







Review

Leveraging the Therapeutic Role of Nanotechnology in Osteoporosis Management: Current Progress and Perspectives

Mansi Malik¹ , Pooja Yadav¹ , Kapil Dangi^{1,2} ,
Anita Kamra Verma^{1,3,*} 

¹Nano-Biotech Lab, Kirori Mal College, University of Delhi, Delhi, India

²Department of Zoology, Deshbandhu College, University of Delhi, Delhi, India

³Delhi School of Public Health, Institution of Eminence, University of Delhi, Delhi, India

*Corresponding author: akverma@kmc.du.ac.in

Article History

Received:
12 March 2025

Revised:
9 June 2025

Accepted:
30 June 2025

Published online:
30 July 2025

Published in Issue:
2 January 2026

© 2026 The Author(s). Published by the OICC Press under the terms of the [CC BY 4.0, Creative Commons Attribution License](https://creativecommons.org/licenses/by/4.0/), which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

Abstract:

Osteoporosis (OP) is a bone degenerative disease, wherein progressive deterioration of microarchitecture of bones make them porous, fragile and brittle leading to bone hollowing. OP is characterized by decrease in bone mineral density (BMD) wherein spine, shoulder, hip, wrist bones are more prone to fracture risks that causes high morbidity and socio-economic burden. This necessitates early diagnosis of OP and prediction of fragility fracture risk. Conventional diagnostic methods, include Dual-Energy X-ray Absorptiometry (DXA), do not give accurate predictions of risk of fractures as minor changes in bone structure are often overlooked. The fact that most fractures occur at non-osteoporotic BMD values, despite the operative diagnosis being based on BMD, is an obstacle in management of OP. With the advent of artificial intelligence, a series of reports suggest deep learning applications in screening and diagnosis of OP. Deep learning methods can emerge as a promising method for detection and diagnosis of osteoporotic fractures via machine learning (ML).

The ever-expanding field of nanotechnology has witnessed rapid development of its potential application for OP treatment. While traditional therapies for OP are effective, their use are severely limited due to reduced bioavailability, non-specific distribution coupled with adverse effects. Nanotherapeutics have emerged as a promising approach for managing OP. The unique physicochemical properties of nanoparticles include tunable surface characteristics, ultra-small size, high surface-to-volume ratio that empower them to overcome the confines of traditional therapies. Nanotechnology applications in OP therapeutics are still in the early phases, with more research needed to fully uncover its potential.

Keywords: Artificial intelligence; Biomaterial scaffolds; Bone mineral density; Bone regeneration; Machine learning; Nanotechnology; Osteoporosis (OP)

Cite this article: Malik M, Yadav P, Dangi K, Verma, AK. Leveraging the Therapeutic Role of Nanotechnology in Osteoporosis Management: Current Progress and Perspectives. Int. J. Nano Dimens. 2026;17(1): 1-19. <https://doi.org/10.57647/j.ijnd.2026.1701.01>

1. Introduction

Osteoporosis (OP) is a progressive systemic skeletal disorder characterized by a reduction in bone mineral density (BMD) and compromised bone microarchitecture, leading to increased bone fragility and susceptibility to fractures [1]. It causes bones to become more porous and brittle, which lowers BMD and increases the fracture

risks. Spine, hip, wrist and shoulder bones are most adversely affected in this disease. Low BMD and increased bone fracture are one of the main characteristics of OP [2]. OP leads to long-term complications, including stooped posture, persistent pain, skeletal deformities, functional impairment, and psychological impacts such as depression, collectively diminishing quality of life [3]. OP is becoming extremely common as the life

expectancy is increasing globally.

OP is reported in all gender, ethnicities and different age groups; however, post-menopausal women are at notably higher risk. The various OP risks factors are outlined below in (Table 1) by S. Misner, et al. (2017, 2018) [4]. Women are at high risk after menopause which is referred to as post-menopausal OP (PMO). An estimated 200 million women worldwide, including 75 million across Europe, Japan, and the United States, are affected by PMO [5].

Bones are hard, compact rigid tissues that enables the body to perform multiple functions. Outermost layer of bone is referred to as cortical bone, it plays the major weight-bearing function in the body and is extremely resistant to bending and torsion [6]. The trabecular or cancellous bone is the innermost layer of bone; it is spongy and highly vascularized in nature consisting of bone marrow [7]. Osteoblasts, osteoclasts, osteocytes, fibroblasts are the main cellular components that altogether constitutes bone microenvironment. Osteoblasts are specialized mesenchymal-derived cells responsible for bone formation through the process of osteogenesis, contributing to new bone synthesis and the growth of existing bone tissue. In contrast, osteoclasts, derived from hematopoietic precursors, mediate bone resorption via osteoclastogenesis, a process that involves the degradation and remodeling of bone matrix [8]. These cells play a crucial role in bone remodelling. In a healthy individual these cells function in normal manner, to repair all the flaws and cracks, maintaining healthy bones [9]. However, when bone remodelling activity gets imbalanced i.e., when bone resorption by osteoclast exceeds bone formation by osteoblast, it results in pathophysiological changes leading to low BMD, loss in trabecular region of bone making them more porous, brittle and enhancing risks of fracture, altogether causing OP in an individual. Apart from the osteoclast and osteoblast activities, various systemic factors (hormones) such as estrogen, calcitonin, parathyroid hormone, testosterone contribute key role in remodelling of bone and thereby sustaining the skeletal homeostasis. Estrogen plays a critical role in regulating bone remodeling, as its receptors are expressed on both osteoblasts and osteoclasts [10]. The marked decline in estrogen levels during menopause disrupts the balance between osteogenesis and bone resorption, favoring increased bone turnover and contributing to the pathogenesis of osteoporosis.

At present no active treatment for OP is prescribed rather its treatment and prevention can be addressed by using home remedies for its management. OP prevention involves taking steps to change the environment and way of living so that a high peak BMD is maintained [11]. A regular healthy diet plan, regular exercise, avoiding risk factors like alcohol abuse and smoking is advised to all who are at an increased risk of disease. Conversely, treatment involves intervention for patients who have established OP that could lower down the chances of subsequent fractures [12].

Hormone-based therapies have shown considerable

efficacy in the management of osteoporosis, particularly in peri- and postmenopausal women. Hormone Replacement Therapy (HRT) remains a key therapeutic approach, significantly reducing the risk of both vertebral and nonvertebral fractures across various dosing regimens [13]. HRT contributes to the preservation of BMD throughout the skeletal system and helps normalize bone remodelling dynamics. Additionally, Selective Estrogen Receptor Modulators (SERMs), lasofoxifene, raloxifene and bazedoxifene, Selective Tissue Estrogenic Activity Regulators (STEARs) like tibolone have demonstrated efficacy in improving BMD at both femoral and vertebral sites. Furthermore, the Tissue-Selective Estrogen Complex (TSEC), which combines conjugated estrogens with bazedoxifene, not only attenuates bone turnover and increases BMD but also alleviates climacteric symptoms associated with menopause [14].

These recent medications and therapies for OP treatment have several adverse side effects causing renal impairment and acute kidney toxicity. HRT have potential risks of breast cancer, thrombosis, hot flushes, vaginal bleeding, stroke, cardiovascular disease, thromboembolism and various other complications have been reported with the use of SERMs [15]. In light of these challenges, alternative strategies employing biomaterials, particularly nanoparticles, have been explored for therapeutic applications of OP and enhanced bone regeneration. Nanoparticles fall within the range of 1 to 100 nm, exhibiting a high surface area-to-volume ratio because of their nanoscale dimensions [16]. Nanoparticles are used as vehicle for site-specific drug delivery due to their small size. Drugs are either encapsulated or adsorbed within nanoparticles, thereby increasing their biostability [17]. Since bone is a nanocomposite, utilization of nanomaterials for bone tissue regeneration and OP treatment serves as an effective approach. Nanomaterials also serve as osteoconductive agents that stimulates stem cells differentiation to an osteolineage [18]. For instance, calcium phosphate-based nanomaterials interact with integrin receptors on mesenchymal stem cells (MSCs), leading to activation of focal adhesion kinase (FAK) signalling pathways. This activation upregulates key transcription factors such as Runx2 and Osterix, which drive the osteogenic markers expression including collagen type I, alkaline phosphatase, osteocalcin, culminating in matrix mineralization and osteoblast differentiation [19].

2. General understanding of OP for developing nanotherapeutics

2.1 Etiology

Strength of bone is determined by the two critical components: bone mineral density (BMD) and bone quality. While BMD remains the clinical gold standard for diagnosing osteoporosis and evaluating initial fracture risk, emerging evidence indicates that BMD alone may not comprehensively predict fracture susceptibility or monitor therapeutic efficacy. Consequently, the concept of

bone quality has gained prominence, as it encompasses both material and structural attributes that contribute to overall bone strength [20].

Structural properties are largely influenced by bone geometry—specifically the size and shape of the bone—as well as its microarchitectural organization, including thickness of trabecular, trabecular connectivity, also thickness or porosity. On the other hand, material properties are defined by parameters such as the mineral-to-matrix ratio, hydroxyapatite crystal size (mineralization), collagen composition (including collagen type and cross-linking patterns), and the extent of microdamage or micro-fracture accumulation [21].

Moreover, estrogen deficiency following menopause has been strongly correlated with accelerated bone loss and increased bone turnover, significantly elevating fracture risk. These alterations in bone remodelling dynamics can be broadly classified as:

2.1.1 Primary OP

Primary OP is linked with the process of aging and deficiency of sex hormones. Estrogen deficiency in post-menopausal women results in lower BMD [22]. Aging results in degradation of trabecular region of the bone making them porous and brittle, therefore resulting in reduced bone mass. With advancing age, increased levels of sex hormone-binding globulin (SHBG) lead to the inactivation of estrogen and progesterone, resulting in decline of BMD in males [23].

2.1.2 Secondary OP

Numerous coexisting conditions and/or medicines can lead to secondary OP. It results due to imbalance of sex hormones, calcium and vitamin D levels [24]. BMD has been seen to drop off quickly within three to six months of starting glucocorticoid medication. Secondary OP may occur due to different reasons in different genders [25]. In male individuals, OP is more frequently linked to excessive alcohol consumption, use of glucocorticoids and hypogonadism. A study has indicated that the males undergoing androgen-deprivation therapy (ADT) are at an increased risk of OP. In females, 78% of chances of secondary OP were caused by calcium metabolism disorders and hyperparathyroidism [26].

2.2 Epigenetics associated with OP

Research has identified several genes that contribute to risk of developing of OP. These genes primarily regulate processes involved in maintenance and development of bone, as well as calcium and vitamin D metabolism, both of which are vital for skeletal health [27]. Three genes are reported to be involved with maintenance of bone health as variations in them may affect the bone densities.

- i) **Vitamin D Receptor (VDR) Gene:** Variations in this gene affects vitamin D metabolism, influencing calcium absorption and bone mineralization [28].
- ii) **COL1A1 and COL1A2 Genes:** These genes encode type I collagen, a major structural protein in bones. Mutations in these genes can lead to *osteogenesis imperfecta* and other bone disorders [29].
- iii) **LRP5 Gene:** This gene is crucial for bone formation and density. Mutations in LRP5 are linked to high bone mass or, conversely, to *osteoporosis pseudo glioma* syndrome [30].

Research indicates that epigenetic modifications can influence genes involved in bone remodelling. For instance, alterations in the expression of the RUNX2 gene, which is essential for bone formation, can result in changes to density and structure of bone.

Beyond DNA sequence variations, epigenetic modifications also play a crucial role in health of bone. Epigenetics involves modification in expression of gene without any alterations in the sequence of DNA frequently through mechanisms like DNA methylation and histone modification. Overall, the crosstalk between bone health and genetics is highly complex, and further research is essential to understand holistically how the genetic factors contribute to the development of OP [31].

2.3 Environmental factors affecting OP

Osteoporosis (OP) is a complex, multifactorial skeletal disorder that arises from the interplay between genetic determinants and environmental influences, bone homeostasis. While genetic plays a foundational role, recent investigations emphasize the significance of environmental and lifestyle-related factors—such as chronic psychosocial

Table 1. List of various factors affecting osteoporosis.

Uncontrollable factors	Controllable factors
Post menopause	Intake of balanced diet
Hormone levels	Intake of Calcium and Vitamin D rich diet
Old age	Diet rich in vegetables and fruits
Gender mainly females	Proper medications
Genetics	Consumption of alcohol
Environmental factors, exposure to low level of sunlight	Smoking
Body structure, having thin and small body structure	Weight loss
Family history	Maintaining healthy everyday lifestyle

stress, physical inactivity, and diets deficient in essential nutrients for modulating bone metabolism. Despite awareness of these ecological determinants, the impact of environmental pollutants, particularly airborne contaminants, on bone health remains inadequately explored. This represents a critical gap in current knowledge, as bone tissue serves as a long-term depot for heavy metals acquired through environmental and dietary exposure. Metals such as lead (Pb), cadmium (Cd), mercury (Hg), and aluminum (Al) accumulate in the skeletal matrix by replacing calcium within hydroxyapatite crystals, rendering the bone a biological repository for toxic substances throughout the lifespan [32]. Lead exposure, in particular, has been associated with multiple deleterious skeletal effects, including suppression of 1,25-dihydroxyvitamin D synthesis, enhanced osteoclastic bone resorption, and impaired osteoblastic bone formation. These combined effects contribute to net bone loss and reduced bone mineral density, thereby aggravating the risk of osteoporosis [33, 34].

