Review

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Osteoporosis therapy using nanoparticles: a review

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Abstract

Osteoporosis, characterized by low bone density and increased risk of fractures, represents a major healthcare challenge. Anti-resorptive and anabolic medications are now used to treat osteoporosis in an effort to reduce bone loss and increase bone mass. Innovative methods are required since current therapies have drawbacks. Promising options for improving bone health and medicine delivery are provided by nanotechnology. Bisphosphonates with tetracyclines and oligopeptides, among other compounds that target the bone, make it easier to provide a particular medication to bone tissue. Additionally, nanocarriers are essential for the administration of both organic and inorganic nanoparticles in the treatment of osteoporosis. Drug encapsulation and controlled release may be done in a variety of ways using organic nanoparticles. Inorganic nanoparticles have special qualities that help in medication transport and bone repair. This review explores the potential of nanoparticle-based strategies in the treatment of osteoporosis.

Keywords: Bone-targeting, drug delivery system, nanoparticles, osteoporosis

Introduction

Reduced bone mass and microstructural degeneration of bone tissue are the hallmarks of osteoporosis, a degenerative skeletal illness that also increases bone fragility and fracture risk. According to WHO guidelines, osteoporosis is considered to be present when a patient's bone mineral density is 2.5 standard deviations or more below the average bone mass for young, healthy persons[1]. In adults, bone is reformed by a coordinated process in which bone-forming osteoblasts create and mineralize new bone matrix while bone-resorbing osteoclasts destroy old bone[2]. Osteoporosis results from disturbances in this physiological mechanism that cause a loss in bone mass. Regrettably, there are significant limitations to existing osteoporosis therapies, including inadequacies and long-term safety concerns[3]. There is currently no adequate treatment for osteoporosis-related bone thinning[4]. The only effective treatments for osteoporosis are anti-resorptive medications, which slow down excessive bone resorption (the main cause of primary osteoporosis), and anabolic agents, which successfully rebuild the lost bone mass caused by excessive resorption[5]. Bone diseases have emerged as the most common degenerative illnesses and a significant public health issue in many countries[6], which has stoked interest in both prevention and therapy. Over the age of 50, osteoporosis is thought to afflict one in three women and one in five men, according to the International Osteoporosis Foundation[7]. The higher incidence of osteoporosis in females than in males can be attributed to the loss of female sex hormones 'estrogens' after menopause, as the ovarian follicular reserve ends at menopause[8]. In fact, this illness causes a bone to shatter every three seconds. This issue has significant socioeconomic and human costs. The economic cost of events and previous fragility fractures, which are mostly caused by osteoporosis, was calculated at €29 billion in the five biggest EU nations (Germany, France, Italy, UK, and Spain) and €38,7 billion in the 27 other EU nations[9]. The aim of this review is to highlight various drug delivery approaches for the treatment of osteoporosis using nanoparticles by illustrating the challenges, promises, and limitations of this new approach.

HIGHLIGHTS

- The bone-targeting medication delivery systems is one of the creative ways to improve osteoporosis treatment .
- Methods of using nanoparticles to create drugs for the treatment of osteoporosis.
- The proven that the use of nanomaterials significantly enhances the treatment of osteoporosis.

Current osteoporosis therapies

For the treatment of osteoporosis, a variety of medications and therapeutic techniques have been examined (Fig. 1). Anti-resorptive medications, which work against osteoclasts and either anabolic steroids or bone-forming accelerators, which are aimed

