Review Article



# Recent advances in the application of nanotechnology in joint arthroplasty: a narrative review

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**Background and Objective:** Osteoarthritis (OA) is a multifactorial disease, involving biomechanical, inflammatory, and metabolic processes that ultimately impact the structure and function of a joint. Current therapeutic options can improve symptoms and prolong the time to surgery, yet they are not curative and are limited by their systemic side-effects and their inability to provide site-specific delivery. Nanomedicine takes advantage of the unique properties held by technology on the nanoscale (1–100 nm), including surface effects and quantum effects, that allow for novel mechanical, thermal, and magnetic functions. The primary aim of this narrative review is to summarize the recent advances made in nanotechnology and their uses in joint arthroplasty.

**Methods:** This narrative review was performed following a computerized search of the electronic database on PubMed in September 2024. Papers related to the use of nanotechnology in orthopaedic arthroplasty surgery were included for review.

**Key Context and Findings:** Nanotechnology holds the promise of optimizing OA treatment, refining the implants used during joint arthroplasty, and aiding in the diagnosis and treatment of post-operative joint infections. With the increasingly aging population and growing demand for joint replacement, this review aims to cover the novel applications of nanoparticles (NPs) within the realm of joint replacement surgery.

**Conclusions:** Future studies are needed to further investigate the clinical translation of NPs in joint arthroplasty. Additionally, the potential of NPs needs to be considered within their limitations and their safety profile that is still being defined.

**Keywords:** Nanoparticles (NPs); nanotechnology; osteoarthritis (OA); total joint replacement (TJR); joint implants

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## Introduction

Originally introduced by the Nobel Prize laureate Richard Feynman in 1959, nanotechnology involves the use of particles at the nanoscale (1–100 nm) (1). The small size and large surface area of nanoparticles (NPs) introduces many unique properties, with the ability to be further specialized with surface modifications (2,3). Properties such as enhanced mechanical, thermal, and magnetic functions allow NPs to be advantageous in cellular uptake, directed drug-delivery, and imaging (4,5). These advances hold the potential to revolutionize medicine and the ability to

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**Table 1** The search strategy summary

| Items | Specification |
|---|---|
| Date of search | From September 1 to September 30 2024 |
| Database | PubMed |
| Search terms used | The research was conducted using the following keywords: "Nanotechnology", "Nanoparticles", "Orthopaedic Surgery", "Joint Arthroplasty", and "Joint Replacement" |
| Timeframe | 2000 to 2024 |
| Exclusion criteria | Non-English language publications |
| Selection process | First author completed selection process |

diagnose and treat patients. Thus, over the past decade, nanotechnology has been rapidly gaining success and popularity in the medical world (6).

Orthopaedic surgery is one area of medicine with emerging interest in the applications of nanotechnology, with recent research focused on the potential uses of nanomedicine in implants, osteoarthritis (OA) treatment, bone regeneration, and infection management (7). Total joint replacements (TJRs) represent some of the most frequently performed surgeries in the world, with OA being a primary contributing factor (8,9). As the population continues to age, the incidence of joint replacement is expected to continue rising, with a growth of 71% for total hip arthroplasty (THA) and 85% for total knee arthroplasty (TKA) expected by the year 2030 (10). With the rapidly growing literature on the uses of nanotechnology in orthopaedics, there remains room to discuss the applications of this new technology within the realm of joint surgery. While numerous studies have explored nanotechnology in arthroplasty, there is no clear synthesis of how these interventions compare with conventional strategies in clinical contexts. This review focuses on the applications of nanomedicine in the treatment of joint disease, primarily recent advances in OA management and TJR. We present this article in accordance with the Narrative Review reporting checklist (available at https://aoj.amegroups.com/article/view/10.21037/aoj-24-50/rc).

## Methods

This narrative review was performed following a computerized search of the electronic database on PubMed in September 2024. The search was limited to English-language studies published between 2000 and 2024 in PubMed. Search terms included the following keywords: "Nanotechnology", "Nanoparticles", "Orthopaedic Surgery", "Joint Arthroplasty", and "Joint Replacement". Abstracts were originally screened to assess for applicability and inclusion into the review, with further publications pulled from the referenced materials within these initial inclusions. The selection process was completed by the first author. The specific search summary is reported in *Table 1*.

