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Innovations and Challenges in Osteoporosis: A Review of Current and Future Strategies

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ABSTRACT: Osteoporosis is a chronic skeletal disorder characterized by reduced bone mass and microarchitectural deterioration, leading to increased fragility and fracture risk. This review provides a comprehensive overview of the pathophysiology, diagnostic approaches, and therapeutic strategies for osteoporosis, highlighting the advancements in research and emerging treatment paradigms. Key findings emphasize the critical role of hormonal regulation, molecular pathways such as RANK/RANKL/OPG and Wnt/β-catenin signaling signaling, and the influence of inflammation on bone remodeling. Current pharmacological treatments, including anabolic and anti-resorptive agents, have been explored alongside promising innovations such as dual-action drugs, sclerostin inhibitors, and nanoparticle-based delivery systems. Additionally, herbal therapies have been discussed as complementary alternatives, offering bioactive compounds that modulate bone remodeling pathways.

Emerging technologies, such as 3D-printed bone models and CRISPR-Cas9 gene editing, are transforming preclinical research, addressing the limitations of traditional models, and bridging the gap to clinical applications. Despite these advancements, challenges such as adherence to therapy, accessibility to low-resource settings, and ethical considerations in animal research remain significant barriers. Future research should focus on developing standardized protocols for novel therapies, conducting large-scale clinical trials, and leveraging personalized medicine and artificial intelligence to optimize osteoporosis care. This review underscores the need for a multidisciplinary approach to effectively address the global burden of osteoporosis, reduce fracture risk, and improve the quality of life of affected individuals

INTRODUCTION

Osteoporosis is an extensive bony ailment that is analytically identified by diminished bone mineral density and skeletal filaments. This can preside to buildup bone brittleness, which can accelerate imminent fragmentation [1]. Various factors contribute to the increased risk of osteoporosis and fractures. Women are more susceptible than men because of their lower peak bone mineral density (BMD), and the risk increases with age as bone resorption surpasses bone formation. Slim individuals with lean bone structures and certain racial groups, such as Asians and Whites, are at a higher risk, while African Americans tend to have a lower risk [2]. A family history of osteoporosis or hip fracture further increases the risk of osteoporosis. Hormonal changes, including reduced estrogen levels after menopause, low testosterone levels in men, and

abnormal menstrual cycles play a significant role [3]. Poor diets lacking calcium, vitamin D, or adequate protein can lead to bone loss, while specific diseases such as hyperthyroidism, rheumatoid arthritis, or gastrointestinal disorders exacerbate this risk. The prolonged use of certain medications, such as glucocorticoids or cancer treatments, also contributes to bone fragility [4]. Additionally, lifestyle factors such as physical inactivity, smoking, and excessive alcohol consumption further weaken bones and increase the risk of fracture [5,6].

2. DIAGNOSIS OF OSTEOPOROSIS

Bone formation markers play a vital role in the evaluation of bone metabolism. Alkaline phosphatase (ALP), derived from the bone and liver, serves as a reliable serum marker and provides normal liver function. Bone-specific alkaline phosphatase (BALP) is a sensitive indicator of bone metabolism. Procollagen type 1 N-terminal propeptide (P1NP) is a serum marker of bone formation, specifically in osteoblasts and fibroblasts. The presence of procollagen type 1 C-terminal propeptide (P1CP) indicates COL1A1 synthesis, which is essential for bone matrix formation. Osteocalcin, produced by bones and thrombocytes, serves as a late marker for bone formation and provides insights into bone remodeling processes [7,8].

Bone resorption markers are essential for the assessment of collagen turnover and bone loss. Hydroxyproline (HYP) and hydroxylysine (HYL), which originate from the bone, skin, cartilage, and soft tissue, are non-specific urinary markers of collagen turnover. Pyridinoline (PYD) is another non-specific urinary marker, while deoxypyridinoline (DPD), which is also found in urine, specifically reflects bone resorption. Bone sialoprotein (BSP) serves as a serum biomarker for resorption and osteoporosis. Osteopontin, found in the bone and blood, functions as a prognostic marker for postmenopausal osteoporosis. Tartrate-resistant acid phosphatase 5b (TRACP 5b), detected in the plasma and serum, is an enzyme marker for bone resorption [1,2]. Collagen degradation products, such as carboxy-terminal (CTX-1) and amino-terminal crosslinked telopeptides of type 1 collagen (NTX-1) found in urine and serum, are critical resorption markers. Cathepsin K (CatK), a specific serum biomarker, highlights bone resorption activity. These markers collectively aid in evaluating bone turnover and the risk of osteoporosis [11,12].

