

Hormonal remodeling and molecular mechanisms in postmenopausal osteoporosis: Pathogenesis and therapeutic implications (Review)

WENJUN LIU^{1,2*}, ZHENGZHENG LI^{1,3*}, PENGLIN WANG^{1,3*}, JIAHAO ZENG^{1,3},
HAIMIN ZENG^{1,3}, YINING XIE^{1,3}, RUHUI YANG^{1,3}, LIU YANG¹,
SIJIAN LIN¹ and CHENYU ZHANG¹

¹Department of Rehabilitation Medicine, The Second Affiliated Hospital, Jiangxi Medical College,
Nanchang University, Nanchang, Jiangxi 330006, P.R. China; ²Department of Endocrinology and Metabolism,
The First Affiliated Hospital of Nanchang University, Nanchang, Jiangxi 330006, P.R. China;

³The Second Clinical Medical College, Jiangxi Medical College, Nanchang University, Nanchang, Jiangxi 330006, P.R. China

Received March 11, 2026; Accepted October 15, 2026

DOI: 10.3892/ijmm.2026.6027

Abstract. Postmenopausal osteoporosis (PMO) is a prevalent metabolic bone disorder characterized by accelerated bone loss, reduced bone mineral density, and increased fragility fracture risk. Although estrogen deficiency is considered a central driver of PMO, increasing evidence indicates that bone loss after menopause results from broader endocrine remodeling involving multiple hormones. Estrogen decline

and the accompanying rise in follicle-stimulating hormone (FSH) are characteristic of the menopausal transition. Alterations in the parathyroid hormone (PTH)-vitamin D axis, oxytocin (OT) and calcitonin (CT) may also influence skeletal homeostasis, although their patterns and causal contributions are less consistently established in postmenopausal women. These pathways are discussed as interacting components of an endocrine framework with differing levels of supporting evidence. These coordinated hormonal alterations disrupt bone remodeling through several mechanisms, including impaired bone mechanical homeostasis, dysregulated osteoimmune interactions, altered calcium metabolism, and gut microbiota-bone axis imbalance. Collectively, these changes promote osteoclast activation, suppress osteoblast function, and accelerate skeletal deterioration. Current therapeutic approaches, such as hormone replacement therapy, bisphosphonates, selective estrogen receptor modulators, and PTH analogs, have improved the management of PMO but remain limited by safety concerns or restricted long-term efficacy. Emerging approaches, including FSH blockade, selected phytoestrogen-related interventions, modified CT delivery, and OT-related pathways have different levels of supporting evidence; most specific experimental strategies require human efficacy and safety validation before clinical application. An improved understanding of hormonal interactions and endocrine network remodeling may facilitate the development of more precise and individualized strategies for the prevention and treatment of PMO.

Correspondence to: Professor Chenyu Zhang, Department of Rehabilitation Medicine, The Second Affiliated Hospital, Jiangxi Medical College, Nanchang University, 1 Minde Road, Donghu, Nanchang, Jiangxi 330006, P.R. China
E-mail: 18607002558@163.com

*Contributed equally

Abbreviations: PMO, postmenopausal osteoporosis; BMD, bone mineral density; OT, oxytocin; OTR, OT receptor; CT, calcitonin; FSH, follicle-stimulating hormone; PTH, parathyroid hormone; PTHrP, PTH 1 receptor; HRT, hormone replacement therapy; WHI, Women's Health Initiative; FF, follicular fluid; HPO, hypothalamic-pituitary-ovarian; BMSCs, bone marrow MSCs; SERMs, selective estrogen receptor modulators; OCN, osteocalcin; OPG, osteoprotegerin; BTMs, bone turnover markers; FDA, Food and Drug Administration; SDG, Secoisolariciresinol diglucoside; SWD, Siwu decoction; TCM, traditional Chinese medicine; VAS, visual analogue scale; rhPTH, recombinant human PTH; sCT, Salmon CT; OVX, ovariectomized; SCFAs, short-chain fatty acids; MSCs, mesenchymal stem cells; ER α , estrogen receptor α ; KDM6B, lysine demethylase 6B; HOXC6, homeobox C6; BMP2, bone morphogenetic protein 2; Treg, regulatory T cell; FSHR, FSH receptor; HSP90 α , heat shock protein 90 α ; RANKL, receptor activator of nuclear factor- κ B ligand

Key words: PMO, hormonal remodeling, estrogen deficiency, bone remodeling, HRT, therapeutic strategies

Contents

1. Introduction
2. Hormonal changes in postmenopausal women
3. Effect of hormonal changes on the development of osteoporosis in postmenopausal women
4. Therapeutic strategies for PMO
5. Discussion

1. Introduction

Postmenopausal osteoporosis (PMO) is a metabolic bone disease caused primarily by estrogen deficiency, which manifests as an accelerated bone remodeling imbalance (1). The sudden drop in estrogen levels during the menopausal transition promotes differentiation and activation of osteoclasts, resulting in a rate of bone resorption that exceeds the rate of bone formation (2). This hormonal change leads to rapid bone loss during the perimenopausal period, ultimately resulting in reduced bone mineral density (BMD), deterioration of microarchitecture, impaired bone strength, and susceptibility to fragility fracture. Densitometric osteoporosis is defined by a dual-energy X-ray absorptiometry (DXA) T-score of -2.5 or lower; a hip or vertebral fragility fracture can also establish a clinical diagnosis irrespective of BMD (3,4). However, as the population ages, osteoporosis and associated fractures are rapidly becoming an important public health problem, and epidemiological data indicate a high burden of disease: ~20% of women aged 50 years or older in the United States, and 30% of women aged ≥ 65 years, meet the criteria for osteoporosis as defined by the DXA (5). In China, the prevalence of osteoporosis was 20.6% among women aged 40 years or older in a nationwide population-based study (6). Fragility fractures can cause persistent pain, functional impairment and loss of independence. Hip fractures are particularly serious and are associated with increased short-term mortality in older women (7).

