355 Xinqiao Road, Dinghai District, Zhoushan, Zhejiang, 316000, People's Republic of China, Tel +86-580-2615027; +86-580-2615024, Fax +86-580-2616545, Email liangwq@usx.edu.cn; zjy2038689@sina.com

International Journal of Nanomedicine downloaded from https://www.dovepress.com/
For personal use only.

Abstract: Nanotechnology has profoundly transformed medical science, with orthopedics experiencing significant advancements in diagnostic techniques, drug delivery systems, and tissue regeneration. The complex nature of orthopedic tissues presents substantial challenges for conventional therapeutic interventions, but the development of nanomaterials with specialized chemical, physical, and biological properties has facilitated the creation of novel treatment modalities. Nanotechnology has significantly advanced orthopedic care by enabling targeted drug delivery, enhanced implant performance, and improved diagnostic tools. This review uniquely integrates recent breakthroughs in biocompatible nanomaterials, focusing on their clinical translation and regulatory challenges. It highlights the complexity of orthopedic tissues and the limitations of conventional therapies, emphasizing how nanomaterials address these through controlled drug release, and improved tissue regeneration. Key sections address advancements in drug delivery systems, innovative implant technologies, toxicity issues, and biocompatibility considerations. It also explores the existing regulatory landscape, challenges in clinical approval, and future directions for the successful translation of nanotechnologies in orthopedic care.

Keywords: orthopedics, nanomaterials, toxicity of nanomaterials, biocompatibility, orthopedic implants, drug delivery, diagnostics, rheumatoid arthritis, osteoporosis, osteoarthritis

Introduction

Orthopedic disorders represent the second leading cause of disability worldwide, imposing a significant economic burden. In the United States alone, these conditions account for an estimated $880 billion annually in healthcare costs.[1] Bone-related disorders have risen markedly in recent years, with osteoporosis now affecting over 50% of Americans aged 50 and older.[2] In time diagnosis and management of bone-related disorders are critical to minimizing both morbidity and, in certain cases, mortality. While these conditions are not always directly life-threatening, complications, particularly in older adults, can significantly increase health risks. For instance, osteoporotic fractures, especially of the hip, are associated with high morbidity and a notable rise in mortality due to subsequent immobility and related complications. Among the most prevalent musculoskeletal disorders are rheumatoid arthritis (RA), osteoarthritis (OA), and osteoporosis (OSP), with a higher incidence observed in adult women. RA, an autoimmune condition, is characterized by chronic joint inflammation and often leads to progressive disability if left untreated.[3] Osteoarthritis (OA) is the most common degenerative joint disorder, characterized by alterations in chondrocyte morphology and a progressive

Received: 6 March 2025
Accepted: 27 June 2025
Published: 21 July 2025

© 2025 Xia et al. This work is published and licensed by Dove Medical Press Limited. The full terms of this license are available at https://www.dovepress.com/terms.php and incorporate the Creative Commons Attribution – Non Commercial (unported, v4.0) License (http://creativecommons.org/licenses/by-nc/4.0/). By accessing the work you hereby accept the Terms. Non-commercial uses of the work are permitted without any further permission from Dove Medical Press Limited, provided the work is properly attributed. For permission for commercial use of this work, please see paragraphs 4.2 and 5 of our Terms (https://www.dovepress.com/terms.php).

decline in the extracellular matrix (ECM). This degeneration often leads to significant biomechanical dysfunction and joint instability, contributing to impaired mobility and quality of life.[4]

In contrast, osteoporosis is the gradual and progressive degradation of bone microarchitecture and a reduction in bone mineral density. This condition significantly elevates the risk of fractures, particularly in older adults.[5] Osteosarcoma survival rates significantly decline from an initial 70–80% to approximately 20–30% once the disease progresses to a metastatic stage.[6,7] The complex anatomical structure of orthopedic tissues presents considerable challenges for the effective pharmacological treatment of related disorders.[8] In recent years, nanotechnology has emerged as a valuable tool in the diagnosis and treatment of bone-related disorders, offering promising avenues for improved clinical outcomes.[9] The active application of nanotechnology has resulted in significant advancements in drug delivery systems and diagnosis, facilitating more targeted and efficient therapeutic intervention.[10]

Nanomedicine leverages nanoparticles in the treatment of bone disorders, offering numerous advantages.[11] These include increased drug concentration at the specific site of action, reduction in unintended drug distribution, enhanced transport of large drug quantities, improved solubility for hydrophobic compounds, and the ability to modify nanoparticle surfaces for precise and controlled delivery.[12] Achieving optimal therapeutic outcomes depends on the precise regulation of growth factor levels within biomaterial scaffolds, especially at the interfaces with healthy tissue.[13] Different nanomaterial-based drug delivery systems, including metallic nanoparticles (AuNPs), quantum dots (QDs), carbon nanotubes (CNTs), micelles, polymeric nanoparticles, liposomes, and dendrimers, have significantly advanced drug delivery and healthcare applications.[14–16] These delivery systems have been increasingly utilized to enhance the efficacy and precision of conventional therapies for bone-related disorders. Nanomaterials and nanocomposites have found extensive application in treating various bone conditions, including osteoarthritis, osteosarcoma, bone tumors, osteoporosis, autoimmune diseases, and bone regeneration and tissue repair.[17,18]

Despite notable advancements, persistent knowledge gaps significantly limit the clinical translation of nanotechnology-based orthopedics. These include incomplete understanding of long-term biocompatibility, particularly immune responses such as macrophage polarization and inflammasome activation, as well as the degradation behavior of nanomaterials through hydrolytic and enzymatic pathways.[19] Systemic toxicity, especially from metallic (titanium, silver) and polymeric (PLGA, PCL) nanoparticles, also remains inadequately characterized, with emerging evidence of off-target accumulation in secondary organs (liver, spleen) and potential epigenetic implications.[20] Addressing these gaps requires robust, standardized toxicokinetic models capable of predicting in vivo behavior over extended periods.[21]

To provide a comprehensive understanding of the field, this review is structured around different orthopedic conditions where nanotechnology has demonstrated promising therapeutic potential. Subsequent sections explore recent advancements in nano drug delivery systems, including condition-specific strategies summarized in tabular form. It further discusses the application of nanomaterials in orthopedic implants and diagnostics, supported by illustrative figures. Critical aspects such as nanoparticle toxicity mechanisms, biocompatibility evaluation, and standardized assessment methods are discussed in detail. In addition, regulatory considerations, the advantages and limitations of nanomaterials, and current challenges with potential solutions are addressed to provide a translational perspective. Finally, it concludes by summarizing key insights and future directions for safe and effective clinical integration of nanotechnology in orthopedic care.

This review provides a comprehensive overview of recent innovations in nanotechnology-based drug delivery for orthopedic disorders, with a focus on their clinical utility and therapeutic promise.

Osteoarthritis

Osteoarthritis is a prevalent joint disorder and a leading cause of disability worldwide, with an increasing global prevalence.[22] Osteoarthritis (OA) involves complex pathological changes within the synovial joint, including degeneration of hyaline cartilage, subchondral bone remodeling, synovial tissue hypertrophy, increased angiogenesis, and instability of tendons and ligaments. These alterations collectively impair joint function and drive disease progression.[23] Systemic osteoarthritis therapies face major limitations, including rapid clearance after intra-articular injection, poor cartilage targeting, and significant side effects from repeated high-dose administration, gastrointestinal, renal, and cardiovascular complications. Moreover, conventional drug delivery systems lack precision, often failing to

reach inflamed or degraded tissue effectively, which compromises therapeutic outcomes. These challenges limit the long-term efficacy of current treatments and highlight the need for more targeted and sustainable delivery strategies.[24]

Nanotechnology-based drug delivery systems have been widely investigated to enhance the pharmacokinetics and pharmacodynamics of osteoarthritis treatments. Biocompatible and biodegradable materials, such as hydrogels and polymeric nanoparticles, enable effective therapy with minimal toxicity.[25] This approach aims to deliver targeted and sustained therapeutic effects, minimizing systemic side effects and offering long-term benefits. By improving delivery precision, nanotechnology holds considerable promise in advancing osteoarthritis treatment.[26]

A recent investigation aimed to develop kartogenin-loaded nanocrystal-polymer particles as a controlled release system for the effective treatment of OA. These particles demonstrated a significant drug loading capacity and prolonged release over an extended period, enhancing therapeutic efficacy. Kartogenin, a small heterocyclic compound, is known for its potential in protecting and regenerating cartilage, making it a promising candidate for OA management. The fabrication process involved encapsulating kartogenin nanocrystals within a biodegradable polymer matrix, ensuring both stability and sustained release properties. Preclinical testing in a murine model of mechanistic OA revealed that the kartogenin-loaded polymeric particles exhibited superior biological activity as compared to simple kartogenin solution, resulting in improved therapeutic outcomes. These findings suggest that the development of this nanocrystal-polymer particle system could significantly advance drug delivery techniques for osteoarthritis, offering more effective treatments. Further investigation in vivo is warranted to fully evaluate the clinical potential and safety of this novel drug delivery platform.[27] He et al developed and documented a cationic multi-arm avidin nanocarrier to facilitate the targeted transport of various small-molecular OA drug.[28] The compact size and favorable electrostatic properties of avidin facilitate its deep penetration into the cartilage.[29] The study by Kang et al focused on the development of thermoresponsive nanospheres synthesized from chitosan oligosaccharide conjugated with pluronic F127 and a carboxyl group. These nanospheres were engineered to facilitate the simultaneous and independent co-release of diclofenac and kartogenin within a single system, aiming to provide a combination therapy for osteoarthritis. The nanospheres demonstrated an initial rapid release of diclofenac, followed by a sustained release of kartogenin in response to temperature variations. Both in vitro and in vivo studies revealed that these temperature-responsive nanospheres possess dual functionalities, anti-inflammatory and chondroprotective properties, making them promising candidates for osteoarthritis treatment.[30]

Osteosarcoma

Osteosarcoma, the most prevalent malignant bone tumor, presents treatment challenges due to the adverse effects of chemotherapy and the development of drug resistance.[31] Advancements in nanotechnology have led to the development of nanoparticles that can target bone tumors, deliver drugs and genes precisely, and ensure controlled release. This improves drug efficacy, extends circulation time, and reduces side effects.[32] Hyaluronic acid nanogels loaded with cisplatin and doxorubicin showed promising results in treating osteosarcoma, offering prolonged circulation and enhanced stability. The combination therapy demonstrated synergistic effects, improving tumor targeting and treatment efficacy.[33] Au et al created pH-responsive nano metal-organic structures for targeted delivery of zoledronate in cancer bone metastases. Using folate to enhance tumor uptake, they achieved an 80–85% improvement in antitumor efficacy, attributed to better drug absorption and extended release.[34]

Osteoporosis

Osteoporosis (OSP) is a condition characterized by weakened bones, often caused by hormonal changes and deficiencies in vitamin D or calcium, which leads to reduced bone density and increased fracture risk.[35] OSP results from an imbalance in bone maintenance, marked by increased osteoclast activity and accelerated bone remodeling. Elevated cytokines and pro-inflammatory factors promote bone resorption while inhibiting bone formation.[36] OSP is classified into primary and secondary types based on its etiology. Primary osteoporosis is associated with aging and reduced sex hormone production, while secondary osteoporosis arises from other underlying health conditions. Primary osteoporosis is further subdivided into postmenopausal osteoporosis (type I), which involves increased bone resorption due to estrogen deficiency, and age-related osteoporosis (type II), characterized by a decline in bone density due to impaired bone formation.[37]

The systemic administration of anti-osteoporotic drugs often leads to adverse effects due to off-target interactions with various tissues, highlighting the need for new therapeutic agents that offer better efficacy, fewer side effects, and more convenient administration methods. Nanomaterial-based drug delivery systems present a promising alternative for osteoporosis treatment, as they allow for controlled drug release, increased drug concentration at targeted sites, reduced side effects, and enhanced bone regeneration. A study developed a drug delivery system using mesoporous hydroxyapatite nanoparticles modified with poly(N-isopropylacrylamide) brushes, which were loaded with simvastatin to address local deficiencies caused by osteoporosis.[38]

Ryu et al developed alendronate-conjugated nano-diamonds as a targeted treatment for osteoporosis. The study demonstrated that these nano-diamonds specifically accumulate in bone tissue, exhibit a strong affinity for hydroxyapatite, and enhance alkaline phosphatase activity. Additionally, they showed effective bone targeting in vivo, highlighting their potential for improving osteoporosis therapy through a synergistic approach.[39] Nagai et al created transdermal formulations of solid raloxifene nanoparticles to address its low bioavailability. The addition of a permeation enhancer facilitated significant skin absorption, leading to notable therapeutic effectiveness in treating osteoporosis in an ovariectomized rat model.[40]

Nanotechnology has been utilized to improve the bioavailability of calcium supplements, potentially reducing the risk of osteoporosis.[41] The use of nano-hydroxyapatite (HA) crystals offers promising opportunities for enhancing the effectiveness of HA supplements in osteoporosis management.[35] The study conducted by Luiz et al shown that nano-HA has the potential to augment the process of new bone creation during the early stages of healing in vivo.[42] Polymethylmethacrylate (PMMA) is commonly used as bone cement in clinical settings for its rapid curing time and mechanical durability, particularly in the treatment of osteoporotic vertebral compression fractures (OVCFs).[43] However, its use is associated with post-surgical complications, including monomer toxicity, excessive rigidity, and thermal necrosis due to high polymerization temperatures.[44,45] To improve the biocompatibility of polymethyl methacrylate (PMMA) bone cement, zirconium dioxide (ZrO_2) and barium sulfate ($BaSO_4$) nanoparticles were incorporated into the PMMA matrix. Functionalized $BaSO_4$ nanoparticles increased osteoblast adhesion two-fold compared to unmodified $BaSO_4$, while both functional and non-functional ZrO_2 nanoparticles enhanced osteoblast adhesion by approximately 1.5 times compared to unmodified ZrO_2. The addition of these nanoparticles showed a positive correlation with osteoblast adherence and cell viability, compared to unmodified PMMA.[46] Calcium Phosphate Cement (CPC) is known for their exceptional biocompatibility and structural resemblance to real bone.[47] The clinical application of CPC is often constrained by challenges related to its injectability, degradation rate, and low mechanical strength. A study aimed at overcoming these limitations incorporated silica nanoparticles into CPC. The results demonstrated that nanosilica enhanced osteoblast proliferation, improved mechanical strength, and shortened handling time. Additionally, the introduction of colloidal silica particles reduced the setting time of the cement, with higher silica concentrations further decreasing cement porosity.[48]

Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a chronic, progressive systemic autoimmune disorder characterized by symmetrical joint inflammation, which results in cartilage degradation, bone erosion, swelling, and pain.[49] These symptoms lead to joint deformity and impaired physical function. Additionally, as the condition progresses, RA may progressively affect other organs.[50] There are three primary factors, namely genetic, environmental, and autoimmune, that play a significant role in predisposing individuals to rheumatoid arthritis (Figure 1).[51]