The World Health Organization (WHO) classifies bone density levels based on hip bone mineral density (BMD) T-scores. A T-score between +1 and -1 indicates normal bone density, while a score between -1 and -2.5 reflects low bone mass (osteopenia). Osteoporosis was diagnosed with a T-score of -2.5 or lower, and severe osteoporosis was defined by a T-score of -2.5 or lower with a history of fractures. Individuals with low T-scores have an increased risk of fractures, necessitating regular monitoring and consultation with healthcare professionals to adopt appropriate therapeutic measures [13,14].

3. GLOBAL BURDEN OF OSTEOPOROSIS

Osteoporosis is a matter of universal civic wellbeing. However, to date, no wide-ranging study has been conducted. The main Objective of World Health Organization [WHO] is to accomplish osteoporosis in 6.3% of men and 21.2% of women aged 50 years and above worldwide [15]. Based on the current global population of individuals with osteoporosis, 500 million men and women were affected. Approximately 25.5 million Women and 6.5 million men were affected among 32 million people with Osteoporosis in Europe27+2 countries over the age of 50. The phenomenon of this organized review is to establish the prevalence of Osteoporosis in Total European population, which was reported to be 5.6% among 22.1% of women, and 6.6% of men were affected with osteoporosis [16]

Osteoporosis in 71 Asia-Pacific countries (319 million) is projected to be at high risk of fracture by 2040. The overall population will grow by 24% between 2013 and 2050. The population over 50 years of age will grow by an average of 144%. More Advanced Countries, such as Europe and the Americas, were affected by 51%, and Western Pacific and Southeast Asia affected 49% of cases with osteoporosis [17]

3.1. Global Statistics

Osteoporosis is Substantial economic impact. The annual cost associated with Osteoporosis in the European Union is estimated to be 37 billion euros. The Clinical Costs of Osteoporosis in the United States were estimated to be 13.7 to 20.3 billion dollars [18]. It is also predicted that most elderly individuals have an immense hazard of broken bones, and the Arabian Gulf region has a high prevalence of vitamin D deficiency due to lack of sunlight, resulting in significantly lower bone density among females as compared to Western populations [19,20].

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Osteoporosis is a remarkable global health issue affecting millions of people worldwide. The Mortality rate was not particularly Up-to-date, But alarming statistics in the European Union have reported approximately 43,000 deaths annually. In the United States, the annual mortality rate of osteoporosis is approximately 20-30% population was reported [15,21].

3.2. Indian Statistics

India is a Culturally disparate sovereign nation worldwide, with multiple dietary varieties, and there can be regional discrepancies in the Occurrence of Osteoporosis. In this retrospective study, the statistical differences in all four regions, including the west, north, east, and south regions, the distribution of statistical results was reported as 16.3% in the western region, 16.4% in the north region, 18.4% in the east region, and 20.7% in the south region. According to the data, the prevalence of osteoporosis was greater in South Indian Women than in West Indian Women because of insufficient availability of nutritional status and resources in rural India [22].

However, the Mortality rate of Osteoporosis in India is not apparent. However, some regular consequences of fractures, such as vertebral and hip fractures, were described in the Delhi Vertebral Osteoporosis Study [DVOS]. The prevalence of vertebral fractures among Postmenopausal Women and the geriatric population was reported to be approximately 17.1%. Hip fracture rates have also been reported, with 159 fractures per 100,000 women over 50 years of age being predominantly affected in North India. Among females and males, the presence of osteoporosis was higher in females than in males [19.4% vs. 17.3%] owing to the high skeletal density in males [23].

4. PATHOPHYSIOLOGY OF OSTEOPOROSIS

Osteoporosis is a placid bone disease that leads to reduced peak bone tissue, typically causing excessive bone resorption, which leaves the bone and enters systemic circulation [24]. Hence, the formation of pores in cortical bones develops, which increases the risk of fractures. These are two other aspects of weak bones, such as osteopenia, which is typically a precursor to Osteoporosis and Osteomalacia, where there is a lack of minerals in a bone that is caused by severe vitamin D deficiency, which causes softening of the bone [25].