## NP characterization

### *NP classification*

NPs are defined by the International Organization for Standardization as objects on the nanoscale (1–100 nm) where the dimensions of the short and long axes do not significantly differ (11). These particles come in an array of shapes and sizes, varying from cylindrical to spherical to conical (12). Their structure can be uniform or layered, typically including three layers: a surface layer, the shell layer, and a core (13). NPs can be further categorized based on their composition, typically falling under one of three classes: organic, carbon-based, or inorganic (12) (*Figure 1*).

Organic NPs are composed of proteins, lipids, polymers, or carbohydrates, often formed via non-covalent intermolecular interactions (14,15). This allows them to be bio-degradable and easily cleared from the body, with common examples including micelles and liposomes (12). These NPs are often used to encapsulate therapeutic drugs, allowing them to be released in a controlled manner and reducing cytotoxicity (16). These characteristics make organic NPs advantageous in targeted drug delivery and cancer therapy (12).

Carbon-based NPs are comprised solely of carbon atoms and include examples such as carbon black NPs, carbon quantum dots, and nanodiamonds (17-19). The

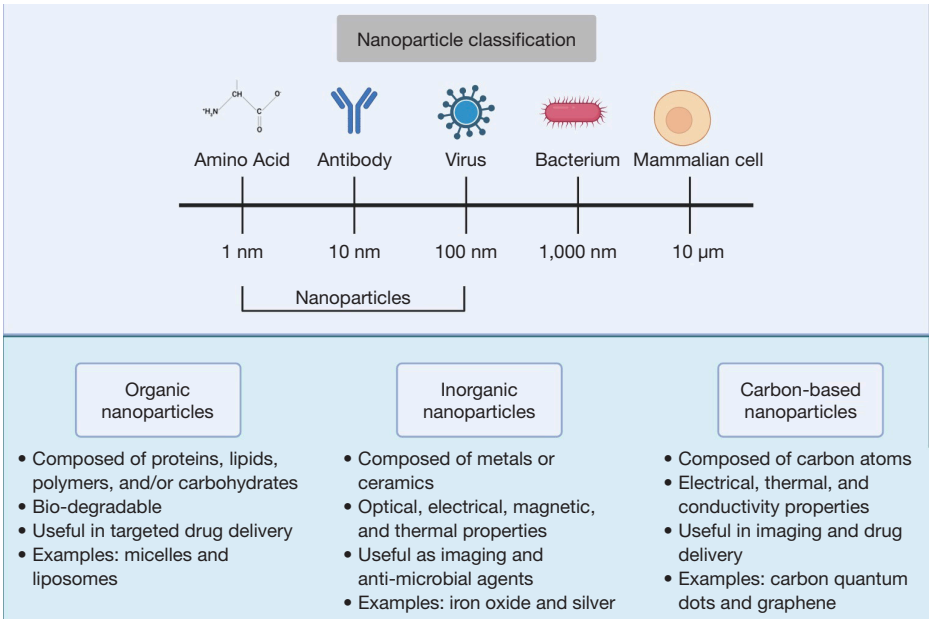


**Figure 1** Nanoparticle classification.

$sp^2$-hybridized carbon bonds allow for unique properties within this class of NPs, including electrical conductivity, thermal properties, magnetism, and high strength (20). These characteristics makes them incredibly useful in applications such as imaging, tissue engineering, and drug delivery (21,22). Furthermore, carbon dots have fluorescent emissions with lower cytotoxicity compared to normal fluorescence markers, making them useful as imaging probes (23).

Lastly, inorganic NPs include all particles not composed of organic or carbon-based materials, usually metals or ceramics (12). Metal NPs possess optical and electrical properties due to their localized surface plasmon resonance characteristics, as well as thermal and magnetic effects, giving them a broad range of applications (13). Some areas of utility include contrast agents during magnetic resonance imaging, cell labeling, drug delivery, and as antimicrobial agents against microorganisms (24). Ceramic NPs are useful in imaging and catalytic processes due to their high stability created during successive heating and cooling processes (13,25). Semiconductor NPs carry characteristics between those of metals and nonmetals, thus also contributing to a wide array of uses (13,26).

### *NP production*

The production of NPs can be broadly classified into two main categories: top-down synthesis and bottom-up synthesis (13). During top-down synthesis, a larger molecule is degraded into smaller components, which are ultimately transformed into NPs (13). Contrastingly, bottom-up synthesis involves creating NPs from simpler building blocks (13).

