REVIEW ARTICLE

# Emerging therapies for the treatment of osteoporosis

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## ABSTRACT

Osteoporosis is a chronic disease of the osseous system characterized by decreased bone strength and increased fracture risk. It is due to an imbalance in the dynamic ongoing processes of bone formation and bone resorption. Currently available osteoporosis therapies like bisphosphonates, selective estrogen receptor modulators (SERMs), and denosumab are anti-resorptive agents. Parathyroid hormone analogs like teriparatide are the only anabolic agents currently approved for osteoporosis treatment. The side-effects and limited efficacy of the presently available therapies has encouraged extensive research into the pathophysiology of the disease and newer drug targets for its treatment. The novel anti-resorptive agents being developed are newer SERMs, osteoprotegerin, c-src (cellular-sarcoma) kinase inhibitors, $\alpha_v\beta_3$ integrin antagonists, cathepsin K inhibitors, chloride channel inhibitors, and nitrates. Upcoming anabolic agents include calcilytics, antibodies against sclerostin and Dickkopf-1, statins, matrix extracellular phosphoglycoprotein fragments activin inhibitiors, and endo-cannabinoid agonists. Many of these new drugs are still in development. This article provides an insight into the emerging drugs for the treatment of osteoporosis.

**Key Words:** Anabolic agent, anti-resorptive agent, bone formation, bone resorption, osteoporosis

## INTRODUCTION

Osteoporosis is a chronic disease of compromised bone strength that affects post-menopausal women. The disease increases the risk of fragility fractures due to decreased bone density and quality. The World Health Organization defines osteoporosis as a bone mineral density (BMD) measurement of 2.5 standard deviations or more below the population mean BMD of sex-matched young adults, i.e., a *t*-score of $\leq -2.5$.[1] It has been estimated to affect 200 million women world-wide, approximately one-tenth of women aged 60, one-fifth of women aged 70, two-fifths of women aged 80 and two-thirds of women aged 90. According to statistics compiled by the International Osteoporosis Foundation, more than 75 million people in the United States, Europe, and Japan have osteoporosis. 1 in 3 women over 50 experience osteoporotic fractures, as compared to 1 in 5 men.[2] In 2003, there were approximately 26 million people with osteoporosis and this number is projected to increase to 36 million by 2013.[3] These fractures not only take a heavy economic toll but also lead to chronic pain, deformity, depression, disability and death.

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## BONE BIOLOGY

Bone remodeling is a physiological process that maintains the integrity of the skeleton by removing old bone and replacing it with a young matrix. Bone remodeling follows a time sequence that lasts about 6 months. There are 4 stages, (1) activation of osteoclast (bone resorbing cells) precursors that mature into multinuclear osteoclasts under the direction of cytokines and hormones, (2) resorption of bone by osteoclasts causing a resorption cavity – A process that lasts about 3 weeks, (3) reversal of the resorption signal (4) formation of new bone by osteoblasts (bone forming cells) that fills up the resorption cavity with new bone and lasts several months.[4]

### Present therapies and their drawbacks

The bisphosphonates were the first drugs recommended for the treatment and prevention of post-menopausal osteoporosis. However, they often cause gastrointestinal toxicity, including dyspepsia, abdominal pain, gastritis,

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and esophagitis. The other serious side-effects include osteonecrosis of the jaw, femur fracture, and atrial fibrillation. These adverse effects lead to suboptimal patient compliance.[5] Few novel, longer acting and more potent bisphosphonates like ibandronate, risedronate, and zoledronic acid may be given as infrequent, intermittent administration, which have been lately approved by US Food and Drug Administration.[6]

Estrogens had been used for the treatment of osteoporosis, but were found to cause serious side-effects such as breast cancer, endometrial cancer, and thromboembolism.[7] Selective estrogen receptor modulators (SERMs) have been developed which offer the benefit of dissociating the favorable estrogenic effects on bone and the cardiovascular system from unfavorable stimulatory effects associated with breast and endometrial cancer. Raloxifene is currently the only SERM marketed for the prevention and treatment of osteoporosis. Potential side-effects of this drug are increased risk of blood clots, vasomotor symptoms, and hot flushes.[8] Denosumab is an anti resorptive agent which has been recently approved by the FDA in June 2010.[9] It is a human monoclonal antibody that binds receptor-activator of nuclear factor kappa B ligand (RANKL) and inhibits its action, thus inhibiting the activation of osteoclasts.[10] The first effective anabolic agent teriparatide [parathyroid hormone (PTH) 1-34] has been used clinically. However, high cost and daily subcutaneous injections are its major limitations. Thus, there is a need for novel drug therapies for the treatment of osteoporosis.

