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Review Article

Orthopaedics Section

Recent Trends and Scope of Nanotechnology in Orthopaedic Surgery: A Narrative Review

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ABSTRACT

Orthopaedic implants osseointegrate better using nanophase materials because they mimic the natural trabecular bone structure better. Additionally, prostheses with nanophase coatings can lessen bacterial adherence compared to prostheses with traditional surfaces. Improved osseointegration and infection prevention may be possible with nano-coated joint replacement implants. Other potential applications with strong in-vitro findings include rapidly integrating fillers for osteochondral flaws, antitumour selenium-coated endoprostheses, along with potent targeted Drug Delivery Systems (DDSs) for infection prevention and treatment of chronic overuse injuries. It is significant to focus on the use of nanotechnology in artificial joint replacement prostheses, drug delivery utilising nanotechnology, surgical oncology of the skeleton using nanotechnology, bone cell function using nanotechnology, applications in orthopaedic surgery, and, finally, the use of nanotechnology and its potential new fields of study for human welfare. Before nanophase devices are approved for clinical use, significant progress must be made in comprehending the potential health concerns associated with their creation, implantation, and usage habits. However, they have a lot of potential and will probably be helpful to all of us in the future. Nanotechnology is a fast-advancing area, and its applications in orthopaedic surgery are continually expanding. This review article enables academics, clinicians, and other stakeholders to stay up-to-date on the most recent advancements, innovations, and achievements in the integration of nanotechnology into orthopaedic operations. The article also focuses on the challenges of applying nanotechnology in orthopaedics, such as biocompatibility issues, regulatory hurdles, and financial considerations. Simultaneously, it can discuss potential avenues for further research, collaboration, and progress in overcoming these challenges. Discussing the practical applications and clinical consequences of nanotechnology in orthopaedic surgery is crucial. The evaluation can explore on how these improvements will affect patient outcomes, surgical techniques, and overall healthcare practices.

Keywords: Cancer diagnosis, Diagnostics, Drug delivery, Gene delivery, Osseointegration

NTRODUCTION

Nanotechnology involves the creation, manipulation, and integration of resources on a nanoscopic scale, typically less than 100 nanometers, into micro and macro systems [1]. In orthopaedic surgery, nanotechnology offers innovative techniques for various orthopaedic applications. Key applications include the osseointegration of implant materials, meniscus repair and regeneration, treatment of osteochondral defects, and vertebral disk issues. Targeted drug delivery is particularly crucial for treating bone cancer. Bone is structured with a flexible matrix and bound minerals. The bone matrix comprises elastic collagen fibres and ground material. This biocomposite material consists of calcium and phosphate minerals (hydroxyapatite), proteins with type I collagen fibres, and water. Both minerals and organic constituents have nanometer-scale dimensions.

Conventional orthopaedic and dental implants are prone to failure and have a shorter lifespan, especially in young patients. Nanotechnology-developed bone replacements enhance implant strength and longevity. Progress in implant manufacturing has facilitated the development and use of biosensors, sensitive diagnostics, and controlled drug delivery systems. Osseointegration is crucial in stimulating new bone production for secure implant placement. The material properties of the implant should match the mechanical characteristics of the surrounding bone tissue. Successful osseointegration necessitates a direct chemical and physical connection with adjacent bone surfaces, without any fibrous tissue contact. While stainless steel and cobalt chrome alloys offer excellent mechanical qualities, their stiffness can lead to stress-shielding and bone resorption. Osseointegration helps reduce stress and strain at the tissue-implant interface, enhancing implant functionality and longevity [2].

Traditional physical rules do not apply at the nanoscale; nanomaterials exhibit unique and distinct features compared to materials composed of larger particles [3]. Despite having significantly smaller grain sizes than their conventional counterparts, nanophase materials maintain the same basic atomic structure. These entities are distinguished by two defining characteristics: the behaviour of nanophase materials is explained by quantum mechanics, unlike bulk materials explained by classical mechanics, and the surface area increases as the particle size decreases. Particles with a grain size of <100 nm exhibit different behaviours in terms of melting point, conductivity, reactivity, and combustibility compared to larger particles.

