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Review Article

Comprehensive review of postmenopausal osteoporosis: molecular mechanisms, lifestyle interventions and pharmacological advances

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ABSTRACT

Postmenopausal osteoporosis is a major public health concern characterized by decreased bone mineral density (BMD) and deterioration of bone microarchitecture, leading to increased fragility and fracture risk. The condition is primarily driven by estrogen deficiency following menopause, which disrupts the balance between bone resorption and bone formation. This review provides a comprehensive overview of the molecular and physiological mechanisms underlying postmenopausal osteoporosis, including the roles of osteoclast activation, inflammatory cytokines, oxidative stress, and key regulatory pathways such as RANK/RANKL/OPG and Wnt/β-catenin signaling. In addition to the biological mechanisms, the review examines important lifestyle factors that influence bone health, including nutrition, adequate calcium and vitamin D intake, physical activity, and fall-prevention strategies. Evidence supporting weight-bearing and resistance exercise as effective non-pharmacological interventions for maintaining or improving BMD is discussed. The article also reviews current pharmacological treatments for postmenopausal osteoporosis, including antiresorptive agents such as bisphosphonates and denosumab, as well as anabolic therapies such as teriparatide and romosozumab. In addition, the role of hormone replacement therapy (HRT) is considered as a therapeutic option for postmenopausal women. HRT can reduce bone loss by compensating for estrogen deficiency and has been shown to improve BMD and reduce fracture risk. Emerging therapeutic approaches and future directions in osteoporosis research are also highlighted. Understanding the complex interactions among hormonal changes, molecular pathways, lifestyle factors, and pharmacological therapies is essential for improving prevention strategies and optimizing clinical management of postmenopausal osteoporosis.

Keywords: Postmenopausal osteoporosis, Hormone replacement therapy, Bone mineral density, Osteoporosis treatment

INTRODUCTION

Osteoporosis is a chronic bone disease characterized by reduced BMD and structural deterioration of bone tissue, increasing the risk of fractures, particularly in the spine, hip, and wrist.[1] While the condition can affect both genders, it is significantly more common in women, especially during and after the menopausal transition.

The hormonal changes associated with perimenopause and menopause play a central role in the development of osteoporosis.

Perimenopause is the transitional phase that begins with the onset of menstrual irregularities and ends after twelve consecutive months without menstruation during which hormonal fluctuations-especially in estrogen and progesterone-begin to occur. This phase can start as early as the mid-to-late 40s and may last several years. Menopause is officially diagnosed after 12 consecutive months without menstruation and typically occurs between the ages of 45 and 55, with the average age around 51 years.[2] During perimenopause and the early postmenopausal period, women experience a rapid decline in estrogen levels, which is a key regulator of bone metabolism. This drop in estrogen accelerates bone

resorption and reduces bone formation, leading to a significant loss of bone mass-up to 10% in the first five years after menopause.[2,3] This time frame is particularly critical for bone health. Studies show that the most substantial decline in BMD occurs within the first 3 to 6 years following menopause, placing women at a higher risk of developing osteoporosis and experiencing fragility fractures during this window.[1] If preventive measures are not taken during perimenopause, the opportunity to maintain bone mass may be lost by the time osteoporosis is diagnosed later in life.

The burden of osteoporosis is global, but women in low-resource settings are disproportionately affected due to limited access to screening, inadequate nutritional intake, and lower awareness of the disease.[4] Risk factors can be both non-modifiable-such as age, genetics, and ethnicity-and modifiable, including insufficient calcium and vitamin D intake, lack of physical activity, smoking, alcohol use, and prolonged use of corticosteroids.[3] Moreover, recent evidence suggests that adherence to bone-supportive dietary patterns, such as the Mediterranean diet, may help preserve bone density during the menopausal transition.[5]

Despite the availability of diagnostic tools like dual-energy X-ray absorptiometry (DEXA), osteoporosis often remains undetected until a fracture occurs, especially in asymptomatic individuals.[2] Therefore, increasing awareness, early screening during the perimenopausal period, and implementing preventive strategies are essential to reduce the incidence and consequences of osteoporosis in postmenopausal women.

This article explores the pathophysiology, prevalence, risk factors, and prevention of osteoporosis in postmenopausal women, with particular attention to the perimenopausal period as a critical window for intervention.

PATHOGENESIS OF POSTMENOPAUSAL OSTEOPOROSIS

Bone remodeling and estrogen: coordinated cellular dynamics and hormonal regulation

Bone remodeling within basic multicellular units

Bone remodeling occurs in discrete anatomical structures called basic multicellular units (BMUs), where osteoclasts, osteoblasts, and embedded osteocytes orchestrate the removal and replacement of bone matrix. A canopy of bone-lining cells envelops each BMU, maintaining bidirectional communication with osteocytes via gap junctions and paracrine signals. Through extensive dendritic processes, osteocytes sense mechanical strain and microdamage, relaying these cues both to lining cells and to the vascular niche to integrate local and systemic inputs.[6,7]

Under normal conditions, remodeling proceeds through five sequential phases: resting, activation, resorption, reversal, and formation. Activation begins with recruitment of mononuclear pre-osteoclasts to the bone surface, where they fuse into mature, multinucleated osteoclasts. These osteoclasts create a sealed, acidic microenvironment that dissolves mineralized matrix. After resorption, osteoclasts undergo apoptosis, clearing the resorption lacuna and enabling osteoblast recruitment. Osteoblasts then synthesize a collagenous osteoid, which mineralizes to restore bone architecture and mechanical strength.[8]