The Basic mechanism of osteoporosis is that bone has osteoblasts or Bone formation cells with parathyroid hormone are going to increase Macrophage Colony Stimulating Factor [M-CS F] elaboration by these cells, which already express their Rank L [receptor activator of nuclear factor kappa-B] ligand; these cells interact with receptors on osteoclast precursors, causing the transcription of genes that are under the influence of nuclear factor kappa-B leading this towards differentiation, as mentioned by parathyroid hormone, but also by IL-1[interleukin-1], and glucocorticoids begin osteoclast differentiation. Osteoclasts gradually remove more bone; therefore, it is called Bone Resorption [26].

5. CURRENT TREATMENTS OF OSTEOPOROSIS

Osteoporosis treatments are categorized into anabolic agents, anti-resorptive agents, and other therapies, each of which targets specific mechanisms of bone remodeling [27]. **Anabolic agents** stimulate osteoblast activity and promote bone formation by acting on parathyroid hormone receptors or by inhibiting proteins such as sclerostin, which regulate bone growth [28,29]. **Antiresorptive agents** focus on reducing osteoclast differentiation and activity, thereby decreasing bone resorption, including therapies that bind to bone surfaces, regulate hormonal balance, block signaling pathways critical for osteoclast activation, or mimic the effects of estrogen on bone [30,31]. **Other agents** target specialized pathways to simultaneously regulate bone resorption and formation, or enhance calcium absorption and bone mineralization. Integrated mechanisms, such as blocking osteoclast activation through decoy receptors or modulating sclerostin pathways, further refine the balance between bone resorption and formation and support bone health [32,33].

Table 1. Current Treatments of Osteoporosis

S.No.	Category	Mechanism	Examples
1.	Anabolic Agents	Stimulate osteoblast activity and bone formation by acting on PTH1R or inhibiting sclerostin.	Teriparatide, Abaloparatide (PTH1R activation), Romosozumab (sclerostin

2.	Anti-Resorptive Agents	Reduce osteoclast differentiation and activity, decreasing bone resorption.	inhibitor)
	Bisphosphonates	Bind to bone surfaces and inhibit osteoclast activity.	Alendronate, Risedronate, Zoledronic acid, Ibandronate, Pamidronate, Etidronate
	HRT	Regulate bone remodeling by maintaining osteoblast and osteoclast balance.	Estrogen, Testosterone, Calcitonin
	RANK Ligand Inhibitors	Prevent RANKL from binding to RANK on pre-osteoclasts, inhibiting osteoclast differentiation.	Denosumab
	SERMs	Mimic estrogen's action on bone, reducing resorption.	Raloxifene, Bazedoxifene, Tamoxifen
3.	Other Agents	Target specific pathways or provide dual effects on bone resorption and formation.	
	Cathepsin K Inhibitors	Inhibit Cathepsin K, an enzyme critical for osteoclast-mediated bone resorption.	Odanacatib (investigational)
	Strontium Ranelate	Promotes bone formation while inhibiting bone resorption.	Protelos
	Vitamin D Analogues	Enhance calcium absorption and bone mineralization.	Alfacalcidol, Calcitriol
4.	Integrated Mechanisms	Osteoprotegerin (OPG): Acts as a decoy receptor for RANKL, inhibiting osteoclast activation.	
		M-CSF: Supports pre-osteoclast differentiation from hematopoietic stem cells.	
		Romosozumab: Influences these pathways by targeting sclerostin.	

6. CURRENT CHALLENGES IN OSTEOPOROSIS

Challenges and side effects associated with drug therapy for osteoporosis highlight the complexity of long-term treatment. The continuous use of osteoanabolic drugs, such as parathyroid hormone analogs, can lead to hyperparathyroidism, resulting in hypercalcemia and bone loss [3]. Oral osteoporosis medication often causes gastrointestinal discomfort and reduces drug absorption. Anti-sclerostin antibodies may cause injection-site reactions and prolonged drug use can lead to the generation of unwanted biological fragments, causing severe health issues. Due to significant contraindications, certain treatments, such as calcitonin spray, cathepsin K inhibitors, and strontium ranelate, are not recommended [35].A critical issue in long-term therapy is the risk of osteonecrosis of the jaw (ONJ), which is commonly observed in patients taking bisphosphonates or denosumab without drug holidays (DH). DH, typically advised every 1–5 years, allows patients to maintain drug sensitivity, reduce side effects, and prevent complications, such as atypical femur fractures [36]. During this period, treatment adjustments may be made based on recovery, fracture risk, and bone density scores. For instance, oral bisphosphonate therapy often alternates with DH every 1–2 years to mitigate the adverse effects [11].Emerging treatment strategies have focused on optimizing drug delivery and reducing systemic side effects. Subcutaneous injections of monoclonal antibodies and osteoanabolic agents are limited to specific durations, whereas advanced delivery methods, such as nanoparticle-encapsulated drugs, directly target bone tissue and minimize systemic complications [37,38].