2.4 Pathophysiology

Bone tissue undergoes continuous remodelling, with individuals reaching optimum bone mass at about 30 years of age; thereafter, a gradual decline in bone mass begins [35]. While genetics significantly influences peak bone mass, various other factors, including dietary habits, physical activity, and certain diseases or medications, can also affect bone mass (figure 1) [36]. Bone tissue undergoes continuous remodelling throughout life, mediated by osteoblasts and osteoclasts. Osteoclasts facilitate bone resorption whereas osteoblasts mediate osteogenesis occurs when bone resorption exceeds bone formation, resulting in structural deterioration and loss of bone formation [37]. Several local (e.g., growth factors and cytokines) and systemic (hormones) factors such as calcitonin, estrogen, testosterone and parathyroid together maintain the bone homeostasis [38]. Parathyroid hormone enhances osteoblasts differentiation by regulating calcium homeostasis and thus indirectly increases formation of bones [39]. Cytokines, such as receptor activator of nuclear factor kappa-B ligand (RANKL), are crucial mediators in the osteoclastogenic signalling cascade. RANKL is primarily expressed by stromal cells and osteoblasts and it binds to RANK receptor on present on osteoclast precursors. This binding triggers the recruitment of various adaptor molecules, including Tumor Necrosis Factor Receptor Associated Factor 6 (TRAF6) which activates transcription factor nuclear factors kappa B (NF- κ B) and MAP kinase pathway [40]. These transcription factors activate the nuclear factor of activated T-cells cytoplasmic 1 (NFATc1), which is considered as main regulator of osteoclastogenesis. This signalling cascade culminates in the activation of osteoclast-specific genes, promoting the differentiation of pre-osteoclasts into mature osteoclasts and subsequently triggering bone resorption. This signalling cascade culminates in the activation of osteoclast-specific genes, promoting the differentiation of pre-osteoclasts into mature osteoclasts

and subsequently triggering bone resorption [41].

2.5 Diagnosis

Osteoporosis (OP) is primarily diagnosed through the presence of fragility fractures and the assessment of bone mineral density (BMD), typically measured by dual-energy X-ray absorptiometry (DXA), with results expressed as a T-score (Table 2) [42]. The T-score indicates the number of standard deviations by which a patient's BMD differs from that of a young, healthy reference population. According to the World Health Organization (WHO), normal BMD is defined by a T-score between +2.5 and -1.0, osteopenia (low BMD) by a T-score between -1.0 and -2.5, osteoporosis by a T-score below -2.5, and severe osteoporosis by a T-score below -2.5 accompanied by additional clinical risk factors. The WHO has also introduced the FRAX tool for estimating the 10-year probability of fragility fractures [41].

Despite being considered the gold standard, a key limitation of this diagnostic approach is that the majority of fractures occur in individuals with T-scores ranging from -1.0 to -2.5 (osteopenia) or even above -1.0 (normal BMD), thereby reducing its effectiveness as a comprehensive screening tool for osteoporosis [43].

Virtual and physical AI are two subtypes of AI in medicine: the former includes support systems useful for imaging solutions and therapeutic decision-making, while the latter includes insightful prostheses and robotic surgery (figure 2) [44, 45, 46]. Apart from therapeutic decision-making, the virtual subtype of AI presently dominates OP management, with diagnostic tools, bone quality evaluation, fracture risk assessment and fracture detection available or in development [47, 48].

2.5.1 AI applications in OP diagnosis

There is multiple rationale for using opportunistic techniques in the operative diagnosis of OP. For instance, the WHO recommends, measurements of BMD using DXA [49]. Availability of DXA devices is a key factor influencing access to OP screening. Regulatory restrictions and reimbursement policies play a significant role. Accessibility to osteoporosis diagnosis is influenced not only by the availability of DXA units within a country but also by patient-related barriers, including travel distance and transportation limitations. According to a recent survey, the number of DXA units per million population varies significantly, ranging from fewer than 10 units—considered inadequate—to over 50 in some regions [50]. The limited availability of DXA devices in most countries highlights the need for alternative methods. Conventional radiography, being more widely accessible, presents a potential substitute for addressing this challenge [51]. Moreover, if panoramic radiographs suggest signs of OP, patients be referred to medical specialists on recommendation for further evaluation and management [52]. Therefore, there is a compelling need for creating AI-assisted tools to enhance the diagnostic efficacy of these opportunistic OP screening techniques [53]. For instance, convolutional neural

networks (CNNs) have shown promise in diagnosing osteoporosis (OP) using panoramic radiographs. In a pilot study, CNN models achieved an accuracy of up to 86.5% in identifying low bone mineral density regions, demonstrating potential as a screening tool in dental settings [54, 55]. The AUC values varied from 0.98 to 0.99 depending on the CNN [56]. However, two skilled oral and maxillofacial radiologists diagnosed OP, based on radiographs rather than utilising DXA, the gold-standard reference technology [57].

Conventional hand and wrist radiographs have also been used to construct AI-based software solutions for opportunistic OP detection [58]. Indeed, in one work, the algorithm was trained and tested using cancellous texture analysis from the distal radius and cortical radiogram from the third metacarpal bone shaft, with DXA serving as a reference standard with an accuracy of over 89%, the created program may be a viable choice for broader clinical usage.

Other techniques, like as quantitative computed tomography (QCT), computed tomography (CT), and quantitative ultrasonography, have also been suggested for the opportunistic diagnosis of OP [52, 59]. Recent studies have demonstrated that frequent chest CT scans, when analysed using artificial intelligence (AI), can effectively facilitate opportunistic screening for osteopenia and osteoporosis. Several researches have demonstrated that integration of AI with routine chest CT imaging offers significant potential for opportunistic screening of osteopenia and osteoporosis [60, 61].

Recently, a first meta-analysis and systematic review was conducted due to the abundance of imaging-based AI methods for opportunistic OP detection. Seven trials with over 3,000 patients were determined to be qualified for inclusion. The pooled specificity and sensitivity,

using a random effects model, were 0.95 and 0.96, respectively [62]. However, as the authors accurately noted, results should be interpreted cautiously because of the substantial heterogeneity and high risk of bias in patient selection. Nevertheless, it should be mentioned that only three of the seven included research have made use of DXA technology as a reference standard [63].

2.5.2 AI application in Osteoporotic fractures detection

The identification of fractures in standard radiographs is a cornerstone of OP treatment. Thus, it should come as no surprise that a sizable number of software tools for fracture diagnosis that are backed by AI have been created so far [64, 65, 66]. The majority of them usually use a single CNN algorithm, as Inception, Xception, or DenseNet, although occasionally a group of CNNs, commonly called “ensemble,” is employed [67]. It has been generally demonstrated that AI technologies are trustworthy for diagnosing fractures with high accuracy compared to the skilled medical professionals like radiologists or orthopaedics [68]. Lindsey et al. (2018) demonstrated that deep learning models significantly improve fracture detection accuracy in wrist radiographs. When used by emergency clinicians, the AI model increased sensitivity from 80.8% to 91.5% and specificity from 87.5% to 93.9%, with a 47% reduction in misinterpretation rates. These findings highlight AI’s potential to equate or enhance radiologist-level performance in fracture diagnosis [50].

In contrast to the findings from analysis of subgroups that only includes long bones, excluding clavicle, vertebrae and ribs, one meta-analysis reported that the diagnostic efficacy (specificity and pooled sensitivity) was suboptimal when considering all eligible studies. This result holds clinical significance, as it suggests

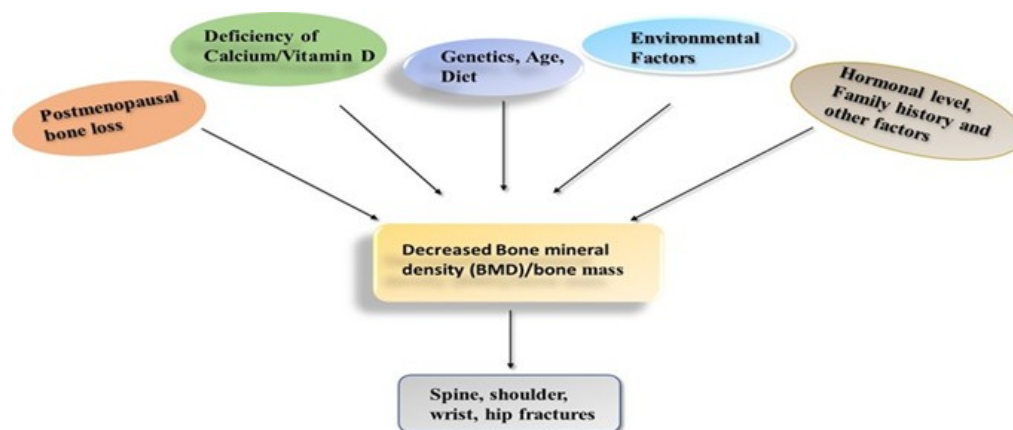


Figure 1. Illustration of various variables impacting BMD thus resulting in fractures and OP.

Table 2. OP defined by WHO. BMD assessment done by DXA and results represented as T-score.

Category	T-score
Normal, healthy condition	-1.0 and above
OP, reduced bone mineral density (BMD)	-2.5 and below
Osteopenia, reduced bone mass	-1.0 to -2.5

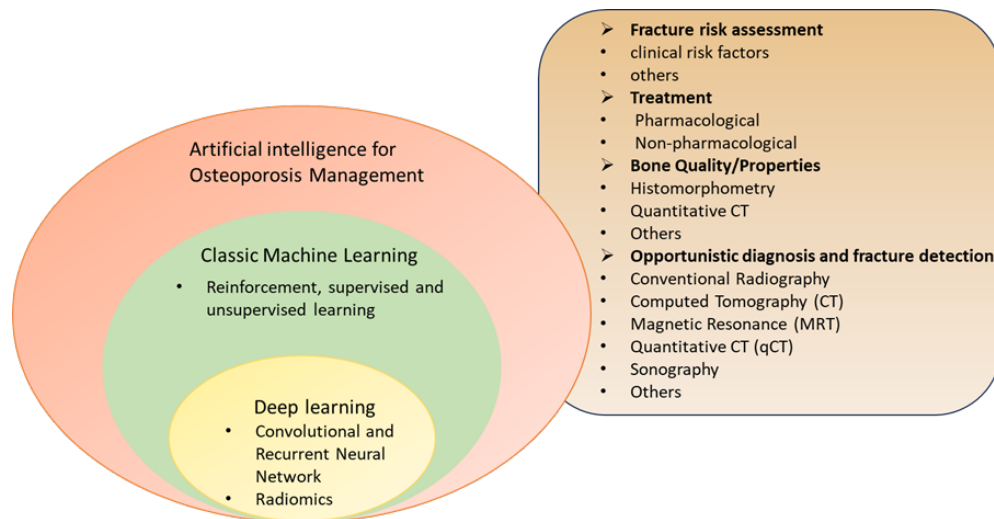


Figure 2. An illustration of AI's hierarchical structure: Machine learning, subfield of AI, gives computer ability to learn on their own without need for explicit programming. Deep learning or end-to-end learning, subfield of Machine learning for medical image feature extraction comprising convolutional and recurrent Neural Networks as its subset.

that fracture detection AI tools may not be fully reliable when the site is of interest, along with surrounding tissue, exhibits greater complexity. Such complexity can hinder accurate classification of the region of interest and the detection of fracture lines [69].

Osteoporotic fractures are the common vertebral fractures, only a fraction of them would be diagnosed right away; the remaining fractures would be found more or less by accident or during the diagnostic assessment of persistent back pain. AI-based technical assistance seems like a sensible addition in raising awareness. As a result, in standard chest and spine radiographs AI developers have recently focused on the automatic diagnosis of vertebral fractures [70, 71, 72, 73].

Recently, an AI-based method was created to automatically detect new osteoporotic vertebral fractures; "new" was defined as occurring within three months of the injury. These AI generated methodologies, as per the authors, may improve the everyday care of osteoporotic patients by lowering the number of new osteoporotic vertebral fractures that are misdiagnosed, without spine surgeons and radiologists in hospitals [74]. However, a major limitation of the algorithm is its inability to detect pathological fractures, such as those associated with metastatic bone disease, despite certain methodological restrictions including a rather limited training data set [75].

In recent years, numerous AI-based technical tools have been designed to predict the risk of fractures [76, 77]. For instance, a new AI-based model for predicting fractures was created and performance was contrasted with that of the nation-specific version of FRAX[®] in newly prospective community-based cohort research [78]. Furthermore, it should be remembered that even while these AI models performed admirably in the community under study, the findings cannot be easily extended to other communities because baseline fracture risks can vary significantly between populations [79, 80].

