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Osteoporosis: A Comprehensive Review of Pathophysiological Mechanisms and Current Therapeutic Approaches

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ABSTRACT

Osteoporosis is a chronic skeletal disorder characterized by decreased bone mineral density and deterioration of bone microarchitecture, leading to increased fracture risk. This review outlines the multifactorial pathophysiology of osteoporosis, emphasizing the impact of estrogen deficiency, oxidative stress, pro- and anti-inflammatory cytokines, and disruption of key molecular pathways such as RANK/RANKL/OPG and Wnt/β-catenin. These factors collectively impair the balance between bone resorption and formation, with glucocorticoid use further exacerbating bone loss. Therapeutic strategies are broadly classified into antiresorptive agents—including bisphosphonates, SERMs, denosumab, calcitonin, and cathepsin K inhibitors—and anabolic agents such as teriparatide, abaloparatide, and statins. Dual-action therapies like romosozumab, along with combination and sequential regimens, offer potential for enhanced efficacy, particularly in high-risk individuals. Despite significant advances, treatment-related adverse effects and limitations persist. The review highlights the necessity for developing safer, more targeted interventions that can restore bone homeostasis with improved long-term outcomes. A mechanistic understanding of bone remodeling and personalized therapeutic strategies remain essential to effectively manage and prevent osteoporosis.

Keywords: Osteoporosis, Bone Remodeling, Estrogen Deficiency, RANK/RANKL/OPG Pathway, Wnt/β-Catenin Signaling, Oxidative Stress, Glucocorticoid-Induced Osteoporosis, Antiresorptive Agents, Anabolic Therapies, Dual and Sequential Treatment Strategies.

1. INTRODUCTION

Osteoporosis is defined by diminished bone mineral density (BMD) along with compromised microarchitecture, increasing fracture risk **(1)**. The WHO defines osteoporosis as a BMD T-score at or below -2.5 using DXA scan (Dual-energy X-ray absorptiometry). An estimated 3 out of 10 women and 1 out of 8 men develop this condition during their lifetime **(2)**, with a global prevalence estimated at 200 million individuals **(3)**. Osteoporosis progresses silently until fractures occur **(4)**. Primary osteoporosis is classified as type I (postmenopausal, estrogen deficiency-induced) or type II (senile, aging-related), while secondary osteoporosis arises from diseases or medications **(5)**. Nearly 50% of

postmenopausal women suffer osteoporotic fractures, with 25% developing vertebral deformities and 15% sustaining hip fractures **(3)**. Bone mass loss primarily drives osteoporosis, influenced by aging or estrogen deficiency, with glucocorticoid therapy exacerbating BMD loss **(6)**.

Bone remodeling involves basic multicellular units (BMUs), where osteoclasts resorb bone and osteoblasts form new matrix, maintaining skeletal integrity. Disruption of this balance underlies osteoporosis **(7)**. Risk factors include genetics, aging, hormonal changes, prolonged glucocorticoid use, poor diet, inactivity, vitamin D deficiency, smoking, and alcohol consumption **(8,9)**.

Therapies include hormone replacement, SERMs (e.g., raloxifene), bisphosphonates (alendronate, risedronate, zoledronic acid), calcitonin, recombinant human parathyroid hormone (rhPTH), strontium ranelate, and denosumab **(10,11)**. However, these treatments have significant drawbacks, such as medication-related osteonecrosis of the jaw (MRONJ), atypical femoral fractures, and decreased serum calcium levels **(12–15)**.

Recent research implicates estrogen deficiency, oxidative stress, pro-inflammatory cytokines, and dysregulation of the RANKL/RANK/OPG and Wnt/β-catenin signaling pathways as key drivers of osteoporosis. Hormonal withdrawal, glucocorticoid therapy, and chronic inflammation contribute to increased osteoclastogenesis and impaired osteoblast function, resulting in imbalanced bone remodeling. Current antiresorptive and anabolic therapies—including bisphosphonates, SERMs, denosumab, teriparatide, and cathepsin K inhibitors—offer therapeutic benefit but are often limited by adverse effects and long-term safety concerns.

This review integrates a comprehensive understanding of osteoporosis pathophysiology and evaluates existing pharmacological strategies, highlighting the need for safer, more targeted approaches that can effectively restore bone homeostasis.