## NEWER DRUGS ANTI-RESORPTIVE THERAPIES

### SERMs

Newer SERMs that are in various stages of drug development include bazedoxifene,[11] lasofoxifene,[12] and arzoxifene.[13] These drugs have shown to be effective in preventing bone loss, preserving bone strength, and reducing total cholesterol levels without evidence of endometrial stimulation and fewer incidences of hot flushes. Bazedoxifene and Lasofoxifene have been approved in Europe but not by US FDA.[14]

### Osteoprotegerin

Osteoclast precursors expressing receptor-activator of nuclear factor kappa (RANK) differentiate into mature bone resorbing cells after activation by RANK ligand (RANK-L secreted by osteoblastic/stromal cells. Osteoprotegerin (OPG) is a decoy receptor for RANKL. It binds to RANKL and prevents its binding to RANK and hence the activation of osteoclasts, thus acting as a natural antibody to the RANKL.[4] It has been demonstrated in preclinical studies that low bone turnover induced by OPG overexpression leads to increased bone mass with no evidence for deleterious effects on bone material properties.[15] In a phase 1 clinical trial, OPG markedly decreased the resorption marker urinary N-terminal telopeptide NTx by 80% by day 4 after a single dose. However, antibodies to OPG seem to appear after its use that may hinder its future use as a treatment for osteoporosis.[16]

### C-src kinase inhibitors

The non-receptor tyrosine kinase c-src plays an essential role in osteoclastic bone resorption. C-src is required for the development of the osteoclast ruffled border, one of the final stages in the maturation of osteoclasts. src-/-mice are osteopetrotic, primarily because of an osteoclast cytoskeletal defect because the cells are unable to form a functional sealing zone and resorptive surface.[17] Preliminary studies with c-src kinase inhibitors show inhibition of bone resorption *in vitro*.[18] Saracatinib is a novel orally available competitive inhibitor of Src kinase shown to inhibit bone resorption *in vitro*. A randomized, double-blind, placebo-controlled, multiple-ascending-dose phase I trial of saracatinib showed that it inhibited osteoclast mediated bone resorption in healthy men without any significant adverse effects.[19]

### $\alpha_V\beta_3$ integrin antagonists

$\alpha_V\beta_3$ integrin receptor or vitronectin receptor is present on the surface of osteoclasts and is required for the attachment of osteoclasts with bone matrix proteins. The interaction between integrin and matrix proteins occurs by means of arginine-glycine-aspartic acid amino acid sequences and disruption of this process impairs osteoclast function. L-000845704 is an orally acting non-peptide antagonist of $\alpha_V\beta_3$ integrin receptor on osteoclasts and causes inhibition of bone resorption. In a phase 2 trial involving 227 women with post-menopausal osteoporosis, L-000845704 significantly decreased bone resorption markers by 40% and increased spine BMD by 3.5% at a dose of 200 mg bid.[20] Preliminary data from *in vitro* studies suggested that a neutralizing antibody $\alpha_V\beta_3$ decreases osteoclast attachment and therefore, bone resorption.[21]

### Cathepsin K inhibitors

Cathepsin K is a cysteine protease that cleaves collagen 1, the major type of collagen in bone and thus helps in bone resorption. It is highly expressed in osteoclasts and its expression is stimulated by RANKL. Notably, cathepsin K levels are elevated in women with post-menopausal osteoporosis.[22] Animal models confirm the important effect of cathepsin K, and deletion of the cathepsin K gene results in osteopetrotic bone in mice.[23] Clinical trials with cathepsin K inhibitors like odanacatib and balicatib have shown a significant dose response increase in the spine and hip BMD and a reduction in bone resorption markers with minimal effect on bone formation markers.[24]