3. Therapeutics for OP

3.1 Non-medical interventions

It includes maintaining calcium homeostasis, vitamin D intake, exercises, no smoking, no alcohol abuse and low caffeine intake [81]. The Institute of Medicine (IOM) recommends that women over 51 and men over 71 should limit their calcium intake to no more than 1,200 mg per day, while the per day calcium intake for male individuals aged 50 to 70 should not exceed 1,000 mg. Vitamin D plays a vital part in sustaining skeletal health and absorption of calcium. According to the IOM, adults aged 70 or above requires 800 IU of calcium per day and individuals between the age of 51 and 70 requires 600 IU of calcium per day [82].

3.2 Pharmacological treatment

OP medications include antiresorptive drugs like bisphosphonates, calcitonin, estrogen agonist/antagonists [EAAs], RANKL inhibitors, denosumab and anabolic drugs that enhances bone formation like teriparatide and decreases bone resorption rate [83]. According to AACE/ACE guidelines, denosumab, zoledronic acid, risedronate, alendronate are treatments for the most of PMO patients who are at increased fracture risks. Bisphosphonates, such as alendronate and zoledronic acid, offer long term skeletal retention and effectively reduce fracture risk but are contraindicated in patients with renal impairment due to their renal excretion. In contrast, denosumab, is preferred in renal insufficiency and demonstrates superior BMD gains and fracture risk reduction compared to bisphosphonates. However, its discontinuation is related with rebound loss of bone and increase in risk of fractures, necessitating careful follow-up. Hence, recommendations for treatment are based on various variables including gender, likelihood of extra risk factors such as coexisting diseases or medications and fracture likelihood likelihood [84]. The high affinity of bisphosphonates for the mineral matrix

of bone, along with their capacity to inhibit resorption of bone mediated by osteoclast, leads to reduced turnover of bone and increased mass of bone. Bisphosphonates inhibit bone resorption by blocking osteoclast activity in *in-vitro* models but when translated to *in-vivo* model results has revealed complexities [85, 86]. Experiments in early clinical and preclinical settings have examined the application of growth hormones, including bone morphogenetic protein-2 (BMP-2), to encourage development of bone. Hormone-based therapies are designed to combat estrogen deficiency that occurs in ageing women and men to target bone regeneration [87]. Numerous scaffold-based treatments have exposed to improve bone differentiation and decrease rate of bone of resorption in addition to hormone-based treatments [88].

3.3 Emerging therapies

Monoclonal antibodies against sclerostin like Romosozumab and cathepsin K inhibitor are novel mechanisms which are some of the new emerging therapies. The process of bone production is slowed down by sclerostin, a protein secreted by osteocytes in the skeletal tissue that inhibits osteoblast activity and proliferation. During bone resorption, activated osteoclasts produce a powerful protease called cathepsin K (CatK), which breaks down the mineral components and degrades the bone matrix [83, 89]. The FDA disapproved Romosozumab, a humanized monoclonal antibody that targets and inhibits sclerostin for treating OP in July 2017, as it leads to adverse cardiovascular events [90]. Blosozumab and BPS804 are two other anti-sclerostin monoclonal antibodies that are being developed and evaluated. Odanacatib is a drug that selectively inhibits CatK; however, its production was halted by Merck in 2016 due to its association with an elevated risk of stroke. Mineral based therapies and bioactive coating implants are focusing on reducing bone loss and enhancing new bone formation [91]. Existing titanium or ceramic bone implants have been studied for bioactive coatings to promote new bone development. Calcium-based mineral therapies utilise calcium phosphate, hydroxyapatite, or bisphosphonates loaded within scaffolding material to promote stem cells differentiation into osteo-lineage [92]. Hydrophilicity, biocompatibility and biodegradability are some of the characteristics which should be kept in mind while designing the scaffolding materials [93]. Materials such as dextran, pullulan, poly (ethylene glycol) (PEG), silica, chitosan and poly(lactic-co-glycolic acid) (PLGA) are being utilized in the treatment of OP (figure 3) [94].

4. Drawbacks associated with OP treatment

Recent medications that are in use for OP treatment have several adverse side effects on the patients. Generally, bisphosphonates are excreted by kidneys, but if a patient have a condition of renal impairment, bisphosphonates will keep on accumulating in the body resulting in toxicity [95]. As a result, bisphosphonates should not be administered to patients whose creatinine clearances are

below the established recommendations. While hormone replacement therapy (HRT) remains effective in improving BMD with reduced fracture risk, its use is limited due to serious long-term risks such as thromboembolism, stroke, and hormone-sensitive cancers. It is generally recommended only for early postmenopausal women when benefits clearly outweigh the risks [96]. HRT is not recommended for patients above 60 years of age, as it have a potential risk of breast cancer and other complications outweighing its advantages. Also, protective impact of HRT on BMD disappears at an unpredictable rate once the therapy is terminated [97]. Various clinical trials on SERMs such as raloxifene have reported hot flashes, vaginal bleeding, worsening of pre-existing hypertriglyceridemia, venous thromboembolism, stroke death and cardiovascular diseases [103]. Calcitonin is also not recommended a first-line treatment for OP due to insufficient evidence demonstrating its effectiveness in reducing nonvertebral fractures as suggested by the Women Health Initiative (WHI) and Million Women's Study [a101].

5. Nanotherapeutics for OP treatment

In light of the aforementioned issues, alternative approaches utilizing biomaterials, especially nanoparticles, explored for treatment of OP and bone regeneration enhanced. Nanotechnology is an innovative strategy owing to its immense applications ranging from novel fabrications of nanomaterials to sophisticated nanobiosensing and revolutionizing for nanodiagnostics [104]. Nanotechnology offers multiple advantages in delivery of therapeutics including sustained drug release, site-specific drug delivery, increased bioavailability and biocompatibility with low toxicity [105]. Compared to macro-sized particles, nanomaterials have a large surface area to volume ratio since they are typically in the nanometer range (1-100 nm). Because of their small size, a large percentage of their atoms reside on the surface of nanoparticles (NPs), which results in size-dependent characteristics [106]. High surface reactivity and efficient targeted intracellular delivery are the outcomes of this property. The bioavailability and biostability of drugs can be enhanced via their encapsulation in NPs. Furthermore, NPs can be chemically modified to increase tissue selectivity or therapeutic loading while concurrently lowering dosage without impairing efficacy of the therapies [107]. Furthermore, NPs can be chemically modified to increase tissue selectivity or therapeutic loading while concurrently lowering dosage without impairing efficacy of the therapies. Given that bone is a nanocomposite, incorporating nanoparticles is a suitable strategy for promoting bone regeneration in OP treatments (Table 3) [108].

By enabling targeted drug delivery and sustained release, which enhance bioavailability and minimize side effects, nanotechnology-based therapies for osteoporosis (OP) provide benefits over traditional treatments like bisphosphonates, hormone replacement therapy (HRT), and calcium supplement [109]. In contrast to conventional medication delivery methods, bone tissue can be

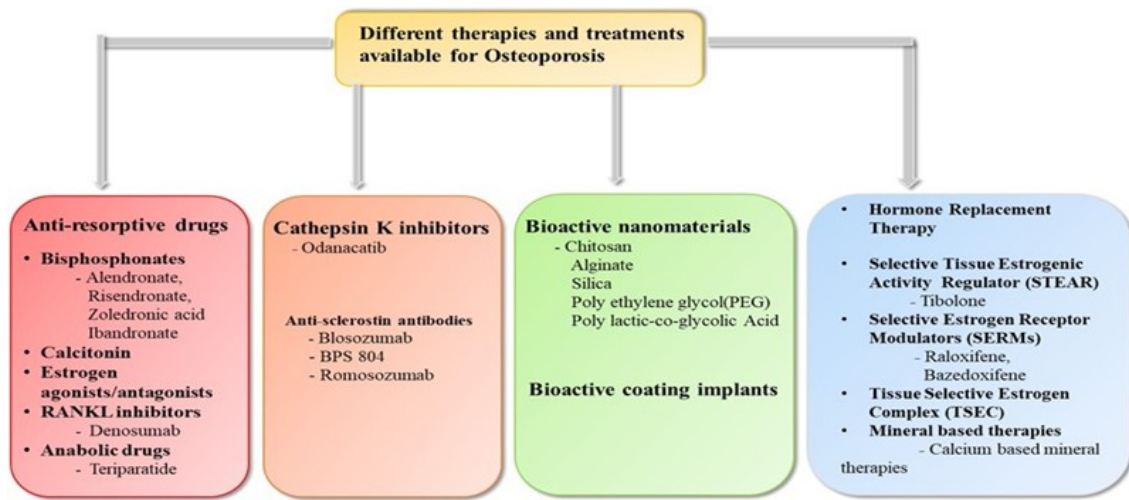


Figure 3. Schematic representation of different therapies and treatment options available for OP.

precisely targeted by nanoparticles, reducing off-target effects [110]. However, while conventional therapies have well established safety profiles, nanoparticle-based treatments still face concerns over long-term toxicity, tissue accumulation, and immune responses. Despite these challenges, nanotechnology holds promise in overcoming the limitations of traditional therapies, offering more effective and localized treatment options for OP, provided that further research into safety and scalability is conducted [100, 111].

5.1 Nanomaterials for OP therapeutics

Nanomaterials have been developed for treatment of OP. Mesoporous silica nanoparticles (MSNs) loaded with β -estradiol showed improved *in vitro* osteoconductivity on a titanium substrate, according to a recent study by Hu et al. (2010). Kang et al. (2012) also studied

in an *in vivo* mouse model, that RGD-tetrapeptide sequences, 17-amino-11-hydroxyandrost-1,4-diene-3-one and a succinyl spacer constituting a nano-delivery system enhanced bone mineral density (BMD) without any known risk of endometrial hyperplasia or thrombosis [112]. Cao et al. (2014) used chitosan nanoparticles (NPs) containing the growth factor BMP-2 for sustained release in a significant lesion in an *in-vivo* research on rabbits. BMP-2 loaded Chitosan NPs promoted osteogenesis and angiogenesis by delivering the BMP2 gene to mesenchymal stem cells, leading to elevated BMP2 protein expression. This upregulation activates the Smad1/5/8 signalling pathway, which in turn the expression of ALP and osteocalcin increased known as osteogenic markers, culminating in enhanced mineralization and formation [113]. However, the mechanical qualities of these scaffolds were not found to be opti-

Table 3. Current Nanomaterials-based strategies for OP treatment.

Strategy	Nanomaterials used	Advantages	Disadvantages
Accelerated Bone Regeneration	-Nano-hydroxyapatite (nHA) -Synthetic silicate nanoparticles (Si NPs) - Layered double hydroxides (LDHs)	Enhance mechanical strength of scaffolds also Promote osteoblast proliferation & differentiation	- High Si NP concentration may be cytotoxic - Limited data on LDH toxicity and cellular effects [98]
Regulation of Bone Remodelling	- Bisphosphonates - Calcium phosphate based materials - Synthetic silicates	Reduce osteoclast activity <i>in vitro</i> and Encourage Oste lineage stem cell differentiation	- Poor osteoclast inhibition <i>in vivo</i> - Limited success of anti-resorptive therapies [99]
Therapeutic Delivery	- Nanocarriers (e.g., liposomes, polymeric NPs) - Drug-loaded calcium phosphate or silicate NPs	Support bone formation and enable targeted drug release [100]	- Potential risks: thrombosis, cancer, endometrial hyperplasia [101]
Combinatorial Nanoengineered Approaches	- Combining nanomaterials (e.g., nHA, Si NPs, LDHs) - Combined with hydrogels & osteo inductive factors	Synergistic effects on osteogenesis and Scaffold design mimics bone ECM	- Early-stage research - Limited data on <i>in vivo</i> efficacy and scalability [102]

mal for treating weight-bearing bones because of porosity. Thus, different nanomaterials used for osteoporosis therapy—such as mesoporous silica, chitosan, and hydroxyapatite nanoparticles—offer distinct advantages and limitations. Mesoporous silica provides controlled drug release but lacks biodegradability and mechanical strength. Chitosan is biocompatible and biodegradable but unsuitable for weight-bearing bones due to its poor mechanical properties. Hydroxyapatite mimics bone composition and supports osteogenesis, though its clinical translation is limited by brittleness and scalability issues. Overall, while these materials show potential, challenges like long-term safety, *in vivo* toxicity, and regulatory approval remain significant barriers to clinical application. Also, overall, protein-based therapies using nanomaterials have showed potential for OP treatment but long-term use of hormone-based therapies are constrained due to thrombosis, cancer and various other risks associated with high dosage and extended use of them [99].