For example, a volume of one cubic meter (m^3) filled with cubes of one cubic meter has a total surface area of six square meters (m^2). However, if the same volume is filled with cubes of one cubic nanometer (nm^3), the total surface area would be six thousand square meters (m^2). Due to this fundamental principle, nanotechnology has the potential to become “the transformative technique of this decade” in the orthopaedic device sector. Important potential applications in orthopaedics have been identified through both fundamental scientific research and translational studies. This study examines the current and future use of nanotechnology in orthopaedics, specifically in Total Knee Replacement (TKR), orthopaedic trauma surgery, cancer treatment, prevention and management of orthopaedic surgery-related infections, soft tissue regeneration, and orthopaedic DDSs has been examined both currently and in the future.

Orthopaedics is a promising field for the application of nanotechnology because Hydroxyapatite (HA), Haversian systems, and collagen fibrils are all nanocompounds. Therefore, orthopaedics presents an ideal opportunity for the utilisation of nanotechnology [4]. During orthopaedic surgeries, complex interactions often occur on a microscopic scale between the biomaterials used and the host tissue. By using biomaterials derived from nanoparticles (NPs) and nanostructures, one can significantly enhance the effectiveness of such interactions through material modifications at the nanoscale. This forms the basic rationale for the majority of applications of nanotechnology in orthopaedic research.

The utilisation of nanotechnology in orthopaedic research holds significant promise as it offers the potential to improve the mechanical properties and biocompatibility of implantable orthopaedic devices. Nanostructured implants and prostheses provide increased mechanical strength, improved resistance to wear and corrosion, potential for drug delivery, and the capacity to serve as scaffolds for tissue regeneration [5].

Research in nanomedicine is currently receiving substantial funding now that nanotechnology has established itself in the medical field. Despite the theoretical advantages of nanotechnology, much of the productive in-vitro and laboratory-based research has not yet been applied in clinical settings. Concerns arise regarding the toxicity of NPs produced as wear debris. At the nanoscale, metals often exhibit different behaviours and material characteristics compared to the microscale. Issues with Metal-On-Metal (MOM) hip replacements are attributed to nanoscale metal ions. Consequently, conventional implants that have been enhanced with nanotechnology for specific properties are preferred over NP implants.

By addressing this issue, the problem of NPs falling freely and damaging tissue is avoided. It has been suggested that regulations are necessary in light of these problems. Despite mentioning the yet-unproven medical benefits, toxicity potential, and prohibitive costs associated with producing nanostructured implants and prosthetics, companies are still hesitant to do so [6].

The main uses of nanotechnology in the field of orthopaedics include the following areas of research of academic interest: i) the development of DDSs that are effective in delivering antibiotics along with chemotherapeutic agents; ii) improving surface preparation of implants and prostheses to enhance the integration of bone and minimise the formation of biofilms; iii) the creation of regulated drug-eluting systems to address infections related to implants; iv) the utilisation of tissue engineering techniques to prepare scaffolds for treatment.

This review focuses on the utilisation of nanotechnology in artificial joint replacement prostheses, the use of nanotechnology in pharmaceutical delivery, nanotechnology and surgical oncology of the skeleton, nano-based technology and the functioning of bone cells, applications in orthopaedic surgery, and lastly, nano-based technology and its potential new fields of investigation. This review also provides an opportunity to explore collaborations between nanotechnologists, material scientists, and orthopaedic surgeons. Interdisciplinary collaboration is crucial for translating nanotechnology advancements into practical applications in orthopaedic surgery. Through a survey of recent developments and applications, the current review aims to provide scholars, physicians, and policymakers with a comprehensive overview of nanotechnology in orthopaedic surgery.

Nanotechnology is utilised in surgical specialties to enhance surgical instruments, suture materials, imaging, targeted drug therapy, visualisation techniques, and wound healing tactics. These applications are clinically significant. Managing burn injuries and scars is a significant area of nanotechnology application. Technology is vital in the prevention, diagnosis, and treatment of a vast range of orthopaedic diseases and in the functional recovery of patients. Nanotechnology has improved clinical trials, research, patient care standards, and the development of safe medical equipment. In the years to come, these advancements may yield positive long-term outcomes in several surgical specialties, including orthopaedic surgery [7].