2. PATHOPHYSIOLOGY OF OSTEOPOROSIS:

2.1. Overview of Bone biology:

Bone is a metabolically active connective tissue comprising an organic matrix (collagen type I, sulfated proteoglycans, adhesive glycoproteins like osteonectin and osteocalcin) and an inorganic matrix (hydroxyapatite, calcium, bicarbonate, citrate, magnesium, potassium, sodium) **(16–18)**. Hydroxyapatite confers rigidity (50–70% of bone mass), while the organic matrix (20–40%) imparts elasticity **(19).**

The cellular constituents of bone tissue comprise osteoprogenitor cells, osteoblasts, osteocytes & osteoclasts. Osteoprogenitor cells, which arise from mesenchymal stem cells, serve as precursors to osteoblasts, synthesizing the matrix, and osteocytes, which regulate intercellular signaling **(20,21)**. Osteoclasts, originating from monocyte–macrophage precursors, are specialized in degradation of bone tissue **(22)**. The mature skeleton is predominantly composed of cortical (~80%) and trabecular (~20%) calcified tissue, with cortical bone structured into osteons (Haversian systems) **(19)**.

2.2. Bone remodeling and imbalance:

Bone modeling adapts skeletal morphology to physiological and mechanical demands, while remodeling involves sequential resorption, reversal, and formation phases (Figure 1) **(23–25)**.

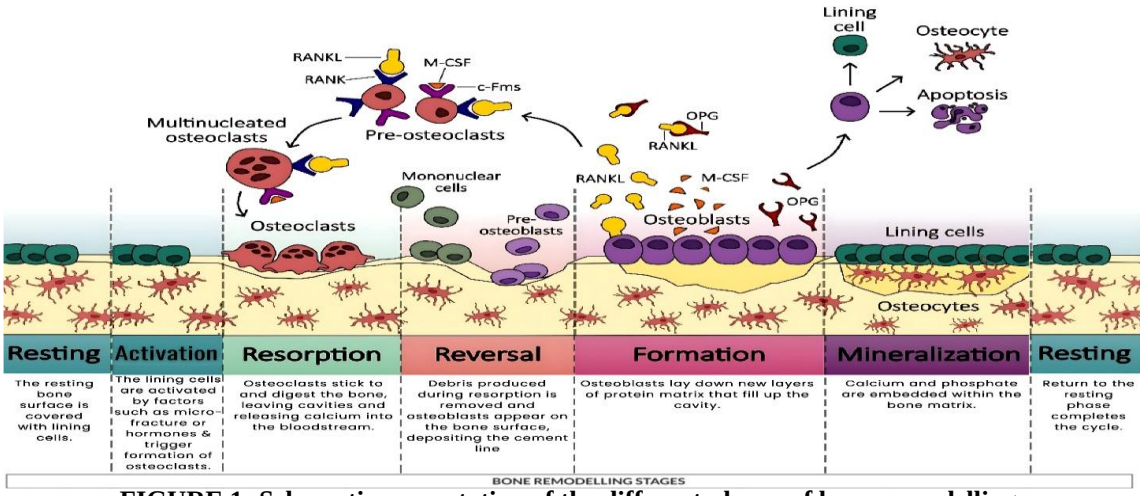

FIGURE 1: Schematic presentation of the different phases of bone remodelling.

Osteoclasts are activated by RANKL and M-CSF signaling, leading to bone resorption. Osteoblasts then fill the resorbed cavities by synthesizing new matrix and promoting mineralization. Regulatory molecules like OPG, RANKL, and M-CSF orchestrate this process to maintain skeletal homeostasis.

Resorption involves preosteoclast migration, fusion into multinucleated osteoclasts, and matrix degradation, followed by reversal with mononuclear cell recruitment of osteoblasts and subsequent bone formation. Resorption lasts ~2 weeks, reversal phase of 4–5 weeks, and then formation up to 4 months **(26).**

Biochemical markers such as alkaline phosphatase (ALP), osteopontin (OPN), osteocalcin (OC), and Type I collagen assess bone formation. ALP facilitates mineralization, OPN regulates mineralization via calcium binding, OC binds hydroxyapatite, and collagen I forms the primary structural framework **(27–29)**.

Imbalance:

An imbalance between resorption and formation results in decreased bone density and disrupted mineral homeostasis, leading to osteoporosis. Maintaining bone homeostasis requires precise regulation of cellular and molecular pathways **(30)**.

2.3. Cellular mechanisms and molecular pathways:

Bone remodeling is chiefly regulated by the RANK/RANKL/OPG axis and the canonical Wnt/β-catenin signaling pathway **(31,32)**.