5.2 Nanomaterials for regulating bone remodelling

The focus of current osteoporotic therapies is to enhance new bone growth and reduce bone resorption. Alendronate is one of the clinical and experimental bisphosphonates that has been utilized to actively decrease osteoclast activity, thereby reducing bone resorption [114]. Among the nanomaterials explored for the OP treatment, various mineral-based nanomaterials like hydroxyapatite, calcium phosphate, silica closely mimic bone composition and exhibit strong osteoconductivity, promoting bone regeneration, is proving to be a promising candidate. Calcium phosphate stimulates activity of osteoblasts and enhances osteogenesis [115]. In a study by Ignjatovi et al. (2013), modified crystal structure of hydroxyapatite by replacing cobalt for calcium ions and altered diamagnetic material to paramagnetic as calcium-based nanomaterials possess osteoblast-promoting properties [116]. *In-vivo* results of this study has shown enhanced osteogenesis, osteoporotic bone replacement as well as bone regeneration. When osteoblast cells were cultured with hydroxyapatite-coated iron oxide (Fe₃O₄) nanoparticles, a considerable proportion of osteoblasts differentiated into new bone and the degree of mineralization increased, according to a study by Tran et al. (2011) [113, 117]. Additionally, these nanoparticles maintained their magnetic properties, which could allow for potential *in vivo* guidance to osteoporotic bone. Bosco et al. (2015) found out that when alendronate, a bisphosphonate drug co-administered with hydroxyapatite nanocrystal it reduced *in-vitro* osteoclast activity by inducing apoptosis of osteoclast cells also used calcium-based materials that have osteoblast-promoting effect and bisphosphonates as a coating on titanium bone implants [118]. These findings collectively suggest that bioactive molecules should be focused for next generation of OP treatments as they are potent enough to stimulate stem cells differentiation into an osteolineage [119]. Dexamethasone (DEX) and bone morphogenetic protein-2

(BMP-2), as key bioactive agents, are instrumental in directing MSC differentiation toward osteoblast lineages, making them strong candidates for next-generation osteoporosis therapies. DEX promotes osteogenesis primarily by enhancing Wnt/ β -catenin signalling—through up-regulation of FHL-2, which facilitates β -catenin nuclear translocation—and by activating the MAPK pathway, which modulates the key osteogenic transcription factor Runx2. It also induces TAZ expression, a transcriptional coactivator that further amplifies Runx2-driven osteogenic gene transcription [120, 121, 101, 122]. BMP-2 acts through the TGF- β /SMAD signalling cascade, specifically activating Smad1/5/8 proteins to upregulate osteogenic markers like ALP and osteocalcin. Moreover, BMP-2 boosts TAZ levels and synergizes with Wnt/ β -catenin signalling to enhance osteoblast differentiation. These pathways do not function in isolation—TGF- β signalling modulates both BMP and Wnt pathways, and its dose-dependent effects can either promote or inhibit osteogenesis. Collectively, DEX and BMP-2 orchestrate a complex network of intracellular signalling events, providing a robust framework for stem cell-based bone regeneration in osteoporosis therapy [123].

5.3 Nanoengineered biomaterials for accelerating bone regeneration

Polymeric materials like PEG, PLGA, chitosan, alginate, dextran and collagen could be used for bone tissue engineering. Chitosan is most commonly utilized for bone tissue engineering as it structurally resembles glycosaminoglycans (GAGs), one of the main constituents of extracellular matrix (ECM). Study by Tripathi et al. (2012) demonstrated use of nanocopper-zinc (nCu-Zn) composite with nano-hydroxyapatite (nHA) and chitosan [124]. Copper possesses antimicrobial activity and zinc metal have a role in mineralization. In theory, these metal ions and hydroxyapatite should encourage mineralization and stem cell osteo-differentiation while lowering the prospects of bacterial infection after implantation [125]. According, to Saravanan et al. (2013), protein adsorption was improved when keratin nanoparticles synthesized using chicken feathers were added to a chitosan scaffold [126]. However, only cytotoxicity assessments were carried out in that study. Xu et al. (2013) have incorporated nano-hydroxyapatite crystals and reinforced polyetheretherketone (PEEK) with carbon fibres that resulted in osteogenesis and stem cells differentiation [127]. Compared to titanium, the carbon fiber-reinforced PEEK material exhibited enhanced contact in *in vivo* research, while *in vitro* studies demonstrated increased osteolineage formation and mineralization of stem cells [128]. Nanoengineered biomaterials such as chitosan, PEG, and PLGA offer superior biocompatibility and controlled biodegradability compared to traditional bone grafts or rigid synthetic scaffolds like metals and ceramics. These polymers support osteogenesis and cellular integration, yet often lack the mechanical strength needed for load-bearing applications. While *in vitro* studies demonstrate promising outcomes in cell adhesion and

differentiation, *in vivo* results are often less consistent due to immune responses and complex tissue environments [129]. Moreover, despite significant preclinical progress, clinical translation remains limited by scalability, regulatory hurdles, and long-term performance uncertainties. The characteristics of bioactive nanoparticles may be further investigated in future bone tissue engineering research to see how they impact stem cell differentiation and bone repair.

5.4 Multi-component nano-engineered approaches

Using a synergistic approach, implantable scaffolds are likely to be the foundation for OP treatments and bone tissue engineering. The highly intricate designs of these scaffolds promote osteoblast differentiation, cellular adhesion, and infiltration, giving the osteoporotic bone considerable mechanical stability until new bone growth takes place [130].

Currently different approaches are used for OP treatment (a) regulating bone remodelling by nanomaterials (Fig. 4 a), (b) nanomaterials for therapeutic delivery (Fig. 4 b), (c) combinatorial nanoengineered approaches (Fig. 4 c), (d) nanoengineered biomaterials for enhanced bone regeneration (Fig. 4 d). Significant results have been achieved by incorporating bioactive NPs, which can direct cells towards an osteogenic lineage, with mineral-based nanomaterials to regulate bone remodelling [131]. Multi-component nano-engineered approaches enhance bone regeneration by combining osteogenic molecules, nanoparticles, and scaffolds, offering superior mechanical properties and synergistic effects compared to single-material systems. These combinatorial strategies provide a more comprehensive treatment than traditional therapies like bisphosphonates by targeting multiple aspects

of bone healing. However, challenges in clinical translation include controlling the release kinetics, ensuring uniform distribution, and managing potential toxicity. In contrast, non-nano-based treatments lack the precision and multi-targeted approach that nano-engineered systems offer, limiting their effectiveness in complex bone regeneration [85].

While the integration of nanomaterials into bone regeneration strategies holds significant promise, there is a need for comprehensive *in vitro* and *in vivo* studies to evaluate their cytotoxicity, biodistribution, and long-term safety profiles. Last, but not the least, combinatorial nanoengineered methods have also been investigated. The usefulness of multi-component systems for enhancing the mechanical properties has not received much attention [100].

6. Clinical translation challenges

Despite the remarkable progress in developing nano-engineered biomaterials for osteoporosis (OP) treatment, a significant gap persists between promising preclinical outcomes and successful clinical implementation. One of the foremost challenges is the limited number of nanoparticle-based therapies that have advanced to clinical trials, indicating hurdles in translating laboratory findings into viable human treatment. Scalability and reproducibility of nanoparticle synthesis remain key obstacles, as precise control over size, surface chemistry, and drug loading is essential to ensure consistent therapeutic efficacy and safety [132]. Furthermore, immune responses and off-target effects pose substantial risks, especially given the complex and dynamic *in vivo* environment. Another critical concern is cost-effectiveness, as the production of high-quality, GMP-compliant nanoma-

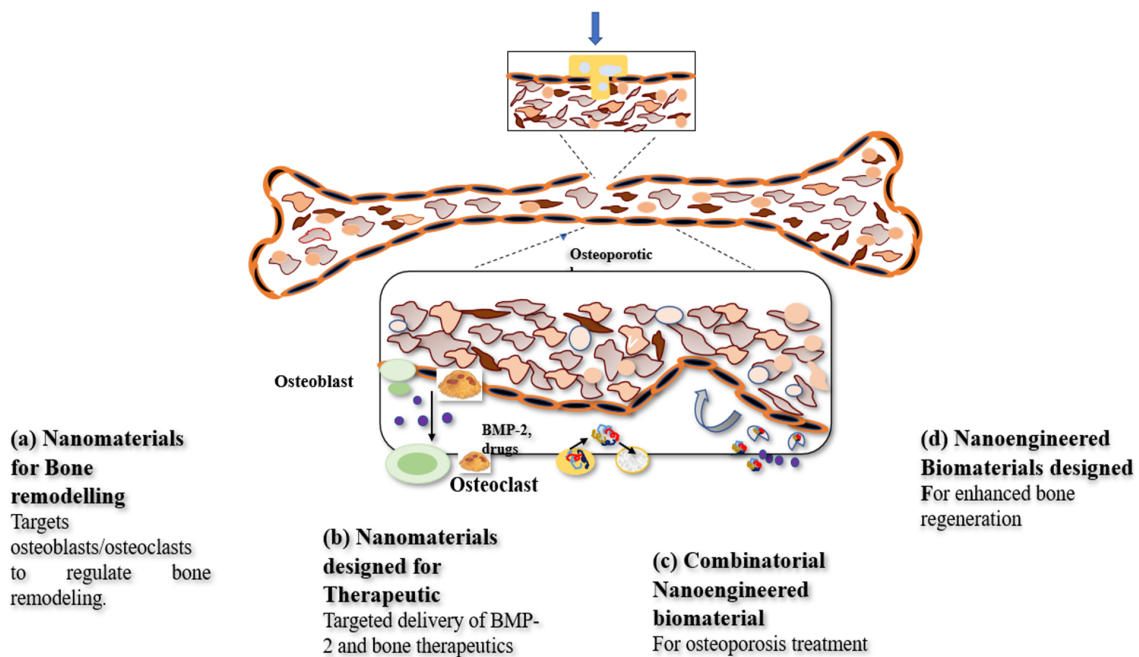


Figure 4. Schematic illustration of different nanomaterials designed for treating OP, (a) nanomaterials for regulating bone remodelling, (b) nanomaterials for therapeutic delivery, (c) combinatorial nanoengineered approach, (d) nanoengineered biomaterials designed for accelerated bone regeneration.

terials at scale often entails significant expense, limiting accessibility. Additionally, regulatory challenges, including lack of standardized evaluation criteria and long approval timelines, hinder the progress of nanoparticle-based OP therapies [133]. Inter-individual variability in nanoparticle uptake, distribution, and metabolism also complicates clinical translation, as factors like age, gender, comorbidities, and genetic background can significantly influence therapeutic outcomes. Addressing these multifaceted challenges requires a coordinated effort across disciplines to establish robust translational pipelines and regulatory frameworks that can bridge the gap between bench and bedside [134].

7. Future directions

Recently, for OP treatment and bone regeneration, a novel class of bioactive nanomaterials has come into existence. Graphene is extensively utilized in industry, neural tissue engineering as it possesses electrically conductive properties. Graphene oxide enhances differentiation of osteogenic markers through the ERK1/2-MAPK pathway activation, resulting in an increased expression of alkaline phosphatase (ALP), RUNX2, and COL1A1. Kalbacova et al. demonstrated that graphene substrates facilitate the attachment of mesenchymal stromal cells and human osteoblasts, indicating the material's potential to support osteogenic processes [135]. Carbon-based material has also shown potential of stem cells differentiation in osteolineage [136]. Nano-hydroxyapatite and silica nanoparticles are examples of inorganic nanomaterials that promote osteogenic stem cells differentiation and aid in osteogenesis. Nano-hydroxyapatite is well documented for mineralization and differentiation of stem cells osteolineage new tissue formation of bone. It is utilized in coating orthopaedic implants to enhance osseointegration [98]. Osteoconductive materials include 2D nanostructures, that can be easily incorporated into the matrix of interest and have completely different properties from the same material's 3D arrangement. Layered double hydroxides (LDHs), silicate nanoparticles and graphene also known as "layered clay" re-emerging as leading candidates for the next generation OP therapeutics and bone tissue engineering [137]. Silicate NPs are becoming a more innovative 2D osteoconductive substance. These have shown the capacity to drive stem cells differentiation into osteoblasts by releasing orthosilicic acid [Si(OH)₄], which enhances type I collagen synthesis and activates osteogenic pathways, including BMP-2/Smad/RUNX2, ERK1/2, and WNT/SHH signalling. These mechanisms collectively contribute to the rise in expression of osteogenic markers and mineralization. These aid as a flexible targeted drug delivery vehicle as particle centres are negatively charged and positive charges are compelled to gather along the edges of the substance [138]. This distribution of surface charge makes it possible for shear-thinning and increases stability in an aqueous solution, making it promising for use in an injectable or 3D-printed osteoconductive system [139]. Artificial silicate nanoparticles have demonstrated

potential in bone tissue regeneration, as their products of degradation—such as sodium, magnesium (Mg²⁺), lithium, and orthosilicic acid (Si(OH)₄)—are biocompatible and can enhance mesenchymal stem cells (MSCs) to osteogenically differentiate eliminating the need for additional growth factor [140]. Si(OH)₄, as mentioned above, reported to promote the formation of collagen and type 1 the Mg²⁺ released during the breakdown of silicates improves cell adhesion to scaffolds. Without osteo-inductive agents like BMP-2 or dexamethasone, the quantities necessary to induce the development of new bone did not reach the hazardous levels even though the silicate nanoparticles in the experiments displayed cytotoxicity at high dosages, further highlighting the novelty of this method for controlling fate of stem cells in bone tissue regeneration [141].

