International Journal of Orthopaedics and Bone Disorders

ISSN Print: 2664-8946
ISSN Online: 2664-8954
Impact Factor: RJIF 5.46
IJOBD 2024; 6(1): 45-54
www.orthopedicsjournals.net
Received: 03-09-2024
Accepted: 04-10-2024

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Orthopaedics nanotechnology: Review with a clinical focus

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DOI: https://doi.org/10.33545/26648946.2024.v6.i1a.36

Abstract
Nanotechnology has been extensively studied for its potential medical applications, particularly in orthopedics. This paper offers an in-depth account of the numerous orthopedic subspecialties where nanomaterials are currently as well as in the future being applied. One of the most promising innovations is the development of nanomaterials as scaffolds, which can enhance the interaction between natural bone and orthopedic implants. In orthopedic surgery, Nanotechnology can transform both diagnostics and treatments. However, further investigation is needed to guarantee the clinical safety of nanomaterials because it is still uncertain how they may affect human health in future generations.

Keywords: Nanomaterials, nanomaterials, orthopaedics, spine, arthroplasty, sports injury

Introduction

Background

Innovative and disruptive technologies have consistently shown the potential to enhance patient outcomes. Among these cutting-edge fields, nanotechnology comes to light as one that can help diagnose and treat complex medical diseases. As initially described by the National Nanotechnology Creativity, Nanotechnology is the exact manipulation and investigation of atomic particles and molecules with sizes between one and one hundred nanometers. Over time, this definition has broadened to include various scientific endeavors and applications [1]. Almost six decades ago, the promise of nanotechnology was originally highlighted by Richard Feynman, who called it "a field in which little is currently being done, but in which a huge amount can be accomplished according to principle" in 1959 [2]. Subsequently, nanotechnology has expanded to include many industries, including personal care products, food packaging, water filtration, and healthcare [3].

Many innovative orthopedic treatments have utilized "nanomedicine," which refers to the application of nanotechnology in medicine. Clinical examples involve enhanced diagnostic techniques, biodegradable materials, degenerative degeneration of disk therapies, and tailored drug administration [4].

Earlier research has provided detailed overviews of biomaterials explored and used in orthopedic nanotechnology [5, 6].

What sets our review apart is its organization by orthopedic subspecialties, focusing on how nanotechnology is applied in clinical orthopedics. While specialty classifications can be subjective, they help highlight the clinical significance of specific advancements, with the understanding that future applications will likely expand into other subspecialties. Our primary goal is to inform musculoskeletal researchers and orthopedic surgeons about current and future nanotechnology uses. Additionally, we will highlight nanotechnology studies currently undergoing clinical trials in every sector.

Fundamentals of Nanotechnology

The combination of several scientific domains, including materials research, microbial biology, semiconductors, and biological tissue engineering has given rise to nanotechnology.

Interestingly, for now, traditional micromaterials are reduced to Nano-sized particles, they often exhibit different physical and chemical properties. For example, the quantum size effect becomes more pronounced as the particle size approaches 100 nm or smaller [7]. When particle size decreases significantly, this effect is observed in the material's electrical properties. When reduced to the microscopic level materials with insulating characteristics at the macroscopic level could exhibit conductive characteristics. Apart from changes in electrical characteristics, a higher surface area-to-volume ratio may also impact the mechanical characteristics. This property is essential because nanoparticles have a large surface area retention that allows for more efficient interactions with the surrounding structures. This enhanced connection leads to a higher rate of Osseointegration of surgical implants by improving the attachment between the prosthesis and the native skeleton [8].

The possibility for more precise therapeutic Nano-engineered materials can target and influence cellular processes, as many of the chemicals take part in the process in which they exist naturally and interact at the nanoscale [10]. This is particularly relevant in orthopedics because bone is a fusion of collagen and hydroxyapatite at the nanoscale [11]. Applying these principles has led to advancements in the functionality and performance of various outcomes, both within the medical field and outside.