2.3.1. Wnt/β-catenin signaling:

The Wnt/β-catenin siganling pathway critically regulates osteoblastogenesis **(31)**. Upon binding to Frizzled and LRP5/6 receptors, Wnt proteins prevent β-catenin degradation, allowing its accumulation and nuclear translocation to regulate target gene expression, promoting osteoblast differentiation, maturation, and survival while inhibiting osteoclastogenesis via OPG upregulation **(33,34)**. Absence of Wnt signaling leads to β-catenin degradation **(30).**

Sclerostin, encoded by SOST, inhibits Wnt signaling by binding LRP5/6 **(35,36)**. LRP5 mutations reduce bone mass **(37)**; variants like p.Gly835Val increase idiopathic juvenile osteoporosis risk **(38)**. Wnt pathway dysregulation contributes to glucocorticoid-induced osteoporosis **(39)**. Romosozumab, an anti-sclerostin antibody, enhances bone formation, but further Wnt-targeted therapies are under investigation.

2.3.2. RANKL/RANK/OPG Pathway:

Osteoblast- and osteocyte-derived RANKL, binds RANK on pre-osteoclasts, promoting development and survival in presence of M-CSF. OPG, secreted by osteoblasts and

osteocytes, serves as a decoy receptor inhibiting RANKL-mediated activation of RANK **(30).**

OPG genetic variants are associated with osteoporosis susceptibility **(40)**, and elevated RANKL correlates with bone turnover markers **(41)**. Denosumab, a RANKL inhibitor, effectively reduces bone resorption **(40)**.

2.3.3. Estrogen deficiency:

Estrogen deficiency enhances bone resorption, especially post-menopause **(42).**

It activates osteoclastogenesis by upregulating c-Jun in precursors and inhibiting osteoblast proliferation via GSK3β-mediated Wnt/β-catenin suppression **(43).**

Estrogen receptors (ERs) in bone cells regulate IL-1, IGF-1, and TGF-β pathways, maintaining bone density **(44).** ERs also suppress bone resorption by modulating RANKL **(45)**. Estrogen deficiency induces the expression of pro-inflammatory cytokines (IL-1, IL-6, TNF) and ROS, promoting osteoclastogenesis and inhibiting osteoblast function **(46–48).**

Hormone replacement therapy, though effective, carries risks of breast cancer and cardiovascular disease **(40),** leading to the development of SERMs like raloxifene and bazedoxifene. While effective in preserving BMD, SERMs carry risks of thromboembolism and stroke **(49,50).**

The ideal SERM would selectively mimic estrogen's bone-protective effects without adverse systemic outcomes, necessitating further research.

2.3.4. Oxidative stress:

It is induced when ROS production surpasses cellular clearance mechanisms, causing cellular apoptosis and dysfunction **(51–53).**

Correlation between Oxidative stress and Osteoporosis:

Elevated ROS disrupt bone metabolism, decreasing BMD and enhancing risk of bone fractures. Females after menopause diagnosed with osteoporosis exhibit higher serum H_2O_2 levels and reduced antioxidant enzymes **(54–56).**

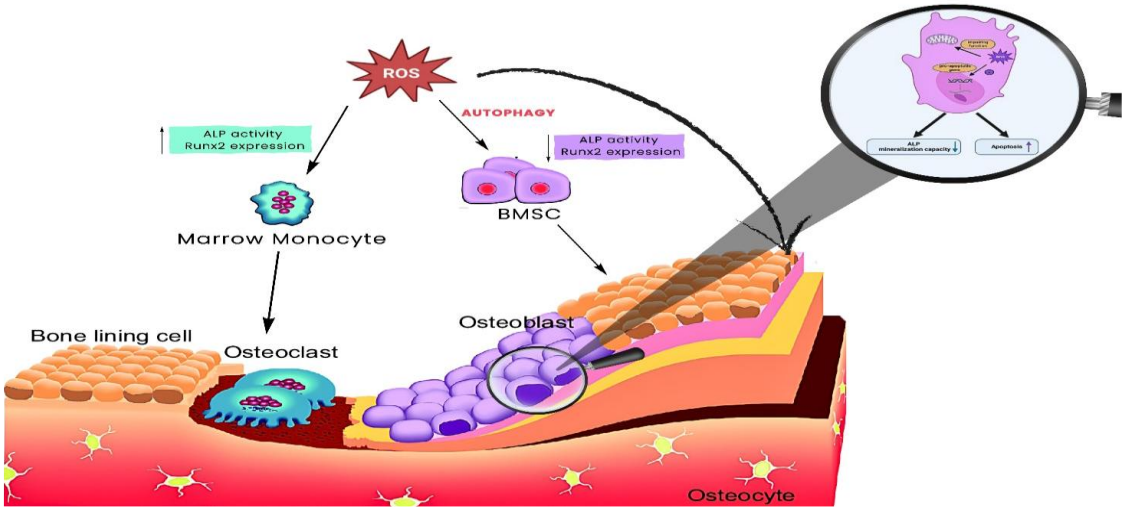

FIGURE 2: The Correlation between Oxidative stress and Osteoporosis.