When designing NPs, it is important to tailor the size, shape, and surface to the desired function of the particle (2). Fine-tuning the size of NPs aids in accumulation at the desired location, prolonging blood circulation half-life, and evasion of the immune system (2). These factors will ultimately determine the efficacy of cellular uptake of the NP (2). One modification often made to NPs is coating them with polyethylene glycol (PEG) to aid in immune system avoidance and therefore prolong circulation (27). While useful in avoidance of immune system clearance, this often poorly impacts the ability of cellular uptake and drug release (28). The addition of ligands to the NP's surface helps ameliorate this effect and aid in active targeting (29).

## Applications of nanotechnology in OA treatment

OA is a debilitating disease, impacting millions of people and costing the USA approximately $100 billion annually (30). Resulting from the progressive loss of articular cartilage, this disease results in changes to the structure and function of the entire joint (30). Age is the primary risk factor for

OA, with 49.7% of individuals ≥65-years-old impacted (31). Additional risk factors include obesity, metabolic disease, and the female gender (30). As the population continues to age, so will the rate of individuals seeking treatment for degenerative joint disease (30,31).

Recent studies have suggested that OA includes biochemical, inflammatory, and metabolic components, complicating the underlying pathophysiology of this disease (30,32,33). As an individual ages, deterioration of the chondrocytes within the articular cartilage of a joint occurs (34). These altered chondrocytes increase production of matrix proteins and matrix-degrading enzymes, contributing to the degradation of the cartilage (34). This process is further aided by the infiltration of mononuclear cells and proinflammatory mediators (34,35). Ultimately, these processes result in joint pain, stiffness, and reduced mobility, impacting a patient's quality of life (36).

Currently, OA can be managed conservatively or surgically, depending on the progression of the disease, patient comorbidities, and patient and surgeon preference (37). Conservative management is usually the preferred initial pathway, with the goal of alleviating symptoms and improving a patient's quality of life (37). First line interventions typically include lifestyle modifications (including exercise therapy and weight management) and pharmacological interventions (including the use of topical and oral non-steroidal anti-inflammatory drugs, intra-articular corticosteroids, and hyaluronic acid injections) (37,38).

While potentially therapeutic, conservative management is unable to cure the underlying disease, thus progression to surgery is usually unavoidable. As recent studies suggest, addressing multifaceted health challenges like frailty requires innovative and accessible technologies that bridge clinical and societal needs (39). Finding novel ways to non-operatively treat OA is of great clinical interest and may help prolong the need for surgical intervention.

### *Nanotechnology treatment advancements*

Conventional drugs, while easily administered via oral routes, require the need for frequent dosing to reach the desired effect (36). Intra-articular injections avoid some of these drawbacks by allowing for improved drug delivery to the desired site and reducing the systemic side-effects (36,40). Despite this, drugs administered intraarticularly are still subject to rapid clearance through enzymatic degradation (36,40). The use of nanocarriers for drug delivery seeks to remove these barriers, allowing for increased site-specific drug delivery and reduced systemic side-effects (7,36). The integration of manual therapy techniques with nanotechnological innovations could provide a synergistic approach to improving patient outcomes, as evidenced by Martínez-Pozas *et al.* (41). Various types of nanotechnology-based drug delivery systems have been developed, including lipid, polymeric, and metallic NPs (7).

#### Lipid NPs

Liposomes are typically comprised of a bilayer of phospholipids and cholesterol enclosing an aqueous center, making them ideal for carrying hydrophobic drugs (42). Their role as drug delivery vehicles serves multiple purposes, including protecting the therapeutic agent from rapid clearance, allowing for controlled drug release, and extending the half-life of the drug (43). Additionally, liposomes can target their delivery site, either actively or passively, thereby improving site-specific delivery and reducing systemic side-effects (44). Active targeting involves the use of interactions between ligands on the surface of the liposomes with receptors present at the target site (45). Passive targeting takes advantage of the microenvironment of the abnormal tissue (46). Inflammatory tissues and tumors typically have highly porous capillaries, preferentially aiding in the accumulation of liposomes at the desired location (46). Recent studies have focused on the application of liposomes in OA treatment.

For example, Williams *et al.* studied the anti-inflammatory effects of methotrexate-loaded vesicles in rats with antigen-induced arthritis, with a more pronounced reduction in swelling seen compared to free drugs (47). This study also demonstrated the importance of the size of liposomes, with greater anti-inflammatory effects witnessed with larger liposomes (1.2 μm) compared to smaller liposomes (100 nm), likely due to the increased clearance of smaller vesicles by the lymphatic system (47).