UTILISATION OF NANOTECHNOLOGY IN ARTIFICIAL JOINT REPLACEMENT PROSTHESES

The lack of successful osteointegration is a significant issue that arises with the rising utilisation of uncemented whole-joint arthroplasties. This is one of the key areas of concern. Despite ongoing efforts to enhance the surface roughness of Prosthetic Joints (PJs) to promote osseous ingrowth or ongrowth, it is important to note that the nanoscale surface remains smooth, which is the critical site for cellular interactions. This promotes fibrous ingrowth rather than bony ingrowth, which ultimately leads to failure at an earlier stage. By increasing the osteoblastic cellular activity, the utilisation of nanotextured surfaces along with nanoengineered implants will help find a solution to the problem. The enhanced interfacial contacts between the implant surface and the host bone are facilitated by the enlarged surface area achieved by the use of nanoengineering techniques, which effectively lower the grain size of the implants. This facilitates the establishment of a strong and reliable osteointegration, which in turn increases the lifespan of the implants. Infection around the PJ is a highly prominent reason for premature joint replacement non fulfillment and subsequent joint replacement surgery. A wide range of methods like antibiotic-loaded cement and several other local DDSs were tried, with fluctuating effectiveness. Previous research has shown evidence of the efficacy of utilising titanium nanotubes to coat prosthetic surfaces. These coatings include the application of nanophase silver or even polypeptide nanofilm right on PJ surfaces to achieve regulated and continued antibiotic flow following surgery, which is effective. It has been demonstrated that there is a reduction in the adhesion and colonisation of bacteria. In light of this, controlled antibiotic-eluting monophasic PJs provide a potential option to address the severe risk presented by infection of the peri-PJ [8].

The Use of Nanotechnology in the Delivery of Pharmaceuticals

Researchers creating nanophase DDSs have focused mostly on treating infections accompanying implants and preventing infections in PJs. Also, this novel approach is useful in diagnostic imaging modalities along with cancer treatment by allowing for a highly targeted attack on cancer cells. It can also promote bone formation when pooled with anabolic drugs, which helps prevent osteolysis around artificial joint surfaces [9]. The growth of injectable medications loaded inside nanospheres proficient in lengthening pharmacological effects is another area of research that shows promise as a fruitful area of investigation. The effectiveness of intra- along with extra-articular (biological and non biological) injections, which are utilised to treat synovitis, arthritic diseases, along with tendinopathies, can be considerably improved as a result of this.

NANOTECHNOLOGY AND SURGICAL ORTHOPAEDIC ONCOLOGY

The applications of nanotechnology in orthopaedic oncology have significant promise to boost diagnostics, conquer treatment resistance, decrease systemic damage to average host cells, along with delivering medications to cancer cells more efficiently. The ability to transport ligands is possessed by NPs. The incorporation of certain ligands that bind to the one-of-a-kind genes created only by tumour cells has the capability to enhance the capacity for accurate and timely diagnosis of primary as well as bone cancers (metastatic malignant). By loading contrast agents onto the NPs, one can boost the precision of targeted tumour imaging and evaluate the survivability of the tumour. This could be very helpful for preoperative valuation and surgical mapping. Additionally, cancer cells can become resistant to treatment by expressing Multidrug Resistance (MDR) proteins on their cell surface. These proteins cause cancer medicine to be pumped out of the cells, lowering the drug concentration inside the cells. Through the use of nanotechnology, vehicles capable of efficiently transporting anticancer medications into cells and delivering the gene sequences necessary to circumvent MDR can be manufactured. Active and passive targeting of cancer cells can be boosted by utilising nanophasic drug delivery devices. After endocytosis, a drug-loaded NP may be associated with surface ligands such as mannose and folic acid through the process of active targeting to identify the cancer cell that is to be targeted. NPs like AuNPs, AgNPs, etc., due to their diminutive size (which enables passive targeting) and their ability to make use of the permeability of cancer cells, make it possible to achieve larger medication concentrations inside cancer cells [10]. The capability to block the procedure of cancer by downregulating particular genes can also be improved by the application of nanotechnology. Employing nanostructures loaded with particles specifically aimed to suppress specific molecular markers can allow for the downregulation of specific molecular markers as well as the fusion oncogenes linked with osteosarcoma and Ewing's sarcoma, respectively [11].