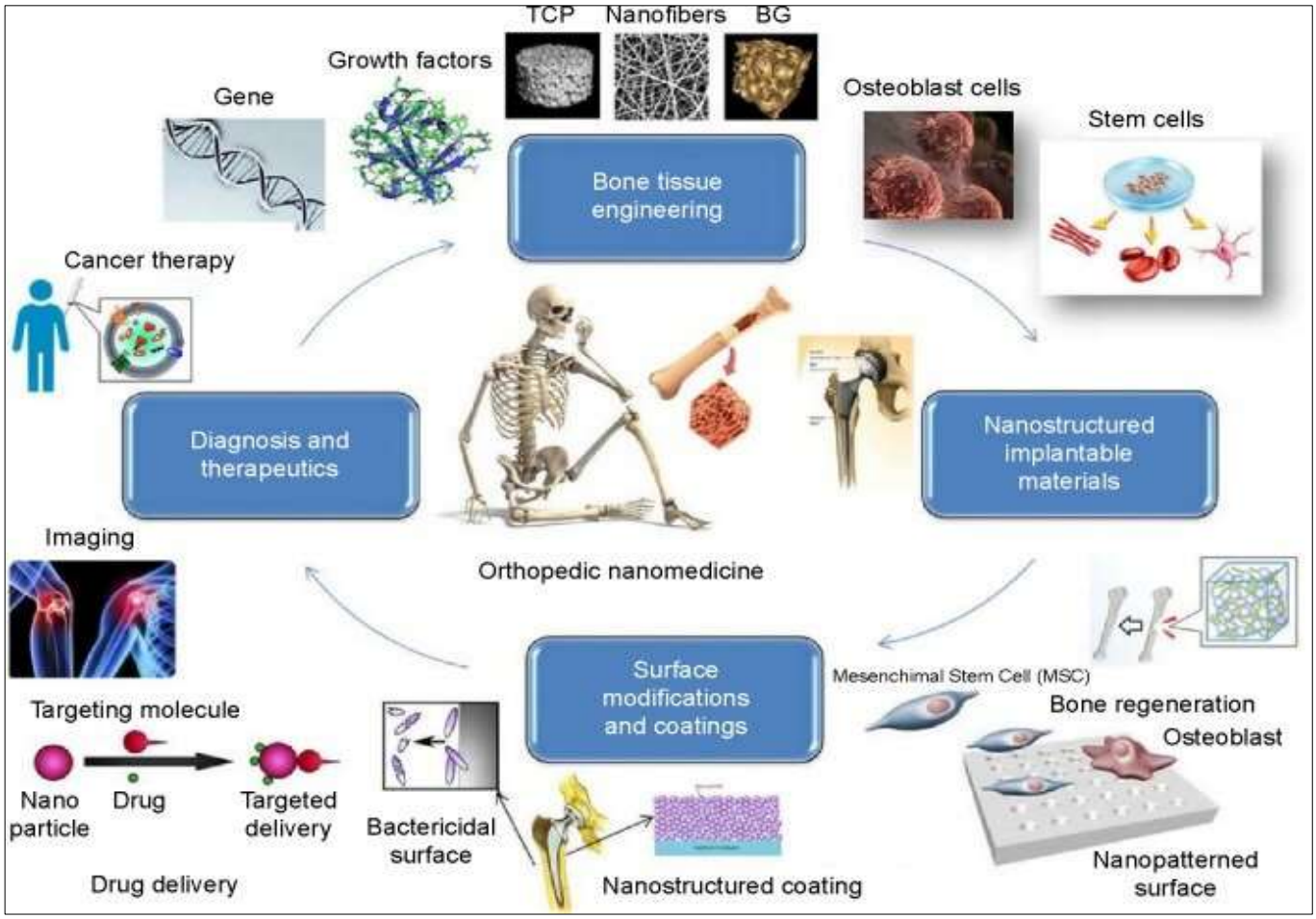

Fig 1: Illustrates the fields and uses of nanomaterials in the field of orthopedics

Spine

Regeneration of Tissue

Degenerated post-discectomy a vertebral recurrence of the disc a rupture, and decreased flexibility of the spine are among the consequences that are frequently linked to surgical procedures for degenerative disc disease, such as discectomy and fusion [12].

Given the inconsistent outcomes and challenges with current therapies, nanotechnology research has emerged as a promising field, investigating innovative cell-based methods, such as tissue engineering, for regenerating intervertebral discs (IVDs). The capacity to transform into a characteristic resembling that of the nucleus pulposus has been demonstrated by novel treatments employing progenitor cell types, including Mesenchymal embryonic (MSCs) [13–16].