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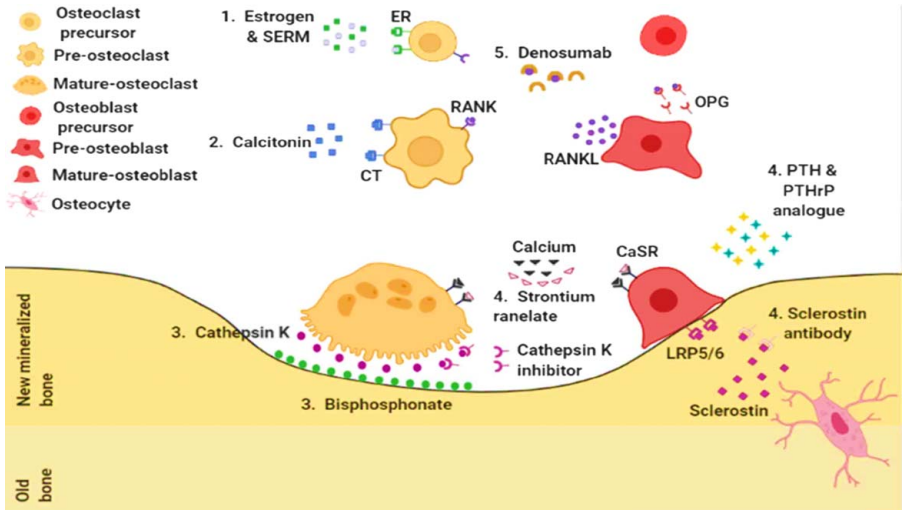

Figure 1. Medications and therapeutic approaches to treat osteoporosis (reproduced from Kim et al[10]). CT indicates calcitonin receptor; CaSR, calcium sensing receptors; ER, estrogen receptor; OPG, decoy receptor osteoprotegerin; PTH, parathyroid hormone; PTHrP, PTH-related protein; RANKL, receptor activator of nuclear factor κB ligand; SERM, second-generation non-steroidal benzothiophene.

to stimulate osteoblasts, make up the majority of therapeutic approaches to prevent fracture and restrict bone loss[11]. Drugs used to treat anti-resorptive disorders primarily work by decreasing osteoclast activity, maintaining bone mass, and boosting bone strength[4]. On the other hand, anabolic medicines have the ability to stimulate the development of new bone and can stop the bone degeneration brought on by the progression of osteoporosis[12].

Anti-resorptive drugs

In recent years, bisphosphonates (BP), which can stop additional bone deterioration in osteoporosis that is already advanced, have dominated the field of osteoporosis treatment. BP inhibits osteoclast activity by inhibiting farnesyl pyrophosphate synthase, a crucial enzyme for membrane protein prenylation and osteoclast detachment from bone[13]. In the end, they cause osteoclasts to undergo apoptosis, which lessens bone resorption[14]. Although these medications have the ability to lower the risk of fracture and bone turnover, their effect on growing or restoring bone mass is very little, at just 2% annually[15]. Moreover, BP is not readily absorbed by the gut and has variable bioavailability. Therefore, it is recommended to take the medication 2 h before breakfast and wait 30 min before taking another medication to reduce the likelihood of interactions with cations like calcium, iron, etc[16]. High dosages must be administered orally, which has a number of adverse effects, including esophagitis[17] from the local impact on the mucosa and jaw necrosis[18] from an overly aggressive suppression of bone resorption. Given this, it is important to understand the effects of long-term BP use. The consequences of utilizing BP in treatments lasting 3, 5, or 10 years have been studied in clinical investigations. Despite 3 years of therapy, they continued to exhibit anti-fracture and bone mineral density-increasing actions[19]. On the other hand, individuals receiving 10 years of therapy as opposed to those receiving just 5 years of treatment reported more severe adverse effects or cessation owing to bad effects[20].

Raloxifene (RLX) is another anti-resorptive medication. RLX is a selective oestrogen receptor modulator that is a second-generation non-steroidal benzothiophene (SERM). In bone, it mimics the effects of oestrogen. By preventing the production of cytokines, which promote bone resorption, RLX prevents bone loss. Although the intestines absorb RLX quickly, it will go through a lengthy pre-systemic glucuronide conjugation. As a result, the achieved absolute bioavailability is quite low.

When the receptor activator of nuclear factor B ligand (RANKL) interacts with its receptor, RANK, which is found on the surface of osteoclasts and osteoclast precursors, osteoclast differentiation is activated[21]. Via preosteoclast fusion and osteoclast survival, this interaction will support osteoclast differentiation. This increases the rate of bone resorption by producing multinucleated mature bone-resorbing osteoclasts[22]. This idea is supported by the creation of a monoclonal anti-RANKL antibody that has been humanized and is presently used to treat osteoporosis[22].