Another class of nanomaterials under investigation are layered double hydroxides (LDHs), which consists of hydroxide sheets interspersed with cationic metal atoms. These nanosheets' layered and ionic structures can be used as delivery vehicles for genetic material and medications, and when they are incorporated into matrices, their qualities are further enhanced. LDHs has shown the potential for the future development of next generation of OP therapeutics as they can be used as a blank canvas for the integration and regulated release of medications and ions [102].

While nanotechnology and AI present promising avenues for osteoporosis (OP) management, several gaps must be addressed to facilitate clinical translation. Most notably, there is insufficient data for longterm *in vivo* safety of nanoengineered materials, with potential risks like bioaccumulation and systemic toxicity still underexplored. The absence of standardized protocols for nanoparticle toxicity testing and pharmacokinetics further complicates regulatory approvals. Additionally, the concept of personalized nanomedicine remains underdeveloped, despite known inter-individual differences in bone metabolism and nanoparticle response. For AI applications, the need for multicenter clinical validation is urgent to ensure model reliability and generalizability across diverse populations. Bridging these gaps requires interdisciplinary collaboration, regulatory clarity, and robust translational frameworks to bring these innovations from bench to bedside.

8. Conclusion

Hormone-based therapy and osteoclast activity inhibition have been the mainstays of conventional treatment for this degenerative disease. Currently available treatments are focused on strategies that reduces osteoclast activity by using variety of anti-resorptive drugs like bisphosphonates such as alendronate, risendronate, zoledronic acid, and ibandronate, calcitonin, various estrogen agonist/antagonists, RANKL inhibitors like denosumab and variety of anabolic drugs like teriparatide [142]. Also, current research focusses on effective therapy options for OP that combine multiple components of care, osteoclast suppression and osteoblasts differentiation.

However, the heightened risk of thrombosis and different cancer types associated with prolonged hormone therapy has recently highlighted the need to explore new strategies for addressing bone loss in OP [143]. Future OP treatments could be substantially aided by employing nanoparticles in tissue engineering of bone. Current developments in nanotechnology, particularly the application of nanoparticles (NPs), present numerous benefits, including site-specific therapeutic delivery, enhanced bioavailability, biocompatibility, and low toxicity. Various engineered nanoparticles promoting bone remodeling and regeneration hold significant potential to serve as the next generation of OP treatments in the near future [144]. Polymeric materials such as PLGA, alginate, dextran, chitosan, PEG and collagen can be utilized in bone tissue engineering. Additionally, calcium phosphate-based nanoparticles have been combined with silica to develop bioactive coatings that enhance bone regrowth and inhibit the progression of OP. Biomaterial scaffolds are biocompatible, hydrophilic, and intricately integrated with biochemical signals. It has been shown that treatments employing these biomaterial scaffolds can increase bone mineralization levels and encourage osteolineage differentiation of stem cells [145]. When combined with osteo-conductive nanoparticles, biomaterial scaffolds offer promising prospects for guided bone regeneration and represent the next generation of therapeutics aimed at combating the bone loss characteristic of OP [146].

Also, attempts to design ML-based models for recognizing new risk of fracture elements and improves prediction of future, represent reliable research directions. Accurate evaluation of outcomes and their therapeutic implications necessitates adherence to and comprehensive duct for the execution and reporting of machine learning models [147]. In summary, several AI algorithms have been created in few past years to help with OP care, including diagnostic tools, assessment risk of fractures, fracture detection, estimation of bone quality, and therapy nomination. Performance comparisons between these solutions and human medical specialists, where applicable, yield comparable outcomes or even support the AI system [148]. In particular, radiomics, which includes AI-supported opportunistic techniques for evaluating bone mineral density in conjunction with clinical data, seems to hold considerable promise for the early identification of individuals who are more likely to suffer fractures. However, methodological techniques underlying any novel AI algorithm should always be thoroughly examined and rigorously evaluated, even if study findings seem good at first look. Limitations that are regularly seen in AI development research include the utilization of subpar reference criteria or the nomination of characteristics (i.e., variables) that have minimum use in clinical practice. Furthermore, it's not always clear that the AI algorithm designed or selected will perform better than straightforward, conventional statistical techniques [145]. High-calibre clinical research in the area of AI in OP therapy is therefore obviously needed.

This might be accomplished, for example, by creating a globally accepted best practice framework that takes into account healthcare authorities, including those engaged in regulatory procedures, AI developers, OP specialists, and their respective scientific societies.

The potential of AI to completely transform OP treatment may be unleashed if these quality standards are satisfied, and future advantages for doctors, patients, and healthcare in general should become increasingly apparent and significant.

Abbreviations used

BMD	Bone Mineral Density
OP	Osteoporosis
NPs	Nanoparticles
LDHs	Layered double hydroxides
PMO	Post Menopausal Osteoporosis
IOM	Institute of Medicine
HRT	Hormone Replacement Therapy
ML	Machine Learning
AI	Artificial Intelligence
CNN	Convolutional Neural Networks

Acknowledgments

MM is thankful to UGC, Govt. of India for her Junior Research Fellowship (JRF), PY is thankful to DST-Inspire.

Authors contributions

Authors have contributed equally in preparing and writing the manuscript.

Availability of data and materials

The authors declare that the data supporting the findings of this study are available within the paper.

Conflict of interests

The authors assert that they do not have any identifiable conflicting financial interests or personal relationships that might be perceived to influence the work presented in this paper.

References

1. Singh S, Sarma DK, Verma V, Nagpal R, and Kumar M. "From Cells to Environment: Exploring the Interplay between Factors Shaping Bone Health and Disease." *Medicina (B Aires)* 2023; 59:1546. doi: [10.3390/medicina59091546](https://doi.org/10.3390/medicina59091546)
2. LeBoff MS, Greenspan SL, Insogna KL, et al. "The clinician's guide to prevention and treatment of osteoporosis." *Osteoporosis International* 2022; 33:2049–102. doi: [10.1007/s00198-021-05900-y](https://doi.org/10.1007/s00198-021-05900-y)

3. Da P, Coordinatore SM, Supervisore D, et al. "Effects of adapted physical activity on quality of life, physical fitness and fear of falling in people with osteoporosis Effects of APA on QOL, PF and FOF in People with Osteoporosis."
4. Sindel D. "Osteoporosis: Spotlight on current approaches to pharmacological treatment." *Turk J Phys Med Rehabil* 2023; 69:140–52. doi: [10.5606/tftrd.2023.13054](https://doi.org/10.5606/tftrd.2023.13054)
5. Long G, Liu C, Liang T, Zhang Z, Qin Z, and Zhan X. "Predictors of osteoporotic fracture in postmenopausal women: a meta-analysis." *J Orthop Surg Res* 2023; 18:574. doi: [10.1186/s13018-023-04051-6](https://doi.org/10.1186/s13018-023-04051-6)
6. El Miedany Y. "Bone Health: Basic and Applied Bone Biology." *New Horizons in Osteoporosis Management* 2022 :3–47. doi: [10.1007/978-3-030-87950-1_1](https://doi.org/10.1007/978-3-030-87950-1_1)
7. Wawrzyniak A and Balawender K. "Structural and Metabolic Changes in Bone." *Animals* 2022; 12:1946. doi: [10.3390/ani12151946](https://doi.org/10.3390/ani12151946)
8. Bordukalo-Nikšić T, Kufner V, and Vukičević S. "The Role Of BMPs in the Regulation of Osteoclasts Resorption and Bone Remodeling: From Experimental Models to Clinical Applications." *Front Immunol* 2022; 13. doi: [10.3389/fimmu.2022.869422](https://doi.org/10.3389/fimmu.2022.869422)
9. Zhu G, Zhang T, Chen M, et al. "Bone physiological microenvironment and healing mechanism: Basis for future bone-tissue engineering scaffolds." *Bioact Mater* 2021; 6:4110–40. doi: [10.1016/j.bioactmat.2021.03.043](https://doi.org/10.1016/j.bioactmat.2021.03.043)
10. Noirit-Esclassan E, Valera MC, Tremollieres F, et al. "Critical Role of Estrogens on Bone Homeostasis in Both Male and Female: From Physiology to Medical Implications." *Int J Mol Sci* 2021; 22:1568. doi: [10.3390/ijms22041568](https://doi.org/10.3390/ijms22041568)
11. Clark P and Lavielle P. "Are Women Ready to Prevent Osteoporosis? Change Stages for Preventive Behaviors." *Health Education & Behavior* 2021; 48:892–8. doi: [10.1177/1090198121993025](https://doi.org/10.1177/1090198121993025)
12. Kaminsky LA, German C, Imboden M, Ozemek C, Peterman JE, and Brubaker PH. "The importance of healthy lifestyle behaviors in the prevention of cardiovascular disease." *Prog Cardiovasc Dis* 2022; 70:8–15. doi: [10.1016/j.pcad.2021.12.001](https://doi.org/10.1016/j.pcad.2021.12.001)
13. Anagnostis P, Bosdou JK, Vaitis K, Goulis DG, and Lambrinoudaki I. "Estrogen and bones after menopause: a reappraisal of data and future perspectives." *Hormones* 2021; 20:13–21. doi: [10.1007/s42000-020-00218-6](https://doi.org/10.1007/s42000-020-00218-6)
14. Kim BM, Kim SE, Lee DY, and Choi D. "Effect of Tissue-Selective Estrogen Complex on Hip Structural Geometry in Postmenopausal Women: A 12-Month Study." *Front Endocrinol (Lausanne)* 2021; 12. doi: [10.3389/fendo.2021.649952](https://doi.org/10.3389/fendo.2021.649952)
15. Bartl R. "Hormone Replacement Therapy (HRT) and SERMs." *Osteoporosis in Clinical Practice* 2023 :91–8. doi: [10.1007/978-3-031-14652-7_9](https://doi.org/10.1007/978-3-031-14652-7_9)
16. Khan S and Hossain MK. "Classification and properties of nanoparticles." *Nanoparticle-Based Polymer Composites* 2022 :15–54. doi: [10.1016/B978-0-12-824272-8.00009-9](https://doi.org/10.1016/B978-0-12-824272-8.00009-9)
17. Oladipo AO, Lebelo SL, and Msagati TAM. "Nanocarrier design–function relationship: The prodigious role of properties in regulating biocompatibility for drug delivery applications." *Chem Biol Interact* 2023; 377:110466. doi: [10.1016/j.cbi.2023.110466](https://doi.org/10.1016/j.cbi.2023.110466)
18. Wasy leczko M, Wojciechowski C, and Chwojnowski A. "Polyethersulfone Polymer for Biomedical Applications and Biotechnology." *Int J Mol Sci* 2024; 25:4233. doi: [10.3390/ijms25084233](https://doi.org/10.3390/ijms25084233)
19. Li L, Li H, Wang Q, et al. "Hydroxyapatite Nanoparticles Promote the Development of Bone Microtissues for Accelerated Bone Regeneration by Activating the FAK/Akt Pathway." *ACS Biomater Sci Eng* 2024; 10:4463–79. doi: [10.1021/acsbiomaterials.4c00574](https://doi.org/10.1021/acsbiomaterials.4c00574)
20. Felsenberg D and Boonen S. "The bone quality framework: Determinants of bone strength and their interrelationships, and implications for osteoporosis management." *Clin Ther* 2005; 27:1–11. doi: [10.1016/j.clinthera.2004.12.020](https://doi.org/10.1016/j.clinthera.2004.12.020)
21. Ravn P, Cizza G, Bjarnason NH, et al. "Low Body Mass Index Is an Important Risk Factor for Low Bone Mass and Increased Bone Loss in Early Postmenopausal Women." *Journal of Bone and Mineral Research* 1999; 14:1622–7. doi: [10.1359/jbmr.1999.14.9.1622](https://doi.org/10.1359/jbmr.1999.14.9.1622)
22. Xu Z, Yu Z, Chen M, et al. "Mechanisms of estrogen deficiency-induced osteoporosis based on transcriptome and DNA methylation." *Front Cell Dev Biol* 2022; 10. doi: [10.3389/fcell.2022.1011725](https://doi.org/10.3389/fcell.2022.1011725)
23. Zitzmann M. "Testosterone deficiency and chronic kidney disease." *J Clin Transl Endocrinol* 2024; 37:100365. doi: [10.1016/j.jcte.2024.100365](https://doi.org/10.1016/j.jcte.2024.100365)
24. Liang B, Burley G, Lin S, and Shi YC. "Osteoporosis pathogenesis and treatment: existing and emerging avenues." *Cell Mol Biol Lett* 2022; 27:72. doi: [10.1186/s11658-022-00371-3](https://doi.org/10.1186/s11658-022-00371-3)
25. Ciarambino T, Crispino P, Leto G, Mastrolorenzo E, Para O, and Giordano M. "Influence of Gender in Diabetes Mellitus and Its Complication." *Int J Mol Sci* 2022; 23:8850. doi: [10.3390/ijms23168850](https://doi.org/10.3390/ijms23168850)