Several studies have shown that Poly (γ-glutamic acid) Nano complexes, when used during injection therapies, can aid in restoring the native IVD matrix and exhibit anti-inflammatory effects in ex vivo studies [13, 14]. These treatments often use growth factors to promote cell differentiation and proliferation. However, the limited lifespan of these growth factors *in vivo* poses a significant challenge to their long-term effectiveness. The present research aims to produce scaffolds with nanofibrous structures that can promote biologically relevant growth variables and increase the potential of MSCs to tackle this problem. When combined with growth factors such as TGF-β, these support structures have demonstrated promising results in the creation of useful grafts during IVD renewal. Although still a relatively new area of study, advances in

scaffold engineering hold potential for effective nucleus pulposus regeneration [15].

In the context of peripheral nerve injury, traditional surgery has been criticized for being both costly and ineffective. Nanoengineering offers a potentially attractive alternative for treating such injuries, bypassing the need for autografts and thus reducing surgical morbidity. Mechanical qualities can be customized in manufactured conduits constructed of carbon nanostructures and nano frameworks.

And may promote neuron regeneration by enhancing surface topographical interactions, offering an advantage over traditional autografts. [17].

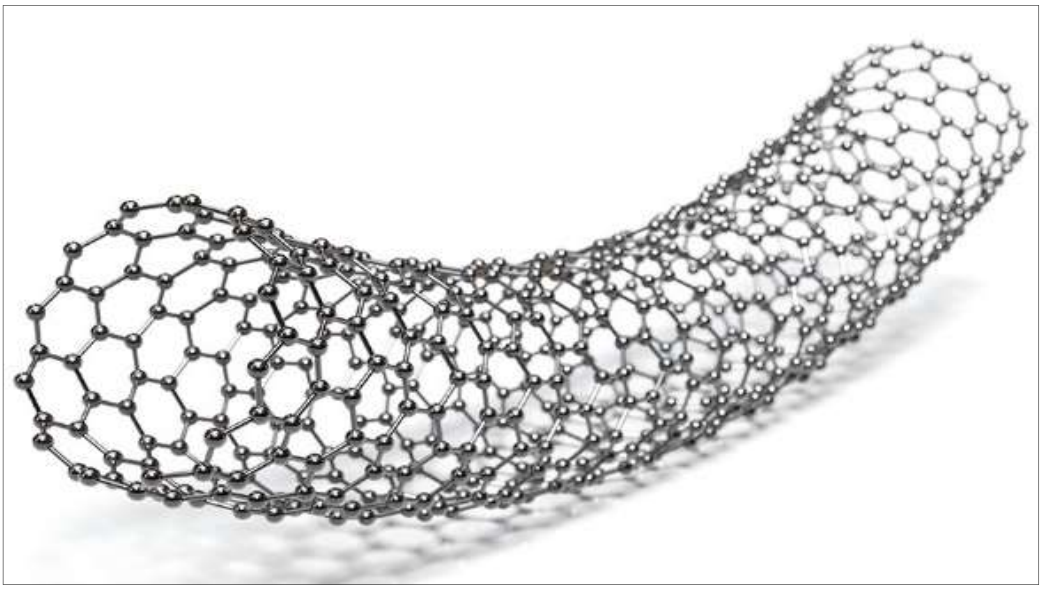

Fig 2: Tiny carbon nanotubes may stimulate the development of new neurons and even imitate the electrical features of insulation (Fig. 2) [9].

Generally speaking, using electrospinning procedures has made it possible to fabricate Nano constructs that faithfully mimic genuine extracellular habitats [18].

Some nanoscale fibers, which are both straightforward and economical, offer more surface area for controlled development, neuron recuperation, stem cells leaving their homes, and absorbing proteins [17]. Common materials used in conduit compositions consist of collagen and silicone. While nanoscale artificial neural conduits are not yet widely used in clinical practice, they represent a promising future direction for nerve regeneration therapy. These artificial conduits could potentially replace auto grafting as the primary treatment option. They might even make it possible for operators to customize the conduits based on the particular kind of nerves that require regeneration—motor, sensory-related, or combination.