Current research suggests that the underlying mechanism causing PMO is estrogen deficiency in menopausal women (8). Under physiological conditions, bone homeostasis is maintained by a dynamic remodeling process that balances osteoblast-mediated bone formation and osteoclast-mediated bone resorption. Estrogen preserves this balance primarily by inhibiting osteoclastogenesis through regulation of the receptor activator of nuclear factor- κ B ligand (RANKL)/osteoprotegerin (OPG) system and suppression of pro-inflammatory cytokines. Meanwhile, estrogen promotes osteoblast differentiation and survival through osteogenic signaling pathways such as Wnt/ β -catenin. In addition, estrogen contributes to systemic calcium homeostasis by enhancing intestinal calcium absorption and reducing renal calcium excretion. Consequently, estrogen deficiency disrupts bone remodeling equilibrium, resulting in increased bone resorption, reduced bone formation, and progressive bone loss characteristic of PMO (9,10). Based on this mechanism, researchers in the Women's Health Initiative (WHI) trial found that hormone replacement therapy (HRT) in healthy postmenopausal women was effective in reducing the risk of bone fractures (11), but that the therapy may increase the risk of cardiovascular disease and breast cancer (12). However, with further research, it has been observed that even with normal estrogen levels, women in the menopausal transition also experience bone loss (13), suggesting that PMO may not be due to estrogen deficiency alone. Other endocrine pathways implicated in postmenopausal skeletal regulation include follicle-stimulating hormone (FSH) (14), oxytocin (OT) (15), the parathyroid hormone (PTH)-vitamin D axis (16,17) and calcitonin (CT) (18). Recent single-cell and multi-omics studies have characterized cellular and molecular changes during ovarian aging in humans and

non-human primates (19-21). These findings inform upstream endocrine remodeling but do not directly establish a causal link between individual ovarian cell programs and postmenopausal skeletal outcomes.

The present narrative review synthesizes evidence on postmenopausal hormonal remodeling and its skeletal consequences, focusing mainly on studies published between 2015 and 2025, with selected updates from 2026 and earlier landmark studies where relevant. Rather than treating individual hormones as independent determinants of bone loss, the available evidence was organized within an integrated endocrine-network framework. In this framework, ovarian aging and the loss of estrogenic feedback represent upstream endocrine changes that interact with alterations in FSH, OT, PTH, CT and vitamin D, while these hormonal signals converge on shared skeletal effector systems, including the basic multicellular unit, osteoimmune pathways, calcium homeostasis and the gut-bone axis. This framework is used to distinguish well-established mechanisms from unresolved controversies, compare the translational maturity of emerging interventions, and identify stage-specific priorities for future research.

2. Hormonal changes in postmenopausal women

Decrease in estrogen levels. The postmenopausal decline in estrogen reflects follicular depletion and age-related changes in granulosa-cell function and intraovarian signaling. The central feature of ovarian ageing is the irreversible reduction of the primordial follicular pool. As the number of follicles decreases to a critical threshold ($<1,000$), the level of estradiol (E2) secreted by the granulosa cells declines precipitously, and the serum E2 concentration in postmenopausal women is usually less than 20 pg/ml (22). Granulosa cells are the main functional unit of estrogen synthesis. Using single-nuclei multi-omics analyses, Jin *et al* (21) found that the abundance of granulosa cells in human aging ovaries was reduced compared with that in young ovaries and that the expression of apoptosis-related genes in granulosa cells was increased. Further studies revealed that this is mainly due to CCAAT/enhancer-binding protein delta (CEBPD)-mediated regulation of senescence genes (21) and mechanistic target of rapamycin (mTOR) signaling (23) leading to an ovarian-specific senescence pathway. In addition to a decrease in granulosa cell number, aging also leads to granulosa cell dysfunction and impaired estrogen synthesis. In a single-cell study of goat ovarian aging, Xu *et al* (24) identified pseudotime-dependent changes in hydroxysteroid 17-beta dehydrogenase 1 (HSD17B1) expression in granulosa cells. These findings suggest altered steroidogenic regulation but do not establish HSD17B1 as a causal driver of estrogen decline in human menopause. The expression level of circular RNA DDX10 (circDDX10) gradually decreased with age, inhibiting the expression of factors related to steroid hormone synthesis in ovarian granulosa cells, leading to insufficient estrogen secretion in the aged ovary (25). Aging also alters cellular communication, with FSH and growth differentiation factor (GDF) signaling depleted in aged granulosa cells and oocytes, reducing the ovarian regulatory effects of gonadotropins (21). New research found that changes in ovarian follicular fluid (FF) cytokine profiles and hormone profiles during the natural human physiological cycle are age-related and independent of

endogenous gonadotropin regulation, with interleukin (IL)-2 and IL-12 in FF correlating with E2 and estrone (E1) in FF in young women (26).

Increase in follicle stimulating hormone (FSH) levels. Hormonal changes in menopausal women include a decrease in estrogen and a corresponding change in FSH. Elevated FSH concentrations during the menopausal transition were documented as early as 1975 (27). This phenomenon is highly correlated with the decrease in estrogen during menopause (28). Follicular depletion reduces ovarian estrogen and inhibin feedback to the hypothalamic-pituitary system, thereby increasing pituitary FSH secretion (28,29). Epidemiological analyses indicate that hormonal shifts characterized by declining E2 and elevated FSH are strongly associated with reduced BMD and increased risk of osteopenia and osteoporosis in postmenopausal populations (30).

Decrease in OT levels. OT is a neuropeptide primarily produced by neurons in the hypothalamus. Lower circulating OT concentrations have been reported in some postmenopausal populations (31). The underlying mechanisms for this decline may include changes in sexual activity, decreased vagal activity, and lower levels of estrogen (32).

Increase in PTH levels. PTH concentrations may increase with aging and disturbances in calcium and vitamin D homeostasis, but secondary hyperparathyroidism is not an inevitable consequence of menopause (33). Eastell *et al* (33) found a 35% increase in PTH with age by collecting blood and testing serum PTH in 51 healthy women between the ages of 26 and 88 years ($P < 0.02$).

CT-related changes. CT inhibits osteoclast-mediated bone resorption, but the pattern and skeletal significance of circulating CT changes after menopause remain less well established than those of estrogen deficiency. Age-related changes in thyroid C cells have been reported in male rats, and estrogen-responsive CT secretion has been demonstrated in fish; these findings cannot be directly extrapolated to postmenopausal women (34,35). Accordingly, a consistent menopause-related decline in CT should not be assumed.

Vitamin D deficiency. Vitamin D synthesis and metabolism can be used to regulate calcium, phosphorus, and bone metabolism, with regulation of the efficiency of intestinal calcium absorption by its active form, 1,25-dihydroxyvitamin D [$1,25(\text{OH})_2\text{D}$], being the most important function (36). A cross-sectional National Health and Nutrition Examination Survey (NHANES) analysis examined associations between vitamin D status and menopausal timing, but it did not establish that vitamin D deficiency causes earlier menopause (37). Vitamin D status remains relevant to calcium homeostasis and skeletal health after menopause (38). Unfortunately, vitamin D deficiency is very common in menopausal women. Vitamin D deficiency in menopausal women may have several contributing factors. First, aging reduces 7-dehydrocholesterol (7-DHC), the precursor for vitamin D_3 synthesis (39). Reduced sun exposure may contribute to low vitamin D status, although exposure patterns vary among populations (40). In addition,

vitamin D transport relies on vitamin D binding protein (DBP) and albumin, whose levels can be influenced by the lower estrogen levels typical of menopause (41). The detailed mechanisms underlying the various hormonal changes that occur in postmenopausal women are shown in Fig. 1.