Nanotechnology and the Functioning of Bone Cells

When biomaterials are implanted in people, interactions between the biomaterial's outermost layer and the nearby bone and soft tissues are important for cell differentiation and osseointegration, which is when bone grows into the surface of the implant. Whenever biomaterials are inserted inside a human body, certain interactions occur. Mesenchymal stromal cells appear to be an early cell type to be introduced when a nanophase biomaterial is added to a biological environment [12]. Nanophase implant surfaces as well as scaffolds may enhance osseointegration by encouraging the differentiation of these stromal cells from mesenchymal tissue and attracting the adhesion molecules necessary for osteoblasts by imitating the nanoscopic, 3D extracellular, and cell surface topography.

For instance, it is believed that type X collagen, due to its well known nano-topographical structure, induces endochondral ossification in the developing embryo. The replication of this process has the potential to facilitate the regulated enhancement of endochondral ossification that takes place in the course of secondary bone repair [13]. A substantial archive of evidence exists demonstrating the efficacy of various nanostructured materials in enhancing osteoblast activity. The materials included in this category consist of nanophase ceramics, namely aluminum oxide, titanium dioxide, carbon, selenium, Ti6AlV, cobalt-chrome alloys, and nanocrystalline diamond. Some in-vitro investigations show a higher degree of osteoid mineralisation on nano surfaces compared to micro-roughened surfaces [14].

An essential role in mediating the identification and activation, as well as osteoblast adherence to the biomaterial, which eventually results in osseointegration, is played by extracellular adhesion molecules like fibronectin and vitronectin. Nanophase implant surfaces interact with fibronectin and vitronectin more efficiently than conventional surfaces do. The biomolecules exhibit conformational alterations in addition to increased adsorption onto the nanosurface [15].

Application of nanomaterial in bone cells: Nanoparticles include the use of cell labelling to increase the scope of research and to enhance and non invasively monitor methods for cell treatment. Additionally, research is ongoing to develop drug-delivery devices with better pharmacologic properties. By enabling the regulated release of bioactive compounds like growth factors or anticancer medications, they improve the treatment outcome. Furthermore, promising gene therapy concepts are needed for intracellular manipulation-based future therapeutic alternatives [16].

When it comes to cell labelling during regenerative therapy, NPs show a lot of promise. Labelling compounds are applied in-vivo, or the cells are tagged ex-vivo and then applied locally or even systemically, depending on the treatment method. Thus, cell labelling makes it possible to detect transplanted cells practically, for example, using Magnetic Resonance Imaging (MRI) [17]. Therefore, cell labelling offers the chance to see and monitor cell travel to the defect site in-vivo as well as evaluate the outcome and role of the transplanted cells within tissue regeneration. This is necessary for a trustworthy assessment of the results of cell treatment. Mesenchymal Stem Cells (MSCs) are considered to enhance tissue regeneration within stem cell treatment because of their remarkable regenerative capacity. The application of MSCs shows promise in a variety of domains, including fracture repair and bone regeneration [18].