Oxidative stress (ROS) impairs bone homeostasis by promoting osteoclast differentiation from marrow monocytes and reducing osteoblast function. It suppresses ALP activity and Runx2 expression in bone marrow stem cells (BMSCs), leading to decreased mineralization and increased apoptosis. Autophagy acts as a regulatory mechanism to counteract ROS-induced damage and maintain osteoblast viability.

Mechanism of Oxidative stress in bone metabolism:

a. Effect on Mesenchymal Stem Cells Derived from Bone Marrow:
   Oxidative stress impairs BMSC proliferation, survival, and osteogenic differentiation by disrupting Wnt/β-catenin signaling and autophagy, reducing ALP activity and Runx2 expression **(57–60)**.
b. Disruption of Osteoblast Activity:
   ROS activate JNK pathways, inducing osteoblast apoptosis, impairing mitochondrial function, and reducing mineralization **(61–63).**
c. Stimulation of Osteoclast Development and Differentiation:
   ROS promote osteoclastogenesis by enhancing RANKL and M-CSF production and TRAP expression **(64).**

Thus, oxidative stress critically disrupts bone remodeling, making antioxidant therapies a promising strategy.

2.3.5. Cytokines and Osteoporosis:

Cytokines are key regulators of immune and inflammatory processes via complex signaling pathways **(65).** In osteoporosis, cytokines—particularly TNF, interleukins (ILs), and various growth factors (GFs)—play critical roles in bone remodeling alongside osteoclasts and osteoblasts. The RANKL/RANK/OPG axis represents a central pathway within these cytokine-mediated mechanisms **(66).** As proteins and glycoproteins secreted by various immune and stromal cells, cytokines facilitate intercellular communication and regulate bone metabolism **(67)**. Cells such as macrophages, B cells, T cells, mast cells, endothelial and stromal cells contribute to bone turnover by secreting cytokines involved in both resorption and formation processes **(68).** Cytokines are typically categorized as either pro-inflammatory, which enhance inflammation, or anti-inflammatory, which suppress it **(65).** Table 1 shows the Effect of Cytokines on osteoporosis.

2.3.6. PTH and Osteoporosis:

Parathyroid hormone (PTH) regulates calcium and phosphate homeostasis **(100).** Chronic PTH elevation, as in primary hyperparathyroidism, induces osteoporosis **(101,102).** PTH acts via PTH1R receptors, activating cAMP/PKA and PLC pathways **(103,104)**. Intermittent PTH exposure activates anabolic cAMP/PKA signaling, promoting osteoblast survival and bone formation. Continuous exposure activates catabolic PLC pathways, enhancing RANKL expression and bone resorption **(104–111)**. Teriparatide, a PTH analog, is effective in increasing bone mass, particularly for glucocorticoid-induced osteoporosis **(112,113)**.

2.3.7. Calcitonin and Osteoporosis:

Calcitonin inhibits osteoclast activity and supports BMD **(114)**.
However, its physiological relevance in humans remains uncertain, as chronic calcitonin alterations minimally affect calcium or bone homeostasis **(115–119)**.
Some studies suggest calcitonin protects under calcium stress and promotes osteoblast activity **(120–122)**, though findings are inconsistent **(123,124)**. Overall, calcitonin's role in skeletal biology remains complex and not fully elucidated.

2.3.8. Glucocorticoid and Osteoporosis:

Glucocorticoids enhance bone resorption and inhibit bone formation **(125)**. They prolong osteoclast survival (↑ RANKL, ↓ OPG) and impair osteoblast proliferation and differentiation **(126,127)**. They also induce osteoblast-to-adipocyte transdifferentiation, disrupt BMP signaling, and promote apoptosis in osteoblasts and osteocytes **(125–128)**. Glucocorticoid-induced osteoporosis leads to higher fracture risk compared to postmenopausal osteoporosis. While antiresorptive therapies are approved, their long-term efficacy remains uncertain.

TABLE 1: Effect of Cytokines on osteoporosis.