Internal surgical implants

Rechargeable Human Fracture Morphogenetic Hormone (rhBMP) expenses and adverse effects may be lessened with the use of the field of nanotechnology which could help facilitate the fusion of the spinal column as well as encourage disc and regeneration of nerves. Improvements to titanium spinal surgical procedures, especially the use of zirconia and titanium oxide nanoparticles have demonstrated promise in terms of augmenting bone growth and reducing degradation in contrast to traditional smooth implants [19]. Additionally, silicon nitrate nanoparticle-enhanced cervical cages, which provide several biomechanical benefits compared to traditional Polyether-Ether-Ketone (PEEK), the first nanotechnology-based interbody fusion device are available on the market since 2014 which is FDA approved [20, 21]. When considering typical titanium and Polyamide cages, it has been shown that the Triton Spine nano-LOCKTM system can induce higher levels of bone-promoting and growth factors that promote angioplasty [22].

This study highlights how nanotechnology may be able to enhance the process of osteogenesis by improving the physical interface involving implants and rock. Administration of rhBMP-2 often leads to adverse effects due to its supra-physiologic dosing. [23]. Nanotechnology is being explored as a way to address these limitations. One approach involves using Peptide Amphiphilic (PA) molecules, which can create intracellular filament-replicating nanofiber aggregates that improve cellular rejuvenation. Studies have shown that using PA nanofiber as a solution scaffold improved average fusion rates and allowed for a tenfold decrease in the amount that was needed of BMP-2 [24, 25]. Current investigations are being conducted to assess the efficacy of this method in stimulating the process of osteogenesis *in vivo*, and to investigate its possible substitution for growth stimulants in spinal fusion procedures [24].

Orthopedic oncology

Therapeutic applications-drug delivery

Significant advancements have been made in extending survival for patients with osteosarcoma and Ewing sarcoma, but challenges such as pharmacokinetics, cytotoxicity, drug resistance, and poor chemotherapy selectivity, issues remain [26]. Through specialized carrier molecules, Nanotechnology offers potential solutions to these problems that increase drug delivery. The nanotechnology-based drug delivery method starts with the development of a Nano molecule that is loaded with the drug. (Fig. 3). Monoclonal antibody, which is a specific ligand is attached to the nano molecule to enable it to target and enter cancer cells. This targeted delivery reduces collateral damage to healthy cells and allows the drug to act directly on the cancerous cells [27]. Different carrier materials, such as titanium, gold, calcium phosphate, and chitosan, are being investigated as drug carriers in nanoparticle form [28]. Lipid nanoparticles, in

particular, are an attractive option for osteosarcoma treatment due to their ability to be administered orally and their demonstrated high absorption rates [29]. This technique has been employed to assess the effectiveness of conventional chemotherapeutic drugs, such as etoposide, against bone metastases in various cancers, yielding promising results [30, 31]. Additionally, silica nanocarriers loaded with doxorubicin and enhanced with zoledronate have shown significant cytotoxicity effects against bone metastatic activity [32]. A recently developed nanoparticle, loaded with gambogic acid and retinoic acid, demonstrated a notably higher rate of apoptosis (28%) in osteosarcoma cells compared to traditional drug delivery methods by Liu *et al*., [33]. Moreover, Zhou *et al*. found that cisplatin loaded into customized Nano carriers exhibited superior anti-cancer activity against osteosarcoma cells while reducing side effects and renal accumulation compared to the free drug form [34]. Despite these encouraging results, research into novel drug carrier strategies utilizing nanotechnology remains in its early stages.

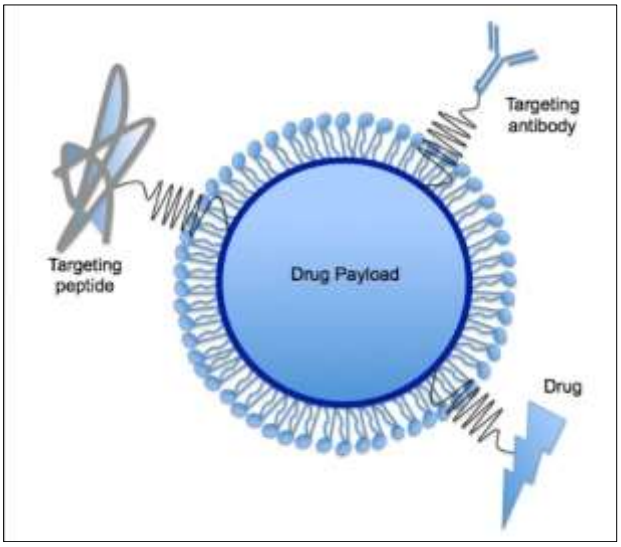

Fig 3: Diagram demonstrating the fundamental principle of drug delivery using nanoparticles. This method not only allows for more precise drug targeting but also control of drug release in treating bone cancer, prosthetic joint infections, and osteomyelitis.