Anabolic drugs

Estrogens and recombinant human parathyroid hormone (rPTH) are anabolic drugs that promote bone growth and have been shown to be effective against osteoporosis[23,24]. By boosting bone mass, a daily dose of rPTH has been shown to be more effective than BP medication. This medication is utilized for its potential to inhibit osteoblast apoptosis and stimulate bone growth[25]. Nevertheless, long-term therapy is only effective for 24 months due to the increasing risk of hypercalcemia and tumours from extended hormone delivery and the requirement for daily injections[26]. The injection of growth factors such as bone morphogenetic proteins has also been investigated as a method of promoting bone development (BMPs). They boost bone strength and density and encourage bone growth[5,27]. To obtain therapeutic results, however, supraphysiological dosages are required, which might have unfavourable consequences such as excessive bone growth, inflammation, or even cancer[27]. The

systemic administration of BMPs was further constrained by their brief half-lives[28].

Small interfering RNA (siRNA)-mediated gene silencing has more recently been applied to the treatment of bone diseases, including osteoporosis. The amount of research into this treatment has significantly grown because of its many benefits[29]. With this kind of treatment, siRNA was directed against the genes that had been found to suppress bone growth without altering bone resorption. To promote bone production significantly, siRNA must be administered at large concentrations, which increases the likelihood of negative effects on non-skeletal tissues[30]. Considering these factors, the numerous side effects of the various existing medications are one of the most significant and enduring issues with osteoporosis therapy. It is obvious that each produced medicine requires the creation of unique delivery mechanisms.

Nanotechnology for bone release and drug delivery

Medicines that are administered systemically are circulated throughout the body after being absorbed into the bloodstream. They barely enter bone tissue and quickly leave the body. Drugs permeate bone less than other tissues because bone has less vascularization than other organs like the brain, liver, or kidney[31,32]. As a result, they are often delivered in high doses delivered, which may cause systemic toxicity. A controlled drug delivery device that could administer the medication selectively to bone tissue would make it safer and more efficient[33]. Drug delivery systems (DDS) are intended to lessen the possibility of hazardous side effects while enhancing the therapeutic efficacy of medications. Recently, there has been an increase in interest in using nanoparticles as DDS to treat bone disorders. The therapeutic substance would then be released into the bone tissue by the drug carrier, either promoting bone formation or reducing bone resorption. DDS maximizes drug dosages in this way, guards against biodegradation, and reduces exposure to non-target cells[34]. For instance, when treated with oestrogen, the drug's transport to tissues other than bone can have a variety of consequences, including endometrial and breast cancer, intrauterine bleeding, an increase in uterus weight, and more[35,36]. An estradiol-prodrug was recently created by conjugating estradiol to an Aspoligopeptide carrier. They discovered that it was selective to bone and even had a long-lasting impact on bone while avoiding estradiol's negative side effects. In addition to extending medication intervals, the deployment of this targeted bone delivery method will improve patients' quality of life[37].

A targeted medicine delivery device distributes the medication at a chosen location. The most crucial components of a medication delivery system for treating bone illnesses are the carriers and the bone-targeting moieties[36].

Bone-targeting molecules

Finding compounds with a high affinity for bone is crucial for directing nanoparticles there. It is well-recognized that hydroxyapatite (HA), which is its main component, makes up the mineralized matrix of bones[38]. Bone would be a viable target for selective delivery because HA crystals are found there in significant quantities[39]. Consideration should be given to substances that have a strong affinity for HA.

Bisphosphonate with tetracycline

Tetracycline and bisphosphonate can be employed as bone-targeting molecules because of their high affinity for the calcium found in HA[35]. As tetracycline has a high affinity for calcium, it was the first drug employed. It is an antibiotic, but because of its strong affinity for bone, which stained children's teeth yellow, paediatric medicine stopped using it. Despite this, it is still used as an adult antibacterial and a bone-targeting compound. As a result, smaller compounds are known as tetracycline analogues were created with comparable bind capabilities to tetracycline[40]. Neale and colleagues attempted to minimize the tetracycline structure in order to lessen any negative effects brought on by the drug's biological action. Although the changes lost their biological action, they could still bind HA[41]. Despite these attempts, its low stability after chemical changes and complex chemical structure ruled against its utilization. Contrary to tetracycline, bisphosphonates have gained popularity as bone-targeting molecules recently. Due to their strong affinity for HA, ability to bind to areas with osteoclastic activity, and capability to block bone resorption, they are frequently utilized to treat osteolysis disorders. These facts make it possible to target and treat the illness with the same chemical[42].