The various diagnostic modalities utilized for rheumatoid arthritis (RA) encompass traditional radiography, ultrasonography (US), computed tomography (CT), and magnetic resonance imaging (MRI).[53] RA diagnosis using imaging criteria requires assessing the number and size of affected joints and the duration of synovitis. Patients must have involvement of at least two medium or large joints, one small joint, or synovitis lasting more than six weeks.[54] Conventional radiography, particularly X-ray, is the primary method for assessing structural damage in RA joints.[55] Radiographic scans of healthy individuals show intact joints with clear cortical bone boundaries. Markides et al effectively tracked the movement of stem cell populations in arthritic joints of mice using superparamagnetic iron oxide nanoparticles (SPIONs) combined with magnetic resonance imaging (MRI). This approach allowed for the

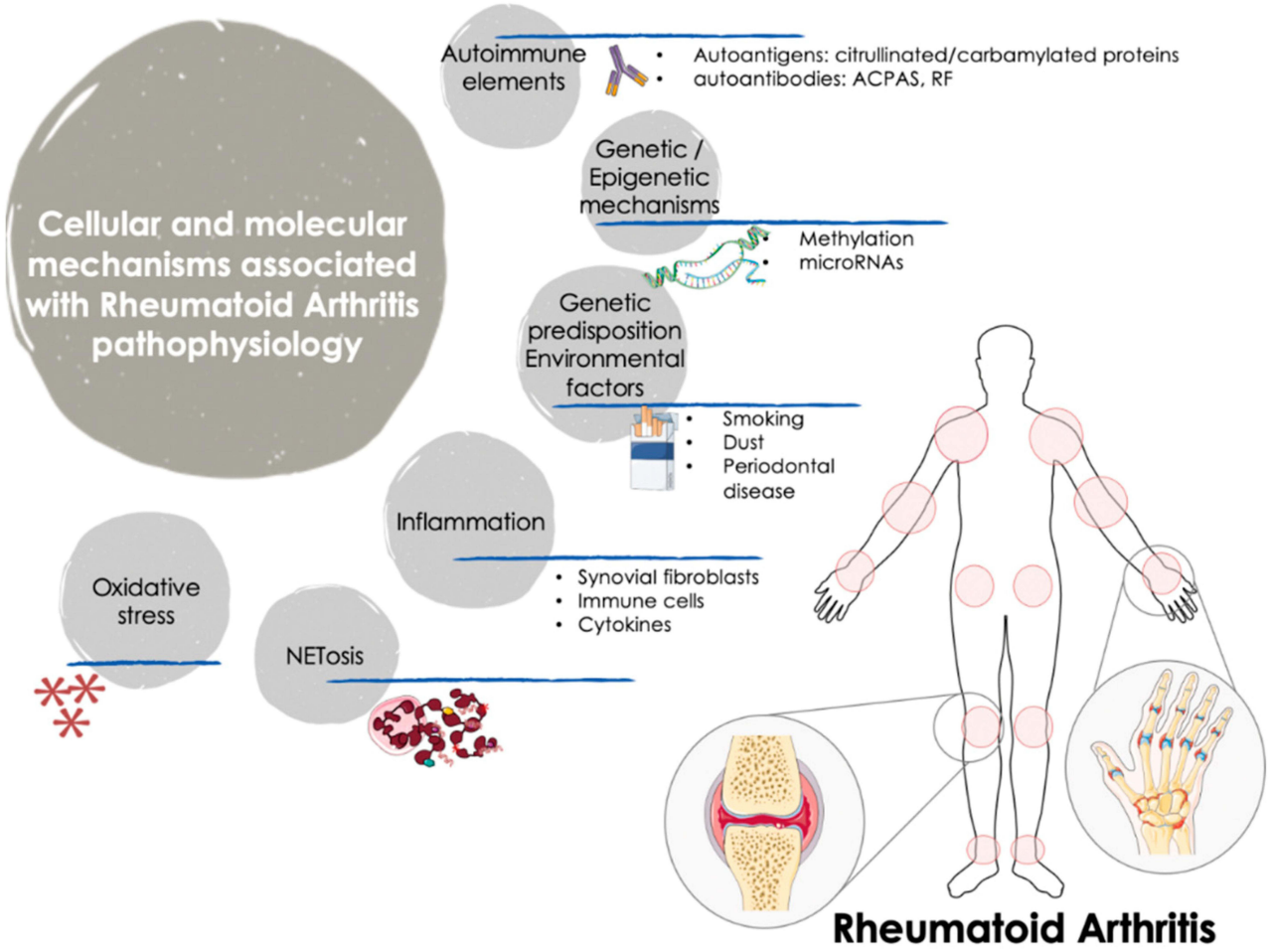

Figure 1 Cellular and molecular mechanisms in RA pathogenesis: RA development involves genetic and environmental interactions triggering autoimmune responses, characterized by autoantigens, autoantibodies, and inflammatory mediators released by activated immune cells. Emerging evidence has implicated additional mechanisms, such as oxidative stress, NET formation, and regulatory layers of gene expression including epigenetic modifications (eg, DNA methylation) and post-transcriptional control by microRNAs, in RA pathogenesis. Adapted from Lopez-Pedrera C, Barbarroja N, Patiño-Trives AM, et al. Effects of biological therapies on molecular features of rheumatoid arthritis. Int J Mol Sci. 2020;21(23):9067. Under the terms and conditions of the Creative Commons Attribution (CC BY) license (http://creativecommons.org/licenses/by/4.0/).[52]

successful monitoring of mesenchymal stem cells (MSCs) within rheumatic joints in murine models of RA.[56] Chen et al developed a specialized nanoparticle platform for labeling and monitoring T cells in vivo, utilizing carboxylated-PEG-SPIONs (IOPC), which can be easily conjugated with amide-containing compounds. The team successfully conjugated IOPC with an anti-CD3 monoclonal antibody and created MRI contrast agents capable of selectively binding to T cells.[57] Magnetic fibrin nanoparticles (MFNPs) have been utilized for the early detection of RA. Periyathambi et al attached folic acid to MFNPs (FA-MFNPs) to target activated macrophages in the synovial knee joints of rats. The study demonstrated that these nanoparticles exhibit high specificity as MRI contrast agents, effectively identifying phagocytic macrophages within joint tissues.[58]

Nanoparticles, including liposomes, micelles, polymeric NPs, and metallic or biomaterial-based carriers, hold significant promise for the targeted delivery of therapeutic agents in the treatment of RA (Table 1).[59–62] These systems are designed to leverage specific properties that enhance passive targeting, particularly through selective accumulation at sites of inflammation within the joints.[63] For example, studies have shown that nanoparticles in the size range of 45–115 nm exhibit varying levels of anti-inflammatory efficacy, with 115 nm particles demonstrating the greatest effect.[64] The aggregation of nanoparticles in inflamed tissues is influenced by several physicochemical properties, including surface charge, hydrophilic or hydrophobic characteristics, and particle structure or size.[65]

Nanoparticles composed of chitosan demonstrate considerable potential in enabling the targeted delivery of pharmaceutical agents to arthritic tissues. A key issue with non-targeted drug delivery is the potential for drug accumulation in

Table 1 Illustrates the Prevailing Passive Targeted Drug Delivery Systems Employed for RA Treatment Within the Past Five Years

Nanocarriers	Drug	Models	Advantages	Reference
PEG-liposomes	Dex	Mice model	Increased anti-RA activity	[66]
PCL-PEG micelles	Dex	Rats model	Therapy was both safe and efficient.	[60]
Lecithin/sodium glycocholate-micelles	Dex palmitate	Rats model	Increased bioavailability and reduced joint irritation.	[67]
Carbon nanotubes (CNTs)	MTX	NA	The effectiveness of FLS was significantly enhanced.	[68]
IL1raK72-CS Nanoparticles	IL1ra	Rats model	Exhibited an extended duration of action.	[69]
Chitosan NPs	Hydroxychloroquine	Rabbit	Improved stability, controlled drug release	[70]
Gold NPs	Diclofenac	Rat, Mouse	Biocompatibility, precise targeting to inflammatory sites	[71]
Albumin-based NPs	Etanercept	Mouse	Reduced immunogenicity, prolonged circulation	[72]
Polymeric Micelles	Tocilizumab	Mouse	Controlled release, enhanced cellular uptake	[73]
Folic acid-conjugated NPs	Methotrexate	Rat	Targeted delivery to macrophages in synovial joints	[74]

organs like the liver, kidneys, and spleen. However, non-targeted agents like iron-saturated bovine lactoferrin (Fe-bLf) and curcumin are preferred due to their minimal adverse effects on other tissues. In contrast, drugs like methotrexate, which exhibit potent therapeutic effects, are deliberately directed towards arthritic tissues to enhance their efficacy.[8] Numerous studies have investigated the use of methotrexate in targeted therapies. One such study developed dextran sulfate-grafted-MTX (DS-g-MTX) to selectively target the scavenger receptor, which is overexpressed on macrophages, as a potential treatment for RA. The DS-g-MTX micelles, with a diameter of approximately 100 nm, demonstrated promising potential for efficient active targeting in collagen-induced arthritis (CIA) models, both in vitro and ex vivo.[75]

Curcumin shows promise as a therapeutic agent for the treatment of osteoporotic conditions (OSP); however, its clinical application is hindered by limitations such as poor solubility, physicochemical instability, low bioavailability, rapid degradation, and suboptimal pharmacokinetics. To address these challenges, nano-formulations have been proposed to enhance its efficacy. Notably, the development of a complex comprising gold nanoparticles and cyclodextrin incorporating curcumin has demonstrated effectiveness in inhibiting osteoclastogenesis from bone marrow-derived macrophages. This drug delivery system functions through the inhibition of the RANKL activator, thereby improving curcumin's therapeutic outcomes.[76] Rheumatoid arthritis agents like low-density lipoprotein, dextran sulfate, hyaluronic acid, and folic acid are employed to target inflammation-associated cells and macrophages.[77,78] Table 2 provides a comprehensive overview of the diverse applications of nanodrugs in the context of delivering therapeutic agents to cartilage and bone tissues.

Table 2 Bone and Cartilage Drug Delivery Systems Using Nano-Formulations

Disease	Nanodrugs	Outcomes	Reference
Osteoarthritis	The fusion of insulin-like growth factor 1 (IGF-1) with a heparin-binding domain (HpB)	The study observed a decrease in cartilage degradation in Lewis rats of the male gender.	[79]
Osteoarthritis	The lipid nanoparticles (NPs) loaded with diacerein (DC) and altered with chondroitin sulfate were utilized in this study.	The Charles Foster rat exhibits an increased ability for cartilage regeneration.	[80]
Osteoarthritis	The anti-Hif-2α siRNA was condensed using polyethyleneimine (PEI) that was modified with a cationic amphipathic peptide (CAP).	The study observed a substantial decrease in the process of cartilage degradation within the joints of male Chinese Kun Ming mice.	[81]

(*Continued*)

Table 2 (Continued).

Disease	Nanodrugs	Outcomes	Reference
Osteoarthritis	The utilization of alginate-chitosan polymeric nanocarriers for encapsulating iron-saturated bovine lactoferrin.	The study resulted in a substantial alteration of disease-modifying activity through its impact on gene expression.	[82]
Rheumatoid arthritis	The incorporation of MTX and SPIONs superparamagnetic iron oxide nanoparticles into anti-CD64 antibody-conjugated PLGA (poly(lactic-co-glycolic acid)) nanoparticles.	Nanoparticles (NPs) have the potential to enhance the efficacy of methotrexate (MTX) while minimizing harm to unaffected tissues and organs. Furthermore, they offer a non-invasive and targeted imaging modality for rheumatoid arthritis.	[83]
Rheumatoid arthritis	Ascorbyl palmitate, an antioxidant, used to make MTX-Aspasomal formulation	Enhanced tissue penetration, diminished adverse effects, and lower toxicity shown in Wistar rats.	[84]
Rheumatoid arthritis	The incorporation of MTX inside a nanogel matrix composed of mPEG−P (LP-co-LC)	This study explored the reduction-responsiveness and glutathione-triggered release behavior of MTX.	[85]
Rheumatoid arthritis	Dextran sulfate was grafted with MTX.	Exceptional scavenger receptor (SR) targetability, increased accumulation, and effective inflammatory suppression in activated RAW 264.7 cells.	[75]
Osteoporosis	The siRNA complexed with polyethyleneimine (PEI) and encapsulated within nanosized poly(lactic-co-glycolic acid) (PLGA) capsules.	The inhibition of osteoclast growth and the decrease in osteoclast activity.	[86]

Nanotechnology in Orthopedic Implants

The use of nanoparticles in orthopedic applications has gained significant attention due to their unique properties, including enhanced surface area, potential for targeted drug delivery, and molecular interactions with biological systems. However, successful integration requires a comprehensive understanding of their synthesis, characterization, and optimization. Nanoparticles can be synthesized through various techniques, such as chemical vapor deposition, sol-gel methods, electrospinning, and bio-inspired synthesis, each offering distinct advantages in size control, surface modification, and scalability.[87] The synthesis method directly impacts the physicochemical properties of nanoparticles, which are essential for their functionality in orthopedic applications. After synthesis, nanoparticles undergo thorough characterization to assess their size distribution, morphology, surface charge, and chemical composition. Common characterization techniques, transmission electron microscopy (TEM), scanning electron microscopy (SEM), dynamic light scattering (DLS), and X-ray diffraction (XRD), ensure the structural integrity and reproducibility of the particles.[88] These analyses are pivotal for confirming the nanoparticles' suitability for clinical applications, particularly in ensuring their safety and therapeutic efficacy. In addition to characterization, the optimization of nanoparticles is a crucial step to enhance their performance for orthopedic use.[89] This encompasses refining parameters such as particle size, surface functionalization, drug encapsulation efficiency, and controlled release kinetics, all of which significantly affect the biocompatibility, cellular uptake, and therapeutic outcomes in bone regeneration and tissue repair.[90] The optimization process aims to maximize the nanoparticles' potential for targeted therapy, offering improved precision in drug delivery and supporting the regeneration of damaged orthopedic tissues.[90] A deeper understanding of these factors is fundamental for advancing nanoparticle-based therapies, ensuring that they meet the rigorous demands of clinical practice in orthopedics.

Recent advancements in nanotechnology have significantly enhanced the performance of orthopedic implants through strategic material selection, surface modifications, mechanical reinforcement, and smart drug delivery systems. Nanostructured titanium alloys, produced via severe plastic deformation (SPD) techniques, exhibit superior strength and ductility, making them ideal for load-bearing applications.[91] Nanophased hydroxyapatite (nHAp) ceramics demonstrate improved fracture toughness and bioactivity, promoting osseointegration.[92] Surface modifications, such as titanium dioxide (TiO_2) nanotube arrays, have been shown to enhance osteoblast adhesion, proliferation, and differentiation, as

well as reduce bacterial colonization, thereby improving implant stability and longevity.[93] Incorporating nanocomposites like graphene oxide/hydroxyapatite (GO/HAp) and carbon nanotube-reinforced HAp into implant materials has led to increased elastic modulus and fracture resistance, while maintaining biocompatibility and promoting bone ingrowth.[94] Additionally, mesoporous silica nanoparticles (MSNs) have been utilized for controlled and sustained release of osteoinductive factors such as bone morphogenetic protein-2 (BMP-2) and dexamethasone, facilitating enhanced osteoblast differentiation and bone regeneration in both in vitro and in vivo models.[95] These innovations collectively contribute to the development of next-generation orthopedic implants that are not only mechanically robust but also biologically active and therapeutically responsive, addressing the complex demands of bone repair and regeneration.