APPLICATIONS IN ORTHOPAEDIC SURGERY

Mature bone possesses inorganic mineral sizes around 50 nm, 25 nm, and 4 nm, indicating a rather large surface area at the nanoscale level. In contrast, contemporary orthopaedic implant surfaces exhibit a high degree of smoothness at the nano-scale level. Smooth surfaces tend to promote the proliferation of fibrous tissue over bone, but the presence of a nanotextured surface may facilitate bone formation. The use of a nanotextured substance may lower the danger of implant rejection. Along with the advantages of nanophase HA, Nanocrystalline hydroxyapatite CoCrMo, (Cobalt, Chromium, Molybdenum) and nanoengineered titanium promote osteoblast adhesion greater than their traditional counterparts [19,20]. Surfaces with HA nanostructures and many other nanostructured surfaces exhibit this distinct cellular activity. It is assumed that it is a direct effect of these surfaces' smaller grain sizes [21]. The outcomes of using nanocrystalline HA material as a filler for bone shortages have been promising. This was an adequate bone transplant substitute for metaphyseal defects, as demonstrated by a series of distal radius fractures [22]. Similar encouraging outcomes were seen in another investigation by that group when the procedure was employed to treat metaphyseal deficits in tibial plateau fractures. A series of proximal tibia fractures also showed that this was a suitable replacement for bone grafts in metaphyseal abnormalities [23]. Nanophase silicon appears to prevent the development of cancerous osteoblasts at the implant-tissue interface when administered to titanium implants for orthopaedics on a nanometric scale [24].

Orthopaedic traumatologists are showing a substantial amount of interest in nanophase silver as a source of research interest [25]. Silver's antimicrobial properties have made it a traditional treatment for wounds for many generations. Over the last decade, the introduction of nanophase silver dressings into the commercial sphere has shown their superior efficacy in terms of both wound infection prevention and wound healing stimulation, surpassing the performance of conventional silver-based or plain dressings. In a similar vein, the integration of nanophase silver into titanium orthopaedic implants' surface, namely titanium nanotubes, exhibits prompt and potent bactericidal along with antiadhesive properties, which can last for up to 30 days [26].

Injuries to the nerves in the body's periphery may also be helped by nanotechnology. According to a study, type I collagen scaffolding impregnated with nanophase silver greatly increases the amount of adsorbed proteins necessary for nerve repair while also shortening the time required for nerve regeneration. In an investigation, nanosilver-coated along with untreated type I collagen scaffolds were compared in a group of rabbits with an artificially produced 10 mm sciatic nerve lesion. Thicker myelin sheaths, better nerve transmission, and greater amounts of laminin adsorption were all seen in the group impregnated with nanosilver [27].

Nano Formulation-based Drug Delivery

Currently, a significant amount of effort is focussed on developing more accurate methods of drug delivery. In the treatment of tendinopathy, gold can serve as an efficient transcutaneous DDS for iontophoresis. This finding implies that the use of nanophase gold can enhance the effectiveness of diclofenac as a transcutaneous anti-inflammatory medication. In addition to nanophase gold, nanofiber Poly-L-Lactic Acid (PLLA) has remarkable potential as a nanoscale DDS. When nanofibre PLLA is used as the delivery mechanism for Bone Morphogenetic Protein (BMP)-2.12, large calvarial bony defects heal in a short amount of time, along with an increase in the expression of osteoblastic lineage cells.

Additionally, in a study by Li H et al., researchers used a biodegradable polypeptide nanofilm coating on overall joint prostheses to deliver cefazolin into a simulated Total Joint Replacement (TJR) environment. They found that this resulted in a decreased bacterial load and a better osteoblastic response. The ability of *Staphylococcus aureus*, often known as *S. aureus*, to adhere to a bare nanofilm implant surface was significantly lower than its ability to adhere to a traditional prosthesis [28].

NANOTECHNOLOGY AND ITS POTENTIAL NEW FIELDS OF INVESTIGATION OR NANOTECHNOLOGY'S SAFETY AND POTENTIAL FUTURE RESEARCH AREAS IN ORTHOPAEDIC SURGERY

One of the most important outstanding questions in nanotechnology is its applicability in healthcare settings. Due to implanted nanomaterials' degradation, NPs may be released into the body over time. At this point, the impact that NPs have on one's health is largely unknown. The metabolic processes of NPs involve several organ systems, including the circulatory system, hepatic system, and renal system, potentially leading to inflammatory responses and oxidative stress. There is evidence indicating a correlation between nanoparticulate particles and heightened cytotoxicity in the brain and lungs [29,30]. On the other hand, an opposing viewpoint posits that nano debris may have beneficial outcomes.