### Chloride channel inhibitors

An acidic environment within the sealing zone of osteoclasts facilitates optimal activity of bone-resorbing proteases and is hence required for process of osteoclastic bone resorption. Passive movement of chloride through chloride channel (ClCN7) located in the cell membrane of the osteoclast is required for secretion of acid from osteoclasts. Type 7 transmembrane ClCN7 is specifically found in the osteoclasts.[25] *In vitro* studies of osteoclasts from human patients with inactivating ClCN7 mutations depict normal osteoclastogenesis, but a 80-90% reduction in the bone-resorbing activity of the cells.[26] *In vitro* studies have also shown that ClCN7 inhibitors decrease osteoclast acidification and inhibit the formation of resorption pits and inhibit bone resorption in ovariectomized rats without inducing obvious toxicity.[27]

### Nitrates

The role of nitric oxide (NO) in skeletal homeostasis has been realized lately. Augmentation of osteoblast function[28] and inhibition of osteoclast development and function[29] by NO has been depicted by *in vitro* studies. Low-dose isosorbide mononitrate acts as a NO donor and has shown to decrease markers of bone resorption while increasing the markers of bone formation in post-menopausal women.[30] Another pharmaco-epidemiological case-control study also indicates less incidence of fractures in persons receiving nitrates. Thus, NO donor drugs may be effective in the treatment of osteoporosis.[31]

## ANABOLIC THERAPIES

### PTH-related peptide therapies

In an attempt to overcome the compliance issues associated with teriparatide, alternative methods of PTH administration (transdermal, nasal) have been tested. A clinical trial of transdermal PTH (TPTD patch) on post-menopausal women significantly increased total hip BMD as compared to both placebo patch and teriparatide injection in a dose-dependent manner.[32] A nasal spray formulation of PTH (1-34) also showed encouraging results in a 3-month, uncontrolled, open-label pilot study in 90 osteoporotic subjects.[33] ZT-031 (ostabolin-C), a cyclic 31-amino acid PTH analog, administered by daily SC injections to post-menopausal women with osteoporosis resulted in a dose-dependent increase in bone density without significant adverse events.[34] Other PTH formulations with anabolic effects on the skeletal system are PTH-related protein 1-36 (PTHrP [1-36]),[35] an analog of PTHrP (BA058, formerly BIM44058),[36] and a PTH-Fc fusion protein in which PTH (1-34) is fused to the Fc fragment of human immunoglobulin $G_1$ IgG1.[37] These strategies are still under investigation and may be developed as a potential treatment of osteoporosis in the upcoming years.

### Calcium-sensing receptor antagonism

Calcium-sensing receptor antagonists (calcilytics) are a new drug class of orally administered agents that stimulate endogenous PTH release and have bone forming action. JTT-305/MK-5442 and SB-423557 are two calcilytics that were shown to increase bone formation and prevent bone loss in ovariectomised rats.[38,39] ATF 936 and ronacaleret are still under clinical trials for the establishment of their role in the treatment of osteoporosis.[40,41]

### Sclerostin neutralizing antibodies

The Wingless-type (Wnt) mouse mammary tumor virus integration site pathway plays an important role in bone formation and regeneration. Low density lipoprotein receptor-related protein (LRP) 5 and LRP6 function as coreceptors in Wnt pathway. Sclerostin, a protein secreted by osteocytes, binds to coreceptors LRP5/6 and inhibit their association with Wnts, thus acting as an inhibitor of this pathway.[42] Treatment with a monoclonal antibody to sclerostin (Scl-AbII) is seen to markedly increase bone formation on trabecular, periosteal, endocortical, and intracortical surfaces in animal studies.[43] The subcutaneous administration of a single dose of AMG 785, a human recombinant sclerostin antibody, to healthy men and post-menopausal women showed dose-related increases in bone formation markers with a dose-related decrease in one bone resorption marker in a clinical study.[44]

### Dickkopf-1 (Dkk-1) inhibiton

Dkk-1 is another negative regulator of the Wingless-type mouse mammary tumor virus integration site WNT signaling pathway that acts by directly binding to LRP5 and LRP6. Blocking these receptors lead to inhibition of osteoblastogenesis in various osteogenic cell lines.[45] A human monoclonal antibody to Dkk-1 has been tested in ovariectomised monkeys and found to stimulate bone formation,[46] suggesting promise as a skeletal anabolic agent. However, the performance of these antibodies in humans is awaited.