3. Effect of hormonal changes on the development of osteoporosis in postmenopausal women

Effect of reduced estrogen levels on osteoporosis

Bone mechanical homeostasis mediated by reduced estrogen.

Bone remodeling requires the coordinated activity of multiple cell types, including osteocytes, osteoblasts, osteoclasts, bone lining cells, and bone marrow mesenchymal stem cells (BMSCs). Osteoclasts, osteoblasts, osteocytes and bone lining cells, together with the local vasculature, form the basic multicellular unit (BMU), with osteal macrophages (osteomacs) also contributing to the local remodeling environment. Communication among these cells through direct contact and autocrine/paracrine signaling coordinates bone resorption and formation. Under mechanical loading, these cellular interactions contribute to bone remodeling, fracture repair and regeneration (42,43).

Bone tissue contains numerous osteocytes, which form an interconnected network via extended dendrites to facilitate mechanotransduction. Estrogen deficiency post-menopause increases osteocyte apoptosis. However, selective estrogen receptor (ER) modulators (SERMs), as reported by Huber *et al* (44), can protect osteocytes from apoptosis after estrogen withdrawal. Estrogen deficiency also impairs osteocyte function by altering their paracrine activity, as shown by Geoghegan *et al* (45), leading to an increased RANKL/OPG ratio. Lewis *et al* (46) used ovariectomy to model menopausal ovarian failure and found that reduced estrogen lowers osteocyte mechanosome numbers and weakens osteocyte Ca^{2+} signaling. This explains the diminished bone adaptability to mechanical stimulation. Osteocytes are also the principal source of sclerostin, a glycoprotein encoded by the SOST gene. Sclerostin binds to the Wnt co-receptors low-density lipoprotein receptor-related proteins 5 and 6 (LRP5/6) and inhibits canonical Wnt/ β -catenin signaling, thereby suppressing osteoblast differentiation and bone formation. Because estrogen deficiency alters osteocyte viability, mechanosensation and paracrine signaling, dysregulation of the osteocyte-sclerostin axis may contribute to impaired bone formation and remodeling imbalance after menopause (47,48). Osteoblasts serve as bone forming cells and mineralizers (49). Estrogen enhances alkaline phosphatase activity (50) and boosts osteocalcin (OCN) expression (51), thereby contributing to the normal functioning of osteoblasts. Osteoclasts are essential for bone remodeling through their bone-resorbing function. Experimental work by Guo *et al* (52) showed that estrogen suppresses osteoclast formation and bone resorption through microRNA (miR)-27a-mediated regulation of peroxisome proliferator-activated receptor γ and adenomatous polyposis coli. When subjected to mechanical stress, BMSCs can differentiate into osteoblasts or chondrocytes. Estrogen supports the osteogenic differentiation of BMSCs through several transcriptional and epigenetic mechanisms. In cultured human BMSCs, including cells obtained from women

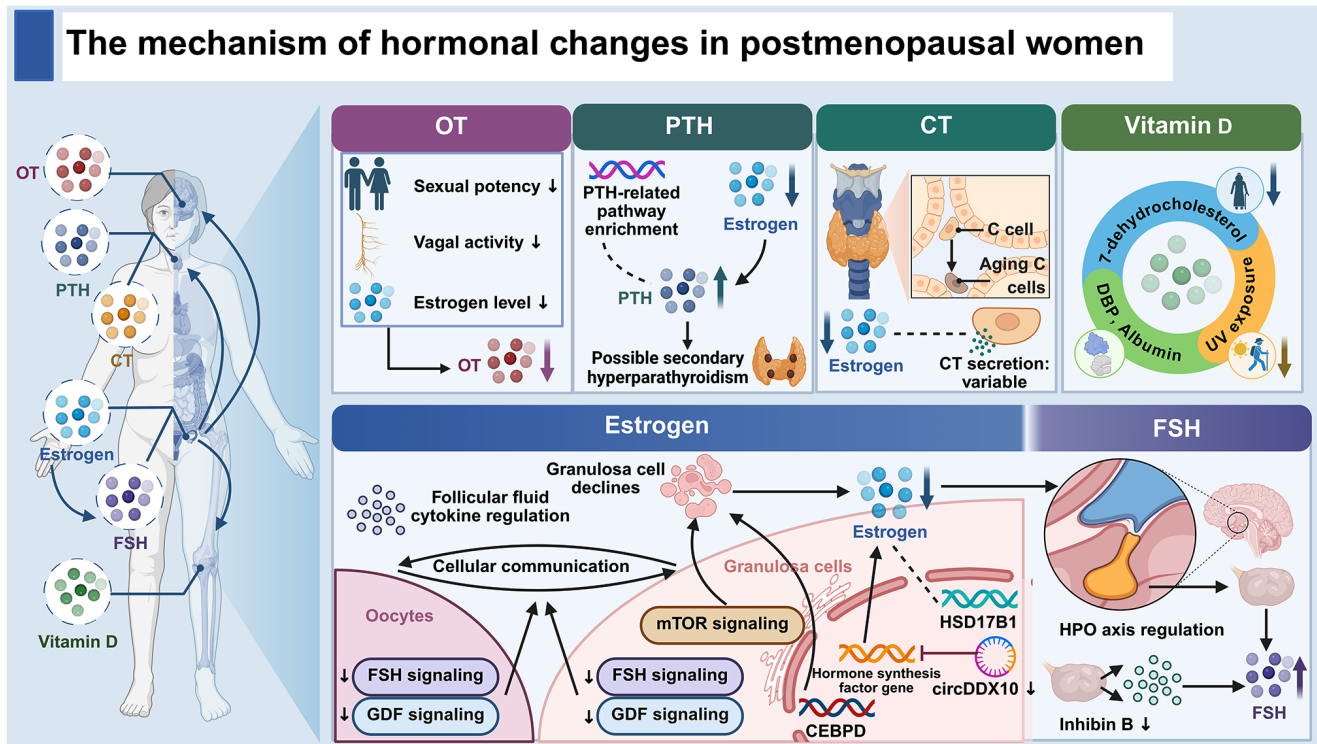


Figure 1. Mechanisms of hormonal changes in postmenopausal women. Ovarian aging drives the decline in estrogen production through multiple interrelated mechanisms: Progressive granulosa cell loss mediated by mTOR signaling and CEBPD-regulated senescence programs; impaired steroidogenic function of granulosa cells caused by downregulated circDDX10 and altered HSD17B1 expression; and disrupted oocyte-granulosa cell communication due to depleted FSH and GDF signaling, combined with age-related changes in follicular fluid cytokine profiles. The attenuated negative feedback of estrogen on the HPO axis, together with reduced inhibin B secretion, collectively leads to elevated circulating FSH levels. Decreased circulating OT levels are associated with reduced sexual activity, attenuated vagal activity and lower estrogen concentrations. Age-related enrichment of PTH-related pathways and loss of direct estrogenic suppression may result in possible secondary hyperparathyroidism. CT secretion patterns vary across individuals, which is attributable to age-related morphological and functional changes in thyroid C cells and withdrawal of estrogenic stimulation. Vitamin D status is regulated by reduced cutaneous 7-dehydrocholesterol, insufficient UV exposure and altered levels of carrier proteins DBP and albumin. CEBPD, CCAAT/enhancer-binding protein delta; circDDX10, circular RNA DDX10; CT, calcitonin; DBP, vitamin D-binding protein; FSH, follicle-stimulating hormone; GDF, growth differentiation factor; HPO, hypothalamic-pituitary-ovarian; HSD17B1, hydroxysteroid 17-beta dehydrogenase 1; mTOR, mechanistic target of rapamycin; OT, oxytocin; PTH, parathyroid hormone; UV, ultraviolet.