Oligopeptides

Moreover, several investigations discovered molecules that may distinguish between surfaces that promote bone growth and those that promote bone resorption. According to studies, aspartate's eight repeating sequences (Asp_8) preferentially attach to surfaces that promote bone resorption, whereas $(AspSerSer)_6$ demonstrated favourable binding to surfaces that promote bone formation[30]. This makes it feasible to utilize one portion or the other, depending on the medicine being used. If it is an anti-resorptive drug, Asp_8 should be utilized as a guide to the surface of bone resorption; if it is an anabolic agent, $(AspSerSer)_6$ should be used as a guide to the surface of bone creation[43].

Nanocarriers for treating osteoporosis

In recent years, it has been discovered that nanoparticles are prospective carriers for effective therapeutic delivery in the treatment of bone diseases see (Table 1). As bone is a nanocomposite, the creation of nanoparticles is appropriate for bone repair in osteoporosis patients. They can enhance pharmacokinetic, pharmacodynamic, biodistribution, and targeting, as well as protect drugs from biodegradation[36] in addition to this

Table 1

An overview of a therapeutic medication delivery system for bones.

Therapy	Moiety targeting bones	Carrier	References
Ethinylestradiol	[a]	Liposomes	[45]
RLX	[a]	Chitosan NPs	[24]
Thermolysis	ALN	Fe_3O_4 NPs	[46]
RANK siRNA	[a]	MBG´s	[22]
RANKL siRNA	AspSerSer6	Cationic liposomes	[47]
RIS	RIS	ZnHA NPs	[16]
ALN	ALN	HA NPs	[48]

[a]There is no indication of the targeted moiety.

ALN, Alendronate; MBG, nanospheres of mesoporous bioactive glass; RANKL, receptor activator for nuclear factor κB ligand; RIS, risedronate; RLX, raloxifene; siRNA, small interfering RNA.

dimensional similarity. They can improve therapeutic loading, increase tissue selectivity, and decrease dosages without compromising therapy efficacy because of their capacity to be chemically changed[44].

Organic nanoparticles for the treatment of osteoporosis

Liposomes

The first nano-delivery method that was successful in finding a therapeutic use was liposomes[46,49]. Typically, lipid molecules with a hydrophilic head group and a hydrophobic tail self-assemble to form liposomes. Cholesterol is added to the liposome, which enhances the mechanical properties by reducing membrane permeability[45]. This structure enables the loading of pharmaceuticals with various solubilities by allowing an aqueous core to be encased inside a phospholipid bilayer. The bilayer membrane would include hydrophobic chemicals, whereas the watery core would contain hydrophilic agents[50]. The quick absorption by the reticuloendothelial system (RES), which results in a short circulation half-life, is one of the main drawbacks of liposomes. Polyethylene glycol-lipid (PEG-lipid) coupled with the bilayer can be added to reduce RES absorption and enhance bloodstream time[51].

A new generation of liposomes was developed in recent years for the targeted delivery of genes to cure bone disorders. By employing an ovarectomized rat model, Lu and colleagues synthesized an ethinylestradiol liposome (EEL) and looked at how it affected postmenopausal osteoporosis. They came to the conclusion that EEL was more successful than free ethinylestradiol at stimulating the quantity of calcium deposited in bone, as well as boosting osteoblast activity and active bone production[45]. $(AspSerSer)_6$ was connected by Zhang and colleagues to a cationic liposome that contained an osteogenic siRNA. This siRNA specifically targets Plekhol, a suppressor of osteogenic lineage activity[52]. A single or more amines can be found in the polar head of cationic lipids, which are the building blocks of cationic liposomes. These liposomes spontaneously bind and compress DNA to create complexes that have a strong affinity for cell membranes and can carry plasmids into cells[53]. As an alternative to modifying bone resorption, this enables the delivery of therapeutic cargos (such as siRNAs) to the target osteogenic linage cells[30]. Neutral liposomes are less toxic, have a longer half-life in circulation, and interact with proteins less than cationic liposomes. To address these issues, neutrally charged lipoplexes can be added to the cationic liposome system. Similar to this, Hengst and colleagues developed liposomes with the bone-targeting moiety of cholesteryl-trisoxyethylenebisphosphonic acid (CHOL-TOE-BP), a novel custom-made bisphosphonate derivate. These liposomes were created to treat conditions that affect the bones, such as osteoporosis[54].