### Statins

Statins have been identified as enhancers of the bone morphogenetic protein-2 gene expression and bone formation *in vivo*. Increase of osteoblast number and promotion of osteoblastic differentiation, leading onto increased bone formation by simvastatin has been seen in animal models.[47] The beneficial effect of statins on bone formation has also been depicted in clinical studies.[48] However, the dose required for enhancing bone formation is much higher than that of hypolipidemic action. Thus, there is a need to develop potent and preferably bone-specific statin-related molecules.

### Matrix extracellular phosphoglycoprotein (MEPE) fragments

MEPE is highly expressed in differentiated osteoblasts and osteocytes and acts as an endogenous inhibitor of bone mineralization. Thus, deletion of the MEPE gene in mice leads to an increase in the number and activity of osteoblasts leading to increased bone mass.[49] But it has been seen that MEPE 242-264, a fragment of MEPE stimulate new bone formation and fracture healing in preclinical studies.[50] These data suggest that full-length MEPE and MEPE fragments derived from proteolytic cleavage may exert opposite effects on bone metabolism and thus inhibitors of the actions of full-length MEPE and peptide fragments of the protein, may both be efficacious as skeletal anabolic agents.

### Activin inhibitiors

Activin, a member of growth and differentiation factor protein family is a negative regulator of bone mass that stimulates bone resorption and inhibits bone formation. ACE-011 is a human glycosylated dimeric fusion protein consisting of ActRIIA (activin receptor IIA) linked to the human IgG1 Fc domain. It has been seen that treatment of monkeys with a soluble form of the activin type IIA receptor markedly increases bone mass and strength. In a phase 1 clinical trial, it has shown to produce a rapid and sustained dose-dependent increase in serum levels of bone specific alkaline phosphatase and a decrease in serum C-terminal telopeptide CTX and tartarate resistant acid phosphotase TRACP-5b levels.[51]

### Cannabinoid agonists

Endocannabinoids and their receptors have been seen to be involved in the regulation of osteoblast differentiation and bone formation. Cannabinoid CB1/2 agonist CP 55,940 and cannabinoid (CB) 2 selective agonists HU 308 have shown stimulation and early differentiation of bone marrow derived osteoblast precursors and enhancement of bone nodule formation in osteoblast cultures *in vitro*.[52] Conversely, treatment with the CB receptor inverse agonist/antagonist AM 251 suppresses osteoblast number and function by acting on CB1 receptors.[53] However, their role in the treatment of osteoporosis will be decided after clinical studies.

## CONCLUSION

The present treatment of osteoporosis largely focuses on decreasing the bone resorption by agents like bisphosphonates, SERMs and denosumab. These classes of drugs are also undergoing refinement to optimize efficacy, safety and patient adherence. Newer intravenous bisphosphonates with long skeletal retention time and SERMs with more selective action on the bones have been lately introduced into clinical practice. The only anabolic agent in clinical practice is PTH analogue, teriparatide. With the better understanding of the pathophysiology of the disease, various new drug targets have been identified. The emerging anti resorptive agents in advanced clinical studies include OPG, c-src kinase inhibitors, $\alpha_v\beta_3$ integrin antagonists, cathepsin K inhibitors, ClCN7 inhibitors and nitrates. Some anabolic therapies like calcilytics, antibodies against sclerostin and Dkk-1, statins, MEPE fragments, activin inhibitiors and endocannabinoid agonists are also present in various stages of clinical drug development. However, the role of these agents in the treatment of osteoporosis would be clear in the upcoming years.

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