Another study of Corciulo *et al.* evaluated the targeting ability of liposomal encapsulated drugs in obesity-induced and post-traumatic OA animal models (48). Studies had previously demonstrated the importance of adenosine in maintaining cartilage by acting at its A2A receptor (48). In this study, Corciulo *et al.* prepared liposomes with adenosine and CGS21680, a selective A2A receptor agonist (48). They found a significant reduction in OA cartilage damage and joint swelling in their OA models, along with reduced expression of the genes associated with matrix degradation in the chondrocytes harvested (48). This study highlights the

 

use of nanotechnology in providing targeted drug-delivery.

### Polymeric NPs

Numerous polymers have been used to develop drug delivery systems, including chitosan, starch, and polylactic acid (49). These polymeric materials can be easily structurally modified, allowing for directed drug delivery similar to liposomes (49). Maudens *et al.* investigated the use of nanocrystal-polymer particles (NPPs) developed with kartogenin, a molecule capable of protecting and regenerating cartilage (50). In this study, *in vitro* experiments demonstrated the high-drug loading ability and extended drug release over a 3-month period of these NPs (50). *In vivo* experiments in a murine OA mouse model then compared the kartogenin NPPs to a kartogenin solution, with higher levels of bioactivity seen with the NPPs (50). This innovative idea holds the promise of improving OA treatment by reducing conventional drug clearance and promoting cartilage protection.

Kang *et al.* developed thermo-responsive polymeric nanospheres, capable of allowing dual drug delivery in a single system (51). These nanospheres were loaded with diclofenac within the inner core while kartogenin was covalently cross-linked on the outer surface, allowing for immediate release of the diclofenac and controlled release of the kartogenin independently based on temperature change (51). The dual function of these drugs demonstrated both anti-inflammatory and chondroprotective effects on OA in both *in vitro* and *in vivo* experiments (51).

### Metallic NPs

Metals such as silver, copper, zinc, and iron have been widely used in various medical applications, including imaging and drug delivery (52). Their possession of anti-inflammatory and anti-bacterial properties make them extremely useful in areas such as wound healing and burn management (52). Metallic NPs can be synthesized via physical, chemical, or biological methods with their properties dependent on their size and composition (53). Alloy NPs composed of two or more metals have been shown to have enhanced properties and more stable structures when compared to monometallic NPs (53). This provides them with a more diverse portfolio of applications, including strong photocatalytic and magnetism effects (53). Recently, studies have focused on their applications in orthopaedics (52). A study conducted by Sang *et al.* evaluated the use of silver NPs in type II collagenase-induced knee OA in a mouse model (52). They found a significant reduction in synovial hyperplasia and neutrophil infiltration, suggesting a novel way of treating OA (52).

While most of the drug delivery and potential regenerative aspects of nanotechnology are largely theoretical at this stage, there are plausible mechanisms that hold promise for the future. One invention that is actively being used in orthopaedic clinics is extended-release triamcinolone acetonide (Zilretta®) (54). This intra-articular injection is currently approved for management of knee OA in the USA, with excellent results demonstrated during clinical trials. This formulation involves the slow release of triamcinolone acetonide from poly lactic-co-glycolic acid (PLGA) microspheres into the synovium, prolonging the effects of the corticosteroid and reducing systemic side-effects (54). Clinical trials showed improved pain, stiffness, and physical function when compared to a placebo and triamcinolone acetonide crystalline suspension (CS), with similar tolerability to these alternatives (54).

## Application of nanotechnology in joint replacement implants

### *Optimization of bone integration*

Total joint arthroplasty aims to improve joint mobility and decrease pain associated with OA by replacing all or part of the joint with an artificial device (55). Achieving osseointegration of the implant is an important goal of surgery, otherwise there is a high risk of implant failure due to aseptic loosening (55). In addition to insufficient initial fixation being a leading cause of aseptic loosening, loss of mechanical fixation over time and biological loss of fixation due to osteolysis are other contributors to failure (56).