Coupling between resorption and formation is governed primarily by the osteoprotegerin (OPG) and receptor activator of nuclear factor κB ligand (RANKL) signaling axis. RANKL, a member of the tumor necrosis factor (TNF) superfamily, exists in both membrane-bound and soluble forms and is predominantly produced by osteoblast-lineage cells, T and B lymphocytes and also released from apoptotic osteocytes. Upon binding to its cognate receptor RANK on osteoclast precursors, RANKL induces receptor trimerization and facilitates the recruitment of TNF receptor–associated factor (TRAF) adaptor proteins, with TRAF6 playing a pivotal role. This interaction initiates downstream signaling cascades, notably the NF-κB and mitogen-activated protein kinase (MAPK) pathways, culminating in the induction of nuclear factor of activated T cells c1 (NFATc1), the principal transcriptional regulator of osteoclastogenesis. NFATc1 amplifies its own expression through an autoregulatory loop and synergizes with AP-1 and other transcription factors to drive the expression of key osteoclastic genes, including cathepsin K, tartrate-resistant acid phosphatase (Acp5), and the αvβ3 integrin, all of which are essential for bone matrix adhesion and resorptive function. Osteocytes, as the principal mechanosensors, upregulate RANKL in response to microdamage and hormonal changes-most notably estrogen deficiency—thereby initiating osteoclastogenesis. Stromal cells and other osteoblastic lineage cells also contribute to the local RANKL pool. While OPG also belonging to the TNF receptor superfamily acts as a soluble decoy receptor and binds RANKL with high affinity, preventing RANKL from engaging its signaling receptor RANK on osteoclast precursors and mature osteoclasts to restrain excessive resorption.[9,10]

Osteoclast-osteoblast coupling mechanisms

Following matrix degradation, two complementary coupling pathways recruit and activate osteoblasts:

Growth factor liberation

Degradation of bone matrix releases abundant growth factors, including transforming growth factor-β (TGF-β), insulin-like growth factors, and bone morphogenetic proteins. These factors diffuse to the reversal surface, enhancing osteoblast proliferation and differentiation.[11,12]

Direct cell-cell and paracrine signals

Mature osteoclasts express ephrinB2, which engages EphB4 on osteoblast precursors. This bidirectional signaling simultaneously suppresses further osteoclast activity and promotes osteoblast maturation. Additionally, osteoclast-derived mediators such as Wnt10b, BMP6, and sphingosine-1-phosphate (S1P) augment osteoblast survival and functional capacity.[13,14]

Estrogen as a hormonal regulator of bone homeostasis

Estrogen exerts multifaceted control over bone remodeling by targeting each major cell type-osteocytes, osteoclasts, and osteoblasts-and by modulating systemic factors that influence mineral metabolism (Figure 1).

Effects on osteocyte viability and signaling

Estrogen sustains osteocyte viability and normal remodeling dynamics. In vitro, 17β-estradiol protects MLO-Y4 osteocyte-like cells from apoptosis via activation of the nitric oxide/cGMP/PKG pathway, leading to phosphorylation and inactivation of the proapoptotic BAD (Bcl-2-associated death promoter) protein.

Loss of estrogen increases osteocyte apoptosis, which in turn elevates RANKL availability-both by release of RANKL from dying cells and by induction in neighboring viable osteocytes. Sclerostin is also secreted by osteocytes along with RANKL that blocks Wnt/β-catenin signaling in osteoblast-lineage cells. This reduces osteoblast differentiation, proliferation, and activity, lowering synthesis of bone matrix and decreasing bone formation shifts the remodeling balance toward more bone resorption.[15] *In vivo*, hypoestrogenic premenopausal women treated with gonadotropin-releasing hormone analogues exhibit a fourfold rise in osteocyte DNA strand breaks; a similar surge in apoptosis occurs in both cancellous and cortical compartments of ovariectomized rodents. Importantly, administration of a pan-caspase inhibitor in ovariectomized mice abrogates osteocyte death and prevents the associated increase in endocortical resorption, confirming apoptosis as a key trigger for estrogen-deficiency-induced bone loss. Unexpectedly, conditional deletion of estrogen receptor α (ERα) in osteocytes does not increase their apoptosis or bone resorption, suggesting possible compensation by ERβ or incomplete ERα excision in residual cells.

Direct and indirect actions on osteoclasts

Early autoradiographic and immunocytochemical analyses demonstrated ER expression in both osteoclast precursors and mature osteoclasts, establishing a basis for direct hormonal regulation.[13] Estrogen binding to osteoclastic ERα triggers pro-apoptotic signaling, shortening osteoclast lifespan and diminishing resorptive capacity. Genetic models in which ERα is specifically ablated in osteoclasts-using cathepsin-K-or LysM-Cre drivers-exhibit prolonged osteoclast survival and reduced trabecular bone mass, directly demonstrating that estrogen signaling limits osteoclast lifespan and activity.[16,17] Mechanistically, estrogen downregulates and dephosphorylates the AP-1 transcription factor c-Jun, impairing RANKL/M-CSF-stimulated osteoclast differentiation. In human monocytes, estrogen promotes assembly of an ERα–BCAR1 scaffold that sequesters TRAF6, thereby blunting NFκB activation downstream of RANKL and further inhibiting osteoclastogenesis and apoptosis of osteoclasts.