Items with anticancer effects are used therapeutically.

For individuals who have had bone cancer surgery, implants for orthopedic surgery are frequently utilized. Traditional materials aren't meant to stop cancer from spreading or coming back, though.

Consequently, research is focused on developing implants that support healthy bone formation and inhibit cancer progression. Selenium has demonstrated such properties, and selenium nonmaterial implants have been shown to enhance normal bone function at the implant-tissue interface while preventing the formation of malignant osteoblasts [35]. Selenium nanomaterials have improved alkaline phosphatase activity, calcium deposition, bone proliferation, and adhesion compared to untreated titanium implants. Recently, nanostructured magnesium alloy implants, refined through grain modification, have also shown anti-tumor effects. These implants have been observed to reduce the viability and adhesion of human osteosarcoma cells, highlighting their potential in combating cancer while supporting bone health [36].

Diagnostic applications

In diagnostic of cancer, the application of nanotechnology relies on the ability of specific genetic alterations to bind with nanoparticle-ligand complexes, enabling comprehensive cellular imaging. Cancerous cells when a contrast substance is added to these complicated systems, tumor cells with specific abnormalities can be seen [27]. For instance, this imaging strategy has been investigated with a mutation in the malignant marker p15 gene, which is frequently linked to pulmonary metastases in sarcoma. This technique might make it easier to identify a cancer's propensity for metastatic spread early on [37]. This method may help identify the possibility of metastatic cancer early on in a malignancy. Chemotherapeutics could be started before the onset of clinical symptoms by combining this method with medication delivery based on nanotechnology, which could lower patient lethality.

Detecting nanomaterials with fluorescent probes may enhance cancer response assessment following therapy [38]. This approach could offer greater accuracy in measuring residual tumors after resection than traditional histology analysis [39].

In arthroplasty

Substitute substance

Although primary surgical replacement of joints is generally successful, the implants have an extended lifespan. The ultimate objective of the field of nanotechnology is to create reliable and efficient body substances that will prolong the life of implants and prevent infection. By altering particular outer features of surgical procedures, a single can improve the communication between the titanium post and the bone underneath it (Fig. 4).

For example, nanotextured implant surfaces can enhance osteoblast function and facilitate osseointegration [5]. The severe plastic deformation (SPD) process, which subjects titanium implants to high stress and reduces metal grains to the nanoscale, has enhanced titanium implants' mechanical properties and biocompatibility [40]. Issues concerning breakage limitations have restricted the use of Ultra-High Molecule Weight Polycarbonate (UHMWPE) inserts in replacement.

However, nanotechnology is being investigated as a means to enhance.

The UHMWPE material's durability. Carbon nanotube integration has demonstrated potential in producing a new composite and this material may eventually be used as a tibial component or acetabular lining [41]. Altering the surface nanostructure of implants can enhance their functionality, increase their longevity, and increase their capacity to withstand both passive and active fatigue.

Cement

The application of nanostructures to improve widely used bone cement mixes such as Poly methyl Methacrylate (PMMA).

While antibiotics are often added to bone cement to prevent infection, they are known for their limited half-life [42]. The distribution of drugs and monitored release may be improved by including nanotechnology-based antibiotic carriers in traditional PMMA concrete, such as nanoparticles of fatty acids, silica, and mud nanotubes [43, 44, 45]. In addition, research is looking into the antibacterial qualities

of non-antibiotic nanotechnology additions such as dendrimers, silver, and chitosan.

PMMA also induces inflammatory reactions, leading to fibrous encapsulation and inflammation, potentially causing implant failure [46, 47]. Osteointegration is enhanced and osteoblast differentiation is stimulated when nanostructured material additives are added to PMMA bone cement, according to research [48, 49]. Cement often contains ceramic particles to improve X-ray transparency, such as silica and ammonium sulfate. At the point of contact between the implant and bone, these particles could, however, negatively impact biocompatibility [50].