Artificial intelligence (AI) and machine learning have revolutionized osteoporosis management. AI tools enhance radiological diagnostics, detect vertebral fractures, and assess bone mineral density using advanced imaging techniques, such as CT, MRI, and DEXA absorptiometry [39,40]. Deep-learning algorithms enable precise evaluation of fractures and support physicians in devising personalized treatment plans. AI-driven drug development also paves the way for next-generation therapies, offering a promising approach to address the challenges of osteoporosis management [41,42].

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7. HERBAL APPROACHES TO TREAT OSTEOPOROSIS

Herbal therapies are gaining recognition as a promising alternative for managing osteoporosis, valued for their natural origin, minimal side effects, and potential to target multiple pathways involved in bone remodeling. Rich in bioactive compounds, plants can modulate osteoblast and osteoclast activity, presenting an effective complementary or substitute option to conventional treatments (Table 2) [43-50].

Table 2. Medicinal Plants for the management of Osteoporosis

S.No.	Examples	Potential Benefits	Mechanisms of Action
1.	*Acanthopanax senticosus*	Adaptogenic properties that may support bone health.	Enhances bone metabolism and reduces bone resorption [51,52].
2.	*Actaea racemosa*	Traditionally used for menopausal symptoms, supports bone density.	Mimics estrogenic activity, beneficial in postmenopausal osteoporosis [53].
3.	*Allium cepa*	Positive effects on bone metabolism.	Antioxidant properties that protect bone cells [4].
4.	*Asparagus racemosus*	Supports bone health, traditionally used in Ayurvedic medicine.	Promotes osteoblast activity and bone formation [55].
5.	*Camellia sinensis*	Compounds in green tea support bone density.	Antioxidant effects reduce bone resorption [56].
6.	*Cissus quadrangularis*	Promotes bone healing and improves bone strength.	Enhances osteoblast activity and suppresses osteoclast differentiation [57].
7.	*Cornus mas*	Antioxidant properties that contribute to bone health.	Protects bone cells from oxidative damage [58].
8.	*Nigella sativa*	Black seed with various health benefits, including bone density improvement.	Enhances bone metabolism through anti-inflammatory and antioxidant effects [59].
9.	*Olea europaea*	Olive leaves and oil have protective effects on bones.	Supports bone mineralization and reduces oxidative stress [60].
10.	*Opuntia ficus-indica*	Beneficial effects on bone metabolism.	Modulates bone turnover by promoting bone formation and inhibiting resorption [61].
11.	*Pinus pinaster*	Antioxidant properties that may support bone health.	Protects against oxidative stress-induced bone degradation [62].
12.	*Trifolium pratense*	Contains isoflavones that mimic estrogen, supporting bone density.	Acts as a phytoestrogen, reducing bone loss in postmenopausal osteoporosis [63].

Table 3. Phytochemicals for the management of Osteoporosis

1.	Isoflavones	Found in red clover and soy; mimic estrogen, supporting bone health.	Modulates hormonal pathways to maintain bone density [64].
2.	Ginsenosides	Compounds from ginseng that promote bone formation.	Stimulate osteoblast activity and suppress osteoclastogenesis [65].

3.	Epimedium prenyl flavonoids	Enhance bone metabolism and promote bone strength.	Stimulate osteoblast activity and inhibit osteoclast differentiation [66].
4.	Tocotrienols	A form of vitamin E that supports bone health.	Antioxidant properties protect bone cells from oxidative damage [67].

Table 4. Mechanism of action of Phytochemicals to treat Osteoporosis

1.	Promotes osteoblast activity	Supports bone formation and improves bone mineralization.
2.	Inhibits osteoclast activity	Reduces bone resorption and prevents excessive bone loss.
3.	Provides antioxidant and anti-inflammatory protection	Protects bone cells from oxidative stress and inflammation, which can exacerbate bone degradation.
4.	Modulates hormonal pathways	Mimics estrogen's effects to maintain bone density, particularly in postmenopausal women [68-71].