Estrogen also exerts potent indirect effects by modulating the bone microenvironment: it suppresses RANKL expression in osteoblasts and in T and B lymphocytes, reducing the primary osteoclastogenic stimulus. Concomitantly, estrogen enhances secretion of OPG from stromal cells and osteoblasts, shifting the RANKL/OPG ratio to favor inhibition of osteoclast differentiation and activation.[18] In estrogen-replete states, proinflammatory cytokines-interleukin-1, interleukin-6, TNF-α-and mediators such as macrophage-colony stimulating factor and prostaglandins are kept in check; estrogen deficiency unleashes their overproduction, fueling enhanced osteoclastogenesis and bone resorption.[19,20]

Promotion of osteoblast survival and function

Estrogen directly extends osteoblast lifespan by inhibiting apoptosis. In vitro studies reveal that 17β-estradiol activates the Src/Shc/ERK signaling cascade while downregulating JNK activity. These pathways converge on downstream transcription factors-Elk-1, C/EBPβ, CREB, and c-Jun/c-Fos-to promote osteoblast survival, matrix production, and mineralization.

Systemic modulation of mineral homeostasis

Beyond cellular targets within bone, estrogen attenuates parathyroid hormone sensitivity in bone, limiting PTH-driven resorption, and stimulates calcitonin release, which directly suppresses osteoclastic activity. Estrogen also enhances intestinal calcium absorption and reduces renal calcium excretion, thereby maintaining adequate mineral availability for bone formation.[21]

Thus, through a combination of direct cellular effects and systemic actions, estrogen is indispensable for maintaining the tightly regulated balance of bone resorption and formation. By preserving osteocyte viability, promoting osteoclast apoptosis, extending osteoblast lifespan, and modulating mineral homeostasis, estrogen safeguards skeletal integrity and prevents bone loss.

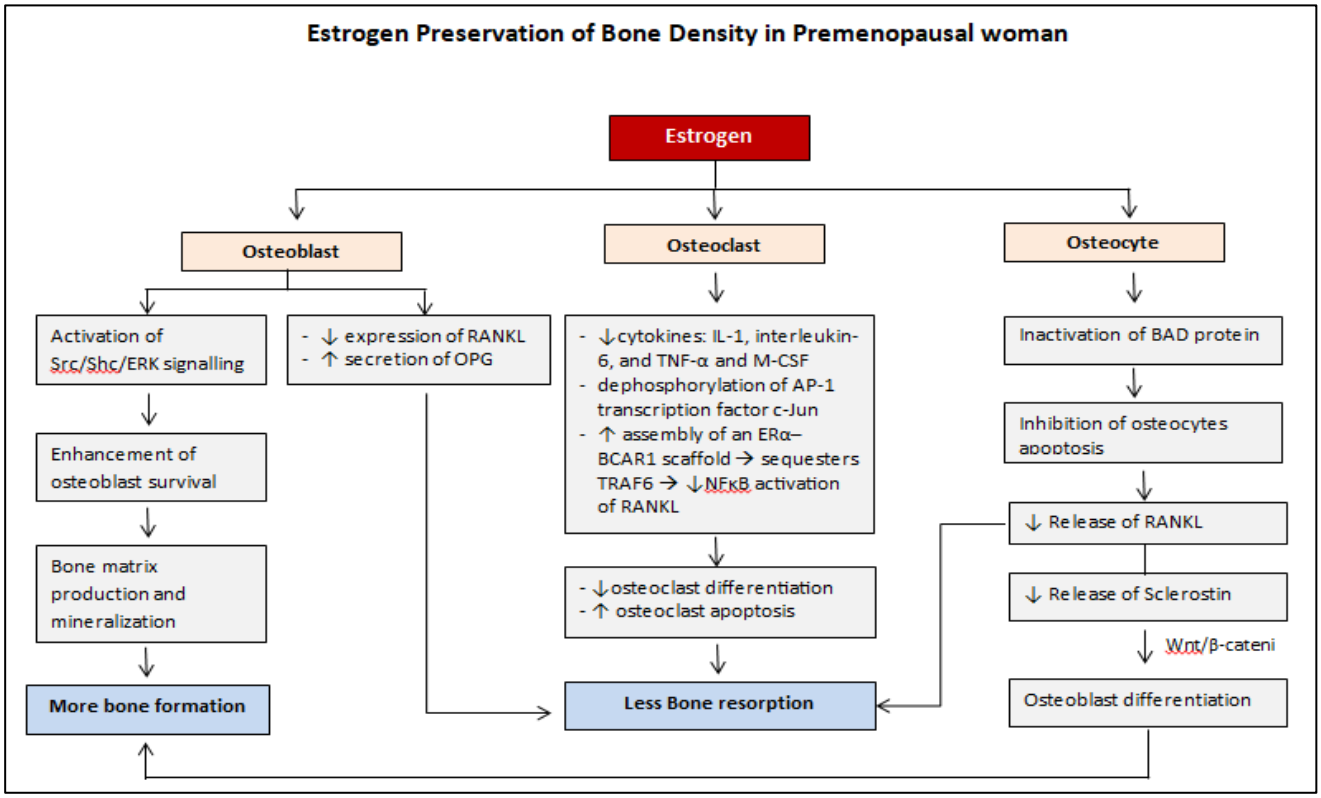

Figure 1: Estrogen preservation of bone in premenopausal woman. Loss of estrogen (eg, menopause) removes these coordinated protective mechanisms, shifting remodeling toward net resorption and increasing osteoporosis risk.