26. V VN, B K, C VI, et al. "Does mild form of subclinical hypothyroidism needs treatment?" *Endocrine Abstracts* 2022; 83. DOI: [10.1530/endoabs.83.TO1](https://doi.org/10.1530/endoabs.83.TO1)
27. Li Z, Zhang J, Xu T, Hao Z, and Li Y. "Mechanism of histone demethylase KDM5A in osteoporotic fracture healing through epigenetic regulation of the miR-495/SKP2/Runx2 axis." *Molecular Medicine* 2025; 31:65. DOI: [10.1186/s10020-025-01098-5](https://doi.org/10.1186/s10020-025-01098-5)
28. Senosi MR, Fathi HM, Baki NMA, Zaki O, Magdy AM, and Gheita TA. "Bone mineral density, vitamin D receptor (VDR) gene polymorphisms, fracture risk assessment (FRAX), and trabecular bone score (TBS) in rheumatoid arthritis patients: connecting pieces of the puzzle." *Clin Rheumatol* 2022; 41:1333–42. DOI: [10.1007/s10067-022-06048-8](https://doi.org/10.1007/s10067-022-06048-8)
29. Selina A, Kandagaddala M, and Thomas N. "COL1A1 and COL1A2 Gene Variants Causing Osteogenesis Imperfecta in a Major Referral Center of India." *Am J Med Genet A* 2025; 197. DOI: [10.1002/ajmg.a.64023](https://doi.org/10.1002/ajmg.a.64023)
30. Zhang ZL, Qin YJ, He JW, et al. "Association of polymorphisms in low-density lipoprotein receptor-related protein 5 gene with bone mineral density in postmenopausal Chinese women." *Acta Pharmacol Sin* 2005; 26:1111–6. DOI: [10.1111/j.1745-7254.2005.00173.x](https://doi.org/10.1111/j.1745-7254.2005.00173.x)
31. Morris JA, Kemp JP, Youtlen SE, et al. "An atlas of genetic influences on osteoporosis in humans and mice." *Nat Genet* 2019; 51:258–66. DOI: [10.1038/s41588-018-0302-x](https://doi.org/10.1038/s41588-018-0302-x)
32. Pizzorno J. "Environmental Toxins Are a Major Cause of Bone Loss The PATH AhEAd." 2021; 20
33. Al-Ghafari A, Elmorsy E, Fikry E, Alrowaili M, and Carter WG. "The heavy metals lead and cadmium are cytotoxic to human bone osteoblasts via induction of redox stress." *PLoS One* 2019; 14:e0225341. DOI: [10.1371/journal.pone.0225341](https://doi.org/10.1371/journal.pone.0225341)
34. Kostenuik P. "On the evolution and contemporary roles of bone remodeling." *Marcus and Feldman's Osteoporosis* 2021 :727–72. DOI: [10.1016/B978-0-12-813073-5.00031-9](https://doi.org/10.1016/B978-0-12-813073-5.00031-9)
35. Rinonapoli G, Pace V, and Ruggiero C. "Obesity and Bone: A Complex Relationship." *Int J Mol Sci* 2021; 22:13662. DOI: [10.3390/ijms222413662](https://doi.org/10.3390/ijms222413662)
36. Nasma F, Behera J, Tyagi P, Debnath N, Falcone JC, and Tyagi N. "The potential link between the development of Alzheimer's disease and osteoporosis." *Biogerontology* 2025; 26:43. DOI: [10.1007/s10522-024-10181-z](https://doi.org/10.1007/s10522-024-10181-z)
37. Mennitti C, Farina G, Imperatore A, et al. "How Does Physical Activity Modulate Hormone Responses?" *Biomolecules* 2024; 14. DOI: [10.3390/biom14111418](https://doi.org/10.3390/biom14111418)
38. Chen T, Wang Y, Hao Z, Hu Y, and Li J. "Parathyroid hormone and its related peptides in bone metabolism." *Biochem Pharmacol* 2021; 192:114669. DOI: [10.1016/j.bcp.2021.114669](https://doi.org/10.1016/j.bcp.2021.114669)
39. Kitaura H, Marahleh A, Ohori F, et al. "Role of the Interaction of Tumor Necrosis Factor- α and Tumor Necrosis Factor Receptors 1 and 2 in Bone-Related Cells." *Int J Mol Sci* 2022; 23:1481. DOI: [10.3390/ijms23031481](https://doi.org/10.3390/ijms23031481)
40. Jiang T, Xia T, Qiao F, Wang N, Jiang Y, and Xin H. "Role and Regulation of Transcription Factors in Osteoclastogenesis." *Int J Mol Sci* 2023; 24:16175. DOI: [10.3390/ijms242216175](https://doi.org/10.3390/ijms242216175)
41. Imeri B, Gheitasi M, Khaledi A, and Mozafaripour E. "Bone Mineral Density and Content among Iranian Elite Male Athletes in Different Sports." *Arch Bone Jt Surg* 2023; 11:212–7. DOI: [10.22038/ABJS.2022.67195.3196](https://doi.org/10.22038/ABJS.2022.67195.3196)
42. Thurner GC, Haybaeck J, and Debbage P. "Targeting Drug Delivery in the Elderly: Are Nanoparticles an Option for Treating Osteoporosis?" *Int J Mol Sci* 2021; 22:8932. DOI: [10.3390/ijms22168932](https://doi.org/10.3390/ijms22168932)
43. Guan J, Li Z, Sheng S, et al. "An artificial intelligence-driven revolution in orthopedic surgery and sports medicine." *International Journal of Surgery* 2025; 111:2162–81. DOI: [10.1097/JS9.0000000000002187](https://doi.org/10.1097/JS9.0000000000002187)
44. Topol EJ. "High-performance medicine: the convergence of human and artificial intelligence." *Nat Med* 2019; 25:44–56. DOI: [10.1038/s41591-018-0300-7](https://doi.org/10.1038/s41591-018-0300-7)
45. Meng Y, Yang Y, Hu M, Zhang Z, and Zhou X. "Artificial intelligence-based radiomics in bone tumors: Technical advances and clinical application." *Semin Cancer Biol* 2023; 95:75–87. DOI: [10.1016/j.semcancer.2023.07.003](https://doi.org/10.1016/j.semcancer.2023.07.003)
46. Khorati AA, Shahid Z, Fok M, et al. "Artificial intelligence and the orthopaedic surgeon: A review of the literature and potential applications for future practice: Current concepts." *Journal of ISAKOS* 2024; 9:227–33. DOI: [10.1016/j.jisako.2023.10.015](https://doi.org/10.1016/j.jisako.2023.10.015)
47. Pickhardt PJ, Lee SJ, Liu J, et al. "Population-based opportunistic osteoporosis screening: Validation of a fully automated CT tool for assessing longitudinal BMD changes." *Br J Radiol* 2019; 92:20180726. DOI: [10.1259/bjr.20180726](https://doi.org/10.1259/bjr.20180726)
48. Deshpande N, Hadi MS, Lillard JC, et al. "Alternatives to DEXA for the assessment of bone density: a systematic review of the literature and future recommendations." *J Neurosurg Spine* 2023; 38:436–45. DOI: [10.3171/2022.11.SPINE22875](https://doi.org/10.3171/2022.11.SPINE22875)

49. Clynes MA, Westbury LD, Dennison EM, et al. "Bone densitometry worldwide: a global survey by the ISCD and IOF." *Osteoporosis International* 2020; 31:1779–86. DOI: [10.1007/s00198-020-05435-8](https://doi.org/10.1007/s00198-020-05435-8)
50. Dimai HP. "New Horizons: Artificial Intelligence Tools for Managing Osteoporosis." *J Clin Endocrinol Metab* 2023; 108:775–83. DOI: [10.1210/clinem/dgac702](https://doi.org/10.1210/clinem/dgac702)
51. Farhadi Nia M, Ahmadi M, and Irankhah E. "Transforming dental diagnostics with artificial intelligence: advanced integration of ChatGPT and large language models for patient care." *Frontiers in Dental Medicine* 2025; 5. DOI: [10.3389/fdmed.2024.1456208](https://doi.org/10.3389/fdmed.2024.1456208)
52. Yang J, Liao M, Wang Y, et al. "Opportunistic osteoporosis screening using chest CT with artificial intelligence." *Osteoporosis International* 2022; 33:2547–61. DOI: [10.1007/s00198-022-06491-y](https://doi.org/10.1007/s00198-022-06491-y)
53. Ghasemi N, Rokhshad R, Zare Q, Shobeiri P, and Schwendicke F. "Artificial intelligence for osteoporosis detection on panoramic radiography: A systematic review and meta analysis." *J Dent* 2025; 156:105650. DOI: [10.1016/j.jdent.2025.105650](https://doi.org/10.1016/j.jdent.2025.105650)
54. Gaudin R, Otto W, Ghanad I, et al. "Enhanced Osteoporosis Detection Using Artificial Intelligence: A Deep Learning Approach to Panoramic Radiographs with an Emphasis on the Mental Foramen." *Medical Sciences* 2024; 12:49. DOI: [10.3390/medsci12030049](https://doi.org/10.3390/medsci12030049)
55. Aurna NF, Yousuf MA, Taher KA, Azad AKM, and Moni MA. "A classification of MRI brain tumor based on two stage feature level ensemble of deep CNN models." *Comput Biol Med* 2022; 146:105539. DOI: [10.1016/j.combiomed.2022.105539](https://doi.org/10.1016/j.combiomed.2022.105539)
56. Anandan R, C.L K, Ganesan A, and Aniyan KY. "Strut and radio-morphometric analysis of mandibular trabecular structure in pre-and post-menopausal women to aid in the diagnosis of osteoporosis." *J Oral Biol Craniofac Res* 2024; 14:273–9. DOI: [10.1016/j.jobcr.2024.03.002](https://doi.org/10.1016/j.jobcr.2024.03.002)
57. Chawla SK and Malhotra D. "Prediction of Osteoporosis Using Artificial Intelligence Techniques: A Review." 2023 :181–98. DOI: [10.1007/978-981-99-0601-7_15](https://doi.org/10.1007/978-981-99-0601-7_15)
58. Zeng C, Guo B, Zhang S, et al. "Age-related changes in lumbar bone mineral density measured using quantitative computed tomography in healthy female cynomolgus monkeys." *Quant Imaging Med Surg* 2023; 13:2038–52. DOI: [10.21037/qims-22-763](https://doi.org/10.21037/qims-22-763)
59. Fang Y, Li W, Chen X, et al. "Opportunistic osteoporosis screening in multi-detector CT images using deep convolutional neural networks." *Eur Radiol* 2021; 31:1831–42. DOI: [10.1007/s00330-020-07312-8](https://doi.org/10.1007/s00330-020-07312-8)
60. Sharma G, Sharma A, Krishna M, Ahluwalia P, and Gautam G. "Diagnostic performance of minichromosome maintenance 5 (MCM5) in bladder cancer: A systematic review and meta-analysis." *Urologic Oncology: Seminars and Original Investigations* 2022; 40:235–42. DOI: [10.1016/j.urolonc.2022.03.001](https://doi.org/10.1016/j.urolonc.2022.03.001)
61. Wang S, Tong X, Cheng Q, et al. "Fully automated deep learning system for osteoporosis screening using chest computed tomography images." *Quant Imaging Med Surg* 2024; 14:2816–27. DOI: [10.21037/qims-23-1617](https://doi.org/10.21037/qims-23-1617)
62. Ahern DP, McDonnell JM, Riffault M, et al. "A meta-analysis of the diagnostic accuracy of Hounsfield units on computed topography relative to dual-energy X-ray absorptiometry for the diagnosis of osteoporosis in the spine surgery population." *The Spine Journal* 2021; 21:1738–49. DOI: [10.1016/j.spinee.2021.03.008](https://doi.org/10.1016/j.spinee.2021.03.008)
63. Kutbi M. "Artificial Intelligence-Based Applications for Bone Fracture Detection Using Medical Images: A Systematic Review." *Diagnostics* 2024; 14:1879. DOI: [10.3390/diagnostics14171879](https://doi.org/10.3390/diagnostics14171879)
64. Chung SW, Han SS, Lee JW, et al. "Automated detection and classification of the proximal humerus fracture by using deep learning algorithm." *Acta Orthop* 2018; 89:468–73. DOI: [10.1080/17453674.2018.1453714](https://doi.org/10.1080/17453674.2018.1453714)
65. Gitto S, Serpi F, Albano D, et al. "AI applications in musculoskeletal imaging: a narrative review." *Eur Radiol Exp* 2024; 8:22. DOI: [10.1186/s41747-024-00422-8](https://doi.org/10.1186/s41747-024-00422-8)
66. Ahmad F, Farooq A, and Ghani MU. "Deep Ensemble Model for Classification of Novel Coronavirus in Chest X-Ray Images." *Comput Intell Neurosci* 2021; 2021. DOI: [10.1155/2021/8890226](https://doi.org/10.1155/2021/8890226)
67. Meena T and Roy S. "Bone Fracture Detection Using Deep Supervised Learning from Radiological Images: A Paradigm Shift." *Diagnostics* 2022; 12:2420. DOI: [10.3390/diagnostics12102420](https://doi.org/10.3390/diagnostics12102420)
68. Lindsey R, Daluiski A, Chopra S, et al. "Deep neural network improves fracture detection by clinicians." *Proceedings of the National Academy of Sciences* 2018; 115:11591–6. DOI: [10.1073/pnas.1806905115](https://doi.org/10.1073/pnas.1806905115)
69. Baekkeskov S, Nielsen JH, Marner B, et al. "Autoantibodies in newly diagnosed diabetic children immunoprecipitate human pancreatic islet cell proteins." *Nature* 1982; 298:167–9
70. Wiklund P, Buchebner D, and Geijer M. "Vertebral compression fractures at abdominal CT: underdiagnosis, undertreatment, and evaluation of an AI algorithm." *Journal of Bone and Mineral Research* 2024. DOI: [10.1093/jbmr/zjae096](https://doi.org/10.1093/jbmr/zjae096)