Pro-inflammatory cytokines:	**Effect on Osteoblast**	**Effect on Osteoclast**	**Effect on Osteocytes**	**Overall Bone Impact**	**References:**
TNF-α	Induces RANKL and M-CSF production at low concentrations. Impairs osteoblast function and inhibits bone formation at high concentrations. Downregulates IGF-1 and RUNX2 expression, suppressing osteoblast differentiation.	Promotes osteoclastogenesis. Upregulates RANK signaling and c-Fos expression.	Upregulates RANKL and sclerostin expression. Promotes osteoclast formation both in vitro and in vivo.	↑ Bone resorption ↓ Bone formation (osteoblast inhibition)	(69–72)
IL-1β	Triggers p38 MAPK activation, promoting bone resorption. Reduces osteoblast viability.	Facilitates osteoclast maturation and multinucleation.	Elevates sclerostin secretion. Triggers osteocyte apoptosis. Amplifies osteocyte-mediated osteoclastogenesis.	↑ RANKL, bone loss, osteoclast activity ↓ Bone formation rate	(73–80)
IL-1α	-	Upregulates RANKL expression, enhancing osteoclastogenesis.	Promotes osteocyte survival. Modulates bone homeostasis through Ca^{2+} and NO signaling.	↑ Bone loss, osteoclast activity ↓ OPG (Osteoprotegerin)	(66,75,81–84)
IL-6	Suppresses osteoblast differentiation.	Directly and indirectly stimulates osteoclast development. Limits the differentiation of osteoclast progenitors.	Plays a crucial role in the interaction between osteocytes and bone metabolism. Modulates bone remodeling and osteoclastogenesis. Promotes osteocyte-mediated osteoclastic differentiation through the JAK2/STAT3 pathway.	↑ Osteoclast differentiation, bone resorption, osteogenic capacity. ↓ Osteoblast differentiation, bone trabecular volume.	(77,85–89)
Anti-inflammatory cytokine	Effect on Osteoblast	Effect on Osteoclast	Effect on Osteocytes	Overall Bone Impact	References:
IL-10	Inhibits osteogenic activity in bone marrow.	Restricts the differentiation of osteoclast progenitors. Inhibits RANK-induced osteoclast formation.	Modulates bone metabolism and osteoclastogenesis. Suppresses bone resorption by upregulating OPG. Downregulates RANKL and	↑ Bone formation, but also bone fragility. ↓ Osteoclast differentiation, bone resorption, bone loss, and bone mineralization.	(79,90–92)

			CSF-1 expression. Synergizes with IL-4 to enhance osteoblast differentiation and mitigate inflammation.		
IL-4	-	Directly and indirectly inhibits osteoclast formation. Suppresses the resorptive activity of mature osteoclasts.	Modulates osteocyte-bone interactions. Cooperates with IL-10 to enhance osteoblast differentiation. Promotes an anti-inflammatory phenotype in macrophages. Suppresses osteoclastogenesis.	↑ Osteoprotegerin (OPG), leading to reduced bone resorption. ↓ RANKL, osteoclastogenesis, & bone resorption. Th2 cells induced by IL-4 prevent bone loss.	(79,93–96)
IL-13	-	Suppresses osteoclast formation and bone resorption.	Contributes to bone remodeling. May influence osteocyte function and metabolism through its anti-inflammatory properties. Potentially regulates osteocyte activity and bone homeostasis.	↑ Bone formation, resorption control, mass preservation, & bone tissue strength. ↓ Bone loss.	(97–99)

3. CURRENT TREATMENT OR THERAPEUTIC STRATEGIES FOR OSTEOPOROSIS:

Osteoporosis treatments are broadly classified into two categories: antiresorptive drugs ("bone resorption inhibitors") that reduce bone breakdown, and anabolic agents ("bone formation accelerators") that stimulate bone formation **(129)**.

3.1. Antiresorptive medications:

Antiresorptives suppress osteoclastogenesis and activity, lower bone turnover, and enhance mineralization, thereby restoring bone homeostasis. Key antiresorptive therapies include bisphosphonates, SERMs, calcitonin, and denosumab **(130)**.

3.1.1. Bisphosphonates:

Bisphosphonates are first-line agents for osteoporosis **(131)**. Nitrogenous bisphosphonates include, alendronate, risedronate, ibandronate, and zoledronate, disrupt osteoclast function via inhibition of the mevalonate pathway **(132)**. Structurally analogous to pyrophosphate, they bind hydroxyapatite at active bone resorption sites **(133)**.