*Abbreviations: ERα=estrogen receptor alpha; OPG=osteoprotegerin; RANKL=receptor activator of nuclear factor κB ligand; TRAF6=TNF receptor associated factor 6; NF-κB=nuclear factor kappa B; AP-1=activator protein 1; BAD=Bcl-2 associated death promoter; M-CSF = macrophage colony-stimulating factor.

MENOPAUSE AND OSTEOPOROSIS: MECHANISMS DRIVING BONE LOSS

Estrogen deficiency and BMU imbalance

At menopause, the abrupt decline in circulating estrogens destabilizes the tightly regulated remodeling cycle within BMUs. Although global markers of both bone resorption and formation rise initially, each BMU exhibits a persistent lag in osteoblast-driven refilling. In practice, the rate of matrix deposition cannot match the accelerated excavation by osteoclasts, producing a net deficit in bone mass and implicating estrogen deficiency not only in increased resorption but also in impaired bone formation.[22]

Molecular mediators of enhanced resorption

Loss of estrogen receptor signaling in osteoclast-lineage cells directly heightens osteoclastic lifespan and activity. Concomitantly, estrogen withdrawal upregulates pro-osteoclastogenic cytokines-interleukin-1, interleukin-6, and tumor necrosis factor-α-and increases macrophage colony-stimulating factor (M-CSF) expression. Stromal cells and osteoblasts also produce more RANKL, tipping RANKL/osteoprotegerin ratio in favor of resorption. Under physiological conditions, estrogen directly promotes osteoblastic expression of matrix proteins (e. g. type I collagen) and coupling factors that synchronize bone formation with prior resorption.[22]

Immune cell contributions to rapid bone loss

Estrogen deficiency expands TNF-α–producing T lymphocytes, which fuel osteoclastogenesis. In ovariectomized rodents, mice lacking mature T cells (nude mice) are protected from cortical bone loss, whereas other T-cell-deficient strains exhibit site- and strain-specific outcomes. These observations highlight the immune context-dependent nature of T-cell-mediated resorption in estrogen-deprived bone.[23]

Oxidative stress and impaired osteogenesis

Both advancing age and estrogen withdrawal elevate reactive oxygen species (ROS) and oxidative-stress markers within bone. ROS antagonize Wnt/β-catenin signaling by diverting β-catenin from T-cell factor (TCF)-mediated transcription toward FoxO-driven antioxidant programs. Resulting shift shortens osteoblast and osteocyte lifespan while promoting osteoclast differentiation. Antioxidant therapy in ovariectomized mice restores Wnt signaling and mitigates bone loss, positioning ROS as central mediator of estrogen-deficiency-induced osteoporosis.[16,20]

NF-κB dysregulation in osteoblasts

Estrogen withdrawal markedly increases NF-κB activity in osteoblastic cells, further uncoupling formation from resorption. Pharmacologic inhibition of NF-κB *in vivo* narrows this gap by upregulating Fos-related antigen-1 (Fra-1), a transcription factor critical for bone matrix synthesis, and by restoring osteoblast function in estrogen-deficient states.[12]

CLINICAL PHASES OF POSTMENOPAUSAL BONE LOSS

Postmenopausal bone loss unfolds in two temporally and mechanistically distinct phases.

Early, rapid phase (0-4 years post-menopause)

Driven directly by estrogen deficiency and disproportionate loss of trabecular bone due to uncoupled resorption over formation.

Late, steady phase (>4-8 years post-menopause)

Reflects age-related decline in osteoblast number and function and affects both cortical and trabecular compartments, occurring in both sexes. This biphasic pattern underscores the unique impact of menopause on bone turnover, followed by an age-associated deceleration in formation.

OSTEOPOROSIS INTERVENTIONS IN POSTMENOPAUSAL WOMEN

The management of postmenopausal osteoporosis is multifaceted and requires an evidence-based, individualized approach aimed at reducing fracture risk and preserving skeletal integrity. According to international guidelines (Endocrine Society, national osteoporosis foundation [NOF], 2020; WHO, 2023), optimal care combines lifestyle modification, adequate nutritional support, and pharmacologic therapy when indicated.[24] These interventions aim to slow bone resorption, stimulate bone formation, and improve BMD. Long-term management also includes periodic monitoring using dual-energy X-ray absorptiometry (DEXA) and biochemical markers of bone turnover to assess therapeutic efficacy and safety.

PREVENTION AND MANAGEMENT OF OSTEOPOROSIS IN POSTMENOPAUSAL WOMEN

Step 1: Risk assessment

Evaluate clinical risk factors, see Table 1 (age, menopause status, family history, low body weight, previous fractures).

Use FRAX or QFracture tools to estimate 10-year fracture risk. Consider baseline DEXA scan for women ≥65 years or younger with risk factors.