Nanomaterials offer a promising approach in orthopedic grafts, potentially reducing the need for biological bone elements. Extensive research in bone tissue engineering has focused on nanoparticles to enhance osteointegration, stimulate osteoblast activity, and address bone pathologies (Figure 2). Various nanoscale materials, including nanorods, carbon nanotubes, nano-cubes, quantum dots, nanoflowers, and metal-organic frameworks, have been investigated for medical implants.[96,97] The integration of implants into bone tissue has been enhanced through nanotextured surfaces, which promote osteoblast functionality and proliferation. Additionally, the application of severe plastic deformation (SPD) has demonstrated potential for improving the mechanical properties and biocompatibility of titanium implants.[98,99]

Table 3 highlights various nanoparticle types used in orthopedic implants, while also emphasizing the associated challenges such as biodistribution, long-term biocompatibility, and non-specific absorption. Nanoparticle-based implants

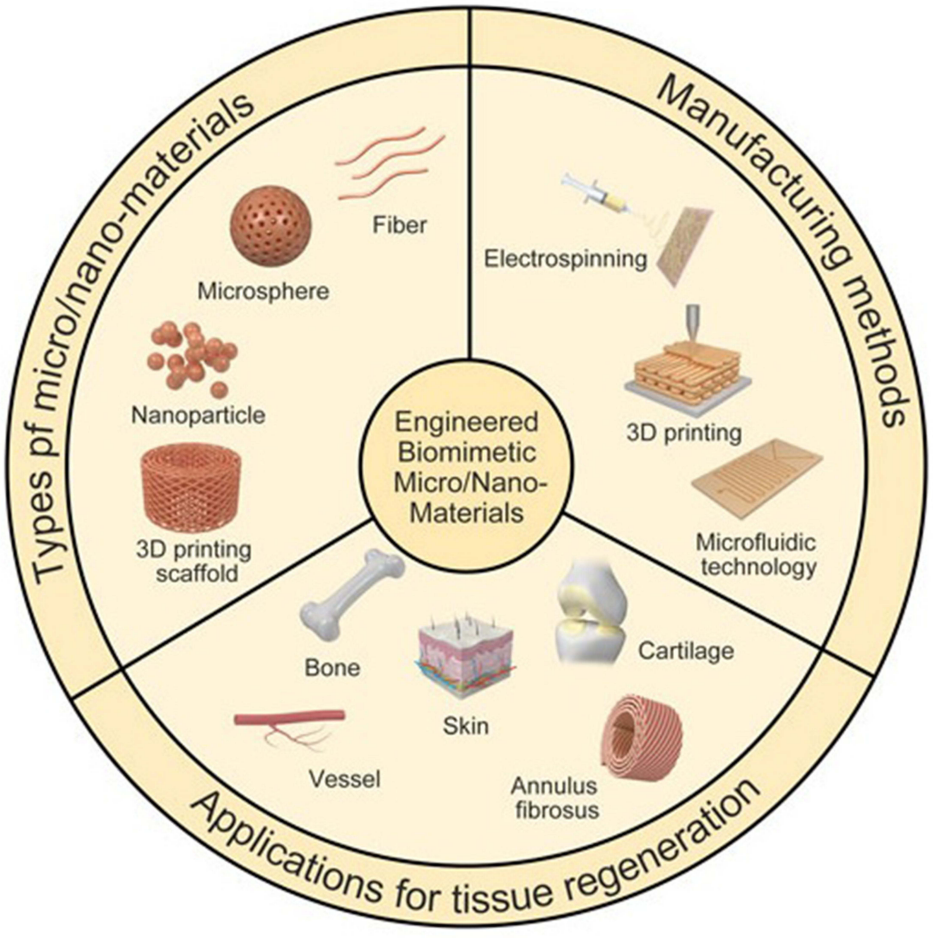

Figure 2 Schematic representation of micro/nano-engineered materials and their applications in tissue regeneration. There are diverse structural formats including nanofibers, nanoparticles, microspheres, and 3D-printed scaffolds designed to mimic natural tissue architecture, with representative applications in bone healing, and tissue engineering. Adapted from Han F, Meng Q, Xie E, et al. Engineered biomimetic micro/nano-materials for tissue regeneration. Front Bioeng Biotechnol. 2023;11:1205792. under the terms and conditions of a creative commons licence 4.0 (http://creativecommons.org/licenses/by/4.0/).[100]

Table 3 Comparative Analysis of Different Nanoparticle Types in Orthopedic Implants and Scaffolds for Bone Regeneration

Nanoparticle Type	Application in Orthopedics	Key Findings	Challenges/Limitations	References
Gold Nanoparticles (AuNPs)	Bone regeneration, implant coatings	Enhanced osteointegration, reduced bacterial adhesion, and controlled drug release.	Potential toxicity due to accumulation in the liver and spleen, challenges in large-scale production.	[104]
Silver Nanoparticles (AgNPs)	Antimicrobial coatings for implants	Effective antimicrobial properties, reduced infection rates in bone implants.	Cytotoxicity at higher concentrations, concerns over long-term exposure and biocompatibility.	[105]
Hydroxyapatite Nanoparticles (HA)	Bone scaffolds, drug delivery systems	Improved bone regeneration, enhanced cell adhesion, and osteogenic differentiation.	Slow degradation rate, challenges in maintaining long-term stability and functional degradation.	[106]
Magnetic Nanoparticles (MNPs)	Drug delivery, targeting, and imaging	Stimuli-responsive, allows magnetic targeting for localized drug delivery.	Limited biocompatibility and possible long-term accumulation in tissues, issues with controlling magnetic field effects.	[107]
Polymeric Nanoparticles (PLGA, PCL)	Controlled drug delivery, scaffolds	Good biocompatibility, enhanced drug loading, and sustained release.	Potential for incomplete degradation and delayed clearance, issues with batch-to-batch consistency.	[108]
Carbon Nanotubes (CNTs)	Scaffold reinforcement, drug delivery	Increased mechanical strength of scaffolds, improved cell infiltration, and bone regeneration.	Poor biocompatibility, risk of fibrous encapsulation, difficulty in surface functionalization.	[109]
Quantum Dots (QDs)	Imaging, drug delivery systems	Enhanced imaging capabilities, drug loading, and controlled release.	Potential cytotoxicity, concerns over long-term stability in biological environments.	[110]
Cerium Oxide Nanoparticles (CeO_2)	Bone regeneration, oxidative stress reduction	Antioxidant properties, promoting osteoblast differentiation and bone healing.	Limited long-term studies, potential accumulation in tissues, and high surface reactivity.	[111]
Dendrimers (Polyamidoamine)	Targeted drug delivery systems	High drug loading capacity, enhanced tissue penetration, and controlled release.	Potential toxicity due to their cationic surface charge and incomplete biodegradation.	[112]
Calcium Phosphate Nanoparticles	Bone tissue engineering, scaffolds	Promotes bone mineralization, osteogenic differentiation of stem cells.	Slow resorption rates, difficulty in achieving optimal material properties.	[113]

offer an increased surface area, promoting a favorable environment for bone regeneration and reducing the risk of infections. The use of nanoparticles in implants often requires a coating that functions as a scaffolding mechanism. Studies have shown that extracellular adhesion proteins interact more effectively with nanophase implant scaffolds than with traditional implant surfaces, enhancing protein absorption and creating conditions that support osteoblast adhesion, bone growth, and implant integration with bone.[101] A study by Kon et al demonstrated the effectiveness of nanocomposite implants in treating osteochondral knee abnormalities. Additionally, nanomaterial-based scaffolds have been utilized to improve treatments for peripheral nerve damage.[102] Silver-impregnated collagen scaffolds are used to enhance protein absorption, thereby facilitating nerve healing and accelerating the regeneration process.[103]

Personalized nano-orthopedic implants, especially those integrating 3D-printed scaffolds with bioactive nanomaterials, are revolutionizing bone regeneration therapies. Recent advances focus on the design of nanocomposites to enhance both mechanical strength and biological performance.[114] For example, PLA scaffolds reinforced with Graphene Oxide (GO) and Hydroxyapatite (HAp) have demonstrated ~40 MPa compressive strength and accelerated osteoblast differentiation due to synergistic bioactivity.[115] Similarly, Carbon Nanotube (CNT)-reinforced PCL scaffolds showed a 300% increase in tensile modulus while retaining high porosity essential for bone ingrowth.[116] Silica nanoparticles (SiO_2), when incorporated into alginate/gelatin hydrogels, enhanced angiogenesis and mineralization, key for vascularized bone tissue.[117] These innovations are often realized via high-resolution 3D printing technologies Digital Light Processing (DLP) enables <50 μm accuracy in fabricating nano-TiO_2-based craniofacial implants.[114] Furthermore,

biofunctionalization and therapeutic integration into scaffolds is a growing area. Mesoporous silica nanoparticles (MSNs) have enabled sustained release of growth factors like BMP-2 and TGF-β from 3D-printed constructs,[118] aiding in guided tissue regeneration. In terms of antimicrobial function, Ag-nanoparticle-coated Ti-6Al-4V implants significantly reduced bacterial biofilm formation (>90%), addressing a major post-operative complication.[119] In vivo performance is also promising complete trabecular bone regeneration within 12 weeks in rabbits using β-TCP/nano-ZnO scaffolds.[120] Additionally, multi-material 3D printing approaches—such as PEEK/nanodiamond composites—have improved load-bearing capacity in spinal implants.[121] Clinically, FDA-cleared implants like OsteoFab® now feature nano-surface modifications to improve osseointegration.[122] Together, these advances underline a paradigm shift where nanomaterial-enhanced, patient-specific implants offer superior osteointegration, strength, and biological function.

Recent studies have highlighted the importance of understanding the degradation rates and long-term biocompatibility of nanomaterials used in bone tissue engineering. For instance, polyhydroxybutyrate-chitosan/graphene oxide nanocomposite scaffolds exhibited approximately 30% degradation over 100 days, indicating a controlled degradation profile suitable for bone regeneration applications.[123] Additionally, nanocomposite hydrogels incorporating strontium and iron-substituted hydroxyapatite demonstrated sustained degradation without causing acute inflammation or adverse effects in vivo, suggesting their potential for long-term application in bone repair.[124] Moreover, magnesium-based composite calcium phosphate cements have shown enhanced compressive strength and controllable degradation rates, promoting osteogenesis and angiogenesis in vertebral defect models, with no observed systemic toxicity.[125] Furthermore, graphene oxide/chitosan/hydroxyapatite composite membranes have been reported to enhance osteoblast adhesion and guided bone regeneration, with degradation rates aligning with bone healing timelines.[126] However, challenges remain in comprehensively assessing the long-term biocompatibility of various nanomaterials, necessitating further research to establish standardized evaluation methods and ensure their safe clinical application.

The incorporation of Artificial Intelligence and Machine Learning into orthopedic nanomedicine provides a robust platform for accelerating rational design, reducing translational attrition, and advancing toward truly personalized therapeutic solutions.[127] Future research should prioritize the development of interoperable AI frameworks and open-access, well-annotated datasets to ensure the reliability and generalizability of predictive models in clinically relevant scenarios. Artificial Intelligence (AI) and Machine Learning (ML) are increasingly recognized as transformative computational tools in the modeling, prediction, and optimization of nanoparticle behavior within complex biological systems pertinent to orthopedic applications. Unlike conventional trial-and-error methodologies, these data-driven approaches enable the systematic and precise design of nanomaterials, thereby improving both efficacy and efficiency in preclinical development.[128]

In the context of nanoparticle engineering, a variety of ML algorithms including random forest classifiers, support vector machines (SVMs), and artificial neural networks can be trained on large-scale datasets comprising physicochemical properties and associated biological responses (particle size, morphology, surface charge, ligand specificity versus cellular uptake, cytotoxicity, and targeting precision). Such models facilitate high-throughput in silico screening of formulation parameters, allowing for the rational identification of optimal nanoparticle configurations tailored to specific orthopedic targets such as osteoblasts, chondrocytes, or macrophages. Moreover, AI-driven predictive models have demonstrated the capability to simulate nanoparticle degradation kinetics under variable physiological conditions, such as altered pH in synovial fluid or elevated pro-inflammatory cytokine levels, by leveraging historical degradation datasets. Deep learning techniques have also been applied to histological imaging and fluorescence microscopy data for automated quantification of biodistribution and tissue penetration, thereby minimizing observer bias and enhancing reproducibility.[129–131]

Reinforcement learning (RL) algorithms offer additional promise in dynamically regulating drug release profiles in smart-responsive nanocarriers. Through feedback loops informed by biosensors integrated within orthopedic implants or wearable devices, RL systems can modulate delivery mechanisms (swelling behavior, pore activation) in real-time, aligning therapeutic action with patient-specific biological cues such as inflammatory progression or tissue regeneration phases.[132] The integration of AI supports the creation of "digital twins"personalized computational avatars of patients that can be utilized to simulate and optimize nanoparticle-based treatment regimens prior to clinical application. This

approach holds particular relevance in orthopedics, where variability in mechanical load, tissue architecture, and metabolic state presents challenges to standardized therapy.[133]

In recent years, significant advancements have been made globally in the field of orthopedic nanotechnology. In Germany, researchers have focused on developing nanocrystalline hydroxyapatite-based bone cements to improve bone regeneration and implant stability. A notable study investigated the osteogenic capacity of nanocrystalline bone cement in a weight-bearing defect at the ovine tibial metaphysis. The findings indicated that the nanocrystalline hydroxyapatite-based bone cement enhanced bone regeneration and provided long-term stability, making it a promising candidate for clinical applications in orthopedic surgeries.[134] Japanese researchers have made significant strides in enhancing implant osseointegration through the application of nHA composite coatings. A study explored the effects of a novel nHA coating on additively manufactured Ti-6Al-4V alloy implants. The results demonstrated that the nHA coating improved bone ingrowth and initial fixation, thereby enhancing the implant's biological performance. This advancement holds promise for improving the success rates of orthopedic implants, particularly in complex surgical procedures.[135] In Singapore, the development of smart-responsive nanomedicines has opened new avenues for targeted drug delivery in orthopedic applications. These nanomedicines can release therapeutic agents in response to the acidic environment of tumors or inflamed tissues, thereby enhancing the efficacy of treatments while minimizing systemic side effects.[136] The application of such smart nanomedicines in orthopedic settings could lead to more effective management of implant-related infections and inflammation.