Liposomes PLGA-nanoparticles. Due to their large cargo capacity and nano-size, rigid nanoparticles have more promise as a delivery mechanism than liposomes. Because of their superior host non-toxicity, biocompatibility, and tunable breakdown rates, synthetic biodegradable polymers like copolymer poly (lactide-co-glycolide) and poly-lactide have been widely employed for the fabrication of nanoparticles[55]. By altering the molecular weight, porosity, particle size, copolymer ratio, and manufacturing conditions, varied drug release patterns may be achieved[34]. The capability of PLGA to be functionalized and altered to allow the attachment of biological molecules is another benefit[56]. Moreover, it has received FDA approval for several biological uses. The swelling and regulated degradation duration (about 1-6 mo) of PLGA, as well as its molecular interaction capability with the payload[34], make it the ideal material for the creation of controlled delivery systems. Jiang and colleagues created PLGA-based nanoparticles with a brief poly-aspartic acid sequence that have been demonstrated to only interact with hard tissues. To investigate the dispersion and binding potential of the nanoparticles, fluorescein isothiocyanate (FITC) was attached to them. Studies conducted *in vitro* and *ex vivo* showed that FITC-poly-Asp nanoparticles had a specific binding affinity for bone tissue[49]. When the nanoparticles build-up in bone niches, the local medication concentration can be increased, lowering adverse effects and extending the therapeutic window. Using PLGA-PEG copolymers and Aspn-based bone-targeting moieties, Fu and colleagues created bone-targeting nanoparticles in a manner similar to this (1–3). The best apatite binding was demonstrated by asp3-nanoparticles[57]. Moreover, Cong and colleagues created PLGA-PEG nanoparticles and functionalized them with the bisphosphonate alendronate (ALN) as a bone-targeting moiety.

Liposomes chitosan NPs. Because of its characteristics, including non-toxicity, ecological safety, and biodegradability with biocompatibility, chitosan is one of the most often utilized polymers in drug delivery[24]. Chitosan, a copolymer of 2-acetamido-2-deoxy-D-glucopyranose and 2-amino-2-deoxy-D-glucopyranose that is abundantly found in nature, is created by deacetylating chitin[58,59]. Since it contains amino groups, it may be protonated at low pH levels, making it soluble in water. On the other hand, the polymer becomes insoluble when the pH rises above six because the chitosan amines get deprotonated[60]. Chitosan and tripolyphosphate were used in an ionic gelation procedure by Saini *et al*.[24] to create nanoparticles. The nanoparticles were created as a result of interactions between the positive amino groups of chitosan and the negatively charged tripolyphosphate[61,62]. The medication raloxifene was then loaded into nanoparticles to create a novel formulation for raloxifene's intranasal administration for osteoporosis treatment. The polymer's mucoadhesive properties enabled the nanoparticle to adhere to the nasal mucosa, allowing for the direct transport of the medication into the bloodstream. Eventually, it was determined that raloxifene-loaded chitosan nanoparticles may be a cutting-edge method of treating osteoporosis[24].

Inorganic nanoparticles for the treatment of osteoporosis

Hydroxyapatite nanoparticles

One of the main components of the matrix of human bones and teeth is HA, a bio-mineral. HA has high osteoconductive characteristics and is biocompatible and biodegradable[60]. Early research has shown that nanoscale HA encourages osteoblast bioactivity, which improves bone repair[63]. In this aspect, the nanocarrier itself promotes bone mass deposition and bone tissue growth. HA-based nanoparticles that can carry medications and bone minerals to bone tissue were created by Hwang *et al*.[48] Three alginate layers of poly (allylamine) were applied layer by layer to the nanoparticles' surfaces to functionalize them. Next, ALN was conjugated at the outermost layer, giving it the ability to bind bone tissue. ALN was employed as an anti-resorptive medication as well as a targeted substance. The HA serves as a core for the nanoparticles, and once within the bone matrix, they induce osteoconduction, which raises bone density[48].