Table 1: DXA screening by age group with frequency and DXA details.

Age group (in years)	Factors favoring DXA screening	Screening frequency and DXA details
40-49	• Early menopause (<45 years) • Previous fragility fracture • Long-term use of steroids	Usually, no screening unless risk factors are present: Screen with DXA if any risk factors Screening frequency: Normal BMDEvery 5-10 years Osteopenia: Every 2-4 years Osteoporosis: Every 1-2 years, or as directed by your doctor Sites measured: Lumbar spine, total hip, femoral neck.
50-64	Risk factors: • Family history of hip fracture • Low body weight (<57 kg/127 lbs) • Previous fracture after age 50 • Medications affecting bone	
≥65	DXA recommended for all the women	

Step 2: Nutritional optimization and lifestyle

One of the most critical components of prevention and management is nutritional optimization**.** Adequate intake and proper absorption of calcium, vitamin D, magnesium, and vitamin K2 are essential for supporting skeletal health and preventing further bone loss.[24]

The following Table 2 summarizes the key nutrients involved in bone health, their general roles in osteoporosis management, and supporting references:

Table 2: Essential nutrients for osteoporosis prevention and management.

Nutrient	Bioactive/ preferred forms	Recommended dosage	Crucial role in bone health	References
Calcium	Calcium citrate (preferred), calcium carbonate	1,000-1,200 mg/day (≤500 mg per dose)	Main bone mineral; supports structural integrity; works synergistically with vitamin D	Heaney; Institute of Medicine 2011.
Vitamin D	Cholecalciferol (Vitamin D_3)	800-1,000 IU/day; 50,000 IU/week for deficiency	Enhances calcium absorption; supports bone mineralization and muscle function	Holick et al; Eastell et al[24,25]
Magnesium	Magnesium citrate, glycinate, malate	~320 mg/day (women ≥31 years)	Cofactor for vitamin D activation; supports bone structure and muscle strength; reduces fall risk	Kirkland et al; Castiglioni et al[26,27]
Vitamin K2	MK-7 (preferred), MK-4	90-200 mcg/day (MK-7)	Activates osteocalcin; facilitates calcium binding in bone; reduces vascular calcification	Knapen; Schurgers

Lifestyle

Evidence from both large cohort studies and controlled trials consistently demonstrates that regular physical activity-particularly weight-bearing and resistance exercise-reduces osteoporosis risk and supports bone health in postmenopausal women (Table 3).[14] In a large observational cohort from the Taiwan Biobank involving 30,046 women (mean age 59), regular exercisers exhibited a 17% lower risk of osteoporosis compared with non-exercisers (HR 0.83; 95% CI 0.71-0.97).[28]

Table 3: Recommended physical activities for postmenopausal women with osteoporosis.

Exercise type	Mechanism	Recommended regimen	Practical recommendation / intensity
Weight-bearing (walking, stair climbing, dancing)	Stimulates bone via ground reaction forces. Mechanical loading activates osteocyte signaling pathways, notably Wnt/β-catenin, leading to enhanced bone formation and increased BMD, especially in the spine and hip	30-45 min, 5×/week	Moderate pace walking or stair climbing; dancing with weight shifts; include varied surfaces; low-impact steps for frail individuals
Resistance (weights, bands, squats)	Muscle contractions create strain on bone, activating mechanotransduction pathways that stimulate osteoblast activity, increasing cortical thickness and trabecular bone density	2-3×/week, 2-3 sets of 8-12 reps	Moderate intensity (50-70% of 1-repetition max); focus on controlled movements; emphasize major muscle groups (legs, back, arms); avoid rapid jerky lifts
Impact (jumps, hops)	Strong osteogenic stimulus (spine/hip) High-strain, high-rate forces stimulate periosteal bone formation, enhancing bone geometry and strength at the hip and spine, increases greatly BMD by (2-3%)	1-2×/week, under supervision	Low to moderate jumps: 15-25 cm (6-10 in) for beginners; progress to 30-40 cm (12-16 in) if tolerated; land softly with knees slightly bent; avoid if severe osteoporosis or history of fractures
Balance (Tai Chi, yoga, single-leg stands, heel-to-toe walking))	Fall and fracture prevention Improves proprioception, neuromuscular coordination, and postural reflexes, reducing fall risk and indirectly protecting bone	20–30 min, 3–5×/week	Tai Chi sequences, yoga poses (Tree, Warrior), single-leg stands, heel-to-toe walking, standing on foam pads; progress from supported to unsupported; perform slow, controlled movements
Whole-body vibration	Adjunct for low mobility Low-magnitude mechanical signals stimulate osteocytes and bone formation; improves muscle activation and circulation, supporting bone remodeling	10-15 min, 2-3×/week	Frequency 20-30 Hz; amplitude 1-2 mm; knees slightly bent; short initial sessions (5-10 min) for frail individuals; increase gradually

Practical implications

Interventional studies indicate that regular *multimodal exercise* combining weight-bearing impact (e.g., jumping, hopping, skipping, step-ups), *resistance/strength training* (free weights, machines, elastic bands), and *aerobic/weight-bearing* activities (e.g., brisk walking, stair climbing) performed 2-3 times per week for 30-45 minutes over at least 6-12 months with gradually increased exercise intensity and load significantly improves BMD, mitigates bone loss, enhances muscle strength, and decreases the risk of falls and fractures in postmenopausal women.