71. Liu RW, Ong W, Makmur A, et al. "Application of Artificial Intelligence Methods on Osteoporosis Classification with Radiographs—A Systematic Review." *Bioengineering* 2024; 11:484. doi: [10.3390/bioengineering11050484](https://doi.org/10.3390/bioengineering11050484)
72. Xu F, Xiong Y, Ye G, et al. "Deep learning-based artificial intelligence model for classification of vertebral compression fractures: A multicenter diagnostic study." *Front Endocrinol (Lausanne)* 2023; 14. doi: [10.3389/fendo.2023.1025749](https://doi.org/10.3389/fendo.2023.1025749)
73. Rosenberg GS, Cina A, Schiró GR, et al. "Artificial Intelligence Accurately Detects Traumatic Thoracolumbar Fractures on Sagittal Radiographs." *Medicina (B Aires)* 2022; 58:998. doi: [10.3390/medicina58080998](https://doi.org/10.3390/medicina58080998)
74. Paderno A, Ataíde Gomes EJ, Gilberg L, et al. "Artificial intelligence-enhanced opportunistic screening of osteoporosis in CT scan: a scoping Review." *Osteoporosis International* 2024; 35:1681–92. doi: [10.1007/s00198-024-07179-1](https://doi.org/10.1007/s00198-024-07179-1)
75. Hinzpeter R, Baumann L, Guggenberger R, Huellner M, Alkadhi H, and Baessler B. "Radiomics for detecting prostate cancer bone metastases invisible in CT: A proof-of-concept study." *Eur Radiol* 2022; 32:1823–32. doi: [10.1007/s00330-021-08245-6](https://doi.org/10.1007/s00330-021-08245-6)
76. Sadat-Ali M, Alzahrani BA, Alqahtani TS, et al. "Accuracy of artificial intelligence in prediction of osteoporotic fractures in comparison with dual-energy X-ray absorptiometry and the Fracture Risk Assessment Tool: A systematic review." *World J Orthop* 2025; 16. doi: [10.5312/wjo.v16.i4.103572](https://doi.org/10.5312/wjo.v16.i4.103572)
77. Cohen JF and McInnes MDF. "Deep Learning Algorithms to Detect Fractures: Systematic Review Shows Promising Results but Many Limitations." *Radiology* 2022; 304:63–4. doi: [10.1148/radiol.212966](https://doi.org/10.1148/radiol.212966)
78. Makond B, Pornsawad P, and Thawnashom K. "Decision Tree Modeling for Osteoporosis Screening in Postmenopausal Thai Women." *Informatics* 2022; 9:83. doi: [10.3390/informatics9040083](https://doi.org/10.3390/informatics9040083)
79. Cauley JA, Chalhoub D, Kassem AM, and Fuleihan GEH. "Geographic and ethnic disparities in osteoporotic fractures." *Nat Rev Endocrinol* 2014; 10:338–51. doi: [10.1038/nrendo.2014.51](https://doi.org/10.1038/nrendo.2014.51)
80. Curtis EM, Velde R van der, Moon RJ, et al. "Epidemiology of fractures in the United Kingdom 1988–2012: Variation with age, sex, geography, ethnicity and socioeconomic status." *Bone* 2016; 87:19–26. doi: [10.1016/j.bone.2016.03.006](https://doi.org/10.1016/j.bone.2016.03.006)
81. Babić Leko M, Pleić N, Gunjača I, and Zemunik T. "Environmental Factors That Affect Parathyroid Hormone and Calcitonin Levels." *Int J Mol Sci* 2021; 23:44. doi: [10.3390/ijms23010044](https://doi.org/10.3390/ijms23010044)
82. Charoenngam N, Shirvani A, and Holick MF. "Vitamin D for skeletal and non-skeletal health: What we should know." *J Clin Orthop Trauma* 2019; 10:1082–93. doi: [10.1016/j.jcot.2019.07.004](https://doi.org/10.1016/j.jcot.2019.07.004)
83. Chen YJ, Jia LH, Han TH, et al. "Osteoporosis treatment: current drugs and future developments." *Front Pharmacol* 2024; 15. doi: [10.3389/fphar.2024.1456796](https://doi.org/10.3389/fphar.2024.1456796)
84. Grygorieva NV, Kovalenko VM, KORzh MO, et al. "Guideline for diagnostic, prevention and treatment of postmenopausal osteoporosis." *PAIN, JOINTS, SPINE* 2023; 13:128–54. doi: [10.22141/pjs.13.3.2023.378](https://doi.org/10.22141/pjs.13.3.2023.378)
85. Rogers MJ, Mönkkönen J, and Munoz MA. "Molecular mechanisms of action of bisphosphonates and new insights into their effects outside the skeleton." *Bone* 2020; 139:115493. doi: [10.1016/j.bone.2020.115493](https://doi.org/10.1016/j.bone.2020.115493)
86. Wang R, Liu C, Wei W, et al. "Increased bone mass but delayed mineralization: in vivo and in vitro study for zoledronate in bone regeneration." *BMC Oral Health* 2024; 24:1146. doi: [10.1186/s12903-024-04906-2](https://doi.org/10.1186/s12903-024-04906-2)
87. Cui J, Shibata Y, Zhu T, Zhou J, and Zhang J. "Osteocytes in bone aging: Advances, challenges, and future perspectives." *Ageing Res Rev* 2022; 77:101608. doi: [10.1016/j.arr.2022.101608](https://doi.org/10.1016/j.arr.2022.101608)
88. Qaiser F, Ibrahim M, Mazhar R, and Sohail F. "Nanotechnology: A New Hope for the Cure of Osteoarthritis, Osteoporosis and Rheumatoid Arthritis." *Global Pharmaceutical Sciences Review* 2020; V:25–39. doi: [10.31703/gpsr.2020\(V-I\).04](https://doi.org/10.31703/gpsr.2020(V-I).04)
89. Drake MT, Clarke BL, Oursler MJ, and Khosla S. "Cathepsin K Inhibitors for Osteoporosis: Biology, Potential Clinical Utility, and Lessons Learned." *Endocr Rev* 2017; 38:325–50. doi: [10.1210/er.2015-1114](https://doi.org/10.1210/er.2015-1114)
90. Yu S, Li D, Zhang N, et al. "Drug discovery of sclerostin inhibitors." *Acta Pharm Sin B* 2022; 12:2150–70. doi: [10.1016/j.apsb.2022.01.012](https://doi.org/10.1016/j.apsb.2022.01.012)
91. Codrea CI, Croitoru AM, Baciuc CC, et al. "Advances in Osteoporotic Bone Tissue Engineering." *J Clin Med* 2021; 10:253. doi: [10.3390/jcm10020253](https://doi.org/10.3390/jcm10020253)
92. Simpson CR, Kelly HM, and Murphy CM. "Synergistic use of biomaterials and licensed therapeutics to manipulate bone remodelling and promote non-union fracture repair." *Adv Drug Deliv Rev* 2020; 160:212–33. doi: [10.1016/j.addr.2020.10.011](https://doi.org/10.1016/j.addr.2020.10.011)

93. Sharma S, Sudhakara P, Singh J, Ilyas RA, Asyraf MRM, and Razman MR. "Critical Review of Biodegradable and Bioactive Polymer Composites for Bone Tissue Engineering and Drug Delivery Applications." *Polymers (Basel)* 2021; 13:2623. doi: [10.3390/polym13162623](https://doi.org/10.3390/polym13162623)
94. Kuperkar K, Atanase L, Bahadur A, Crivei I, and Bahadur P. "Degradable Polymeric Bio(nano)materials and Their Biomedical Applications: A Comprehensive Overview and Recent Updates." *Polymers (Basel)* 2024; 16:206. doi: [10.3390/polym16020206](https://doi.org/10.3390/polym16020206)
95. D'Oronzo S, Wood S, and Brown JE. "The use of bisphosphonates to treat skeletal complications in solid tumours." *Bone* 2021; 147:115907. doi: [10.1016/j.bone.2021.115907](https://doi.org/10.1016/j.bone.2021.115907)
96. The North American Menopause Society. "The 2022 hormone therapy position statement of The North American Menopause Society." *Menopause* 2022; 29:767–94. doi: [10.1097/GME.0000000000002028](https://doi.org/10.1097/GME.0000000000002028)
97. Gambacciani M and Levancini M. "Featured Editorial Hormone replacement therapy and the prevention of postmenopausal osteoporosis." *Menopausal Review* 2014; 4:213–20. doi: [10.5114/pm.2014.44996](https://doi.org/10.5114/pm.2014.44996)
98. Kontogianni GI, Coelho C, Gauthier R, et al. "Osteogenic Potential of Nano-Hydroxyapatite and Strontium-Substituted Nano-Hydroxyapatite." *Nanomaterials* 2023; 13:1881. doi: [10.3390/nano13121881](https://doi.org/10.3390/nano13121881)
99. Shi S, Duan H, and Ou X. "Targeted delivery of anti-osteoporosis therapy: Bisphosphonate-modified nanosystems and composites." *Biomedicine & Pharmacotherapy* 2024; 175:116699. doi: [10.1016/j.biopha.2024.116699](https://doi.org/10.1016/j.biopha.2024.116699)
100. Wen C, Xu X, Zhang Y, Xia J, Liang Y, and Xu L. "Bone Targeting Nanoparticles for the Treatment of Osteoporosis." *Int J Nanomedicine* 2024; 19:1363–83. doi: [10.2147/IJN.S444347](https://doi.org/10.2147/IJN.S444347)
101. Zhu S, Chen W, Masson A, and Li YP. "Cell signaling and transcriptional regulation of osteoblast lineage commitment, differentiation, bone formation, and homeostasis." *Cell Discov* 2024; 10:71. doi: [10.1038/s41421-024-00689-6](https://doi.org/10.1038/s41421-024-00689-6)
102. Constantino VRL, Figueiredo MP, Magri VR, et al. "Biomaterials Based on Organic Polymers and Layered Double Hydroxides Nanocomposites: Drug Delivery and Tissue Engineering." *Pharmaceutics* 2023; 15:413. doi: [10.3390/pharmaceutics15020413](https://doi.org/10.3390/pharmaceutics15020413)
103. Bernstein SR, Kelleher C, and Khalil RA. "Gender-based research underscores sex differences in biological processes, clinical disorders and pharmacological interventions." *Biochem Pharmacol* 2023; 215:115737. doi: [10.1016/j.bcp.2023.115737](https://doi.org/10.1016/j.bcp.2023.115737)
104. Shang J, Zhou C, Jiang C, et al. "Recent developments in nanomaterials for upgrading treatment of orthopedics diseases." *Front Bioeng Biotechnol* 2023; 11. doi: [10.3389/fbioe.2023.1221365](https://doi.org/10.3389/fbioe.2023.1221365)
105. Majumder J, Taratula O, and Minko T. "Nanocarrier-based systems for targeted and site specific therapeutic delivery." *Adv Drug Deliv Rev* 2019; 144:57–77. doi: [10.1016/j.addr.2019.07.010](https://doi.org/10.1016/j.addr.2019.07.010)
106. Khan I, Saeed K, and Khan I. "Nanoparticles: Properties, applications and toxicities." *Arabian Journal of Chemistry* 2019; 12:908–31. doi: [10.1016/j.arabjc.2017.05.011](https://doi.org/10.1016/j.arabjc.2017.05.011)
107. Izcı M, Maksoudian C, Manshian BB, and Soenen SJ. "The Use of Alternative Strategies for Enhanced Nanoparticle Delivery to Solid Tumors." *Chem Rev* 2021; 121:1746–803. doi: [10.1021/acs.chemrev.0c00779](https://doi.org/10.1021/acs.chemrev.0c00779)
108. Bauso LV, La Fauci V, Longo C, and Calabrese G. "Bone Tissue Engineering and Nanotechnology: A Promising Combination for Bone Regeneration." *Biology (Basel)* 2024; 13:237. doi: [10.3390/biology13040237](https://doi.org/10.3390/biology13040237)
109. Mo X, Zhang D, Liu K, Zhao X, Li X, and Wang W. "Nano-Hydroxyapatite Composite Scaffolds Loaded with Bioactive Factors and Drugs for Bone Tissue Engineering." *Int J Mol Sci* 2023; 24:1291. doi: [10.3390/ijms24021291](https://doi.org/10.3390/ijms24021291)
110. Keshavarz M, Alizadeh P, Kadumudi FB, et al. "Multi-leveled Nanosilicate Implants Can Facilitate Near-Perfect Bone Healing." *ACS Appl Mater Interfaces* 2023; 15:21476–95. doi: [10.1021/acsami.3c01717](https://doi.org/10.1021/acsami.3c01717)
111. Egwu CO, Alope C, Onwe KT, et al. "Nanomaterials in Drug Delivery: Strengths and Opportunities in Medicine." *Molecules* 2024; 29:2584. doi: [10.3390/molecules29112584](https://doi.org/10.3390/molecules29112584)
112. Mo X, Zhang D, Liu K, Zhao X, Li X, and Wang W. "Nano-Hydroxyapatite Composite Scaffolds Loaded with Bioactive Factors and Drugs for Bone Tissue Engineering." *Int J Mol Sci* 2023; 24:1291. doi: [10.3390/ijms24021291](https://doi.org/10.3390/ijms24021291)
113. Dayanandan AP, Cho WJ, Kang H, et al. "Emerging nano-scale delivery systems for the treatment of osteoporosis." *Biomater Res* 2023; 27. doi: [10.1186/s40824-023-00413-7](https://doi.org/10.1186/s40824-023-00413-7)
114. Qiao K, Xu L, Tang J, et al. "The advances in nanomedicine for bone and cartilage repair." *J Nanobiotechnology* 2022; 20:141. doi: [10.1186/s12951-022-01342-8](https://doi.org/10.1186/s12951-022-01342-8)
115. Chen Y, Wu X, Li J, Jiang Y, Xu K, and Su J. "Bone-Targeted Nanoparticle Drug Delivery System: An Emerging Strategy for Bone-Related Disease." *Front Pharmacol* 2022; 13. doi: [10.3389/fphar.2022.909408](https://doi.org/10.3389/fphar.2022.909408)