with PMO, 17 β -estradiol increased runt-related transcription factor 2 (RUNX2) expression and promoted early osteogenic differentiation, partly through Notch signaling (53). Separately, experiments in human dental mesenchymal stem cells showed that estrogen induced lysine demethylase 6B (KDM6B) through estrogen receptor α (ER α) and promoted osteogenic differentiation through bone morphogenetic protein 2 (BMP2)- and homeobox C6 (HOXC6)-related regulation (54). These findings support distinct estrogen-responsive osteogenic mechanisms in experimental stem-cell models (Fig. 2).

The effects of estrogen on different bone cell populations do not occur in isolation but within an interconnected remodeling network. In addition to the aforementioned direct effects, several coupling mechanisms operate within the BMU. Osteocyte-derived RANKL and sclerostin can regulate both osteoclasts and osteoblasts, bone lining cells contribute to RANKL-mediated osteoclast regulation, osteomacs support osteoblast mineralization, and vascular endothelial cells participate in remodeling through the local blood supply and signals such as vascular endothelial growth factor (VEGF). Thus, the disruption of bone homeostasis associated with estrogen deficiency should be considered in the context of both individual cellular responses and multicellular communication within the BMU (43).

Osteoimmunity mediated by reduced estrogen. Osteoimmunity plays a critical role in maintaining bone homeostasis through cytokines and antibodies secreted by immune cells. Estrogen deficiency not only directly affects osteoblasts and osteoclasts, leading to bone loss, but also disrupts bone homeostasis by influencing osteoimmune cells, including T cells, B cells and macrophages.

In postmenopausal women, estrogen deficiency has been associated with alterations in CD4⁺ T cell subsets, including increased T helper 1 (Th1) and T helper 17 (Th17) activity and elevated circulating levels of tumor necrosis factor- α (TNF- α), interferon- γ (IFN- γ), IL-17 and RANKL (55-57). Importantly, while some evidence is derived from clinical observations in postmenopausal women, the causal signaling pathways have been primarily validated in experimental models. RANKL or TNF- α , together with macrophage colony-stimulating factor (M-CSF), can induce osteoclastogenesis from bone marrow monocytes (58). TNF- α can also regulate bone remodeling through the circular RNA Hmbox1 (circHmbox1)/miR-1247-5p/B-cell lymphoma 6 (Bcl6) axis. TNF- α reduces circHmbox1, which increases miR-1247-5p-mediated suppression of Bcl6, thereby favoring osteoclast differentiation while impairing osteoblast differentiation (59). IFN- γ has context-dependent effects: It can directly inhibit osteoclast precursors, while