Alendronate effectively treats corticosteroid-induced and postmenopausal osteoporosis **(131)**. Risedronate reduces bone turnover by inhibiting osteoclasts without compromising bone porosity **(134)**. Ibandronate's tertiary nitrogen group enhances affinity for hydroxyapatite, reversing estrogen depletion-induced bone loss **(135).** Zoledronic acid, a potent intravenous bisphosphonate, inhibits farnesyl pyrophosphate synthase (FPPS), improving BMD and reducing fractures **(136).** Prolonged bisphosphonate use may overly suppress remodeling, leading to medication-related osteonecrosis of the jaw (MRONJ) and atypical femoral fractures especially post-dental procedures **(137–139).**

3.1.2. Estrogen and SERMs (selective estrogen receptor modulators):

Estrogen stimulates osteoblast activity and upregulates vitamin D_3 and calcitonin but is linked to increased risks of breast cancer and cardiovascular disease, limiting its long-term use. SERMs emerged as alternatives, acting as ER agonists in bone while antagonizing breast and uterine tissues **(140).**

Raloxifene hydrochloride suppresses osteoclast activity as an ER agonist in bone while reducing breast cancer risk. However, adverse events like deep vein thrombosis and pulmonary embolism constrain its clinical use **(141)**.

3.1.3. RANKL inhibitor:

Denosumab, an IgG2 monoclonal antibody of human origin, inhibits osteoclast differentiation by neutralizing RANKL and thereby blocking its binding to RANK on precursors **(142)**. It enhances BMD and reduces vertebral, hip, and non-vertebral fracture risks **(143)**, primarily by increasing bone matrix mineralization through remodeling suppression **(144)**.

Sequential administration following teriparatide yields superior BMD improvements compared to bisphosphonates **(145)**. Denosumab improves both trabecular and cortical bone architecture, unlike bisphosphonates, which predominantly affect trabecular regions **(146)**. However, its effects are reversible after discontinuation **(147)**, and rare serious adverse effects, including atypical fractures and osteonecrosis of the jaw, have been reported **(148)**.

3.1.4. Calcitonin:

A 32-residue peptide, calcitonin is produced by thyroid C cells, regulates calcium by promoting deposition in bone, inhibiting renal reabsorption, and reducing gastrointestinal absorption. It binds osteoclast receptors, activating the cAMP/protein kinase A pathway and CREB-mediated transcription **(149–151)**. Synthetic analogs, particularly salmon calcitonin, are widely used in intranasal,

subcutaneous, or intramuscular forms **(152,153)**.

Despite its efficacy, calcitonin is now a second-line therapy due to nasal irritation, hypocalcemia, and potential prostate cancer risk **(49,154)**. Moreover, its antiresorptive efficacy is inferior to other agents **(155)**.

3.1.5. Cathepsin k inhibitors:

Cathepsin K, secreted by osteoclasts, degrades collagen and bone matrix proteins, playing a central role in bone resorption. Its inhibition selectively suppresses resorption without impairing formation, presenting a novel therapeutic strategy **(156)**.

Odanacatib (MK-0822), an orally administered selective cathepsin K inhibitor, demonstrated dose-dependent lumbar spine and hip BMD improvements over 52 weeks in Japanese osteoporosis patients **(156)**. Other inhibitors, including balicatib and 2H-Pyran-4-propanoic acid derivatives, are under development **(157–160)**.

However, concerns regarding risks of stroke, atypical fractures, and pycnodysostosis necessitate cautious evaluation of long-term safety **(157,160,161)**.

3.1.6. Strontium ranelate:

Strontium ranelate (SrR), composed of two stable strontium ions and one ranelic acid molecule **(162)**, shares atomic properties with calcium, enabling substitution within bone matrix **(163,164)**. Its mechanism likely involves calcium-sensing receptor (CaSR)-mediated promotion of osteoblast differentiation and osteoprotegerin (OPG) production while inhibiting osteoclast activity **(163–166)**.

Despite efficacy, SrR is reserved for severe osteoporosis due to adverse effects, including venous thromboembolism, myocardial infarction, and rare hypersensitivity reactions like DRESS syndrome **(167–171)**.

3.2. Anabolic agents:

Anabolic agents stimulate bone formation but are limited by concerns such as osteosarcoma risk, restricting their use to short-term therapy **(129)**.

3.2.1. PTH analogues:

Teriparatide (PTH 1–34) retains the full biological activity of native parathyroid hormone **(172)**. Administered intermittently, it stimulates osteoblast activity and bone formation during an initial "anabolic window" before resorption markers rise **(173–176)**.