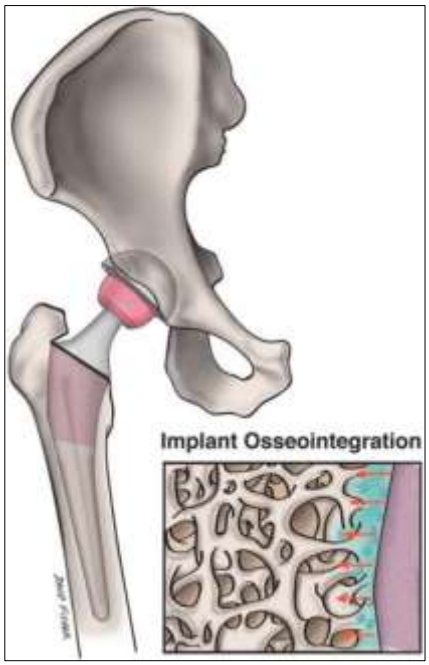

Fig 4: Illustration 4 Comparatively speaking against traditional implants, nanostructured materials implants may be able to better mimic the natural bone habitat and improve implant osseointegration as well as adjacent osteogenesis. The picture shows a close-up of an implanted surface that has been nanoengineered and how it interacts topographically with nearby tissue.

Gilliani *et al*. demonstrated that incorporating these particles with nanoscale modifications improved cytocompatibility and reduced mechanical failure of bone cement [50]. These findings highlight nanotechnology's potential benefits in enhancing bone cement's effectiveness.

Sports Medicine

Chondrogenesis

Cartilage defect repair has been a focus of extensive research in regenerative medicine. When adult cartilage tissue is not repaired correctly, it cannot regenerate fully and may eventually degenerate into osteoarthritis if left untreated. Preclinical studies have shown promising results by enhancing mesenchymal stem cell (MSC) therapy with nanotechnology (Fig. 5), using biocompatible scaffolds to improve native cartilage healing [51–56]. Yaylaci *et al*. synthesized a hyaluronic acid alternative based on nanofibers to promote MSC development toward the chondrogenic lineage without causing the side effects associated with genuine scaffolds [53]. Similarly, Liu *et al*. constructed a Nanofibrous framework that enhanced the subchondral reconstruction of bones and enhanced articular cartilage wound healing using polyethylene glycol (and gelatin [54].

Mahboudi *et al*.'s most recent research [51] showed that a polyether-sulfone framework based on nanofibers dramatically improved the chondrogenic development of mesoderm stem cells (MSCs).

In addition to these findings, various other scaffolds, such as peptide-based materials [52] and injectable hydrogels [57], are being investigated for treating cartilage defects. 28 patients with osteochondral defects were involved in a pilot trial, 70% of the defects were filled with an osteochondral Nano scaffolds graft at the two-year follow-up [56]. However, data from other clinical trials with three-year follow-ups [58] have shown mixed results, and further research is needed to evaluate the safety and effectiveness of these scaffolds. While the broad clinical application of nanotechnology in cartilage regeneration is still in development, studies indicate that using nanoparticles as scaffolds in Rejuvenation tissue technology influences chondrocyte behavioral growth, proliferation, differentiation, and attachment of cells in a beneficial way [59].

Tissue repair

Adhesion formation during tendon operations remains a significant concern, even with the recent advancements in surgical procedures and treatment following surgery.

Nanotechnology and innovations in drug delivery offer potential new approaches to enhance intrinsic and extrinsic tendon healing. Zhao and colleagues devised a technique utilizing hydrosol nanoparticles as drug carriers to facilitate the controlled release of mitomycin-C, a chemotherapeutic agent that helps minimize post-operative adhesions [60]. Through the preservation of durability akin to normal healing a network of this approach demonstrated the capacity to decrease tendon buildup *in vivo*. Another interesting field where nanotechnologies may be used is tendon tissue engineering, which deals mostly with multilayer frameworks.

Research into various scaffolding materials suggests they support better healing, enhance mechanical stability, and may be more suitable alternatives to allograft in tendon regeneration [61–65]. For example, a nanoscale scaffold made of customized silk was developed by Sharif-Aghdam *et al*. and exhibits better collagen synthesis and the survival of cells [66]. Huegel *et al*. also observed improved healing and mechanical strength in rat forearms treated with endogenous nanoscale composites during supraspinatus rehabilitation [61]. While there are currently no clinical trials utilizing nanotechnologies for tendon repair, a great deal of research is being done that highlights the invention's promise for future therapeutic uses [67–69].