According to certain research, HA-based nanoparticles loaded with bisphosphonate risendronate (RIS) increase bone density and enhance bone stiffness and strength. Even at lower dosages of RIS, HA-based nanoparticles loaded with RIS were much more effective than RIS administered alone, which decreased adverse effects[60]. While creating their nanoparticles, Khajuria *et al.*[16] decided to use zinc hydroxyapatite (ZnHA). They made the decision to add zinc to the HA. Several research showed that HA bioactivity was increased by zinc. Because of its similarities to calcium, zinc can take the place of calcium in HA and, subsequently, in bone. Zinc promotes osteogenesis in osteoblasts, inhibits osteoclast activity, and increases bone protein synthesis to promote bone development and mineralization[64]. It's crucial to understand that cytotoxic effects are produced by zinc concentrations of more than 225 mg[65]. In order to target bone, RIS was added to these ZnHA-based nanoparticles. The findings showed that compared to pure RIS or HA/RIS nanoparticles, ZnHA/RIS nanoparticles offer a therapeutic benefit[42].

Bioactive-silica nanoparticles

Dietary silica may have a positive impact on rats' bone growth, according to certain research[64]. In human populations, clinical research found a favourable correlation between dietary silica consumption and bone mineral density (BMD)[66]. Silica is well known for being harmless *in vivo* below 50 000 ppm without causing negative effects in rats[2]. Yet, it is uncertain how silica influences skeletal growth. According to several research, silica nanoparticles would be useful to the skeleton and bioactive[2]. Becket and colleagues investigated how osteoclast and osteoblast differentiation were impacted by 50 nm silica-based nanoparticles. Finally, the study's authors demonstrated that the nanoparticles were physiologically active; *in vitro*, they induced osteoblast development and mineralization while suppressing osteoclast differentiation. The precise mechanics, nevertheless, are not well known. In addition to being a powerful inhibitor of osteoblast differentiation and activity, the nuclear factor kappaB (NF-B) is a transcription factor required for osteoclast differentiation[67]. As a result, NF-B antagonists will encourage osteoblast differentiation and inhibit the production of osteoclasts[64]. After 24 h, these nanoparticles do indeed decrease NF-B signalling, which may provide a partial justification for how nanoparticles can control osteoclast and osteoblast development. Moreover, in-vivo nanoparticles can boost mice's BMD, indicating a potential use for them in the treatment of osteoporosis[2].

Ha and colleagues have looked into the biological mechanism through which silica-based nanoparticles promote osteoblast development and mineralization. They discovered that nanoparticles are ingested via caveolae-mediated endocytosis, stimulating the ERK1/2 signalling pathway, which is required for the conversion of LC3-I to LC3-II and stimulates the formation of autophagosomes. This method stimulates osteoblast development and mineralization even if it is not fully understood[68]. A recent study that discovered that bone mineralization was prevented by inhibiting autophagosome production lends weight to this hypothesis[69].

The use of mesoporous silica nanoparticles (MSNs) as a medication delivery mechanism has also been documented[70]. The mesoporous material MCM-41 was initially proposed as DDS in 2001[71]. In order to target bone areas for the delivery of antiosteoporotic medicines, Sun *et al*. created MSNs anchored by zolendronate[72]. Due to the inherent properties of RNA interference, silencing genes by administering small interfering RNA (siRNA) offers several benefits (RNAi). SiRNA interferes, lowering a certain gene's level of expression. This method has the potential to improve bone tissue production and treat bone diseases[29]. MSNs have the greatest ability to transport compounds like siRNA among all silica-based nanoparticles. In general, siRNAs have a relatively short half-life, have low cell membrane penetration, and are quickly destroyed by RNase. Hence, additional study is required to discover a nanocarrier that may address these issues. MSN research as a prospective delivery vehicle for genetic molecules has risen because of its distinctive features, including high surface area, surface functionality, variable pore size, biocompatibility, and loading capacity[73]. MSNs with calcium added are known as mesoporous bioactive glass nanospheres (MBG). They may be used for regenerating and repairing hard tissue. By administering RANK siRNA, Kim and colleagues showed a unique therapeutic application in which MBGs decrease osteoclastic activities[72].