In the United States, significant progress has been made in developing nanocomposite orthopedic bone cements. European researchers have concentrated on developing nano-hydroxyapatite (nHA) composite coatings for orthopedic implants. These coatings are designed to mimic the natural bone mineral, promoting better osseointegration and reducing the risk of implant failure. The integration of nHA with various polymers and metals has been explored to enhance the mechanical strength and biological compatibility of the implants.[137] A summary of selected ongoing and completed clinical trials relevant to nanotechnology applications in orthopedic care is presented in Table 4 (ClinicalTrials.gov, accessed May 2025). In China, the focus has been on developing smart-responsive nanomedicines for orthopedic applications. Research has been directed towards creating pH-responsive and temperature-sensitive drug delivery systems that can provide localized and controlled release of therapeutic agents. These advancements aim to improve the treatment of bone-related diseases and enhance the healing process post-surgery.[138]

Utilization of Nanotechnology in Diagnostic Applications

Nano-diagnostics utilizes nanostructures for tagging, tracking, and detecting signals, as well as enhancing or modifying them within living organisms. It also involves identifying biologically active chemicals to facilitate rapid disease diagnosis. Borse et al developed a lateral flow immunoassay (LFIA) using fluorescent cadmium telluride quantum dots and a double-antibody sandwich method to detect biomarkers related to inflammation, such as interleukin-6 (IL-6) and C-reactive protein. When compared to traditional ELISA, LFIA showed higher precision and sensitivity,

Table 4 Representative Clinical Trials on Nanotechnology in Orthopedic Applications: Advances in Drug Delivery, Implants, and Biocompatibility (ClinicalTrials.gov, Accessed May 2025)

Trial ID	Study Title	Focus Area	Status	Preliminary Results
NCT04615260	Rate of Bony Fusion Using NanoBone® Synthetic Bone Graft Versus Local Autologous Bone Graft	Bone grafting in orthopedic surgery	Completed	Assessment of bony fusion rates using NanoBone® synthetic bone graft compared to local autologous bone graft.
NCT06249906	Commercial Bone Implant Product Group and Micro-structured Bioceramic Group in Osteoarthritis Knee and Bone Loss	Osteoarthritis and bone loss treatment	Recruiting	Evaluation of commercial bone implant products and micro-structured bioceramic groups in treating osteoarthritis knee and bone loss.
NCT09543210	Nano-Coated Implants for Enhanced Osseointegration	Implant integration	Active, not recruiting	Study of nano-coated implants to enhance osseointegration and reduce implant failure rates.

demonstrating its potential for accurately assessing graft conditions.[139] Jin et al developed a non-invasive nanosensor for measuring nitric oxide levels, enabling real-time monitoring of osteoarthritis progression. The nanosensor was created by encapsulating 4-amino-5-methylamino-2′,7′-difluorofluorescein Diaminofluorescein-FM molecules within poly(lactic-co-glycolic acid) nanoparticles, designed for recyclability to enhance sensor functionality. In vitro experiments demonstrated a correlation between increased fluorescence intensity and changes in nitric oxide levels in chondrocytes. In vivo testing confirmed the method's effectiveness in quantifying nitric oxide concentration in the synovial fluid of a rodent osteoarthritis model.[140]

Recent advancements have introduced atomic force microscopy as a technique for examining the micromechanical properties of bone tissue (Figure 3). Hengsberger's study compared AFM with traditional optical microscopy, using a combination of nanoindentation and AFM to analyze compact and trabecular bone tissues. The analysis involved 24 indents on bone structural units, with a maximum stress of 5 mN. The results indicated that AFM effectively assessed the surface properties of biological structures, such as bone structural units, with greater accuracy than optical microscopy. AFM was particularly capable of identifying indentation zones and distinguishing the unique mechanical properties of each bone structural unit, a feature not achievable with optical microscopy.[141]

Mechanism of Nanoparticle Toxicity

The toxicity of nanoparticles presents a significant concern in their biomedical applications, particularly within orthopedics. Due to their diminutive size and increased surface area, nanoparticles interact with biological systems in ways that bulk materials do not, potentially inducing harmful effects. The underlying mechanisms of nanoparticle toxicity are multifactorial, and they largely depend on particle characteristics such as size, shape, surface chemistry, and charge, all of which modulate their interactions with cells and tissues (Figure 4).[143]

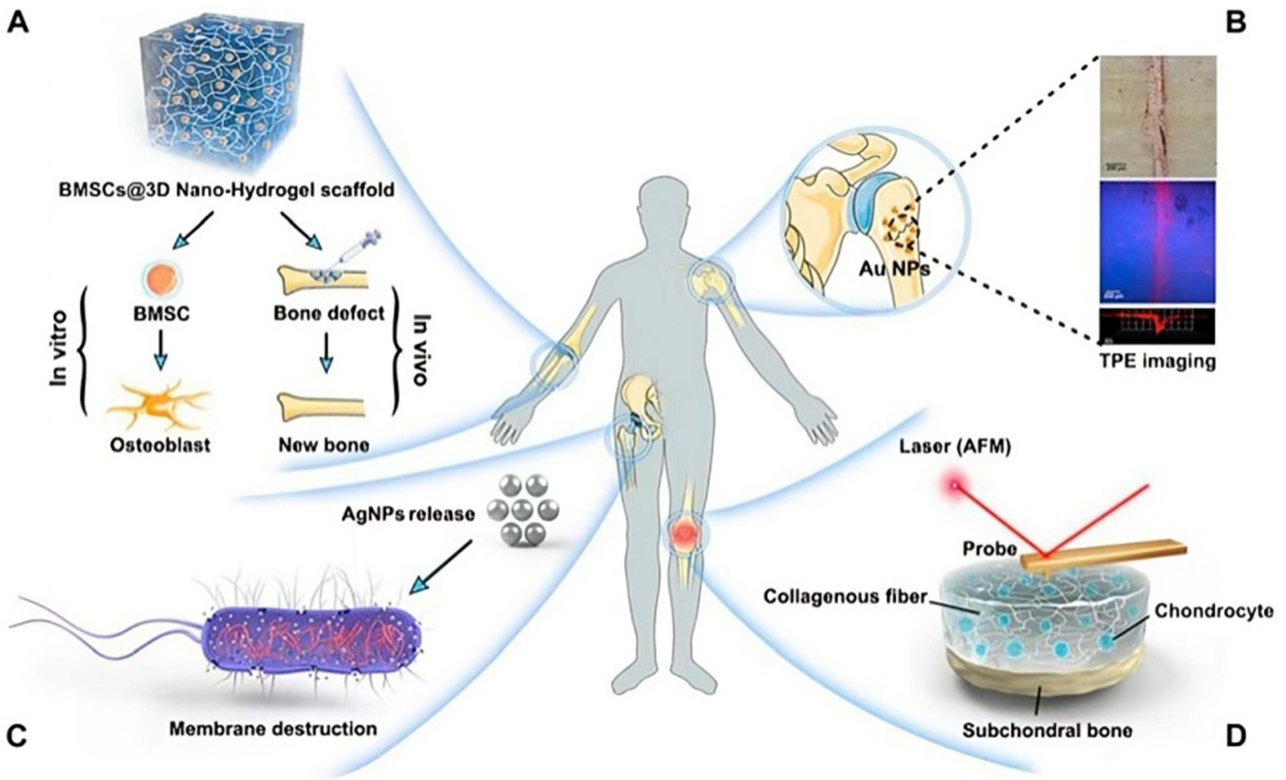

Figure 3 (**A**) Biomimetic tissue renewal nanoparticles, which are characterized by their innovative design, aim to mimic natural biological processes in order to regenerate damaged tissues. (**B**) Nanoparticulate magnetic resonance imaging (MRI) contrast agents offer a high-resolution imaging technique for skeletal disorders with less radiation exposure. (**C**) Development and manufacturing of drug delivery systems that incorporate nanotechnology to achieve specified functionality. (**D**) The application of Atomic Force Microscopy (AFM) in the preliminary diagnosis and nanomechanical analysis of degenerative joint diseases. Adapted from Qiao K, Xu L, Tang J, et al. The advances in nanomedicine for bone and cartilage repair. J Nanobiotechnology. 2022;20(1):141. under the terms and conditions of a Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/).[142]

A primary mechanism contributing to toxicity is the generation of reactive oxygen species (ROS), which results from the highly reactive surfaces of nanoparticles. When nanoparticles enter biological systems, they can interact with cellular components and induce oxidative stress, which damages cellular structures like lipids, proteins, and DNA. This oxidative damage can lead to serious pathological consequences, including cell dysfunction, inflammation, and apoptosis. In orthopedic applications, where tissue regeneration is crucial, such cellular disruptions may impede healing and lead to negative effects in patients.[145]

Another key pathway of nanoparticle toxicity involves the induction of inflammatory responses. Nanoparticles, particularly those with certain surface properties or charges, may be perceived as foreign by the immune system. This recognition activates immune cells, leading to the release of pro-inflammatory cytokines, chemokines, and other mediators. The resulting inflammatory cascade can lead to both local and systemic inflammation, undermining the regenerative capacity of tissues and potentially exacerbating post-surgical recovery. Chronic inflammation can also promote long-term complications, including fibrosis and tissue damage, which can hinder successful implant integration and healing.[146]

The cellular uptake of nanoparticles is another pivotal factor in determining their toxicity. Due to their small size, nanoparticles can easily traverse cellular membranes through processes such as endocytosis. Once internalized, nanoparticles can accumulate in organelles, such as the mitochondria, nucleus, and lysosomes, where they disrupt normal cellular function. This disruption may lead to mitochondrial dysfunction, interference with intracellular signaling pathways, and even genetic damage. For orthopedic applications, this cellular perturbation could impair the tissue's ability to regenerate or repair itself, potentially leading to complications in the healing process.[147]

In addition, the biopersistence of nanoparticles in tissues poses significant risks. Due to their high surface area-to-volume ratio, nanoparticles may not be effectively cleared by the body, leading to prolonged retention in organs such as

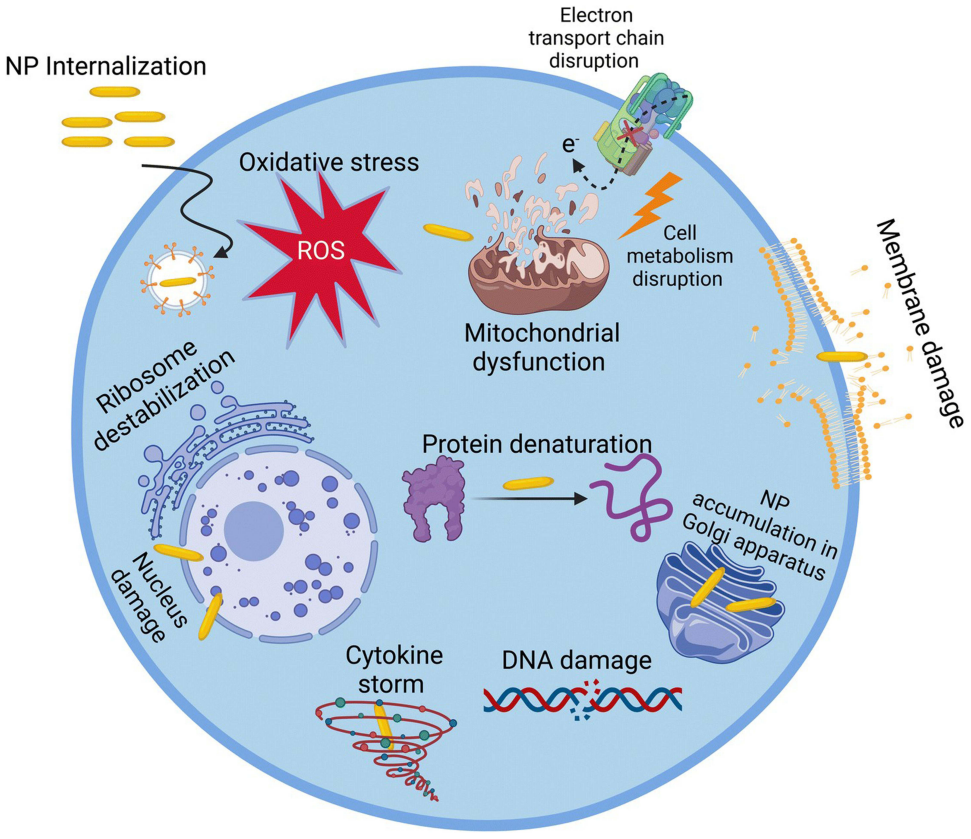

Figure 4 Cytotoxicity assessment of nanoparticles in orthopedic applications, evaluating their impact on cell viability, proliferation, and morphology. Adapted from Awashra M, Młynarz P. The toxicity of nanoparticles and their interaction with cells: an in vitro metabolomic perspective. Nanoscale Adv. 2023;5(10):2674–2723. under the terms of Creative Commons Attribution 3.0 Unported Licence (http://creativecommons.org/licenses/by/4.0/).[144]

https://doi.org/10.2147/IJN.S523462

the liver, spleen, and kidneys. Over time, this accumulation can result in chronic inflammation, fibrosis, and potential organ toxicity. The clearance rates of nanoparticles and their degradation products are critical determinants of their safety and must be carefully studied to understand long-term implications.[148]

The shape and surface charge of nanoparticles are critical factors influencing their biological behavior. For example, rod-shaped nanoparticles have been found to cause more significant cytotoxic effects compared to spherical particles. This may be attributed to their enhanced ability to penetrate cell membranes or exert mechanical stress on cellular structures. Furthermore, nanoparticles with a positive surface charge are generally more cytotoxic, as they have a stronger affinity for the negatively charged components of the cell membrane, facilitating their entry into cells and potentially causing damage.[149]

Biocompatibility and Toxicity Assessment of Nanomaterials

Nanotechnology research is advancing rapidly; however, despite the significant benefits of nanocomposites, their nanoscale size presents potential risks, such as tissue penetration and cellular infiltration, which raise concerns about safety and long-term biological effects.[150] Current research suggests that the incorporation of different nanostructures into composites can result in either toxicity or exceptional biocompatibility, depending on factors such as chemical composition, geometry, and integration method. The reduced size of nanoparticles increases their surface area and energy, raising concerns about their interaction with biological systems and potential toxicity.[151] Nanocomposites are notably smaller than many cells and cellular organelles, which allows them to be internalized into these structures and potentially interfere with cellular functions, and many nanocomposites contain metal components that may pose risks. For example, research has shown that silver ions can induce oxidative stress, raising concerns about their potential toxicity in biological systems.[152] Elements like lead (Pb), copper (Cu), nickel (Ni), cobalt (Co), and zinc (Zn) exhibit different degrees of cytotoxicity when exposed to cell cultures. For instance, the release of zinc ions from titanium dioxide nanotubes at a relatively high concentration of 0.36 parts per million (ppm) has been shown to induce stem cell death.[153,154]