Teriparatide, the first FDA-approved anabolic agent **(112)**, improves BMD but is limited by high cost, injectable administration, and potential side effects like dizziness, nausea, and concerns about osteosarcoma with prolonged use, thus therapy is capped at two years **(177–179).**

3.2.2. PTHrP (PTH related protein) analogues:

Parathyroid hormone-related protein (PTHrP), produced by mesenchymal stem cells (MSCs), acts via PTH1R, similar to PTH **(180–182)**.

PTHrP analogues preferentially activate the RG conformation of PTH1R, resulting in stronger anabolic signaling compared to PTH **(183–187)**.

Abaloparatide, a synthetic PTHrP analogue, significantly increases BMD and reduces fracture risk with fewer hypercalcemia incidences compared to teriparatide **(188,189)**.

However, side effects like GI disturbances, myalgia, and osteosarcoma risk still limit therapy duration to two years **(177–179,183)**.

3.2.3. Statins:

Statins, primarily used as lipid-lowering agents, inhibit endogenous cholesterol synthesis. Their effects on bone metabolism are dose-dependent: low doses may enhance bone resorption, while higher doses promote bone formation **(190)**.

Lovastatin and simvastatin, notable statins, reduce mevalonate production. Simvastatin, in particular, promotes bone formation by preventing apoptosis in osteoblast and

reducing osteoclast differentiation and resorptive activity **(191)**.

Cheon et al. (2021) demonstrated that pitavastatin suppresses RANKL-induced osteoclastogenesis by modulating Akt, NF-κB, and MAPK pathways, resulting in the suppression of c-Fos and NFATc1—key transcription factors in osteoclast development. Statins also impact bone through reducing cholesterol availability, a precursor for the production of sex steroids **(192)**.

Leutner et al. (2019) observed an association involving statin use, circulating sex steroid concentrations, and osteoporosis risk. While the exact role of HMG-CoA reductase inhibition in osteoporosis remains uncertain, statins have shown benefit in osteoporotic patients, especially those with coexisting cardiovascular or cerebrovascular conditions **(193)**.

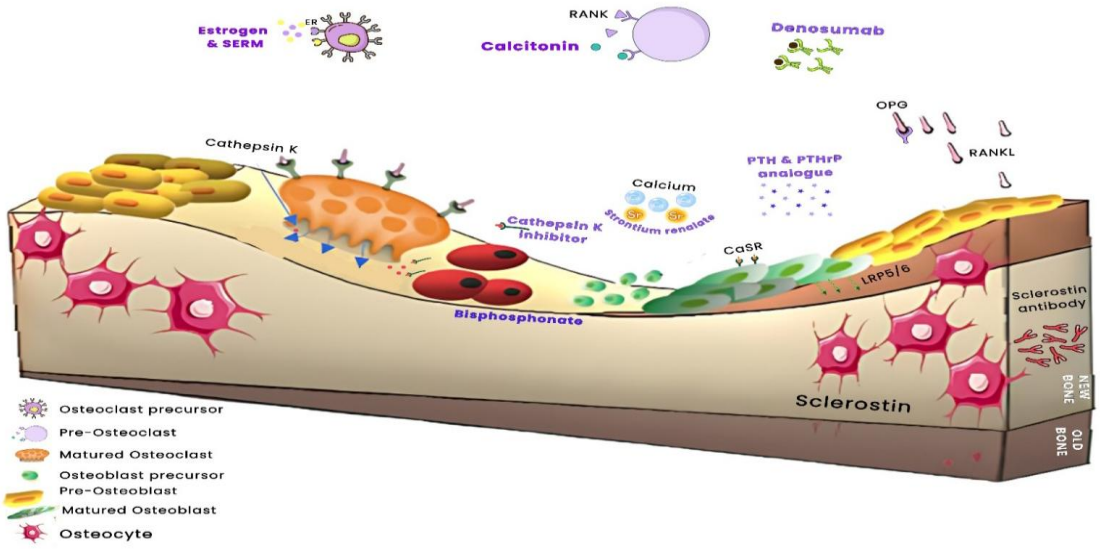

FIGURE 3: Overview of Current Osteoporosis Treatments.

The image illustrates the targets of current osteoporosis therapies. Anti-resorptives like bisphosphonates, calcitonin, and denosumab inhibit osteoclast activity. Estrogen, SERMs, and cathepsin K inhibitors reduce bone breakdown. Anabolic agents such as PTH analogs and sclerostin antibodies stimulate osteoblast function and bone formation. Calcium, strontium ranelate, and CaSR activators aid in maintaining bone mineral density.