Implant-associated osteolysis is the result of inflammatory and enzymatic processes occurring at the implant-bone interface (56). This reaction results from a biological response to implant debris, starting with the development of fibrous tissue, then granulomatous tissue, before progressing to the production of inflammatory mediators which ultimately result in implant failure (56). Thus, finding the optimal implant material is of current interest amongst the orthopaedic community, with ceramic and highly cross-linked polyethylene showing promise in reducing the production of debris particles (56). Despite these advances, osteolysis remains a potential risk following joint replacement of near nanometer sized particles having a true clinical impact. Similarly metal debris from the bearing surface or corrosion at the trunnion can generate

nanometer sized particles leading to pseudotumor and other physiologic effects.

The utilization of nanotextured materials in implants have shown promise in reducing the risk of implant failure by improving osseointegration (55). In nanometric terms, mature bone has a course surface while conventional implants often have a smooth surface at the nanometric level (55). This smoother surface often promotes the growth of fibrous tissue, contributing to the development of aseptic loosening (55). Meanwhile, studies have shown that a nanotextured surface may enhance osteoblast function while reducing fibroblast growth, therefore promoting bone growth and restricting the development of fibrous tissue (55). This nanotextured surface is often achieved via nanotextured hydroxyapatite (HA)-coated surfaces or nano-engineered titanium and cobalt-chromium-molybdenum (CoCrMo) (55). Webster *et al.* conducted an *in vitro* study evaluating the level of osteoblast adhesion to nanophase metals, specifically Ti, Ti6AL4V, and CoCrMo alloys (57). Their results demonstrated an increased rate of osteoblast adhesion to these metals compared to conventional metals, supporting the potential of improved osseointegration during TJR with the use of nano-based implants (57). Furthermore, there have been clinical studies done demonstrating the increased stability of hydroxyapatite (HA)-coated implants following TJRs in patients (58). A meta-analysis performed by Horváth *et al.*, including 11 randomized control trials, compared the effects of HA-coated tibial stems on the stability and functionality of primary TKA. Their results demonstrated that the HA-coating had better stability compared to other uncemented implants, with a statistically significant difference in maximum total point motion of the tibial stem ($P<0.01$). Furthermore, the knee society score was significantly higher for the HA-coated group compared to cementless prosthesis (58).

### *Implant modifications*

The application of bioactive coatings on total joint implants is another area of rapidly growing interest due to their wide array of properties (59,60). The use of diamond-like carbon (DLC) coatings on implants shows great promise given their significant mechanical hardness and antimicrobial effects (60). These coatings provide improved wear resistance to implants and help prevent biofilm formation, a major contributor to periprosthetic joint infection (PJI) (60). The addition of elements, such as silver and copper, to DLC coatings further improve in these mechanical and antimicrobial properties, helping to prolong the life of implants (60-62). Current studies are focused on identifying the ideal level of doping to achieve the desired effects without impacting the durability and mechanics of the DLC (60). Finally, a study by Song *et al.* looked at titanium implants coated with doxycycline-loaded coaxial nanofibers (63). The authors used electrospinning to directly despite the nanofibers onto the titanium implant surface, with a stand single-pass scratch test used to confirm the bonding strength of the coating. Their *in vivo* results in a rat model showed enhanced osseointegration and improved inhibition of *S. aureus* infections compared to the non-nanofiber group (63). Osseointegration was evaluated via scanning electron microscopy, histomorphometry, and micro computed tomography (63). The bone contact surface changes of the nanofiber group was 80% compared to the control group at <5% at measurements made at 2, 4, and 8 weeks post-implantation ($P<0.05$) (63). The doxy released from the nanofiber coating inhibited bacterial growth up to 8-week post-implantation (63).

## Application of nanotechnology in joint infections

PJIs are a serious complication following TJR, resulting in significant patient morbidity and an estimated $1.62 billion cost to the United States' healthcare system (64). The incidence of PJI has grown with the increasing prevalence of joint arthroplasty, with rates up to 4% in the United States (64,65). With the growing interest in nanomedicine comes novel ideas for the prevention and management of PJI.

### *Preventive nanotechnology*

PJI is often a consequence of biofilm formation, which occurs over several sequential steps, involving attachment, maturation, and dispersal of bacteria (66). After introduction into the body, these bacteria are capable of producing proteins that quickly form strong interactions with the host extracellular matrix, making treatment with antibiotics extremely difficult (64). Thus, prevention of PJI from occurring in the first place is an important goal during surgery and perioperative care (64). Data has supported lower infection rates seen with the use of ceramic implants, likely attributed to the smoother surface inhibiting the formation of a biofilm (67,68). As previously discussed, the addition of NP-based coatings to implants has shown great promise in reducing infection by inhibiting biofilm formation (64). In particular, silver NPs have shown active anti-microbial effects against *E. coli* and *S. aureus*, as well as

osteo-integrative capabilities and anti-corrosive properties, making them an ideal elemental choice (66,69,70). These silver NPs also exhibit slow solubilization, therefore preventing toxicity to osteoblasts that may otherwise occur with rapid increases local silver concentrations (71). While still under investigation, these modifications to implants hold the potential for reducing the incidence of PJI.