Metallic and metal oxide nanomaterials offer significant potential for a wide range of bone-related applications, such as the delivery of bioactive compounds, cell labeling, and the improvement of orthopedic implants and scaffolds.[155] Nanoparticles of metallic and metal oxides, when incorporated into orthopedic implants and scaffolds, can be released and quickly respond to changes in the local environment. These responses can be triggered by factors such as temperature fluctuations, pH changes, magnetic fields, and other relevant stimuli.[156] Several studies have shown that metallic ions are released through regular use and corrosion processes. The introduction of these foreign substances into the bloodstream or cellular structures can trigger systemic responses and potential toxic effects.[157] Silver nanoparticles and silver oxide nanoparticles have gained significant use in orthopedics, primarily due to their potent anti-inflammatory properties, which are essential in bone surgery. However, silver nanoparticles have the potential to cause harm to human cells through several mechanisms, including the production of reactive oxygen species, DNA damage, and other adverse effects. The toxicity of these nanoparticles varies depending on factors such as particle size, shape, surface chemistry, accumulation levels, and dosage, with different cell types exhibiting distinct responses to silver nanoparticles.[158,159]

Numerous studies have highlighted the potential of copper nanoparticles in creating materials with exceptional bioactivity and antibacterial properties. This has significant implications for disease prevention and the treatment of bone deformities.[160] Exposure to air causes copper to rapidly transform into copper oxide nanoparticles (CuONPs), which are toxic to human cells. Wang et al found that A549 human lung epithelial cells primarily internalized CuONPs via endocytosis. The nanoparticles, once inside the cells, particularly in the mitochondria and nucleus, induced the formation of reactive oxygen species, leading to cell death and necrosis. These findings suggest that copper and copper oxide nanoparticles may pose significant risks, including gene mutations and disruption of cellular homeostasis.[161]

Gold nanoparticles possess remarkable chemical properties, superior physical characteristics, and excellent biocompatibility, making them highly beneficial for various biomedical applications, including orthopedic implants, medical imaging, and drug delivery. Furthermore, their antibacterial properties further expand their potential in these areas.[162] Gold nanoparticles can be internalized by cells, potentially inducing apoptosis or necrosis. Additionally, these nanoparticles may accumulate in various organs, leading to possible complications. A study by Dykman et al demonstrated that

gold nanoparticles, with sizes ranging from 1 to 2 nm, exhibited acute toxicity across different cell types. This toxicity is likely due to the interaction between the nanoparticles and cellular biopolymers.[163]

Assessment Methods for Biocompatibility of Nanomaterials

Materials used in orthopedic applications must perform effectively in vivo without causing harmful local or systemic effects, such as immune responses, hypersensitivity, inflammation, or carcinogenic reactions. Biocompatibility extends beyond being biologically inert; it also encompasses biofunctionality and long-term stability. The effectiveness of these materials is primarily determined by their properties and how they interact with the biological environment of the target tissues. Important factors include protein adsorption, inflammatory responses, and interactions with blood.[164]

Considering these factors, the biological evaluation of biomaterials involves a variety of tests conducted both in vivo and in vitro. Cytocompatibility assessments examine the biological response of living cells to solutions containing nanomaterial extracts, with a focus on cell survival, proliferation, and metabolic activity. Toxic byproducts from nanomaterials, including metallic ions, reactive substances, and residual monomers, have the potential to negatively affect cellular functions and viability. Cellular damage may manifest as alterations in cellular structure, changes in cell shape, reduced cell adhesion and proliferation, decreased metabolic activity, and, ultimately, cell lysis.[165] The cytotoxicity elution test, also referred to as the MEM elution test, is an in vitro method used to qualitatively assess cytotoxicity. In this procedure, L-929 mouse fibroblast cells are cultured with a test material extract for 48 hours. After the incubation period, the cells are examined microscopically for any morphological changes, cell deformation or lysis. The cellular responses to the material are graded on a scale from 0 to 4, with a biomaterial considered biocompatible if the cellular reaction does not exceed grade 2, which indicates mild reactivity.[166]

The MTT assay is commonly used to evaluate cell viability and growth. There is a positive, linear correlation between the number of viable cells and the intensity of the formazan color produced. Quantitative assessment of viable cells is performed by measuring the absorbance of formazan at 570 nm. A material is considered cytocompatible when the proportion of viable cells is 70% or higher.[167] Genotoxicity assessment plays a crucial role in evaluating the potential risks of nanomaterials, as damage to genetic material can lead to cancer development or disrupt reproductive function by affecting germ cell DNA. Key genotoxicity endpoints include DNA damage, gene mutations, and chromosomal damage, all of which are considered sensitive indicators of genetic harm.[168] Irritation testing, an in vivo assay, assesses the potential of nanomaterials to cause skin irritation. Intracutaneous injections are made on the dorsal region of albino rabbits, and skin reactions such as erythema, edema, scabbing, and bleeding are evaluated at 24, 48, and 72 hours using a standardized scoring system.[169]

The skin sensitization assay evaluates the potential allergenic properties of materials, with the Guinea Pig Maximisation Test (GPMT) being the most widely recognized method. This test involves three phases. In the first phase, known as Stage I (Induction), a biomaterial is injected intradermally into guinea pigs at the designated test site. After a seven-day period, a topical patch is applied. Skin reactions, including erythema and edema, are monitored 24 and 48 hours after the patch is removed. A score of 1 or higher in the test group indicates a tendency for sensitization.[170] Blood compatibility of a medical device is influenced by the material properties of the device, the fluid dynamics within it, and the blood's coagulation tendencies. Hemocompatibility testing focuses on key factors such as coagulation, hemolysis, hematology, platelet function, and the complement system. This evaluation is typically conducted using in vitro models that replicate static, agitated, or shear flow conditions, where fresh human blood is incubated with biomaterials. Hemocompatibility markers are assessed both before and after the incubation of the experimental material.[171]

Techniques and Methods for Addressing Toxicity of Nanomaterials

Nanoparticles can induce oxidative stress, inflammation, and even cellular damage due to their high surface area and reactivity. To mitigate these toxic effects, several surface modification techniques have been employed. These modifications primarily aim to enhance biocompatibility and reduce toxicity. For instance, surface functionalization involves coating the nanoparticles with biocompatible materials, such as polyethylene glycol (PEG), which can help to prevent nanoparticle aggregation and reduce their toxicity by decreasing interactions with biological systems. Another technique,

encapsulation, involves enclosing the nanomaterial in a protective coating, such as biodegradable polymers, to control drug release and prevent direct contact with cells, thus reducing cytotoxicity.[172]

These techniques are commonly used to apply coatings and synthesize polymeric layers on the surfaces of metallic implants, thereby improving their performance. The methods can generally be classified into two main categories: physical and chemical modification techniques.[173] Physical modification techniques, such as flame spraying and plasma spraying, alter the implant surface using energetic charges or mechanical tools to apply bioceramic or polymeric materials to metallic implants. Materials commonly used in these processes include hydroxyapatite, tricalcium phosphate, and bioglass for bioceramic coatings, as well as polymers like polycaprolactone (PCL), poly(lactic-co-glycolic acid) (PLGA), and polyethylene glycol (PEG). These processes enhance surface properties at a microscopic level by increasing surface area, improving adhesion, and reducing the risk of inflammation or immune responses. Plasma spraying, for instance, creates a porous structure that promotes osteointegration and minimizes toxicity by fostering beneficial cellular interactions. On the other hand, chemical modification techniques involve immersing implants in reactive solutions to form coatings, such as sol-gel coating, where a precursor solution is applied and dried to form a uniform thin layer. This layer often contains bioceramic materials like hydroxyapatite, bioactive glass, or calcium phosphate, improving biocompatibility and osteoconductivity. Chemical methods can also introduce functional groups that interact with biological tissues, enhancing bioactivity and reducing immune rejection or other toxic effects by precisely controlling the coating composition to optimize material properties.[174]

Regulatory Perspective for Assessing Safety of Nanomaterials

Regulatory organizations worldwide, including the US Food and Drug Administration (FDA) and the European Chemicals Agency (ECHA), are proactively working to establish guidelines and frameworks to evaluate the risks and hazards associated with nanomaterials. The breakdown of nanomaterials or scaffolds can result in the release of nanoparticles, which may either persist within the system or degrade and be eliminated.[175] Throughout the metabolic process, nanoparticles can circulate through various organs, including the bloodstream, liver, and kidneys, potentially causing oxidative stress and inflammation. As a result, it is essential to regulate the clearance rate and assess the cytocompatibility of these nanoparticles with diverse cell types, including hemocytes, stem cells, hepatocytes, and nephrocytes.[176]

The general regulatory perspective provides a broad framework; however, regulatory compliance introduces specific requirements and challenges that add further complexity to the safety assessment of nanomaterials. Key frameworks such as the FDA's Nanotechnology Guidance and ISO 10993 series are central to preclinical evaluation. It outlines tests for in vitro cytotoxicity, addresses irritation and sensitization, and focuses on degradation products of polymeric medical devices.[177,178] These standards mandate a comprehensive assessment of material interactions with biological systems, yet current protocols often fall short in accommodating the unique physicochemical properties of nanomaterials.[179] Furthermore, the absence of harmonized characterization methods, such as dynamic light scattering under physiological conditions and endotoxin detection, complicates reproducibility and regulatory submission.[180] While in vitro and preclinical data are encouraging, clinical translation is obstructed by batch-to-batch variability in nanoparticle synthesis, sterilization-related alterations (gamma irradiation effects on nano-coatings), and ethical concerns such as informed consent for novel biomaterial-based interventions.[181] Emerging strategies such as Quality-by-Design (QbD) frameworks and organ-on-chip technologies present promising avenues to address translational challenges and facilitate the transition from laboratory research to clinical application.[182]

The US Food and Drug Administration (FDA) approved the Patient Specific Talus Spacer, a 3D-printed cobalt chromium implant, in 2021. This implant, designed for talus bone replacement in cases of avascular necrosis, marks an important milestone in orthopedic nanotechnology.[183] Similarly, The use of nanomaterial-based coatings, such as silver nanoparticle (AgNP) coatings, has been extensively explored for orthopedic implants due to their antimicrobial properties and potential to enhance osseointegration, leading to improved patient outcomes. While the European Medicines Agency (EMA) does not explicitly list individual nanoparticle-based coatings, several nanomaterials have been approved for

medical use and are being investigated for their benefits in orthopedic applications, including improved infection resistance and bone integration.[184]

A comprehensive evaluation of the biodistribution and pharmacokinetics of nanoparticles is essential to assess their viability for use in clinical applications.[185] However, similar limitations of in vitro assessments can be observed in studies that thoroughly investigate the systemic toxicity of nanoparticles on the metabolism and immune system in mice, following administration through various routes, including intravenous, topical, subcutaneous, inhalation, intraperitoneal, and oral methods.[186] Thus, further research is essential to establish a more robust correlation between the in vitro and in vivo effects of nanoparticles, especially in relation to their manufacturing process.

Challenges and Solutions for the Application of Nanomaterials in Orthopedics

Despite the significant promise of nanomaterials in orthopedic applications, several critical challenges must be addressed to facilitate their effective clinical translation. Long-term safety remains a primary concern, as nanoparticles can potentially trigger inflammatory responses, oxidative stress, or accumulate in tissues over time. This underscores the need for developing biocompatible and bioresorbable nanomaterials, validated through extensive in vivo studies to assess systemic and immunological effects. Additionally, inconsistencies in nanoparticle synthesis arising from non-standardized manufacturing methods can lead to variable physicochemical properties and biological performance. Establishing standardized manufacturing protocols and stringent quality control measures is essential to ensure reproducibility. Patient-specific variability, including differences in metabolic profiles, immune responses, and orthopedic tissue architecture, further complicates treatment outcomes. Addressing this requires a shift toward personalized nanomedicine, where therapeutic strategies are tailored based on individual patient parameters.

Importantly, the integration of AI and ML into nanomaterial research offers a powerful approach to overcome several of these translational challenges. AI can optimize nanoparticle design by predicting structure-function relationships, simulating degradation behavior, and improving targeting specificity. Moreover, AI-assisted models can help personalize treatment by analyzing patient data to suggest optimal nanocarrier configurations and drug release profiles. Such intelligent systems can accelerate discovery, reduce experimental costs, and support real-time clinical decision-making. Overcoming remaining barriers will also require strong interdisciplinary collaboration between clinicians, material scientists, bioengineers, and regulatory bodies to align scientific innovation with clinical and ethical standards. High production costs and scalability limitations further restrict broad implementation; thus, developing economically viable and environmentally sustainable manufacturing approaches. Finally, early and continuous dialogue with regulatory agencies will be essential for navigating approval processes and establishing clear guidelines for clinical use.

Conclusion

Nanotechnology, though still in its early stages, holds transformative potential for orthopedics, offering novel solutions in diagnostics, therapeutic interventions, and research. Key breakthroughs, such as the development of advanced nanomaterials for targeted drug delivery and smart-responsive implants, promise to significantly enhance clinical outcomes. These innovations could improve implant precision, boost therapeutic efficacy, reduce infection risks, and facilitate better bone and tendon healing. However, challenges such as nanotoxicity, immune compatibility, and long-term stability need further investigation to ensure safe and effective clinical translation. This review contributes to the existing body of knowledge by providing a comprehensive analysis of nanotechnology's potential in orthopedics, while identifying key unresolved issues, such as regulatory barriers and the translation of preclinical findings into clinical practice. Furthermore, it highlights the need for continued research in personalized nanomedicine, 3D-printed nanocomposite implants, and AI-assisted nanomaterial design. As nanotechnology advances, overcoming these challenges will be crucial for its widespread adoption in orthopedic care, ultimately transforming both the prevention and treatment.

Data Sharing Statement

This is a review article and all relevant information is provided in the article.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This work was supported by Zhejiang Provincial Natural Science Foundation of China (QN25H040001 to LYX), Medical and Health Research Project of Zhejiang Province (2020KY999 to HDD, 2023KY393 to QPL), Traditional Chinese Medicine Science and Technology Projects of Zhejiang Province (2022ZB380 to JYZ, 2022ZB382 to WQL, 2023007231 to CYJ), Science and Technology Project of Zhoushan (2023C31020 to LL, 2023C31019 to HJZ), Research Fund Projects of The Affiliated Hospital of Zhejiang Chinese Medicine University (2021FSYYZY45 to WQL).

Disclosure

The Authors declare that they have no competing or other interests that might be perceived to influence the results and/or discussion reported in this paper.