Effect of reduced estrogen levels on osteoporosis

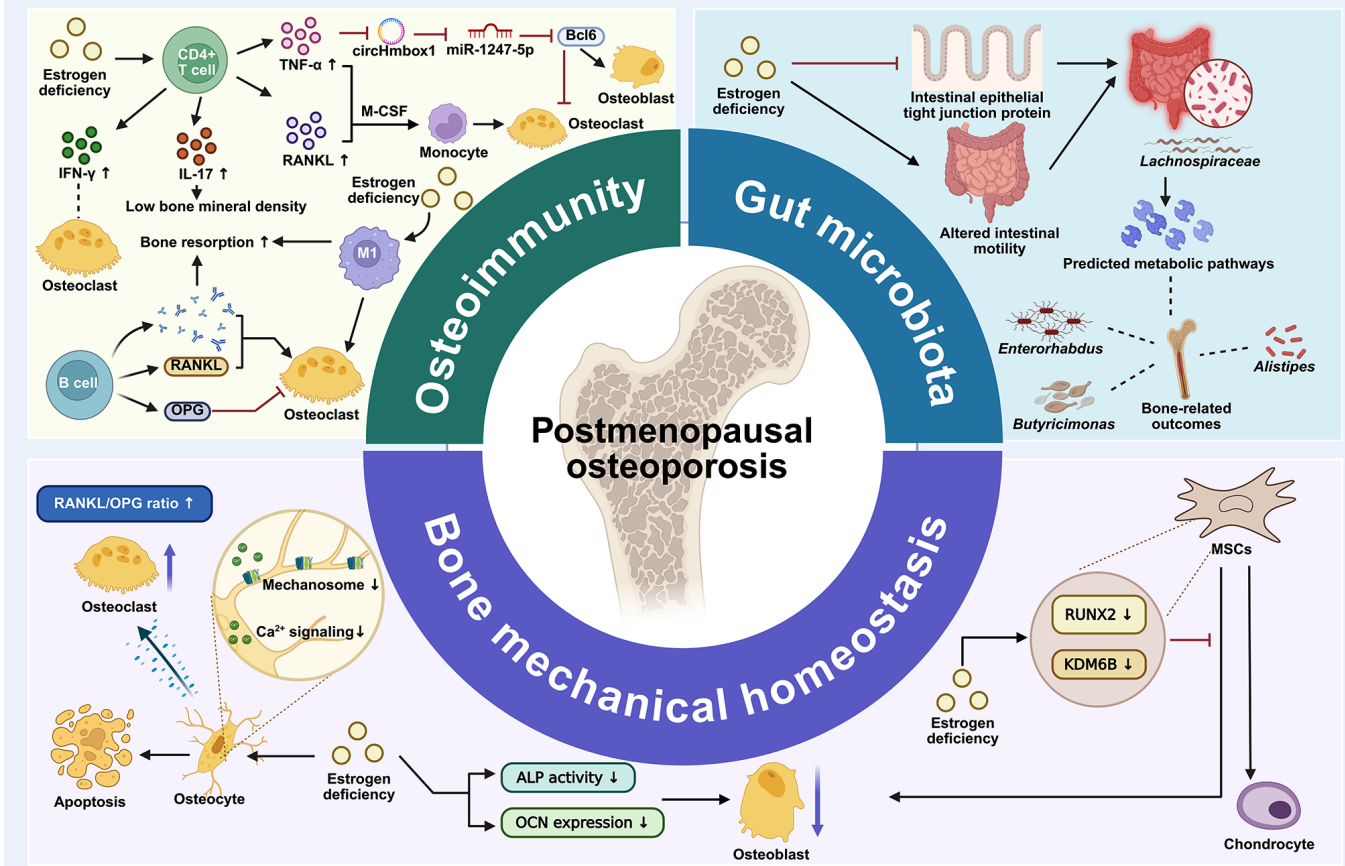


Figure 2. Effect of reduced estrogen levels on osteoporosis. Estrogen deficiency promotes postmenopausal osteoporosis via three interconnected pathophysiological modules. i) Osteoimmunity: Estrogen deficiency increases CD4⁺ T cell-derived TNF-α, IL-17 and IFN-γ; TNF-α suppresses the circHmbox1/miR-1247-5p/Bcl6 axis to impair osteoblast differentiation, while TNF-α and RANKL, together with M-CSF, drive osteoclastogenesis from monocytes. IFN-γ exerts context-dependent effects on osteoclast formation. B cells regulate osteoclast activity via RANKL and OPG secretion, and M1-polarized macrophages enhance bone resorption. ii) Gut microbiota: Estrogen deficiency reduces intestinal epithelial tight junction protein expression and alters intestinal motility, leading to microbial dysbiosis. Lachnospiraceae and its predicted metabolic pathways are associated with bone-related outcomes, while Enterorhabdus, Alistipes and Butyricimonas show associations with bone alterations. iii) Bone mechanical homeostasis: Estrogen deficiency increases osteocyte apoptosis, reduces osteocyte mechanosome abundance and Ca²⁺ signaling, and elevates the RANKL/OPG ratio to activate osteoclasts; it also decreases osteoblast ALP activity and OCN expression. The MSC module summarizes separate estrogen-responsive osteogenic mechanisms involving RUNX2 in human bone marrow MSCs and KDM6B in human dental MSCs. ALP, alkaline phosphatase; Bcl6, B-cell lymphoma 6; Ca²⁺, calcium ion; circHmbox1, circular RNA Hmbox1; IFN-γ, interferon-gamma; IL-17, interleukin-17; KDM6B, lysine demethylase 6B; M1, classically activated macrophage; M-CSF, macrophage colony-stimulating factor; OCN, osteocalcin; OPG, osteoprotegerin; RANKL, receptor activator of nuclear factor-κB ligand; RUNX2, runt-related transcription factor 2; TNF-α, tumor necrosis factor-alpha; MSCs, mesenchymal stem cells; miR, microRNA.

indirectly promoting osteoclastogenesis through T-cell activation and increased osteoclastogenic cytokine production. In experimental estrogen-deficiency models, the net effect can favor bone resorption (60). IL-17 is associated with low BMD in postmenopausal women, suggesting that it may be a key target for osteoporosis (61). In collaboration with T cells, B cells are equally involved in the progression of PMO. In PMO, B cells contribute through two main mechanisms: secreting RANKL and OPG to modulate osteoclast differentiation and activation (62) as well as producing antibodies that stimulate bone resorption (63). Estrogen influences the M1/M2 macrophage ratio by inhibiting M1 macrophage polarization and promoting M2 macrophage polarization through its interaction with the ER. When estrogen levels are sufficient, it helps maintain a balanced macrophage profile. However, in its absence [for example, in ovariectomized (OVX) models], M1 macrophages

dominate, which can lead to increased osteoclastogenesis and bone resorption (1) (Fig. 2).

Bone loss induced by estrogen deficiency through the gut microbiota. Gut flora is a key microecosystem in the body. In recent years, researchers have proposed the concept of the 'gut-bone' axis, revealing a close relationship between gut flora and PMO (64). Human observational data link the menopausal transition to changes in intestinal permeability and inflammation (65). Experimental studies also suggest altered gastrointestinal motility after estrogen withdrawal (66). These changes can alter gut flora composition, potentially leading to dysbiosis. Meng *et al* (67) demonstrated that estrogen deficiency markedly reduces gut microbiota species richness and alters β-diversity. Notably, certain bacteria, including *Helicobacter rodentium*, *Lachnospiraceae 10-1*, *Lachnospiraceae A4* and *Lactobacillus reuteri*, show

significantly enhanced relative abundance. Interestingly, Chen *et al* (68) found that recipient mice receiving fecal transplants from postmenopausal patients with normal bone mass exhibited *Lachnospiraceae* and *Oscillibacter* enrichment, whereas recipient mice receiving fecal transplants from patients with PMO exhibited *Halobiforma*, *Enterorhabdus*, *Alistipes* and *Butyricimonas*, suggesting donor- and model-dependent associations between microbial composition and skeletal outcomes. In recipient mice, enrichment of *Halobiforma*, *Enterorhabdus*, *Alistipes* and *Butyricimonas* was also associated with altered TNF- α and IL-17A expression in serum and bone tissue, linking gut dysbiosis to the osteoimmune pathways (68). Using Mendelian randomization, Zeng *et al* (69) reported associations of *Lachnospiraceae* NK4A136 and *Oxalobacteraceae* with lower osteoporosis risk, and associations of *Pasteurellaceae*, *Pasteurellales* and *Ruminococcaceae* UCG004 with higher risk. These findings depend on the assumptions of the genetic instruments and require validation across populations. *Lachnospiraceae* was associated with alterations in purine metabolism, including changes in inosine, xanthine and uric acid levels in the OVX model. These metabolic changes were correlated with BMD. Functional prediction suggested enrichment of purine-metabolism-related enzymes (70). Associations between microbial taxa, predicted metabolic functions, and bone-related outcomes have also been reported in experimental and human studies (70-72). These findings do not yet establish uniform protective or pathogenic roles for individual taxa or demonstrate that the inferred metabolic pathways mediate bone loss in humans (Fig. 2). Associations between specific microbial taxa and bone health are not consistent across studies. A previous systematic review showed substantial variation in osteoporosis-associated microbial profiles across cohorts, including population-dependent differences in *Alistipes* (73). Such heterogeneity may be related to differences in population characteristics, diet, menopausal stage, sequencing methods and analytical approaches (73). Therefore, individual taxa cannot yet be consistently classified as protective or pathogenic in PMO.