3.3. Dual action therapy:

3.3.1. Anti-sclerostin antibody:

Romosozumab is an FDA-approved monoclonal antibody that targets sclerostin, exerting dual actions by reducing bone resorption and promoting bone formation **(186)**. By inhibiting sclerostin, it activates the canonical Wnt signaling pathway, enhancing β-catenin activity, which increases osteoprotegerin (OPG) production in osteoblasts and downregulates RANKL, thereby inhibiting osteoclastogenesis **(36,186,194)**.

This mechanism results in both anabolic and antiresorptive effects. Administered subcutaneously, anti-sclerostin therapy has been linked to adverse effects, including elevated risks of stroke, myocardial infarction, and other cardiovascular events. The FRAME study also raised concerns about a potential link between Wnt signaling activation and cancer **(186,195,196)**. Consequently, long-term use is not recommended.

Comparative studies show romosozumab's superior efficacy over denosumab in increasing bone mineral density (BMD). At 12 months, romosozumab increased lumbar

spine BMD by 12.5%, compared to 7.2% with denosumab. Similar improvements were noted in total hip and femoral neck BMD, supporting romosozumab as a more effective option for postmenopausal osteoporosis **(197)**.

3.3.2. Fluoride:

Fluoride promotes osteoblast proliferation, enhances ALP activity, and stimulates TGF-β1 signaling through ALK5 modulation **(198,199),(200,201)**.

At low doses, fluoride enhances bone formation by inhibiting phosphotyrosine phosphatase and activating mitogenic kinases **(202,203)**, However, high doses are toxic to both osteoblasts and osteoclasts. Given its narrow therapeutic window (serum range 0.15–1.0 mg/L), slow-release formulations are preferred to maximize efficacy and minimize toxicity.

3.4. Combination therapy:

Given the limitations of current osteoporosis treatments, researchers have explored combination therapy, which involves using either two anti-resorptive agents or pairing an anti-resorptive with an anabolic agent. This strategy aims to achieve synergistic effects and improve treatment outcomes.

Several studies have evaluated such combinations, yielding mixed results. For instance, combining PTH with alendronate or SERMs showed no significant improvement in BMD compared to PTH alone. In contrast, the combination of denosumab and teriparatide produced a modest increase in BMD, indicating potential synergy **(168,204–207)**.

Teriparatide has demonstrated efficacy as a monotherapy and in combination with agents like denosumab or abaloparatide. Analogues of PTH and PTHrP are established therapeutic options, used either alone, in combination, or sequentially with anti-resorptive agents **(208)**.

Despite some benefits, combination therapy is associated with increased cost and cumulative adverse effects. Therefore, it is generally reserved for patients at high fracture risk or those unresponsive to monotherapy.

3.5. Sequential therapy:

Sequential therapy, involving staged use of different agents, addresses combination therapy's drawbacks. Transitioning from teriparatide to bisphosphonates maintains BMD gains and fracture reduction **(209,210)**.

The DATA-Switch study showed that teriparatide followed by denosumab further enhanced BMD at spine and hip **(211)**.

ACTIVE Extension revealed sustained fracture protection with abaloparatide followed by alendronate **(212,213)**.

The FRAME and ARCH studies confirmed durable BMD gains and vertebral fracture risk reduction when romosozumab was succeeded by denosumab or alendronate **(195),(214)**.

Sequential therapy thus offers superior fracture prevention and sustained BMD improvement compared to monotherapy.

Nonetheless, serious adverse effects and treatment limitations persist, emphasizing the need for novel therapies that effectively enhance bone biology while minimizing risks **(215–217)**.

4. CONCLUSION

Osteoporosis is a multifaceted disease arising from disrupted bone remodeling, primarily due to estrogen deficiency, oxidative stress, and pro-inflammatory cytokines. Central pathways like RANK/RANKL/OPG and Wnt/β-catenin govern osteoblast and osteoclast activity and are heavily influenced by hormonal changes and reactive oxygen species. Estrogen withdrawal post-menopause, glucocorticoid therapy, and chronic inflammation enhance osteoclastogenesis while impairing osteoblast function and survival.

Current therapies, including bisphosphonates, SERMs, calcitonin, denosumab, and anabolic agents such as teriparatide and abaloparatide, target specific components of bone metabolism. While these agents improve bone mineral

density and reduce fracture risk, adverse effects and treatment limitations necessitate cautious long-term use. Newer therapeutic strategies such as cathepsin K inhibitors, anti-sclerostin antibodies, and statins show promise due to their dual-action or bone-anabolic effects.

Declaration by Authors

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