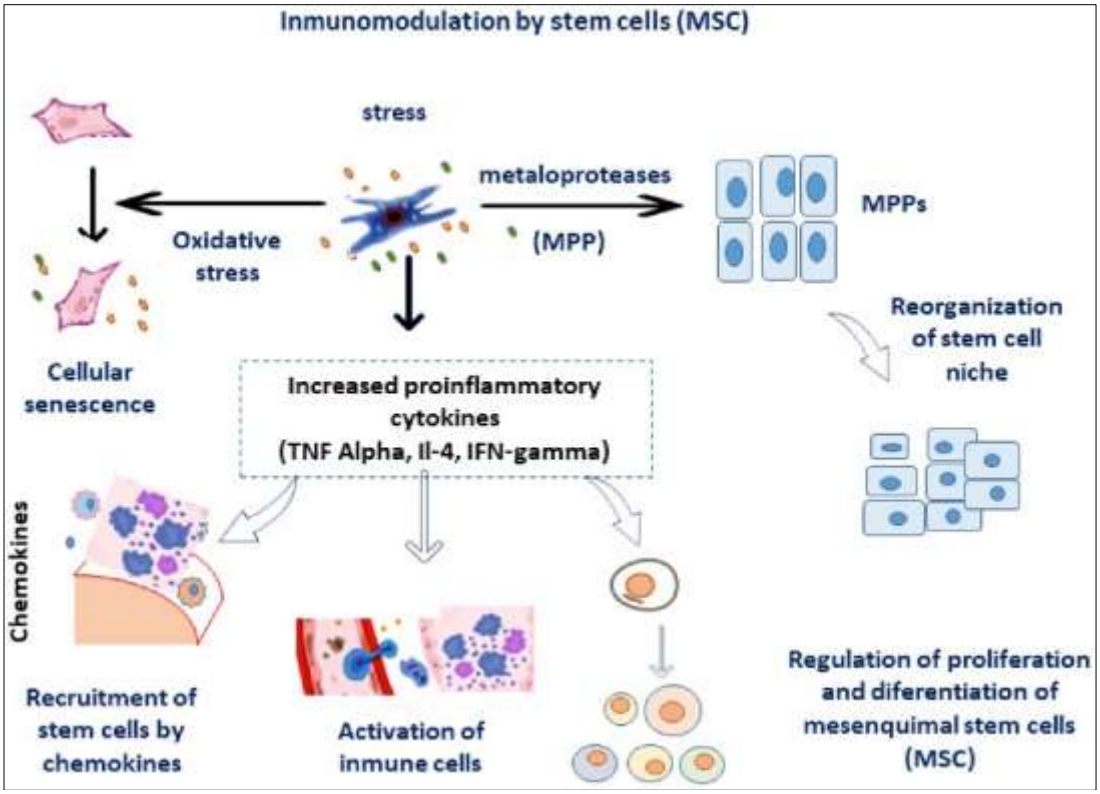

Fig 5: Although the use that human MSCs in rehabilitative procedures to repair osteochondral abnormalities has proven to be somewhat successful, nanotechnology may be able to help these procedures work more effectively. This flowchart illustrates the standard steps involved in treating MSCs employing nanotechnology. Before being cultivated in a growth medium-high heat, MSCs must be first isolated from the patient (a). Once they have developed into chondrocytes, the cells are (b) reimplanted into the patient after being put onto the preferred scaffold material and (c) cultivated in a culture.

Mass transmission

Osteogenic characteristics of materials

Research on nanoparticles is being conducted in musculoskeletal trauma, such as a procedure called to enhance implant bone integration and promote the growth of healthy bone following fractures or non-union situations. When compared with traditional implants, surface alterations and the fact that more closely resemble the bone's normal environment are what give nanostructured implants their developing success in treating injuries. The development of bioactive substrates for the regeneration of bones is the focus of numerous studies accelerating healing and restoring function more efficiently. Numerous research has shown the osteogenic potential of nanofiber scaffolds, showing that they can improve cell migration and support bone repair and development [70–74]. While extensive research is being conducted on the nanostructuring of materials like metals, polymers, ceramics, and composites, their clinical application remains limited due to unresolved safety concerns. Nanotechnology may also offer a promising alternative to bone allografting in managing nonunion deformities.