In addition to microbial composition, increasing attention has been directed toward microbiota-derived metabolites, particularly short-chain fatty acids (SCFAs) such as acetate, propionate and butyrate. These metabolites are produced through microbial fermentation of dietary fibers and are considered key mediators linking gut microbiota to host metabolic regulation. SCFAs have been shown to modulate bone metabolism by inhibiting osteoclast differentiation, promoting osteoblast activity, and regulating immune responses involved in bone remodeling. Experimental studies suggest that SCFAs may reduce bone loss by suppressing osteoclastogenesis and modulating immune pathways such as the regulatory T cell (Treg)/Th17 balance, thereby contributing to the maintenance of bone homeostasis (74-76). Research has shown that the composition of the gut microbiota is significantly altered in women with PMO, accompanied by reduced levels of certain SCFAs (77). These findings support the hypothesis that microbial metabolites act as functional intermediates in the gut-bone axis and may represent potential biomarkers or therapeutic targets in PMO. Several clinical and translational studies have investigated probiotic interventions as a strategy to modulate the gut microbiota and promote bone health. Meta-analyses

of probiotic trials report effects on selected bone-turnover and BMD outcomes, but findings vary by strain, formulation, population and treatment duration (78,79). These results do not establish fracture prevention or justify replacing standard osteoporosis therapy with probiotics.

The gut-bone axis may connect endocrine, immune and metabolic changes in PMO, but taxon-specific mechanisms and clinical benefits of microbiota-directed interventions remain incompletely established. These interactions are summarized in Fig. 2.

Effect of increased FSH levels on osteoporosis. Using NHANES data (1999-2002), Liu *et al* (80) analyzed serum FSH associations with lumbar spine and femoral neck BMD in women aged 35-60. They found a significant non-linear inverse association between serum FSH and lumbar spine BMD exclusively in postmenopausal women (P for non-linearity=0.013), and a comparable link between FSH and osteoporosis risk (P=0.05) (80). Zheng *et al* (81) identified follitropin subunit beta among proteins with high importance in a multivariable predictive model. Predictive importance does not establish a causal skeletal effect of circulating FSH. Mechanistically, FSH binds to the FSH receptor (FSHR) and activates G protein/CCAAT/enhancer-binding protein β signaling in adipocytes, which promotes heat shock protein 90 α (HSP90 α) secretion. Increased extracellular HSP90 α subsequently enhances osteoclast activity and may contribute to increased bone resorption (82). Although observational and genetic analyses support an association between elevated FSH and bone loss, direct human interventional evidence is still lacking. Most mechanistic evidence remains experimental; therefore, the causal skeletal effect of elevated FSH in humans has not yet been established and requires further longitudinal and interventional validation.

Effect of decreased OT levels on osteoporosis. Indeed, OT receptors are widely present on bone tissue and OT regulates bone remodeling by binding to OT receptors on osteoblasts and osteoclasts (83). In normal conditions, E2 triggers the mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK) pathway and OT receptor expression in osteoblasts, boosting OT production. OT then upregulates BMP2 and activating transcription factor 4 promoting osteoblast differentiation and function and forming a synergistic feed-forward loop (15). Reduced estrogen signaling may weaken this feed-forward loop, although its contribution to skeletal outcomes after menopause remains to be established (15). OT has distinct effects on osteoclast formation and mature cell resorptive activity. In experimental models, OT promotes osteoclastogenesis directly and indirectly, including through increased RANKL and reduced OPG expression in osteoblasts. Conversely, OT can suppress resorption by mature osteoclasts through intracellular Ca²⁺ release and nitric oxide synthesis (84). These stage- and cell-dependent effects help explain why changes in osteoclast number do not necessarily translate into equivalent changes in bone resorption; the net therapeutic effect in postmenopausal women remains unproven.

In human studies, Du *et al* (85) linked OT to bone mass (β =0.59, P=0.044) and after age adjustment, to osteoporosis risk (OR: 0.75; 95% CI: 0.63-0.98; P=0.019) in a cross-sectional

study of healthy community dwelling postmenopausal women aged 50-90. In an ovariectomized rat model, OT attenuated bone loss and altered bone-turnover markers and OPG/RANKL mRNA expression (86). Thus, current human evidence supports an association between OT and skeletal status but does not yet establish the therapeutic efficacy of OT supplementation.

Effect of increased PTH levels on osteoporosis. PTH is a key regulator of bone remodeling and exhibits context-dependent effects on skeletal homeostasis. At the cellular level, PTH promotes bone formation by enhancing osteoblast precursor differentiation, inhibiting osteoblast apoptosis, and suppressing sclerostin production, a negative regulator of bone formation (87). However, prolonged elevation of PTH can shift bone remodeling toward resorption by stimulating osteoblast- and osteocyte-derived RANKL expression and reducing OPG production, thereby promoting osteoclast differentiation. By contrast, intermittent PTH stimulation used in anabolic therapies preferentially enhances osteoblast activity and bone formation (16). In experimental models, PTH reduced miR-19a/b expression, while antagonizing miR-19a/b increased its target TG-interacting factor 1 (Tgif1) and augmented PTH-induced bone gain (88). Apart from the direct effects of PTH, genetic polymorphisms in the patient's own PTH and PTH 1 receptor (PTH1R) genes also influence susceptibility to osteoporosis in menopausal women. By analyzing case-control genetic associations in a cohort of South Indian women, Fernandez *et al* (89) revealed lower heel BMD in women with osteoporosis who had the BstBI-AA recessive genotype. On the other hand, Abdi *et al* (90) selected Arab women as their subjects and discovered that the PTH1R single-nucleotide polymorphism rs1138518 C/T genotype serves as a risk factor for osteoporosis in postmenopausal women. Furthermore, it was observed that the C/T and T/T genotypes are associated with different outcomes in 25-hydroxyvitamin D [25(OH)D] levels, suggesting that PTH1R rs1138518 may play a regulatory role in modulating 25(OH)D levels (90). These population-specific genetic associations require replication and do not establish a functional mechanism or a clinically validated prediction tool.

CT and osteoporosis. CT suppresses osteoclast-mediated bone resorption, which can be reflected by reduced urinary hydroxyproline excretion (91). For osteoclasts, CT rapidly disrupts the osteoclast ruffled border, inhibits osteoclast motility and promotes detachment from bone (18). Although CT has a well-established role in regulating osteoclasts, its effects on osteoblasts remain debated. Naot *et al* (92) reported the absence of CT receptors in osteoblasts, whereas Farley *et al* (93) demonstrated CT-mediated promotion of osteoblast proliferation. By contrast, Cornish *et al* (94) showed no increase in mineralized bone area following CT treatment in mice. These studies examined different models and endpoints, including receptor expression, cell proliferation and mineralized bone area, which are not interchangeable measures of a direct osteoanabolic effect. This discrepancy may arise from differences in CT concentrations and incubation durations between studies, highlighting the need for concentration- and time-dependent gradient experiments to characterize CT effects on osteoblasts. Several investigations indicate that CT

primarily acts by inhibiting osteoclast activity, thereby altering the coupling signals between osteoclasts and osteoblasts rather than directly stimulating osteoblast proliferation (92).