116. Ma X, Tian Y, Yang R, et al. "Nanotechnology in healthcare, and its safety and environmental risks." *J Nanobiotechnology* 2024; 22:715. DOI: [10.1186/s12951-024-02901-x](https://doi.org/10.1186/s12951-024-02901-x)
117. Tran N and Webster TJ. "Increased osteoblast functions in the presence of hydroxyapatite-coated iron oxide nanoparticles." *Acta Biomater* 2011; 7:1298–306. DOI: [10.1016/j.actbio.2010.10.004](https://doi.org/10.1016/j.actbio.2010.10.004)
118. Bosco R, Iafisco M, Tampieri A, Jansen JA, Leeuwenburgh SCG, and Beucken JJJP van den. "Hydroxyapatite nanocrystals functionalized with alendronate as bioactive components for bone implant coatings to decrease osteoclastic activity." *Appl Surf Sci* 2015; 328:516–24. DOI: [10.1016/j.apsusc.2014.12.072](https://doi.org/10.1016/j.apsusc.2014.12.072)
119. Wen J, Cai D, Gao W, et al. "Osteoimmunomodulatory Nanoparticles for Bone Regeneration." *Nanomaterials* 2023; 13:692. DOI: [10.3390/nano13040692](https://doi.org/10.3390/nano13040692)
120. Langenbach F and Handschel J. "Effects of dexamethasone, ascorbic acid and β -glycerophosphate on the osteogenic differentiation of stem cells in vitro." *Stem Cell Res Ther* 2013; 4:117. DOI: [10.1186/srct328](https://doi.org/10.1186/srct328)
121. Li Y, Fu G, Gong Y, et al. "BMP-2 promotes osteogenic differentiation of mesenchymal stem cells by enhancing mitochondrial activity." *J Musculoskelet Neuronal Interact* 2022; 22:123–31
122. Grafe I, Alexander S, Peterson JR, et al. "TGF- β Family Signaling in Mesenchymal Differentiation." *Cold Spring Harb Perspect Biol* 2018; 10:a022202. DOI: [10.1101/cshperspect.a022202](https://doi.org/10.1101/cshperspect.a022202)
123. Yu X and Long YC. "Crosstalk between cystine and glutathione is critical for the regulation of amino acid signaling pathways and ferroptosis." *Sci Rep* 2016; 6:30033. DOI: [10.1038/srep30033](https://doi.org/10.1038/srep30033)
124. Samrot AV, Sathiyasree M, Rahim SBA, et al. "Scaffold Using Chitosan, Agarose, Cellulose, Dextran and Protein for Tissue Engineering—A Review." *Polymers (Basel)* 2023; 15:1525. DOI: [10.3390/polym15061525](https://doi.org/10.3390/polym15061525)
125. Wang N, Fuh JYH, Dheen ST, and Senthil Kumar A. "Functions and applications of metallic and metallic oxide nanoparticles in orthopedic implants and scaffolds." *J Biomed Mater Res B Appl Biomater* 2021; 109:160–79. DOI: [10.1002/jbm.b.34688](https://doi.org/10.1002/jbm.b.34688)
126. Saravanan S, Sameera DK, Moorthi A, and Selvamurugan N. "Chitosan scaffolds containing chicken feather keratin nanoparticles for bone tissue engineering." *Int J Biol Macromol* 2013; 62:481–6. DOI: [10.1016/j.ijbiomac.2013.09.034](https://doi.org/10.1016/j.ijbiomac.2013.09.034)
127. Xu A, Liu X, Gao X, Deng F, Deng Y, and Wei S. "Enhancement of osteogenesis on micro/nano-topographical carbon fiber-reinforced polyetheretherketone–nanohydroxyapatite biocomposite." *Materials Science and Engineering: C* 2015; 48:592–8. DOI: [10.1016/j.msec.2014.12.061](https://doi.org/10.1016/j.msec.2014.12.061)
128. Liao C, Li Y, and Tjong SC. "Polyetheretherketone and Its Composites for Bone Replacement and Regeneration." *Polymers (Basel)* 2020; 12:2858. DOI: [10.3390/polym12122858](https://doi.org/10.3390/polym12122858)
129. Wang X, Pan L, Zheng A, et al. "Multifunctionalized carbon-fiber-reinforced polyetheretherketone implant for rapid osseointegration under infected environment." *Bioact Mater* 2023; 24:236–50. DOI: [10.1016/j.bioactmat.2022.12.016](https://doi.org/10.1016/j.bioactmat.2022.12.016)
130. Moore MJ, Lam YT, Santos M, et al. "Evaluation of the Immune Response to Chitosan-graft-poly(caprolactone) Biopolymer Scaffolds." *ACS Biomater Sci Eng* 2023; 9:3320–34. DOI: [10.1021/acsbiomaterials.3c00553](https://doi.org/10.1021/acsbiomaterials.3c00553)
131. Farjaminejad S, Farjaminejad R, and Garcia-Godoy F. "Nanoparticles in Bone Regeneration: A Narrative Review of Current Advances and Future Directions in Tissue Engineering." *J Funct Biomater* 2024; 15:241. DOI: [10.3390/jfb15090241](https://doi.org/10.3390/jfb15090241)
132. Salamanna F, Gambardella A, Contartese D, Visani A, and Fini M. "Nano-Based Biomaterials as Drug Delivery Systems Against Osteoporosis: A Systematic Review of Preclinical and Clinical Evidence." *Nanomaterials* 2021; 11:530. DOI: [10.3390/nano11020530](https://doi.org/10.3390/nano11020530)
133. Liao J, Lu L, Chu X, et al. "Cell membrane coated nanoparticles: cutting-edge drug delivery systems for osteoporosis therapy." *Nanoscale* 2024; 16:8236–55. DOI: [10.1039/D3NR06264C](https://doi.org/10.1039/D3NR06264C)
134. Kumarasamy RV, Natarajan PM, Umapathy VR, Roy JR, Mironescu M, and Palanisamy CP. "Clinical applications and therapeutic potentials of advanced nanoparticles: a comprehensive review on completed human clinical trials." *Frontiers in Nanotechnology* 2024; 6. DOI: [10.3389/fnano.2024.1479993](https://doi.org/10.3389/fnano.2024.1479993)
135. Kalbacova M, Broz A, Kong J, and Kalbac M. "Graphene substrates promote adherence of human osteoblasts and mesenchymal stromal cells." *Carbon N Y* 2010; 48:4323–9. DOI: [10.1016/j.carbon.2010.07.045](https://doi.org/10.1016/j.carbon.2010.07.045)
136. Mahor A, Singh PP, Bharadwaj P, et al. "Carbon-Based Nanomaterials for Delivery of Biologicals and Therapeutics: A Cutting-Edge Technology." *C (Basel)* 2021; 7:19. DOI: [10.3390/c7010019](https://doi.org/10.3390/c7010019)
137. Arrabito G, Bonasera A, Prestopino G, et al. "Layered Double Hydroxides: A Toolbox for Chemistry and Biology." *Crystals (Basel)* 2019; 9:361. DOI: [10.3390/cryst9070361](https://doi.org/10.3390/cryst9070361)
138. Tanaka M, Izumiya M, Haniu H, et al. "Current Methods in the Study of Nanomaterials for Bone Regeneration." *Nanomaterials* 2022; 12:1195. DOI: [10.3390/nano12071195](https://doi.org/10.3390/nano12071195)

139. Chen H, Xue H, Zeng H, Dai M, Tang C, and Liu L. "3D printed scaffolds based on hyaluronic acid bioinks for tissue engineering: a review." *Biomater Res* 2023; 27. doi: [10.1186/s40824-023-00460-0](https://doi.org/10.1186/s40824-023-00460-0)
140. Brokesh AM and Gaharwar AK. "Inorganic Biomaterials for Regenerative Medicine." *ACS Appl Mater Interfaces* 2020; 12:5319–44. doi: [10.1021/acsami.9b17801](https://doi.org/10.1021/acsami.9b17801)
141. Xu G, Shen C, Lin H, et al. "Development, In-Vitro Characterization and In-Vivo Osteoinductive Efficacy of a Novel Biomimetically-Precipitated Nanocrystalline Calcium Phosphate With Internally-Incorporated Bone Morphogenetic Protein-2." *Front Bioeng Biotechnol* 2022; 10. doi: [10.3389/fbioe.2022.920696](https://doi.org/10.3389/fbioe.2022.920696)
142. Martiniakova M, Babikova M, and Omelka R. "Pharmacological agents and natural compounds: available treatments for osteoporosis." *J Physiol Pharmacol* 2020; 71. doi: [10.26402/jpp.2020.3.01](https://doi.org/10.26402/jpp.2020.3.01)
143. Ponzetti M and Rucci N. "Osteoblast Differentiation and Signaling: Established Concepts and Emerging Topics." *Int J Mol Sci* 2021; 22:6651. doi: [10.3390/ijms22136651](https://doi.org/10.3390/ijms22136651)
144. Choi E, Buie JD, Camacho J, Sharma P, and Riese WT de. "Evolution of Androgen Deprivation Therapy (ADT) and Its New Emerging Modalities in Prostate Cancer: An Update for Practicing Urologists, Clinicians and Medical Providers." *Res Rep Urol* 2022; 14:87–108. doi: [10.2147/RRU.S303215](https://doi.org/10.2147/RRU.S303215)
145. Bajwa J, Munir U, Nori A, and Williams B. "Artificial intelligence in healthcare: transforming the practice of medicine." *Future Healthc J* 2021; 8:e188–e194. doi: [10.7861/fhj.2021-0095](https://doi.org/10.7861/fhj.2021-0095)
146. Zhao X, Hu DA, Wu D, et al. "Applications of Biocompatible Scaffold Materials in Stem Cell-Based Cartilage Tissue Engineering." *Front Bioeng Biotechnol* 2021; 9. doi: [10.3389/fbioe.2021.603444](https://doi.org/10.3389/fbioe.2021.603444)
147. Taye MM. "Understanding of Machine Learning with Deep Learning: Architectures, Workflow, Applications and Future Directions." *Computers* 2023; 12:91. doi: [10.3390/computers12050091](https://doi.org/10.3390/computers12050091)
148. Wu Q, Nasoz F, Jung J, Bhattarai B, and Han MV. "Machine Learning Approaches for Fracture Risk Assessment: A Comparative Analysis of Genomic and Phenotypic Data in 5130 Older Men." *Calcif Tissue Int* 2020; 107:353–61. doi: [10.1007/s00223-020-00734-y](https://doi.org/10.1007/s00223-020-00734-y)