Preclinical research has demonstrated that manufactured grafts made with nanotechnology and designed to mimic the body's bone morphology can increase osteoblast adhesion and provide sufficient biomechanical stability [75, 76]. Moreover, ultra-thin nonmaterials called nanosilicates have demonstrated promise in the treatment of bone abnormalities. They have shown extraordinarily high porosity, stiffness, and bone mineralization when included in hydrogels based on collagen [77]. The potential of nanoparticles for future clinical uses is demonstrated by their ability to promote cartilage development and improve the osteointegration of implanted orthopedic devices.

Orthopedic infections

Infection continues to be a major issue in orthopedics, frequently resulting in delayed healing, implant failure, and the necessity for further surgery. Bacterial biofilms are commonly responsible for these infections, and implant removal is usually the only practical solution.

Consequently, current endeavors have focused on developing sophisticated anti-biofilm implants that integrate nanotechnology. As an illustration, an innovative system to deliver drugs for vancomycin embedded in silicon femoral stems demonstrated prolonged absorption for as long as 100 hours [78]. Furthermore, a controlled animal study by Besheli *et al*. demonstrated the efficacy of silk fibroin nanoparticles in managing severe osteomyelitis [79].

Over the last decade, nanophase silver has gained crucial attention in orthopedics and is now used clinically to treat wounds. It has been demonstrated that antifungal nanophase metallic dressings work better for healing and preventing infections than conventional treatments [80].

As Kose *et al*. demonstrated, coating titanium implants with silver Nanopowder reduced bacterial colonization compared to uncoated implants [81]. Recent studies have also shown promise for IL-12 nanocoatings in preventing infections related to open fractures by modulating immune responses [82]. Notably, scientists developed a piece of titanium thumb screw that was coated in silver nanoparticles and successfully stopped biofilm growth in rabbit models [83]. All things considered, nanotechnologies have shown a great deal of promise in reducing surgical site infections

following the reconstruction of joints, trauma patients, and spinal prostheses.

Potential concerns

Despite the promising potential of nanomedicine, as evidenced by early translational research, significant challenges hinder its widespread adoption in orthopedic clinical practice. One primary concern is the limited understanding of the long-term effects of nanoparticle exposure on human health. Some preliminary studies suggest nanomaterials may contribute to oxidative stress, systemic inflammation, and cytotoxicity in the brain and lungs [84]. Conversely, other research indicates that the metabolic byproducts of nanomaterials could potentially enhance cellular health in lung and bone tissue [85]. This uncertainty is compounded by the stringent clinical trial regulations imposed by the US Food and Drug Administration (FDA). These regulations and the financial burden of clinical trials—which can cost hundreds of millions—make it difficult for medical device companies to justify the investment, especially when suitable implants are already available [86]. Additionally, since 2008, just 3% of funding for nanotechnology research has been directed towards exploring its potential health risks [3]. This underscores the necessity for additional research to evaluate the toxicity of nanomaterials before they can be broadly applied in therapeutic settings. Another challenge involves the large-scale production of nanomaterials. Due to their complex structural features, some scientists argue that reliably mass-producing materials smaller than three nanometers are complex. Kelly *et al*. demonstrated that variations in the physical properties and size of components can occur during high-volume production of such small-scale materials [87]. As a result, achieving high-volume, low-cost manufacturing of specific nanomaterials may be challenging without compromising reproducibility.

Conclusion

Musculoskeletal research, therapy, and diagnosis could be revolutionized by nanotechnology, which is currently in its early stages of development. The anticipation that nanostructures would eventually play a major role in clinical care is reinforced by its success in several manufacturing and service industries.

This technology offers numerous innovative applications and can replace many conventional treatments at a lower cost. Nanotechnology could enable more precise treatment methods, resulting in longer-lasting and more effective implants, reduced instances of infection as well as enhanced tendon and regeneration of bone. The future benefits of nanomedicine are beginning to emerge, especially in orthopedics, driven by significant fundamental scientific research. However, further studies are required to understand this promising technology's safety and long-term potential fully.

Competing interests: No conflict

Funding: No funding

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How to Cite This Article
Raj S, Goni V, VB Shrinivas, Kumar M, Aduri TT. Orthopedic nanotechnology: A review with a clinical focus. International Journal of Orthopaedics and Bone Disorders. 2024; 6(1): 45-54.