However, although CT has well-established inhibitory effects on osteoclast-mediated bone resorption, its clinical efficacy in the treatment of osteoporosis in humans appears to be relatively limited. Randomized controlled trials (RCTs) have shown that intranasal salmon CT (sCT) can reduce the risk of vertebral fractures, but it does not significantly decrease the incidence of non-vertebral or hip fractures (95). Accordingly, most current clinical guidelines no longer recommend CT as a first-line therapy for PMO. These findings suggest that although CT plays an important role in the regulation of bone metabolism, its clinical utility in the treatment of osteoporosis remains limited and warrants further investigation. Clarifying the cellular targets and signaling mechanisms of CT will be important for determining its therapeutic relevance in PMO.

Effect of Vitamin D deficiency on osteoporosis. Vitamin D, a fat-soluble vitamin, is crucial for bone metabolism as it enhances intestinal calcium absorption. Chen *et al* (96) investigated the association between vitamin D levels and BMD, bone turnover markers (BTMs), as well as PTH in 8,532 Chinese postmenopausal women. Vitamin D deficiency or insufficiency was present in ~81% of the study population (96). In osteoporotic patients, higher vitamin D levels were positively correlated with BMD at all measured sites and negatively correlated with BTMs, including β -C-terminal telopeptide of type I collagen (β -CTX) and OCN, as well as with PTH levels (96). In line with this result, the study by Al-Rawaf *et al* (97) also identified vitamin D as a key predictor of osteoporosis in postmenopausal women. Current evidence links vitamin D to osteoporosis through three key mechanisms: Regulation of calcium-phosphorus homeostasis (17), immune-mediated modulation of pro-inflammatory cytokine production (17), and vitamin D receptor gene polymorphisms that influence susceptibility to the disease (98). Selected skeletal actions of FSH, OT, PTH, CT and vitamin D are summarized in Fig. 3. The regulatory effects of different hormones and their receptors on postmenopausal bone loss are summarized in Table I.

Hormonal crosstalk and regulatory networks. To integrate the aforementioned hormone-specific evidence, postmenopausal endocrine remodeling can be considered at three analytically distinct but interacting levels. At the upstream level, ovarian aging and the loss of estrogenic feedback establish the endocrine context of menopause. At an intermediate level, alterations involving FSH, the PTH-vitamin D axis, OT and CT modify systemic and local skeletal regulation. At the effector level, these endocrine signals converge on the basic multicellular unit, osteoimmune pathways, calcium homeostasis, and the gut-bone axis, ultimately disturbing osteoblast-osteoclast coupling and favoring net bone loss. This hierarchy should be regarded as an integrative conceptual framework rather than a strictly linear cascade, because several components are linked through feedback loops and the strength of evidence differs among individual pathways. Within this framework, the decline in estrogen is widely regarded as the key endocrine event. Under physiological conditions, estrogen provides negative feedback to the pituitary and helps regulate gonadotropin secretion. With

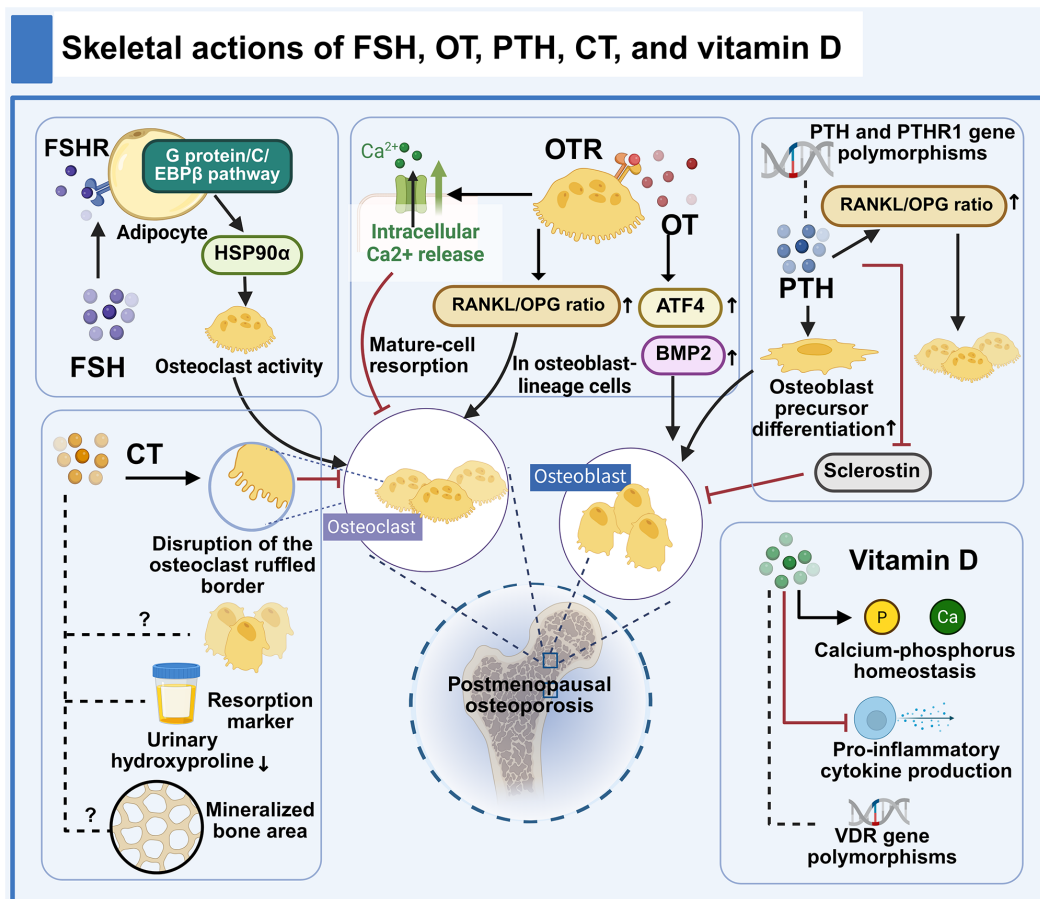


Figure 3. Skeletal actions of FSH, OT, PTH, CT and vitamin D. This diagram summarizes the regulatory effects of five hormonal systems on bone remodeling. FSH binds to FSH receptors on adipocytes and activates the G protein/C/EBP β pathway, which promotes HSP90 α secretion and thereby enhances osteoclast activity. OT signaling upregulates ATF4 and BMP2 to promote osteoblast differentiation; meanwhile, it increases the RANKL/OPG ratio in osteoblast-lineage cells to favor osteoclastogenesis, and on the other hand, induces intracellular Ca²⁺ release in mature osteoclasts to suppress their resorptive function. PTH exerts exposure-dependent biphasic effects: Sustained elevation upregulates the RANKL/OPG ratio to promote osteoclastogenesis, while intermittent administration enhances osteoblast precursor differentiation and inhibits sclerostin to exert anabolic effects. Polymorphisms in the PTH and PTHR1 genes modulate individual susceptibility to osteoporosis. FSH, follicle-stimulating hormone; OT, oxytocin; PTH, parathyroid hormone; CT, calcitonin; HSP90 α , heat shock protein 90 alpha; ATF4, activating transcription factor 4; RANKL, receptor activator of nuclear factor- κ B ligand; OPG, osteoprotegerin; VDR, vitamin D receptor.

progressive ovarian insufficiency and the accompanying fall in estrogen levels, this feedback regulation becomes attenuated, leading to a pronounced rise in FSH (99). As a result, in the postmenopausal state, reduced estrogen and elevated FSH may jointly influence bone cells and favor a shift in bone remodeling toward increased bone resorption.