Prophylactic antibiotics are routinely used during joint replacement surgery to reduce the risk of infection (72). As aforementioned, however, conventional antibiotics face difficulty in disrupting biofilm formation (72). Not to mention the relatively low accumulation of antibiotics at the desired site contributing to their limitations (72). Recent developments have led to the development of antimicrobial NPs, capable of providing improved delivery of antibiotics (72). Feng *et al.* studied the incorporation of doxycycline, a routinely used broad-spectrum antibiotic, into PLGA nanospheres with the use of nanofibrous poly-L-lactic acid (PLLA) scaffolds (73). The *in vitro* studies performed by the authors illustrated controlled release of doxycycline over an extended period, with inhibition of bacterial growth seen for over 6 weeks (73). Their results showed 70% inhibition of *S. aureus* and 40% inhibition of *E. coli* at day 42 in the nanosphere group (73). This was compared to 18% *S. aureus* inhibition and 9% *E. coli* inhibition at the same time point for the adsorbed doxycycline control group (73). Similar studies have demonstrated equal success using PLLA and PLGA scaffolds for antibiotic delivery in animal models (74).

### *Therapeutic nanotechnology*

Even in the setting of optimal operative management, PJI may occur (64). In these cases, reoperation is often necessitated, with a two-stage revision considered the "gold-standard" for treatment (64). While the preferred choice for chronic PJI management, two-stage revisions carry significant patient morbidity and an average mortality rate of 14.4% (75). Thus, NPs present an innovative way of treating PJI given their ability to deliver hydrophilic and hydrophobic drugs while limiting the systemic side-effects seen with large doses of conventional drugs (64,76).

The enhancement of bone cement with NPs for use in cement spacers during revisions has been studied in efforts to improve and prolong local drug delivery. Ayre *et al.* conducted *in vitro* experiments analyzing the incorporation of gentamicin sulfate loaded liposomes into polymethyl methacrylate (PMMA) bone cement (77). Their results showed higher delivery of antibiotics compared to conventional powdered antibiotic cement (77). Furthermore, the antibiotics were released over a 30-day period, allowing for controlled and extended release (77). The overall molecular structure of the cement remained unchanged with the addition of NPs (77). Similar studies have shown comparable results with the integration of silica-based NPs into PMMA cement (78).

Intraarticular injections of NP loaded drugs have shown improvements in penetrating biofilms and treating infections compared to free drugs (64). Fazly Bazzaz *et al.* loaded solid lipid nanoparticles (SLN) with rifampin and conducted *in vitro* experiments evaluating their efficiency against *S. epidermis* biofilm, with results showing a greater effect at eliminating the biofilm compared to free rifampin (79). Another study conducted by Li *et al.* used a mouse model to demonstrate the ability of liposomal encapsulated daptomycin at inhibiting *S. aureus* biofilm growth (80). While this study focused on the treatment of superficial skin infections, it nevertheless shows the ability of a NP drug delivery system being an effective treatment against biofilm in an *in vivo* model (80).

As the incidence of multidrug-resistant bacteria rises, so does the need for novel therapeutic approaches. Bacteriophages, or viruses that infect bacteria, have offered an alternative treatment route given their high bactericidal activity (81). Despite their promise for success, they are limited by bioavailability and stability (82). Combining the selectivity of bacteriophages with the targeted therapy of NPs has shown improvement of bacteriophage efficacy *in vivo* in areas of both bacteria detection and antimicrobial therapy (83). Nanotechnology has previously been used to develop biosensors and probes capable of detecting pathogens (84). Recent studies have focused on ways to combine NPs with phages to aid in pathogen detection (85). One study engineered a phage capable of targeting several bacterial species, including *Escherichia coli*, *Pseudomonas aeruginosa*, *Vibrio cholerae*, and *Xanthomonas campestris* and modified them to react with NPs (85). Gold NPs were then able to form a thiol bond to the phage causing a change in color to the solution indicating the presence of the target bacteria (85).