References

1. Weinstein SL. The burden of musculoskeletal conditions. *JBJS*. 2016;98:1331.
2. Wright NC, Looker AC, Saag KG, et al. The recent prevalence of osteoporosis and low bone mass in the United States based on bone mineral density at the femoral neck or lumbar spine. *J Bone Miner Res*. 2014;29(11):2520–2526.
3. Fan -X-X, Xu MZ, Leung EL, Jun C, Yuan Z, Liu L. ROS-responsive berberine polymeric micelles effectively suppressed the inflammation of rheumatoid arthritis by targeting mitochondria. *Nanomicro Lett* 2020;12:1–14.
4. Peffers MJ, Chabronova A, Balaskas P, et al. SnoRNA signatures in cartilage ageing and osteoarthritis. *Sci Rep*. 2020;10(1):10641. doi:10.1038/s41598-020-67446-z
5. Qayoom I, Teotia AK, Kumar A. Nanohydroxyapatite based ceramic carrier promotes bone formation in a femoral neck canal defect in osteoporotic rats. *Biomacromolecules*. 2019;21(2):328–337. doi:10.1021/acs.biomac.9b01327
6. Ferguson JL, Turner SP. Bone cancer: diagnosis and treatment principles. *Am Fam Physician*. 2018;98(4):205–213.
7. Deep G, Agarwal R. Antimetastatic efficacy of silibinin: molecular mechanisms and therapeutic potential against cancer. *Cancer Metast Rev*. 2010;29:447–463. doi:10.1007/s10555-010-9237-0
8. Roy K, Kanwar RK, Kanwar JR. Molecular targets in arthritis and recent trends in nanotherapy. *Int J Nanomed*. 2015;10:5407–5420. doi:10.2147/IJN.S89156
9. Garimella R, Eltorai AE. Nanotechnology in orthopedics. *J Orthopaed*. 2017;14(1):30–33. doi:10.1016/j.jor.2016.10.026
10. Saeedi M, Eslamifar M, Khezri K, et al. Applications of nanotechnology in drug delivery to the central nervous system. *Biomed Pharmacother*. 2019;111:666–675. doi:10.1016/j.biopha.2018.12.133
11. Sadek AA, Abd-Elkareem M, Abdelhamid HN, et al. Repair of critical-sized bone defects in rabbit femurs using graphitic carbon nitride (g-C3N4) and graphene oxide (GO) nanomaterials. *Sci Rep*. 2023;13(1):5404. doi:10.1038/s41598-023-32487-7
12. Gu W, Wu C, Chen J, et al. Nanotechnology in the targeted drug delivery for bone diseases and bone regeneration. *Int J Nanomed*. 2013;8:2305–2317. doi:10.2147/IJN.S44393
13. Monteiro N, Martins A, Reis RL, et al. Nanoparticle-based bioactive agent release systems for bone and cartilage tissue engineering. *Regener Ther*. 2015;1:109–118. doi:10.1016/j.reth.2015.05.004
14. Lu C, Han HD, Mangala LS, et al. Regulation of tumor angiogenesis by EZH2. *Cancer Cell*. 2010;18(2):185–197. doi:10.1016/j.ccr.2010.06.016
15. Dave V, Sharma R, Gupta C, et al. Folic acid modified gold nanoparticle for targeted delivery of Sorafenib tosylate towards the treatment of diabetic retinopathy. *Coll Surf B Biointerfaces*. 2020;194:111151. doi:10.1016/j.colsurfb.2020.111151
16. Sharma P, Mehta M, Dhanjal DS, et al. Emerging trends in the novel drug delivery approaches for the treatment of lung cancer. *Chem Biol Interact*. 2019;309:108720. doi:10.1016/j.cbi.2019.06.033
17. Jin T, Wu D, Liu XM, et al. Intra-articular delivery of celastrol by hollow mesoporous silica nanoparticles for pH-sensitive anti-inflammatory therapy against knee osteoarthritis. *J Nanobiotechnology* 2020;18:1–15.
18. Hassani Besheli N, Mottaghitalab F, Eslami M, et al. Sustainable release of vancomycin from silk fibroin nanoparticles for treating severe bone infection in rat tibia osteomyelitis model. *ACS Appl. Mater. Interfaces*. 2017;9(6):5128–5138. doi:10.1021/acsami.6b14912
19. Rana S. Mechanistic paradigms of immunotoxicity, triggered by nanoparticles–a review. *Toxicol Mech Methods*. 2025;35(3):262–278. doi:10.1080/15376516.2024.2431687

20. Han J, Mao K, Yang Y-G, et al. Impact of inorganic/organic nanomaterials on the immune system for disease treatment. *Biomater. Sci.* 2024;12 (19):4903–4926. doi:10.1039/D4BM00853G
21. Kreutz A, Chang X, Hogberg HT, et al. Advancing understanding of human variability through toxicokinetic modeling, in vitro-in vivo extrapolation, and new approach methodologies. *Hum Genom*. 2024;18(1):129. doi:10.1186/s40246-024-00691-9
22. Palazzo C, Nguyen C, Lefevre-Colau -M-M, et al. Risk factors and burden of osteoarthritis. *Ann Phys Rehabil Med*. 2016;59(3):134–138. doi:10.1016/j.rehab.2016.01.006
23. Yao Q, Wu X, Tao C, et al. Osteoarthritis: pathogenic signaling pathways and therapeutic targets. *Sig Transduc Targ Ther*. 2023;8(1):56. doi:10.1038/s41392-023-01330-w
24. Evans CH, Kraus VB, Setton LA. Progress in intra-articular therapy. *Nat Rev Rheumatol* 2014;10(1):11–22.
25. Chen M, Wang D, Li M, et al. Nanocatalytic biofunctional MOF coating on titanium implants promotes osteoporotic bone regeneration through cooperative pro-osteoblastogenesis MSC reprogramming. *ACS nano*. 2022;16(9):15397–15412. doi:10.1021/acsnano.2c07200
26. Rahmani Del Bakhshayesh A, Akbarzadeh A, Alihemmati A, et al. Preparation and characterization of novel anti-inflammatory biological agents based on piroxicam-loaded poly-ε-caprolactone nano-particles for sustained NSAID delivery. *Drug Delivery*. 2020;27(1):269–282. doi:10.1080/10717544.2020.1716881
27. Maudens P, Seemayer CA, Thauvin C, Gabay C, Jordan O, Allémann E. Nanocrystal–polymer particles: extended delivery carriers for osteoarthritis treatment. *Small*. 2018;14(8):1703108.
28. Li G, Lu F, Dou X, et al. Polysulfide regulation by the zwitterionic barrier toward durable lithium–sulfur batteries. *J Am Chem Soc*. 2020;142 (7):3583–3592. doi:10.1021/jacs.9b13303
29. Bajpayee AG, Scheu M, Grodzinsky AJ, Porter RM. *J Orthop Res* A rabbit model demonstrates the influence of cartilage thickness on intra-articular drug delivery and retention within cartilage. 2015;33(5):660–667.
30. Kang M-L, Kim J-E, Im G-I. Thermoresponsive nanospheres with independent dual drug release profiles for the treatment of osteoarthritis. *Acta biomaterialia* 2016;39:65–78.
31. Steckiewicz KP, Inkielewicz-Stepniak I. Modified nanoparticles as potential agents in bone diseases: cancer and implant-related complications. *Nanomaterials* 2020;10(4):658.
32. Kılıçay E, Demirbilek M, Türk M, et al. Preparation and characterization of poly (3-hydroxybutyrate-co-3-hydroxyhexanoate)(PHBHHX) based nanoparticles for targeted cancer therapy. *Eur J Pharm Sci*. 2011;44(3):310–320. doi:10.1016/j.ejps.2011.08.013
33. Zhang Y, Wang F, Li M, et al. Self-stabilized hyaluronate nanogel for intracellular codelivery of doxorubicin and cisplatin to osteosarcoma. *Adv Sci*. 2018;5(5):1700821. doi:10.1002/advs.201700821
34. Au KM, Satterlee A, Min Y, et al. Folate-targeted pH-responsive calcium zoledronate nanoscale metal-organic frameworks: turning a bone antiresorptive agent into an anticancer therapeutic. *Biomaterials* 2016;82:178–193.
35. Wei D, Jung J, Yang H, et al. Nanotechnology treatment options for osteoporosis and its corresponding consequences. *Curr Osteo Rep*. 2016;14 (5):239–247. doi:10.1007/s11914-016-0324-1
36. Dubey KA, Chaudhari CV, Bhardwaj YK, Varshney L. Polymers, blends and nanocomposites for implants, scaffolds and controlled drug release applications. *Adv Biomater Biomed Appl* 2017;1–44.
37. Rabiei M, Kashanian S, Samavati SS, Derakhshankhah H, Jamasb S, McInnes SJ. Nanotechnology application in drug delivery to osteoarthritis (OA), rheumatoid arthritis (RA), and osteoporosis (OSP). *J Drug Deliv Sci Technol* 2021;61:102011.
38. Wu T, Sun J, Tan L, et al. Enhanced osteogenesis and therapy of osteoporosis using simvastatin loaded hybrid system. *Bioactive Materials*. 2020;5(2):348–357. doi:10.1016/j.bioactmat.2020.03.004
39. Ryu T-K, Kang R-H, Jeong K-Y, et al. Bone-targeted delivery of nanodiamond-based drug carriers conjugated with alendronate for potential osteoporosis treatment. *J Control Release*. 2016;232:152–160. doi:10.1016/j.jconrel.2016.04.025
40. Nagai N, Ogata F, Otake H, et al. Design of a transdermal formulation containing raloxifene nanoparticles for osteoporosis treatment. *Int J Nanomed*. 2018;13:5215–5229. doi:10.2147/IJN.S173216
41. Xue Y, Zhu Z, Zhang X, et al. Accelerated bone regeneration by MOF modified multifunctional membranes through enhancement of osteogenic and angiogenic performance. *Adv. Healthcare Mater.* 2021;10(6):2001369. doi:10.1002/adhm.202001369
42. Meirelles L, Arvidsson A, Andersson M, et al. Nano hydroxyapatite structures influence early bone formation. *J Biomed Mater Res A*. 2008;87 (2):299–307. doi:10.1002/jbm.a.31744
43. Wang B, Chen H, Peng S, et al. Multifunctional magnesium-organic framework doped biodegradable bone cement for antibacterial growth, inflammatory regulation and osteogenic differentiation. *J Mat Chem B*. 2023;11(13):2872–2885. doi:10.1039/D2TB02705D
44. Gao C, Wei D, Yang H, et al. Nanotechnology for treating osteoporotic vertebral fractures. *Int J Nanomed*. 2015;10:5139–5157. doi:10.2147/IJN.S85037
45. Perni S, Thenault V, Abdo P, et al. Antimicrobial activity of bone cements embedded with organic nanoparticles. *Int J Nanomed*. 2015;10:6317–6329. doi:10.2147/IJN.S86440
46. Khandaker M, Vaughan MB, Morris TL, et al. Effect of additive particles on mechanical, thermal, and cell functioning properties of poly (methyl methacrylate) cement. *Int J Nanomed*. 2014;9:2699–2712. doi:10.2147/IJN.S61964
47. Schröter L, Kaiser F, Stein S, et al. Biological and mechanical performance and degradation characteristics of calcium phosphate cements in large animals and humans. *Acta biomaterialia*. 2020;117:1–20. doi:10.1016/j.actbio.2020.09.031
48. Hesaraki S, Alizadeh M, Borhan S, et al. Polymerizable nanoparticulate silica-reinforced calcium phosphate bone cement. *J Biomed Mater Res B Appl Biomater.* 2012;100(6):1627–1635. doi:10.1002/jbm.b.32731
49. Guo Q, Wang Y, Xu D, et al. Rheumatoid arthritis: pathological mechanisms and modern pharmacologic therapies. *Bone Research*. 2018;6 (1):15. doi:10.1038/s41413-018-0016-9
50. Malmström V, Catrina AI, Klareskog L. The immunopathogenesis of seropositive rheumatoid arthritis: from triggering to targeting. *Nat Rev Immunol*. 2017;17(1):60–75. doi:10.1038/nri.2016.124
51. Sardana Y, Bhatti GK, Singh C, et al. Progression of pre-rheumatoid arthritis to clinical disease of joints: potential role of mesenchymal stem cells. *Life Sci*. 2023;321:121641. doi:10.1016/j.lfs.2023.121641
52. Lopez-Pedrera C, Barbarroja N, Patiño-Trives AM, et al. Effects of biological therapies on molecular features of rheumatoid arthritis. *Int J Mol Sci*. 2020;21(23):9067. doi:10.3390/ijms21239067