The biological basis of these effects lies in mechanotransduction: mechanical strain generated by muscle contraction and gravitational loading increases bone microstrain, activates osteocyte signaling, and promotes osteoblast differentiation and bone formation. Repeated loading cycles enhance bone remodeling efficiency and contribute to improved trabecular architecture and cortical strength.

Step 3. Pharmacologic therapy (if indicated)

Pharmacologic therapy in postmenopausal osteoporosis women should be initiated in women who meet any of the following criteria: a T-score ≤-2.5, a history of fragility fracture (especially vertebral or hip), or osteopenia (T-score between-1.0 and-2.5) with high fracture risk as determined by risk calculators such as FRAX (≥20% for major osteoporotic fracture or ≥3% for hip fracture).[24]

In postmenopausal women, estrogen replacement reduces both circulating and bone marrow levels of sclerostin, a potent inhibitor of Wnt signaling in osteoblasts. This downregulation represents an additional axis through which estrogen sustains bone formation and underscores the multifaceted nature of its anabolic effects. The tight coupling between resorption and formation explains why antiresorptive agents-whether bisphosphonates or RANKL-neutralizing antibodies-produce parallel declines in both processes. By dampening osteoclast activity, these therapies secondarily reduce the release of bone-derived coupling factors, which in turn slows osteoblast recruitment and matrix deposition.[29] Deciphering the molecular interplay among immune cells, oxidative-stress pathways, NF-κB signaling, and sclerostin regulation offers fertile ground for novel osteoporosis treatments. Targeted interventions that preserve osteoblast function or selectively modulate coupling signals may prevent the bone loss more effectively.

FIRST-LINE THERAPY: BISPHOSPHONATES

Bisphosphonates are synthetic analogs of pyrophosphate that bind strongly to hydroxyapatite in bone, particularly at sites of active resorption. During osteoclast-mediated bone resorption, bisphosphonates are internalized by osteoclasts, where nitrogen-containing bisphosphonates inhibit farnesyl pyrophosphate synthase (FPPS) in the mevalonate pathway, preventing prenylation of small GTPases essential for osteoclast function.

This leads to osteoclast apoptosis, decreased bone resorption, and increased BMD and decrease fracture, see Table 4.[30] Bisphosphonates therapy is continued for 3-5 years in most patients, followed by reassessment.

Table 4: Summary of bisphosphonate trials in postmenopausal women with osteoporosis.

Intervention and key trial	Population	Dose and frequency	Treatment duration	Main outcomes, % risk fracture decrease, *(ARR, NNT), BMD
Alendronate-FIT (Black 1996, Bone 2022)[31,32]	2,027 women	5-10 mg PO daily (70 mg weekly)	3 yrs	Vertebral ↓47% (ARR 7%, NNT≈14), Hip ↓51%, BMD: LS +8%, Hip +5%
Risedronate-VERT-MN/ HIP (Harris 1999, McClung 2001)	2,458–9,331 women	5 mg PO daily (35 mg weekly)	3 yrs	Vertebral ↓41% (ARR 5%, NNT≈20), non-vertebral ↓39% (ARR 3.2%, NNT≈31), Hip ↓30% (>80y). BMD: LS +5-6%, Hip +2-3%.
Zoledronic acid-HORIZON-PFT (Black 2007, Reid 2018)[33,34]	7,765 women	5 mg IV yearly	3 yrs	Vertebral ↓70% (ARR 7.6%, NNT≈13), Hip ↓41% (ARR 1.1%, NNT≈91), Non-vertebral ↓25%. BMD: LS +6–7%, Hip +6%.
Ibandronate-BONE (Chesnut 2004)	2,929 women	Oral regimen: 2.5 mg daily OR 20 mg every other day×12 doses every 3 months, IV regimen: 3 mg every 3 months	3 yrs	Vertebral ↓50–60% (ARR 4.9%, NNT≈20), Hip inconsistent. BMD: LS +6%, Hip +2–3%.

*ARR-absolute risk reduction, NNT-number needed to treat, BMD-bone mineral density

SECOND-LINE/ALTERNATIVE: DENOSUMAB (RANKL INHIBITOR)

Denosumab is a fully human monoclonal IgG2 antibody that binds with high affinity to RANKL, key osteoblast/osteocyte-derived cytokine required for osteoclastogenesis. By preventing RANKL from interacting with its receptor RANK on osteoclast precursors and mature osteoclasts, denosumab inhibits osteoclast differentiation, activation, and survival, thereby reducing bone resorption and increasing BMD.[35]

This show decrease in bone turnover markers (CTX, NTX) and significantly reduces vertebral, hip, and non-vertebral fractures in postmenopausal osteoporosis (Table 5).

Table 5: Summary of denosumab trial in postmenopausal women with osteoporosis.

Intervention and key trial	Population	Dose and frequency	Treatment duration	Main Outcomes, % risk fracture decrease, *(ARR, NNT), BMD
Denosumab-Freedom (Cummings 2009, Bone 2021)[35,36]	~7,868 women;	Subcutaneous injection: 60 mg every 6 months	3 yrs (core); up to 10 yrs	Vertebral ↓68% (ARR 4.9%, NNT≈20), Hip ↓40% (ARR 0.5%, NNT≈200), non-vertebral ↓20% (ARR 1.5%, NNT≈67). BMD: LS +9.2%, TH +6%. Rebound risk on abrupt stop.