Metal nanoparticles

The use of thermotherapy in the management of osteoporosis has been appealing. It can result in cell death by rupturing cell membranes and denaturing intracellular proteins[74]. By obliterating osteoclasts by thermolysis, it has been utilized to manage osteoporosis. Fe_3O_4 nanoparticles, which are made of iron (II, III) oxide, are chemically stable, safe, and economical. Their strong magnetic fields may be exploited to raise local temperatures, which in turn causes osteoclast regulation to occur[75]. To improve nanoparticle dispersion in aqueous solvents, Lee and colleagues produced Fe_3O_4 nanoparticles by co-precipitation and coated them with dextran[46]. They then attached ALN to magnetic nanoparticles to give them the ability to adhere to bone surfaces. Two main chemical groups make up ALN: an amino group that inhibits osteoclast activity and a bisphosphonate group with a strong affinity for bone hydroxyapatite. The primary negative side effects, such as nausea, stomach pain, or vomiting, are caused by the amino group. By grafting that group with the nanoparticles, they were able to deactivate it. Because of their affinity for bone, ALN/Dex/Fe3O4 nanoparticles may be phagocytosed by osteoclasts, which leads to radiofrequency-induced thermolysis and osteoclast death[46].

For use in treating osteoporosis, other metal nanoparticles, like Au nanoparticles, have been investigated. Gold nanoparticles have been shown to stimulate osteoblast development and inhibit osteoclast differentiation in recent studies[22]. According to Choi and colleagues, human adipose-derived mesenchymal stem cells are stimulated to differentiate into osteoblasts when exposed to nontoxic doses of chitosan-conjugated-gold nanoparticles (1 ppm) (hADMSCs). Their findings show that mechanical stimulation via chitosan-conjugated AuNP absorption in hADMSCs improves osteoblast development via activation of the Wnt/-catenin signalling pathway. As a result, the build-up of -catenin encourages hADMSCs to differentiate into osteoblast[22] . The synergistic impact of 30 nm Au nanoparticles coupled with ALN on suppressing osteoclast differentiation was demonstrated by Lee and colleagues in their study[22]. Reactive oxygen species (ROS) are crucial for osteoclast development, as we previously discussed[76], and RANKL is a decisive element in this regard. Gold nanoparticles inhibit the development of osteoclasts by

decreasing RANKL's generation of ROS and increasing glutathione peroxidase-1 expression[77].

Comparison of the efficacy of osteoporosis treatment of nanoparticles with other therapies

Nanoparticle-based therapies

Drugs may be delivered directly to bone tissue using nanoparticle technology, enhancing their efficacy and minimizing their negative effects. This focused delivery may enhance the effectiveness of treatments[23,78].

Nanoparticles can protect drugs from degradation, enhancing their stability and bioavailability.

With targeted delivery, lower doses may be required, which reduces the frequency of drug administration.

Personalized medicine: Nanoparticles can be tailored to fit individual patients' needs, which may lead to improved treatment outcomes for specific conditions.

By delivering drugs specifically to bone tissue, nanoparticle-based therapies may reduce the risk of systemic side effects associated with traditional oral medications.

Conventional osteoporosis treatments[79,80]

Bisphosphonates: These medications, such as alendronate and risedronate, are commonly used to treat osteoporosis. They work by slowing bone resorption, reducing the risk of fractures.

Hormone replacement therapy (HRT): Oestrogen therapy is sometimes prescribed to postmenopausal women to help prevent bone loss, but it is associated with certain risks, including an increased risk of breast cancer and blood clots.

Calcium and Vitamin D supplements: These supplements are often recommended to support bone health.

Exercise and lifestyle changes: Weight-bearing exercises and a healthy diet rich in calcium and vitamin D can help maintain bone density.

Effectiveness comparison

Nanoparticle-based therapies have the potential to be more effective in delivering drugs specifically to bone tissue, potentially enhancing osteoporosis treatment outcomes.

Traditional therapies, such as bisphosphonates, have a long history of usage and are often helpful in lowering the risk of fractures and bone loss, but they may also have drawbacks.

The severity of osteoporosis, the patient's overall health, and personal preferences all influence the therapy option.