53. Østergaard M, Boesen M. Imaging in rheumatoid arthritis: the role of magnetic resonance imaging and computed tomography. *La Radiologia Medica*. 2019;124(11):1128–1141. doi:10.1007/s11547-019-01014-y
54. Zhao J, Chen X, Ho KH, et al. Nanotechnology for diagnosis and therapy of rheumatoid arthritis: evolution towards theranostic approaches. *Chin. Chem. Lett* 2021;32(1):66–86.
55. McQueen FM. Imaging in early rheumatoid arthritis. *Best Pract Res Clin Rheumatol* 2013;27(4):499–522.
56. Markides H, Kehoe O, Morris RH, El Haj AJ. Whole body tracking of superparamagnetic iron oxide nanoparticle-labelled cells–a rheumatoid arthritis mouse model. *Stem Cell Res Ther* 2013;4:1–14.
57. Chen C-L, Siow TY, Chou CH. Targeted superparamagnetic iron oxide nanoparticles for in vivo magnetic resonance imaging of T-cells in rheumatoid arthritis. *Mol Imag Biol* 2017;19:233–244.
58. Periyathambi P, Sastry TP, Anandasadagopan SK, et al. Macrophages mediated diagnosis of rheumatoid arthritis using fibrin based magnetic nanoparticles as MRI contrast agents. *Biochim Biophys Acta*. 2017;1861(1):2992–3001. doi:10.1016/j.bbagen.2016.09.018
59. Rahman M, Beg S, Anwar F, et al. Liposome-based nanomedicine therapeutics for rheumatoid arthritis. *Crit Rev Ther Drug Carrier Syst*. 2017;34(4):283–316. doi:10.1615/CritRevTherDrugCarrierSyst.2017016067
60. Wang Q, Jiang J, Chen W, et al. Targeted delivery of low-dose dexamethasone using PCL–PEG micelles for effective treatment of rheumatoid arthritis. *J Control Release*. 2016;230:64–72. doi:10.1016/j.jconrel.2016.03.035
61. Chuang S-Y, Lin CH, Huang TH, Fang JY. Lipid-based nanoparticles as a potential delivery approach in the treatment of rheumatoid arthritis. *Nanomaterials* 2018;8(1):42.
62. Zhang M, Hu W, Cai C, et al. Advanced application of stimuli-responsive drug delivery system for inflammatory arthritis treatment. *Mater Today Bio*. 2022;14:100223. doi:10.1016/j.mtbio.2022.100223
63. Sadek AA, Abd-Elkareem M, Abdelhamid HN, et al. Enhancement of critical-sized bone defect regeneration using UiO-66 nanomaterial in rabbit femurs. *BMC Vet Res*. 2022;18(1):260. doi:10.1186/s12917-022-03347-9
64. Ishihara T, Kubota T, Choi T, et al. Treatment of experimental arthritis with stealth-type polymeric nanoparticles encapsulating betamethasone phosphate. *J Pharmacol Exp Ther*. 2009;329(2):412–417. doi:10.1124/jpet.108.150276
65. Dolati S, Sadreddini S, Rostamzadeh D, et al. Utilization of nanoparticle technology in rheumatoid arthritis treatment. *Biomed Pharmacother*. 2016;80:30–41. doi:10.1016/j.biopha.2016.03.004
66. Ren H, He Y, Liang J, et al. Role of liposome size, surface charge, and PEGylation on rheumatoid arthritis targeting therapy. *ACS Appl. Mater. Interfaces*. 2019;11(22):20304–20315. doi:10.1021/acsami.8b22693
67. Wang X, Feng Y, Fu J, et al. A lipid micellar system loaded with dexamethasone palmitate alleviates rheumatoid arthritis. *AAPS PharmSciTech* 2019;20:1–10.
68. Park J-Y, Hyun JS, Jee JG, Park SJ, Khang D. Structural deformation of MTX induced by nanodrug conjugation dictate intracellular drug transport and drug efficacy. *Int J Nanomedicine* 2021;4943–4957.
69. Ma C, Li B, Zhang J, et al. Significantly improving the bioefficacy for rheumatoid arthritis with supramolecular nanoformulations. *Adv Mater* 2021;33(16):2100098.
70. Singh S, Tiwary N, Sharma N, et al. Integrating nanotechnological advancements of disease-modifying anti-rheumatic drugs into rheumatoid arthritis management. *Pharmaceuticals*. 2024;17(2):248. doi:10.3390/ph17020248
71. Mishra V, Pandey RP, Priyadarshini A, Chang CM, Leal E. *Nanotherapeutics for Inflammatory Arthritis: Design, Diagnosis, and Treatment*. CRC Press; 2024.
72. Garg U, Jain N, Kaul S, et al. Role of albumin as a targeted drug carrier in the management of rheumatoid arthritis: a comprehensive review. *Mol Pharmaceut*. 2023;20(11):5345–5358. doi:10.1021/acs.molpharmaceut.3c00581
73. Wang Q, Qin X, Fang J, et al. Nanomedicines for the treatment of rheumatoid arthritis: state of art and potential therapeutic strategies. *Acta Pharmaceutica Sinica B*. 2021;11(5):1158–1174. doi:10.1016/j.apsb.2021.03.013
74. Li X, Wang H, Zou X, et al. Methotrexate-loaded folic acid of solid-phase synthesis conjugated gold nanoparticles targeted treatment for rheumatoid arthritis. *Eur. J. Pharm. Sci.* 2022;170:106101. doi:10.1016/j.ejps.2021.106101
75. Yang M, Ding J, Feng X, et al. Scavenger receptor-mediated targeted treatment of collagen-induced arthritis by dextran sulfate-methotrexate prodrug. *Theranostics*. 2017;7(1):97. doi:10.7150/thno.16844
76. Yallapu MM, Nagesh PK, Jaggi M, Chauhan SC. Therapeutic applications of curcumin nanoformulations. *AAPS J*.2015;17:1341–1356.
77. Shen ZT, Sigalov AB. Rationally designed ligand-independent peptide inhibitors of TREM-1 ameliorate collagen-induced arthritis. *J Cell Mol Med*. 2017;21(10):2524–2534. doi:10.1111/jcmm.13173
78. Shi Q, Rondon-Cavanzo E-P, Dalla Picola IP, et al. In vivo therapeutic efficacy of TNFα silencing by folate-PEG-chitosan-DEAE/siRNA nanoparticles in arthritic mice. *Int J Nanomed*. 2018;13:387–402. doi:10.2147/IJN.S146942
79. Loffredo FS, Pancoast JR, Cai L, et al. Targeted delivery to cartilage is critical for in vivo efficacy of insulin-like growth factor 1 in a rat model of osteoarthritis. *Arthritis Rheumatol* 2014;66(5):1247–1255.
80. Jain A, Mishra SK, Vuddanda PR, Singh SK, Singh R, Singh S. Targeting of diacerein loaded lipid nanoparticles to intra-articular cartilage using chondroitin sulfate as homing carrier for treatment of osteoarthritis in rats. *Nanotechnol. Biol. Med* 2014;10(5):e1031–e1040.
81. Pi Y, Zhang X, Shao Z, et al. Intra-articular delivery of anti-Hif-2α siRNA by chondrocyte-homing nanoparticles to prevent cartilage degeneration in arthritic mice. *Gene Ther*. 2015;22(6):439–448. doi:10.1038/gt.2015.16
82. Samarasinghe RM, Kanwar RK, Kanwar JR. The effect of oral administration of iron saturated-bovine lactoferrin encapsulated chitosan-nanocarriers on osteoarthritis. *Biomaterials*. 2014;35(26):7522–7534. doi:10.1016/j.biomaterials.2014.04.109
83. Moura CC, Segundo MA, Neves JD, Reis S, Sarmento B. Co-association of methotrexate and SPIONs into anti-CD64 antibody-conjugated PLGA nanoparticles for theranostic application. *Int. J. Nanomed* 2014;4911–4922.
84. Ghosh S, Mukherjee B, Chaudhuri S, et al. Methotrexate aspasomes against rheumatoid arthritis: optimized hydrogel loaded liposomal formulation with in vivo evaluation in Wistar rats. *AAPS PharmSciTech*. 2018;19(3):1320–1336. doi:10.1208/s12249-017-0939-2
85. Feng N, Yang M, Feng X, et al. Reduction-responsive polypeptide nanogel for intracellular drug delivery in relieving collagen-induced arthritis. *ACS Biomater Sci Eng*. 2018;4(12):4154–4162. doi:10.1021/acsbiomaterials.8b00738
86. Sezlev Bilecen D, Uludag H, Hasirci V. Development of PEI-RANK siRNA complex loaded PLGA nanocapsules for the treatment of osteoporosis. *Tissue Eng A*. 2019;25(1–2):34–43. doi:10.1089/ten.TEA.2017.0476

87. Harish V, Ansari MM, Tewari D, et al. Nanoparticle and nanostructure synthesis and controlled growth methods. *Nanomaterials*. 2022;12 (18):3226. doi:10.3390/nano12183226
88. Prasad RD, Prasad RS, Prasad RB, et al. A review on modern characterization techniques for analysis of nanomaterials and biomaterials. *ES Energy Environ*. 2024;23:1087.
89. Kamaly N, Xiao Z, Valencia PM, et al. Targeted polymeric therapeutic nanoparticles: design, development and clinical translation. *Chem. Soc. Rev.* 2012;41(7):2971–3010. doi:10.1039/c2cs15344k
90. Farjaminejad S, Farjaminejad R, Garcia-Godoy F. Nanoparticles in bone regeneration: a narrative review of current advances and future directions in tissue engineering. *J Funct Biomater*. 2024;15(9):241. doi:10.3390/jfb15090241
91. Valiev RZ, Prokofiev EA, Kazarinov NA, et al. Developing nanostructured Ti alloys for innovative implantable medical devices. *Materials*. 2020;13(4):967. doi:10.3390/ma13040967
92. Damiri F, Fatimi A, Magdalena Musuc A, et al. Nano-hydroxyapatite (nHAp) scaffolds for bone regeneration: preparation, characterization and biological applications. *J Drug Delivery Sci Technol*. 2024;95:105601. doi:10.1016/j.jddst.2024.105601
93. Su E, Justin DF, Pratt CR, et al. Effects of titanium nanotubes on the osseointegration, cell differentiation, mineralisation and antibacterial properties of orthopaedic implant surfaces. *Bone Joint J*. 2018;100(1_Supple_A):9–16. doi:10.1302/0301-620X.100B1.BJJ-2017-0551.R1
94. Cheng J, Liu J, Wu B, et al. Graphene and its derivatives for bone tissue engineering: in vitro and in vivo evaluation of graphene-based scaffolds, membranes and coatings. *Front Bioeng Biotechnol*. 2021;9:734688. doi:10.3389/fbioe.2021.734688
95. Ghosh S, Webster TJ. Mesoporous silica based nanostructures for bone tissue regeneration. *Front Mater*. 2021;8:692309. doi:10.3389/fmats.2021.692309
96. Nehra M, Dilbaghi N, Singhal NK, et al. Metal organic frameworks MIL-100 (Fe) as an efficient adsorptive material for phosphate management. *Environment Res*. 2019;169:229–236. doi:10.1016/j.envres.2018.11.013
97. Mehrali M, Thakur A, Pennisi CP, et al. Nanoreinforced hydrogels for tissue engineering: biomaterials that are compatible with load-bearing and electroactive tissues. *Adv Mater* 2017;29(8):1603612.
98. Gusić N, Ivković A, VaFaye J, et al. Nanobiotechnology and bone regeneration: a mini-review. *Int Orthopaed*. 2014;38(9):1877–1884. doi:10.1007/s00264-014-2412-0
99. Serra G, Morais L, Elias CN, et al. Nanostructured severe plastic deformation processed titanium for orthodontic mini-implants. *Mater Sci Eng C Mater Biol Appl*. 2013;33(7):4197–4202. doi:10.1016/j.msec.2013.06.012
100. Han F, Meng Q, Xie E, et al. Engineered biomimetic micro/nano-materials for tissue regeneration. *Front Bioeng Biotechnol*. 2023;11:1205792. doi:10.3389/fbioe.2023.1205792
101. Parchi PD, Cecchini M, Antonini S, et al. How nanotechnology can really improve the future of orthopedic implants and scaffolds for bone and cartilage defects. 2013;3(2).
102. Kon E, Delcogliano M, Filardo G, et al. A novel nano-composite multi-layered biomaterial for treatment of osteochondral lesions: technique note and an early stability pilot clinical trial. *Injury*. 2010;41(7):693–701. doi:10.1016/j.injury.2009.11.014
103. Ding T, Luo Z-J, Zheng Y, et al. Rapid repair and regeneration of damaged rabbit sciatic nerves by tissue-engineered scaffold made from nano-silver and collagen type I. *Injury*. 2010;41(5):522–527. doi:10.1016/j.injury.2009.04.003
104. Li H, Pan S, Xia P, et al. Advances in the application of gold nanoparticles in bone tissue engineering. *J Biol Eng*. 2020;14:1–15. doi:10.1186/s13036-020-00236-3
105. Haugen HJ, Makhtari S, Ahmadi S, et al. The antibacterial and cytotoxic effects of silver nanoparticles coated titanium implants: a narrative review. *Materials*. 2022;15(14):5025. doi:10.3390/ma15145025
106. Mo X, Zhang D, Liu K, et al. Nano-hydroxyapatite composite scaffolds loaded with bioactive factors and drugs for bone tissue engineering. *Int J Mol Sci*. 2023;24(2):1291. doi:10.3390/ijms24021291
107. Santos LF, Silva AS, Mano JF. Magnetic-based strategies for regenerative medicine and tissue engineering. *Adv. Healthcare Mater.* 2023;12 (25):2300605. doi:10.1002/adhm.202300605
108. Ahmed YW, Loukanov A, Tsai HC. State-of-the-art synthesis of porous polymer materials and their several fantastic biomedical applications: a review. *Adv. Healthcare Mater.* 2024;2403743. doi:10.1002/adhm.202403743
109. Pei B, Wang W, Dunne N, et al. Applications of carbon nanotubes in bone tissue regeneration and engineering: superiority, concerns, current advancements, and prospects. *Nanomaterials*. 2019;9(10):1501. doi:10.3390/nano9101501
110. Pechnikova NA, Domvri K, Porpodis K, et al. Carbon quantum dots in biomedical applications: advances, challenges, and future prospects. *Aggregate*. 2025;6(3):e707. doi:10.1002/agt2.707
111. Akhtar H. *Metal Oxide Substituted Polyurethane foams for enhanced craniofacial bone repair: Exploring the properties of Cerium, Zirconium and Copper doped Zinc oxide nanoparticles as potential additive for bone regeneration and angiogenesis* [Doctoral dissertation]. University of Sheffield; 2021.
112. Jeevanandam J, Tan KX, Rodrigues J, et al. Target-specific delivery and bioavailability of pharmaceuticals via Janus and dendrimer particles. *Pharmaceutics*. 2023;15(6):1614. doi:10.3390/pharmaceutics15061614
113. Min KH, Kim DH, Kim KH, et al. Biomimetic scaffolds of calcium-based materials for bone regeneration. *Biomimetics*. 2024;9(9):511. doi:10.3390/biomimetics9090511
114. Wang Z, Agrawal P, Zhang YS. Nanotechnologies and nanomaterials in 3D (Bio) printing toward bone regeneration. *Adv NanoBiomed Res*. 2021;1(11):2100035. doi:10.1002/anbr.202100035
115. Tavakoli M, Emadi R, Salehi H, et al. Incorporation of graphene oxide as a coupling agent in a 3D printed polylactic acid/hardystonite nanocomposite scaffold for bone tissue regeneration applications. *Int J Biol Macromol*. 2023;253:126510. doi:10.1016/j.ijbiomac.2023.126510
116. Feng P, Wang K, Shuai Y, et al. Hydroxyapatite nanoparticles in situ grown on carbon nanotube as a reinforcement for poly (ε-caprolactone) bone scaffold. *Mater Today Adv*. 2022;15:100272. doi:10.1016/j.mtadv.2022.100272
117. Monavari M, Homaeigohar S, Fuentes-Chandía M, et al. 3D printing of alginate dialdehyde-gelatin (ADA-GEL) hydrogels incorporating phytotherapeutic icariin loaded mesoporous SiO2-CaO nanoparticles for bone tissue engineering. *Mater Sci Eng C*. 2021;131:112470. doi:10.1016/j.msec.2021.112470
118. Pamukçu A. *Preparation of Novel Scaffold Systems Reinforced With Mesoporous Silica Nanoparticles for BMP-2 Delivery and In Vitro Investigations* [Master's thesis]. Izmir Katip Celebi University (Turkey); 2021.