Adjunct therapy includes calcium (≥1000 mg/day) and vitamin D (≥400-800 IU/day) supplementation to reduce hypocalcemia risk.[24] Reassessment is required after 5-10 years of Denosumab therapy.

Discontinuation without transition to another antiresorptive (e.g., bisphosphonate) carries a high rebound fracture risk (especially multiple vertebral fractures).[37,38]

ADDITIONAL ANTIRESORPTIVES: SELECTIVE ESTROGEN RECEPTOR MODULATORS (SERMS)

Selective estrogen receptor modulators (SERMs), such as raloxifene, are considered in postmenopausal women who cannot tolerate bisphosphonates or denosumab and who are primarily at risk for vertebral fractures.[24] Raloxifene therapy is best suited for younger postmenopausal women with vertebral osteoporosis and lower overall fracture burden and also has favorable effects on breast cancer risk (Table 6).

Table 6: Summary of raloxifene trial in postmenopausal women with osteoporosis.

Intervention and key trial	Population	Dose and frequency	Treatment duration	Main outcomes, % risk fracture decrease, *(ARR, NNT), BMD
Raloxifene-MORE and CORE (Ettinger 1999, Delmas 2004)[39]	~7,700 women;	60 mg PO daily (120 mg also studied)	4 yrs (MORE), up to 8 yrs	Vertebral ↓30–50% (ARR 3.5%, NNT≈29), No hip benefit. BMD: LS +2-3%, Hip +2%.

However, it does not significantly reduce hip/nonvertebral fractures and increases risk of venous thromboembolism and hot flashes. The therapy can be continued for long-term (≥ 5 years) as benefits persist while discontinuation leads to loss of bone protection.

Anabolic therapies

Anabolic therapies are considered in postmenopausal women at very high risk of fracture (e.g., multiple vertebral fractures, very low T-score <-3.0, fractures despite therapy.[26]

Regimens, duration and sequencing have been summarized in Table 7.

After an anabolic course, therapy must be followed by an antiresorptive (e.g., bisphosphonate or denosumab) to maintain bone density gains.[24,40]

Table 7: Summary of anabolic therapy trials in postmenopausal women with osteoporosis.

Intervention and key trial	Population	Dose and frequency	Treatment duration (months)	Main outcomes % risk fracture decrease, *(ARR, NNT), BMD
Teriparatide (Neer 2001)[41]	1,637 women;	20 µg SC daily	~18-21	Vertebral ↓65% (14% → 5%, ARR 9%, NNT≈11), Non-vertebral ↓53% (6% → 3%, ARR 3%, NNT≈33). BMD: LS +9%, FN +3%.

Continued.

Intervention and key trial	Population	Dose and frequency	Treatment duration (months)	Main outcomes % risk fracture decrease, *(ARR, NNT), BMD
Abaloparatide-ACTIVE (Miller 2016)	2,463 women;	80 µg SC daily	18	Vertebral ↓86% (6.6% → 0.9%, ARR 5.7%, NNT≈18), Non-vertebral ↓43% (4.2% → 2.4%, ARR 1.8%, NNT≈56). BMD ↑ LS, TH, FN.
Romosozumab-FRAME (Cosman 2016)	Postmenopausal osteoporosis;	210 mg SC monthly	12	Vertebral ↓73% (1.8% → 0.5%, ARR 1.3%, NNT≈77), Non-vertebral ↓25% (2.1% → 1.6%, ARR 0.5%, NNT≈200). BMD: LS +13%.
Romosozumab → Alendronate-ARCH (Saag 2017)[44]	High-risk women;	210 mg SC monthly ×12 months → 70 mg PO weekly alendronate	12	Vertebral ↓48% (ARR 3.6%, NNT≈28), Hip ↓38% (ARR 1.2%, NNT≈83). BMD ↑ maintained on alendronate.

HRT

HRT, also referred to as menopausal hormone therapy (MHT), remains one of the most effective strategies to counteract postmenopausal bone loss by restoring biologic estrogen levels and inhibiting osteoclast activity (Shah and Ariel).