In the field of joint replacement, there is currently a lot of discussion on the clinical impact of Metal-on-Metal (MoM) wearing debris. It is believed that nanoscopic metal wear debris, with mean particle sizes ranging from 25 nm to 36 nm, is the primary cause of the toxicity associated with MoM hip replacements. Significant local and systemic repercussions result from dramatically elevated cobalt and chromium ion levels. Nanoscale metal ion wear debris can trigger an inflammatory reaction that is harmful at the level of the prosthesis. Soft tissue may be harmed as a result, and a pseudotumour may develop. Concerns have been raised about the effects on peripheral and central nerve tissue, the cardiovascular and endocrine systems, and their clinical importance, which is still unknown in the case of increased systemic cobalt (Co) and chromium (Cr) ion levels [31].

Drug Delivery

Due to the poor performance of various biomaterials presently utilised for bone replacement or tissue engineering, innovations like the incorporation of bioactive molecules are actively being pursued. Notable proteins can be injected directly into the target region or adsorbed onto a biomaterial surface. Unlike injected proteins, which are typically quickly removed from the body, locally adsorbed proteins are released through desorption or diffusion and may be maintained for longer periods. Nanoparticles are increasingly being investigated as finely adjustable delivery methods for medication release site and timing. Local drug distribution is preferred over systemic administration to reduce undesirable side-effects. Furthermore, proper NP tuning enables temporally regulated, sustained administration based on requirements. The introduction of inhibitory factors to signaling pathways has been described as a viable approach for elucidating previously unknown route functions for research objectives. Furthermore, NP refinement for clinical application in cancer treatment was proven by loading particles with the medication paclitaxel [32].

Gene Delivery

Although many proteins have a clear therapeutic effect on bone metabolism, delivering proteins of interest or growth factors remains a significant challenge due to aggregation, a short lifetime in the bloodstream, and, most importantly, very low efficiency due to short and abrupt release. In this regard, the use of NPs as gene carriers represents a broad and promising field, as the transfection strategy has the potential for long-term expression and hence a prolonged therapeutic effect. Many proof-of-principle experiments have already shown that both inorganic and organic NPs can transfer plasmids into bone cells. In such investigations, a green fluorescent protein-encoding reporter plasmid was typically paired with various carriers, like calcium-doped organosilicate, calcium phosphate NPs, arginine-functionalised HA nanorods, and polymers [33].

The [Table/Fig-1] shows literature findings on the role of nanotechnology in the field of orthopaedic surgery [27,34].

Study	Findings
Dohnert MB et al., [34]	Researchers discovered that when diclofenac was administered with 30 nm gold nanoparticles utilising iontophoresis inside a rat model of Achilles tendinopathy, it effectively decreased the levels of inflammatory cytokines IL1-β along with TNF-α inside the affected region. This reduction was much greater compared to both untreated control groups along with groups that received diclofenac alone.
Ding T et al., [27]	A comparative study was conducted to evaluate the effectiveness of nanosilver-impregnated type I collagen scaffolds relative to control scaffolds inside rabbits having a 10 mm sciatic nerve lesion. The group treated with nanosilver showed an increase in the thickness of their myelin sheaths, enhanced nerve conduction, and greater rates of laminin adsorption.

[Table/Fig-1]: Literature findings on the role of nanotechnology in the field of orthopaedic surgery [27,34].

CONCLUSION(S)

Nanotechnology, although still in its infancy, has established a strong foothold in basic science as well as the preclinical domain of orthopaedic research. As early promising applications of nanotechnology continue to be tested in human clinical trials, its enormous potential is finally starting to become apparent. Extensive research in the fundamental sciences suggests that orthopaedic surgery could hold the key to unlocking many of the exciting theoretical benefits that could be reaped from the application of nanotechnology. Joint replacement implants coated with nanomaterials can enhance the process of osseointegration and effectively combat infections. Prospective applications that exhibit promising in-vitro data include the rapid integration of fillers for osteochondral defects, the utilisation of antitumour selenium-coated endo-prostheses, and the development of effective targeted medication delivery methods for the avoidance of infections and chronic overuse injury therapy.

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- For any images presented appropriate consent has been obtained from the subjects. NA

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