In addition to the potential diagnostic uses, combining phage and NP therapy has also proved promising in therapeutic ventures (83). Encapsulation of phages within polymeric nano and microparticles aids the phage in overcoming environmental obstacles, including degradation by the immune system and low bioavailability (86). This

also allows for controlled release of the phage, with numerous *in vitro* and *in vivo* studies offering promising results (83). Lastly, NPs have been used to kill bacteria through photothermal and photodynamic therapies, by causing localized hyperthermia and oxidative stress respectively (87). The use of NPs comprised of $Cu_9S_8$ and covered in PEG has demonstrated the ability to destroy *S. aureus* biofilms present on titanium surfaces using these therapies (87). Furthermore, photothermal therapy holds the capacity to destroy phages after bacterial identification, reducing the risk of potential transduction or evolution (88). One study evaluated the linkage of phages with gold nanorods via a sulfur bond, forming a "phanorod" (88). The phages were able to target specific bacterial species and photothermal therapy was used for ablation (88). The results demonstrated efficacy against the bacteria with minimal damage to the surrounding tissues (88). While still under investigation, these early studies hold the potential for treatment against localization bacterial infections.

## Conclusions

The use of nanotechnology in medicine is a rapidly growing area of clinical interest, with the US government having contributed nearly $1.4 billion to its research since 2008 (55). Nano-sized molecules contain unique properties, allowing for their utilization in directed drug-delivery and implant design (6,89-92). This holds the promise for increased delivery of drugs to the desired site while simultaneously decreasing the typical systemic side-effects (6,89-92). OA is a devastating disease impacting millions of people worldwide with a cure yet to be discovered (30). This review discussed the recent advances made with nanotechnology in improving conservative management of OA, refining orthopaedic implants, and in the prevention and treatment of joint infections. Current clinical applications in the conservative management of OA include Zilretta®, an intra-articular injection useful in prolonging the effects of corticosteroids. This advancement may provide superior benefits compared to traditional intra-articular injections, helping to improve management of OA and prolong surgical intervention. Further advancements include the integration of nanotechnology coatings in joint implants, which could become the standard of care within the next decade, especially for patients at high risk of infectious complications. These highlights show the potential nanotechnology holds in revolutionizing the treatment of OA and joint arthroplasty.

### *Safety profile of NPs*

While nanotechnology holds the possibility of improving patient care, the question of clinical safety must first be addressed (55). Various organ systems, including the liver and kidneys, are involved in the metabolism of NPs (55). This has raised concerns for potential inflammation, oxidative stress, and cytotoxicity (93). Further concerns surround the development of implant debris leading to increased levels of systemic particles, soft tissue damage, and pseudotumor formation (93). Despite these potential safety concerns, only 3% of the aforementioned $1.4 billion in nanotechnology research funding has been directed to safety concerns (55). Thus, the potential health impacts of NPs are relatively uncertain, with the need for further investigation.

### *Limitations and future implications*

Further limitations of nanotechnology use include the paucity of *in vivo* studies and the high cost of NP production (7). Development of a novel drug is an expensive and timely matter, thus explaining the limited clinical uses of nanotechnology in joint replacement at this time. It currently takes up to two decades for a drug, conventional or nanopharmaceutical, to enter the market after its discovery (94). Even after years of development and testing, only 11.8% of drugs eventually succeed in achieving final approval following clinical trials (95). During this time, it costs approximately $2,870 million to reach the profitable stage of a drug (96). Prior research has shown variability in NP effects *in vitro* versus *in vivo*, thus necessitating extensive testing using animal models before progression to clinical models (94). This, along with the safety and ethical questions surrounding nanotechnology, limits the studies currently available for review (94). Although preclinical studies suggest significant improvements in implant resistance and biocompatibility, randomized controlled trials are needed to evaluate their impact on long-term outcomes, such as joint functionality and patient quality of life (7). Despite these current limitations, nanotechnology has the prospect of impacting joint arthroplasty. Emerging methodologies, such as big data analytics and machine learning, are reshaping the diagnostic landscape, enabling predictive and patient-specific interventions (97,98). Likewise, as research continues to progress, the translation

of these early studies will hopefully translate into clinical applications for nanotechnology.

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## Footnote

*Reporting Checklist:* The authors have completed the Narrative Review reporting checklist. Available at https://aoj.amegroups.com/article/view/10.21037/aoj-24-50/rc

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