Table 5. Emerging Strategies to treat Osteoporosis

Nanoparticle-encapsulated delivery	Ensures targeted drug delivery to bone tissues.	Reduces systemic side effects and enhances bioavailability of plant-based compounds [72,73].
Combination with conventional treatments	Complements existing therapies for a holistic approach to osteoporosis management.	Optimizes bone health through synergistic effects of plant-based and pharmacological treatments [74].

8. INDUCTION METHODS AND PHARMACOLOGICAL MODELS FOR OSTEOPOROSIS

Osteoporosis induction methods in animal models are essential for understanding the pathophysiology of the disease and for evaluating potential treatments. Each method offers unique insights and has specific advantages and limitations [75]. The selection of the appropriate model depends on the specific research objectives and aspects of osteoporosis under investigation. A comprehensive understanding of these models will enhance the translational value of preclinical findings in human osteoporosis [76,77].

Ovariectomy (OVX): It is a prevalent technique used to simulate postmenopausal osteoporosis by surgically removing the ovaries, leading to estrogen deficiency. These hormonal changes accelerate bone turnover and result in bone loss. The OVX model is widely used because of its ability to replicate the rapid phase of bone loss that is observed in postmenopausal women. However, the extent of bone loss can vary among species and the invasiveness of the procedure raises ethical considerations [78].

Glucocorticoid Administration: It involves administration of glucocorticoids to induce osteoporosis, reflecting conditions such as long-term steroid therapy in humans. This method effectively demonstrated the impact of glucocorticoids on bone metabolism, including reduced bone formation and increased resorption. However, the response to glucocorticoids can differ across species and high doses may lead to systemic side effects, complicating the interpretation of bone-specific outcomes [59].

Nutritional Deficiency Models: They Osteoporosis is created by restricting essential nutrients such as calcium or vitamin D, leading to decreased bone mineral density. These models are valuable for the study of the role of nutrition in bone health. However, these studies may not fully replicate the multifactorial nature of osteoporosis, and prolonged deficiency can cause other health issues and confounding results [60].

Disuse Models: They models simulate osteoporosis resulting from immobilization or reduced mechanical loading, such as limb casting or tail suspension in rodents. These models help investigate the effects of mechanical unloading on bone loss.

Nonetheless, they primarily affect immobilized regions, limiting the generalization of findings to systemic osteoporosis [61].

Genetic Models: They use animals with specific gene knockouts or mutations to study osteoporosis. These models provide insight into the genetic factors that influence bone density and strength. However, they often represent rare genetic conditions and may not reflect common forms of osteoporosis in the general population [62].

SUMMARY

Osteoporosis is a significant global health issue characterized by reduced bone mass and structural deterioration, leading to fragility fractures and substantial personal and societal burden. This review has explored the pathophysiology of the disease, emphasizing the role of hormonal regulation, inflammation, and molecular pathways such as RANK/RANKL/OPG and Wnt/β-catenin signaling. Diagnostic advancements, including the use of biochemical markers and imaging techniques like DEXA scans, have improved early detection and risk assessment. Current treatment strategies, including anabolic and anti-resorptive therapies, are complemented by emerging innovations such as sclerostin inhibitors, dual-action drugs, and nanoparticle-based drug delivery systems.

The integration of herbal therapies, leveraging bioactive compounds from plants to modulate bone remodeling pathways, offers promising complementary approaches. Additionally, advancements in research methodologies, including 3D-printed bone models and CRISPR-Cas9, are transforming osteoporosis research and bridging the gap between preclinical and clinical applications.

Despite these advancements, challenges persist, including low therapy adherence, accessibility barriers in resource-limited settings, and ethical concerns in animal research. Addressing these issues is essential to improve outcomes and ensure equitable care.

Future recommendations for osteoporosis management emphasize the need for standardized protocols to integrate emerging therapies, such as sclerostin inhibitors and herbal treatments, into clinical practice. Large-scale, multicentric clinical trials should validate the safety, efficacy, and long-term benefits of novel therapies. Leveraging advanced technologies like AI-driven diagnostics, 3D-printed bone models, and CRISPR-Cas9 gene editing can enhance research precision and treatment efficiency. Efforts to improve patient adherence should focus on simplified regimens, digital tools, and education programs. Addressing socioeconomic barriers by reducing costs, improving healthcare infrastructure, and increasing awareness is crucial for equitable care. Finally, fostering multidisciplinary collaboration among researchers, clinicians, and policymakers is essential for developing holistic approaches to tackle the multifactorial challenges of osteoporosis, reduce its global burden, and improve clinical outcomes.

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