119. Van Hengel I, Gelderman FSA, Athanasiadis S, et al. Functionality-packed additively manufactured porous titanium implants. *Mater Today Bio*. 2020;7:100060. doi:10.1016/j.mtbio.2020.100060
120. Nandi SK, Fielding G, Banerjee D, et al. 3D-printed β-TCP bone tissue engineering scaffolds: effects of chemistry on in vivo biological properties in a rabbit tibia model. *J Mater Res*. 2018;33(14):1939–1947. doi:10.1557/jmr.2018.233
121. Wahab Z. *Surface modification of nanodiamond and its incorporation in nanodiamond/peek nanocomposites* [Doctoral dissertation]. University of South Carolina; 2015.
122. Furlow B, Li H, Pan S. Medical 3-D Printing. *Radiol Technol*. 2017;88(5):519CT–537CT.
123. Motiee E-S, Karbasi S, Bidram E, Sheikholeslam M. Investigation of physical, mechanical and biological properties of polyhydroxybutyrate-chitosan/graphene oxide nanocomposite scaffolds for bone tissue engineering applications. *Int J Biol Macromol*. 2023;247:125593. doi:10.1016/j.ijbiomac.2023.125593
124. Zaczek-Moczydłowska MA, Joszko K, Kavoosi M, et al. Biomimetic natural biomaterial nanocomposite scaffolds: a rising prospect for bone replacement. *Int J Mol Sci*. 2024;25(24):13467. doi:10.3390/ijms252413467
125. Tian F, Zhao Y, Wang Y, et al. Magnesium-based composite calcium phosphate cement promotes osteogenesis and angiogenesis for minipig vertebral defect regeneration. *ACS Biomater. Sci. Eng.* 2024;10(12):7577–7593. doi:10.1021/acsbiomaterials.4c01521
126. Liu S, Li Z, Wang Q, et al. Graphene oxide/chitosan/hydroxyapatite composite membranes enhance osteoblast adhesion and guided bone regeneration. *ACS Appl. Bio Mater.* 2021;4(11):8049–8059. doi:10.1021/acsabm.1c00967
127. Ahmad F, Muhmood T. Clinical translation of nanomedicine with integrated digital medicine and machine learning interventions. *Colloids Surf. B*. 2024;241:114041. doi:10.1016/j.colsurfb.2024.114041
128. Luo Y. Toward fully automated personalized orthopedic treatments: innovations and interdisciplinary gaps. *Bioengineering*. 2024;11(8):817. doi:10.3390/bioengineering11080817
129. Yousaf I. AI and machine learning approaches for predicting nanoparticles toxicity the critical role of physiochemical properties. arXiv preprint arXiv:2409.15322. 2024.
130. Tripathy A, Patne AY, Mohapatra S, et al. Convergence of nanotechnology and machine learning: the state of the art, challenges, and perspectives. *Int J Mol Sci*. 2024;25(22):12368. doi:10.3390/ijms252212368
131. Xiao N, Li Y, Sun P, et al. A comparative review: biological safety and sustainability of metal nanomaterials without and with machine learning assistance. *Micromachines*. 2024;16(1):15. doi:10.3390/mi16010015
132. Jahandoost A, Dashti R, Houshmand M, et al. Utilizing machine learning and molecular dynamics for enhanced drug delivery in nanoparticle systems. *Sci Rep*. 2024;14(1):26677. doi:10.1038/s41598-024-73268-0
133. Dean MC, Oeding JF, Diniz P, et al. Leveraging digital twins for improved orthopaedic evaluation and treatment. *J Exp Orthopaed*. 2024;11(4): e70084. doi:10.1002/jeo2.70084
134. Hamid DMA, El-Ghani SFA, Khashaba MM. Characterization of nano-hydroxyapatite silica gel and evaluation of its combined effect with Solcoseryl paste on bone formation: an experimental study in New Zealand rabbits. *Future Dental J*. 2018;4(2):279–287. doi:10.1016/j.fdj.2018.05.007
135. Yamada M, Ueno T, Tsukimura N, et al. Bone integration capability of nanopolymorphic crystalline hydroxyapatite coated on titanium implants. *Int J Nanomed*. 2012;7:859–873. doi:10.2147/IJN.S28082
136. Ray SS, Bandyopadhyay J. Nanotechnology-enabled biomedical engineering: current trends, future scopes, and perspectives. *Nanotechnol Rev*. 2021;10(1):728–743. doi:10.1515/ntrev-2021-0052
137. Zhao R, Meng X, Pan Z, et al. Advancements in nanohydroxyapatite: synthesis, biomedical applications and composite developments. *Regener Biomater*. 2025;12:rbae129. doi:10.1093/rb/rbae129
138. Liu F, Xue Y, Zhou Y, et al. Trends and advances in antimicrobial surface modification for orthopedic implants (2014–2024). *Tissue Eng Part C Methods*. 2025;31(1):11–25. doi:10.1089/ten.tec.2024.0266
139. Borse V, Srivastava R, Buck CL, Bérubé M, Rolland RM. Fluorescence lateral flow immunoassay based point-of-care nanodiagnostics for orthopedic implant-associated infection. *Gen Comp Endocrinol*. 2019;280:24–33. doi:10.1016/j.ygcen.2019.04.004
140. Jin P, Wiraja C, Zhao J, et al. Nitric oxide nanosensors for predicting the development of osteoarthritis in rat model. *ACS Appl. Mater. Interfaces*. 2017;9(30):25128–25137. doi:10.1021/acsami.7b06404
141. Hengsberger S, Kulik A, Zysset P. A combined atomic force microscopy and nanoindentation technique to investigate the elastic properties of bone structural units. *Eur Cells Mater*. 2001;1:12–17. doi:10.22203/ecm.v001a02
142. Qiao K, Xu L, Tang J, et al. The advances in nanomedicine for bone and cartilage repair. *J Nanobiotechnology*. 2022;20(1):141. doi:10.1186/s12951-022-01342-8
143. Mabrouk M, Das DB, Salem ZA, et al. Nanomaterials for biomedical applications: production, characterisations, recent trends and difficulties. *Molecules*. 2021;26(4):1077. doi:10.3390/molecules26041077
144. Awashra M, Młynarz P. The toxicity of nanoparticles and their interaction with cells: an in vitro metabolomic perspective. *Nanoscale Adv*. 2023;5(10):2674–2723. doi:10.1039/D2NA00534D
145. Cameron SJ, Sheng J, Hosseinian F, et al. Nanoparticle effects on stress response pathways and nanoparticle–protein interactions. *Int J Mol Sci*. 2022;23(14):7962. doi:10.3390/ijms23147962
146. Summer M, Ashraf R, Ali S, et al. Inflammatory response of nanoparticles: mechanisms, consequences, and strategies for mitigation. *Chemosphere*. 2024;363:142826. doi:10.1016/j.chemosphere.2024.142826
147. Ji Y, Wang Y, Wang X, et al. Beyond the promise: exploring the complex interactions of nanoparticles within biological systems. *J Hazard Mater*. 2024;468:133800. doi:10.1016/j.jhazmat.2024.133800
148. Wu T, Tang M. Review of the effects of manufactured nanoparticles on mammalian target organs. *J Appl Toxicol*. 2018;38(1):25–40. doi:10.1002/jat.3499
149. Septiadi D, Crippa F, Moore TL, et al. Nanoparticle–cell interaction: a cell mechanics perspective. *Adv. Mater.* 2018;30(19):1704463. doi:10.1002/adma.201704463
150. Liu W, Webster T. Toxicity and biocompatibility properties of nanocomposites for musculoskeletal tissue regeneration. In: *Nanocomposites for Musculoskeletal Tissue Regeneration*. Elsevier; 2016:95–122.
151. Pan Y-B, Wang S, He X, et al. A combination of glioma in vivo imaging and in vivo drug delivery by metal–organic framework based composite nanoparticles. *J Mater Chem B*. 2019;7(48):7683–7689. doi:10.1039/c9tb01651a

152. Cortese-Krott MM, Münchow M, Pirev E, et al. Silver ions induce oxidative stress and intracellular zinc release in human skin fibroblasts. *Free Rad Biol Med*. 2009;47(11):1570–1577. doi:10.1016/j.freeradbiomed.2009.08.023
153. Okazaki Y, Gotoh E. Metal ion effects on different types of cell line, metal ion incorporation into L929 and MC3T3-E1 cells, and activation of macrophage-like J774. 1 cells. *Mater Sci Eng C Mater Biol Appl*. 2013;33(4):1993–2001. doi:10.1016/j.msec.2013.01.015
154. Liu W, Su P, Chen S, et al. Synthesis of TiO 2 nanotubes with ZnO nanoparticles to achieve antibacterial properties and stem cell compatibility. *Nanoscale*. 2014;6(15):9050–9062. doi:10.1039/c4nr01531b
155. Kyllönen L, D'Este M, Alini M, et al. Local drug delivery for enhancing fracture healing in osteoporotic bone. *Acta biomaterialia*. 2015;11:412–434. doi:10.1016/j.actbio.2014.09.006
156. Walmsley GG, McArdle A, Tevlin R, et al. Nanotechnology in bone tissue engineering. *Nanomedicine*. 2015;11(5):1253–1263.
157. Souza W, Piperni SG, Laviola P, et al. The two faces of titanium dioxide nanoparticles bio-camouflage in 3D bone spheroids. *Sci Rep*. 2019;9 (1):9309. doi:10.1038/s41598-019-45797-6
158. Wang G, Jin W, Qasim AM, et al. Antibacterial effects of titanium embedded with silver nanoparticles based on electron-transfer-induced reactive oxygen species. *Biomaterials*. 2017;124:25–34. doi:10.1016/j.biomaterials.2017.01.028
159. Chairuangkitti P, Lawanprasert S, Roytrakul S, et al. Silver nanoparticles induce toxicity in A549 cells via ROS-dependent and ROS-independent pathways. *Toxicol In Vitro*. 2013;27(1):330–338. doi:10.1016/j.tiv.2012.08.021
160. Bari A, Bloise N, Fiorilli S, et al. Copper-containing mesoporous bioactive glass nanoparticles as multifunctional agent for bone regeneration. *Acta biomaterialia*. 2017;55:493–504. doi:10.1016/j.actbio.2017.04.012
161. Wang Z, Li N, Zhao J, et al. CuO nanoparticle interaction with human epithelial cells: cellular uptake, location, export, and genotoxicity. *Chem Res Toxicol*. 2012;25(7):1512–1521. doi:10.1021/tx3002093
162. Choi SY, Song MS, Ryu PD, Lam AT, Joo SW, Lee SY. Gold nanoparticles promote osteogenic differentiation in human adipose-derived mesenchymal stem cells through the Wnt/β-catenin signaling pathway. *Int J Nanomedicine* 2015;4383–4392.
163. Dykman L, Khlebtsov N. Gold nanoparticles in biomedical applications: recent advances and perspectives. *Chem Soc Rev*. 2012;41 (6):2256–2282. doi:10.1039/c1cs15166e
164. Quinn J, McFadden R, Chan C-W, et al. Titanium for orthopedic applications: an overview of surface modification to improve biocompatibility and prevent bacterial biofilm formation. *iScience*. 2020;23(11). doi:10.1016/j.isci.2020.101745
165. Komeri R, Kasoju N, Kumar PA. In vitro cytotoxicity and cytocompatibility assays for biomaterial testing under regulatory platform. In: *Biomedical Product and Materials Evaluation*. Elsevier; 2022:329–353.
166. Assad M, Jackson N. Biocompatibility evaluation of orthopedic biomaterials and medical devices: a review of safety and efficacy models. *Encycloped Biomed Eng* 2019;281–309.
167. Iqbal H, Keshavarz T. The challenge of biocompatibility evaluation of biocomposites. In: *Biomedical Composites*. Elsevier; 2017:303–334.
168. Kohl Y, Rundén-Pran E, Mariussen E, et al. Genotoxicity of nanomaterials: advanced in vitro models and high throughput methods for human hazard assessment—a review. *Nanomaterials*. 2020;10(10):1911. doi:10.3390/nano10101911
169. De Jong W, Carraway J, Geertsma R. In vivo and in vitro testing for the biological safety evaluation of biomaterials and medical devices. In: *Biocompatibility and Performance of Medical Devices*. Elsevier; 2020:123–166.
170. Kimber I, Basketter DA, Berthold K, et al. Skin sensitization testing in potency and risk assessment. *Toxicol Sci*. 2001;59(2):198–208. doi:10.1093/toxsci/59.2.198
171. Weber M, Steinle H, Golombek S, et al. Blood-contacting biomaterials: in vitro evaluation of the hemocompatibility. *Front Bioeng Biotechnol*. 2018;6:99. doi:10.3389/fbioe.2018.00099
172. Limongi T, Tirinato L, Pagliari F, et al. Fabrication and applications of micro/nanostructured devices for tissue engineering. *Nano-Micro Letters*. 2017;9(1):1–13. doi:10.1007/s40820-016-0103-7
173. Gunputh U, Le H. Composite coatings for implants and tissue engineering scaffolds. In: *Biomedical Composites*. Elsevier; 2017:111–138.
174. Liu Y, Luo J, Chen X, Liu W, Chen T. Cell membrane coating technology: a promising strategy for biomedical applications. *Nanomicro Lett* 2019;11:1–46.
175. Rasmussen JW, Martinez E, Louka P, Wingett DG. Zinc oxide nanoparticles for selective destruction of tumor cells and potential for drug delivery applications. *Expert Opin Drug Deliv* 2010;7(9):1063–1077.
176. Lin G, Li L, Panwar N, et al. Non-viral gene therapy using multifunctional nanoparticles: status, challenges, and opportunities. *Coord. Chem. Rev* 2018;374:133–152.
177. Frisch E, Clavier L, Belhamdi A, et al. Preclinical in vitro evaluation of implantable materials: conventional approaches, new models and future directions. *Front Bioeng Biotechnol*. 2023;11:1193204. doi:10.3389/fbioe.2023.1193204
178. D'Avenio G, Daniele C, Grigioni M. Nanostructured medical devices: regulatory perspective and current applications. *Materials*. 2024;17 (8):1787. doi:10.3390/ma17081787
179. Isibor PO. Regulations and policy considerations for nanoparticle safety. In: *Environmental Nanotoxicology: Combatting the minute Contaminants*. Springer; 2024:295–316.
180. Ramos TI, Villacis-Aguirre CA, López-Aguilar KV, et al. The Hitchhiker's guide to human therapeutic nanoparticle development. *Pharmaceutics*. 2022;14(2):247. doi:10.3390/pharmaceutics14020247
181. Hua S, de Matos MBC, Metselaar JM, et al. Current trends and challenges in the clinical translation of nanoparticulate nanomedicines: pathways for translational development and commercialization. *Front Pharmacol*. 2018;9:790. doi:10.3389/fphar.2018.00790
182. Stavrou M, Phung N, Grimm J, et al. Organ-on-chip systems as a model for nanomedicine. *Nanoscale*. 2023;15(23):9927–9940. doi:10.1039/D3NR01661G
183. Voelker R. 3D-printed implant is approved to replace ankle joint bone. *JAMA*. 2021;325(13):1246.
184. Morimoto T, Hirata H, Eto S, et al. Development of silver-containing hydroxyapatite-coated antimicrobial implants for orthopaedic and spinal surgery. *Medicina*. 2022;58(4):519. doi:10.3390/medicina58040519
185. Ruiz A, Hernández Y, Cabal C, et al. Biodistribution and pharmacokinetics of uniform magnetite nanoparticles chemically modified with polyethylene glycol. *Nanoscale*. 2013;5(23):11400–11408. doi:10.1039/c3nr01412f
186. Jia Y-P, Ma BY, Wei XW, Qian ZY. The in vitro and in vivo toxicity of gold nanoparticles. *Chin. Chem. Lett* 2017;28(4):691–702.

International Journal of Nanomedicine

Dovepress
Taylor & Francis Group

Publish your work in this journal

The International Journal of Nanomedicine is an international, peer-reviewed journal focusing on the application of nanotechnology in diagnostics, therapeutics, and drug delivery systems throughout the biomedical field. This journal is indexed on PubMed Central, MedLine, CAS, SciSearch®, Current Contents®/Clinical Medicine, Journal Citation Reports/Science Edition, EMBase, Scopus and the Elsevier Bibliographic databases. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit http://www.dovepress.com/testimonials.php to read real quotes from published authors.

Submit your manuscript here: https://www.dovepress.com/international-journal-of-nanomedicine-journal