More study is required to prove the long-term safety and efficacy of nanoparticle-based therapies, which are currently in the experimental stage. Due to the potentially higher cost and initially limited availability of innovative therapies, cost, and accessibility may be important considerations.

In the last, therapeutics for osteoporosis based on nanoparticles have shown encouraging results in terms of directly delivering medications to bone tissue and possibly enhancing treatment outcomes. To completely comprehend its efficacy and safety in comparison to standard therapies, additional studies and clinical studies are necessary. To make selections based on their unique circumstances, patients should explore their alternatives with their healthcare professionals.

Challenges and limitations of treating osteoporosis using nanoparticles

Nanoparticle therapy for osteoporosis undoubtedly has a number of drawbacks and issues that need to be resolved by researchers and medical practitioners. The following are some of the major difficulties and restrictions connected with this strategy[81–83].

The main problem is making sure that the nanoparticles are biocompatible and secure for usage within the human body. Some nanoparticles may be poisonous or trigger immunological reactions, both of which might be bad for the patient's health.

It is difficult to achieve precision targeting of nanoparticles to bone tissue while reducing off-target effects. It is very difficult to ensure that nanoparticles will successfully release their payload at the correct site without damaging healthy tissue.

Optimal size and surface characteristics: The behaviour and efficiency of nanoparticles may be influenced by their size and surface qualities. It is difficult to create nanoparticles that have the proper size, surface charge, and use for bone-targeting.

For therapy to be effective, therapeutic chemicals must be loaded into nanoparticles effectively, and their release kinetics must be managed. Technically speaking, achieving appropriate medication loading and release characteristics may be difficult.

Moving from experimental or pre-clinical studies to clinical trials and eventual clinical use is a long and complex process. Regulatory approval, safety evaluations, and large-scale production considerations can present significant barriers.

The cost of manufacturing nanoparticles may prevent their widespread use. Making these medicines more widely available requires the discovery of manufacturing techniques that are both affordable and scalable.

Variations in bone health, genetics, and therapy response are seen in osteoporosis patients. It is difficult to customize nanoparticle-based treatments to each patient's requirements.

Ensuring the long-term safety of nanoparticle-based therapies is essential. This includes monitoring for potential adverse effects that may not be immediately apparent.

There is a chance that, over time, nanoparticle-based therapies for osteoporosis may acquire drug resistance or tolerance.

Informed consent, patient rights, and other ethical and legal issues are brought up by the use of nanoparticles in healthcare.

Collaboration between professionals in nanotechnology, pharmacy, medicine, and regulatory affairs is necessary for the effective development and use of nanoparticle-based medicines. Successful interdisciplinary cooperation might be difficult, yet it is necessary for achievement.

Adoption of nanoparticle-based medicines may be influenced by how the public views and accepts them. Ensuring that patients and the general public trust in the efficacy and safety of these medicines is crucial

The development and widespread use of nanoparticle-based osteoporosis treatments depend heavily on addressing these difficulties and restrictions. To guarantee that these treatments are secure, reliable, and accessible for osteoporosis patients, interdisciplinary cooperation, rigorous testing, and regulatory control are necessary.

Conclusion

Osteoporosis is a condition that has grown to be a global problem, posing clinical, social, and financial challenges. The rise in life expectancy is a major factor in this issue, and health systems

and businesses should be aware of it. As a result, an older population is more likely to develop osteoporosis. The pharmaceutical industry will be very interested in treating osteoporosis because it is a condition that affects an increasing percentage of the population. There are several restrictions with regard to toxicity and bioavailability with current pharmaceutical treatment. New methods for enhancing these medicines' qualities have been made possible by the development of nanotechnology. Bone-targeted nanoparticles have a particularly high potential for therapeutic applications in the delivery of medicines to bone niches. These would extend the therapeutic window, boost local drug concentration, and lessen off-target negative effects. Unfortunately, there has not been much research on the release pattern and the associated mechanism(s), particularly for recently created carriers. Hence, more research concentrating on drug release, safety, and stability is needed and is being driven by the optimization of the carriers. Although more study is required for clinical applications, improving nanotechnology offers the possibility for future therapy solutions.

Ethical approval

Ethics approval was not required for this review.

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