HRT may be delivered orally or transdermally. Oral estrogen undergoes first-pass hepatic metabolism, which increases hepatic production of clotting and inflammatory proteins and potentially elevates cardiovascular risk in susceptible women. Transdermal estrogen bypasses first-pass metabolism, producing steadier estradiol levels with less impact on hepatic coagulation factors and lower risk of venous thromboembolism, making it preferable for some patients (Naik). Although high-quality, long-term fracture outcome data specifically comparing oral versus transdermal delivery in postmenopausal osteoporosis are limited, a very recent transdermal HRT study showed clinically meaningful BMD gains (typically ranging from low single digits up to double-digit percent increases over one to two years depending on site and patient characteristics) compared with oral contraceptives or placebo in amenorrhea-associated bone loss populations-suggesting transdermal HRT's strong bone-protective potential (Medical Xpress). Other research indicates that transdermal and oral estrogen both increase spine and hip BMD in postmenopausal women when compared with controls, and effects may be comparable between routes, though progesterone addition and patient characteristics influence outcomes. In women with a uterus, combining estrogen with a progestogen (such as micronized progesterone) protects the endometrium while maintaining bone benefits similar to estrogen-only therapy. Randomized trials, including the Women's health initiative (WHI), have shown that combined estrogen plus progestin regimens significantly reduce fracture risk, including hip, vertebral, and wrist fractures. In the WHI trial of 16,608 postmenopausal women, combined therapy reduced total fractures by 24% (733 vs. 896; HR 0.76, 95% CI 0.69-0.83), hip fractures by 33% (52 vs. 73; HR 0.67, 95% CI 0.47-0.96), lower arm/wrist fractures by 29% (189 vs. 245; HR 0.71, 95% CI 0.59-0.85), and clinical vertebral fractures by 35% (41 vs. 60; HR 0.65, 95% CI 0.46-0.92) compared with placebo. Meta-analyses and randomized data further confirm that HRT effectively reduces osteoporotic fracture risk, and scoping reviews conclude that menopausal hormone therapy is an effective intervention for preserving BMD when administered at appropriate doses and for extended durations.

Despite clear skeletal benefits, HRT is associated with potential risks that influence clinical decision-making. Adverse outcomes such as increased breast cancer risk with prolonged use, thromboembolic events, and cardiovascular concerns are important, especially in older women or those with multiple comorbidities (Naik). Individualized risk assessment and shared decision-making with patients are essential, taking into account age, time since menopause, baseline fracture risk, and personal and family medical history. Recent policy updates-including changes in FDA labeling reflecting evolving safety evidence for menopause therapies-further underscore the importance of personalized therapy (FDA).

For women near the menopausal transition or within 10 years of menopause onset, HRT remains a viable option for preventing and treating osteoporosis, particularly when non-hormonal therapies are contraindicated or poorly tolerated. Transdermal estradiol, combined with appropriate progesterone, offers robust BMD improvements with potentially better systemic safety profiles than oral routes, though high-quality fracture-specific studies remain limited. Ultimately, HRT should be considered within a broader therapeutic strategy that includes lifestyle optimization, adequate calcium and vitamin D intake, and weight-bearing exercise.

Herbal and plant-based therapy

Several herbal and plant-based interventions have been explored for the prevention and management of postmenopausal osteoporosis, primarily due to their phytoestrogen content or bioactive compounds that may influence bone metabolism. Soy isoflavones, naturally

occurring phytoestrogens, have been shown in randomized trials to modestly improve BMD at the spine and hip and reduce bone turnover markers, although evidence for fracture reduction remains limited.[28] Red clover (Trifolium pratense) contains isoflavones that may exert estrogen-like effects on bone; clinical studies indicate small increases in BMD and improvements in biochemical markers of bone formation, but results are inconsistent. Other herbal agents studied include black cohosh (Cimicifuga racemosa), primarily used for menopausal symptom relief but with some preliminary evidence for bone protection in animal models, and horsetail (Equisetum arvense), which contains silica and antioxidant compounds that may support bone health; however, high-quality clinical trials in humans are scarce. Overall, while these herbal therapies may offer modest bone benefits and are generally well tolerated, their clinical efficacy for fracture prevention is not yet established, and they should be considered complementary to established pharmacologic and lifestyle interventions rather than as primary therapy.

Step 4-Monitoring and follow-up

Monitoring and follow-up is essential to ensure the effectiveness and safety of osteoporosis treatment. Patients should undergo a repeat DEXA scan every 1-2 years to evaluate changes in BMD. Clinicians should regularly assess adherence to therapy and monitor for potential side effects. Bone turnover markers can be measured if additional information about treatment response is needed. For patients on bisphosphonates who have completed 3-5 years of therapy and are at low fracture risk, a temporary "drug holiday" may be considered under clinical supervision.

CONCLUSION

Postmenopausal osteoporosis is driven primarily by estrogen deficiency, which disrupts the balance between bone resorption and formation, leading to accelerated bone loss and increased fracture risk. The early postmenopausal years represent a critical window for intervention, as the most rapid decline in BMD occurs during this period. Pathogenesis involves complex interactions among osteoclasts, osteoblasts, osteocytes, immune mediators, and oxidative stress, with estrogen playing a central protective role. Effective management is multifaceted, combining lifestyle optimization, nutritional support, pharmacologic therapy, and, when appropriate, HRT. Adequate intake of calcium, vitamin D, magnesium, and vitamin K2, along with weight-bearing, resistance, and balance exercises, helps maintain bone strength. Bisphosphonates, denosumab, SERMs, and anabolic agents have demonstrated efficacy in increasing BMD and reducing fractures. HRT remains a highly effective strategy for women near menopause, though individualized risk assessment is crucial due to potential adverse effects. Complementary herbal interventions, including soy isoflavones and red clover, may provide modest benefits but should not replace established therapies.

Ongoing monitoring with DEXA scans, assessment of adherence, and evaluation of bone turnover markers are vital to guide treatment duration, adjust therapy, and consider drug holidays when appropriate. Overall, a personalized, evidence-based approach that combines lifestyle, nutritional, and pharmacologic strategies during the critical perimenopausal and early postmenopausal periods offers the best opportunity to prevent bone loss, optimize skeletal health, and reduce fracture risk in postmenopausal women.

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