In addition, alterations in estrogen levels also disturb the balance among calcium-regulating hormones. Reduced calcium absorption and low vitamin D status may contribute to compensatory PTH elevation, particularly with aging (33,100,101). At the same time, vitamin D metabolism is influenced by both aging and changes in estrogen status. Insufficient vitamin D further impairs intestinal calcium absorption and stimulates compensatory PTH secretion, forming a vitamin D-PTH regulatory loop that ultimately contributes to accelerated bone loss (100,101). At the cellular level, PTH and 1,25(OH)₂D₃ can also increase RANKL expression in osteoblasts, thereby linking hormonal changes to osteoblast-osteoclast communication within the BMU. Vitamin D-related signaling can further stimulate osteoblast-derived VEGF, providing a link between bone formation

and vascular regulation (43). Beyond the classical endocrine axes, several neuroendocrine factors also participate in this regulatory network. For instance, estrogen has been shown to regulate the synthesis of OT and the expression of its receptor. Consequently, the postmenopausal decline in estrogen may indirectly weaken the protective effects of OT on bone tissue (102). These interactions illustrate how distinct endocrine changes can converge on shared skeletal regulatory pathways. However, the strength of supporting evidence differs among individual pathways; the major hormone-related findings are therefore summarized according to their evidence types in Table II.

4. Therapeutic strategies for PMO

HRT. In 2002, the WHI found that the use of combined conjugated equine estrogen and medroxyprogesterone acetate regimens, aimed at improving osteoporosis, led to an elevated risk of cardiovascular events and an increased risk of breast cancer (12). This puts the use of HRT in the limelight. In fact, HRT components are primarily estrogens and/or progestins and

Table I. Major hormones and receptors involved in the regulation of postmenopausal bone loss.

Authors, year	Hormone	Major receptor	Postmenopausal change	Predominant skeletal action of the hormone or pathway	Major regulatory features and supporting evidence	(Refs.)
Khosla <i>et al</i> , 2012; Kular <i>et al</i> , 2012; Fan <i>et al</i> , 2014; Liu <i>et al</i> , 2022	Estrogen (E2)	ER	↓	Inhibits bone loss	Maintains osteocyte survival and osteoblast function and suppresses osteoclastogenesis through mechanisms including RANKL/OPG regulation. Estrogen also supports osteogenic differentiation in mesenchymal stem-cell models through distinct RUNX2-related and ERα/KDM6B-related mechanisms demonstrated in different experimental cell sources	(2,43,53,54)
Liu <i>et al</i> , 2023; Zheng <i>et al</i> , 2025; Huang <i>et al</i> , 2024	FSH	FSHR	↑	Potentially promotes bone loss	Higher FSH levels are associated with lower BMD and greater osteoporosis risk in some human studies. Experimental evidence suggests that FSH/FSHR signaling may enhance osteoclast-related activity through an adipocyte FSHR/G protein/C/EBPβ/HSP90α pathway, although a direct causal role in humans remains to be established	(80-82)
Tamma <i>et al</i> , 2009; Du <i>et al</i> , 2021; Moghazy <i>et al</i> , 2020	Oxytocin	OTR	Lower levels reported in some studies; variable	Context- and stage-dependent	Promotes osteoblast differentiation and function in experimental models and has stage-dependent effects on osteoclasts, promoting differentiation while suppressing the resorptive activity of mature cells. Human observational studies report associations between circulating OT and skeletal measures, but therapeutic efficacy in humans remains unestablished	(84-86)
Silva <i>et al</i> , 2015; Eastell <i>et al</i> , 1991; Fernandez <i>et al</i> , 2022; Abdi <i>et al</i> , 2021	PTH	PTHr1	May increase with aging, vitamin D deficiency, or altered calcium balance	Exposure-pattern-dependent	Regulates osteoblast differentiation, cell survival, and sclerostin production. Sustained elevation may favor increased bone turnover and bone loss, whereas intermittent pharmacological exposure is predominantly anabolic. Selected PTH/PTHr1 variants have been associated with osteoporosis susceptibility in population-specific studies	(16,33, 89,90)
Xie <i>et al</i> , 2020	CT	CTR	Variable; a consistent menopause-specific decrease is not established	Inhibits osteoclast-mediated bone resorption	Primarily suppresses osteoclast-mediated bone resorption by disrupting the ruffled border, reducing osteoclast motility, and promoting detachment from bone	(18)

Table I. Continued.

Authors, year	Hormone	Major receptor	Postmenopausal change	Predominant skeletal action of the hormone or pathway	Major regulatory features and supporting evidence	(Refs.)
Bellavia <i>et al</i> , 2024; Chen <i>et al</i> , 2023; Mondockova <i>et al</i> , 2023	Vitamin D	VDR	Deficiency/insufficiency is common	Adequate vitamin D status is generally protective; deficiency favors bone loss	Supports calcium-phosphorus homeostasis. Observational studies report associations of vitamin D status with BMD, bone turnover markers, and PTH; reported VDR polymorphism associations require population-specific interpretation	(17,96,98)
Changes in OT, PTH, CT, and vitamin D are not uniform across postmenopausal populations. The direction of a serum change should not be interpreted as proof of a causal contribution to bone loss. E2, estradiol; ER, estrogen receptor; ER α , ER alpha; RANKL, receptor activator of nuclear factor- κ B ligand; OPG, osteoprotegerin; RUNX2, runt-related transcription factor 2; KDM6B, lysine demethylase 6B; FSH, follicle-stimulating hormone; FSHR, FSH receptor; BMD, bone mineral density; G protein, guanine nucleotide-binding protein; C/EBP β , CCAAT/enhancer-binding protein β ; HSP90 α , heat shock protein 90 alpha; OT, oxytocin; OTR, OT receptor; PTH, parathyroid hormone; PTHR1, PTH 1 receptor; CT, calcitonin; CTR, CT receptor; VDR, vitamin D receptor; $\square$, postmenopausal increase; $\downarrow$, postmenopausal decrease.						

are primarily used to treat perimenopausal and early menopausal vasomotor symptoms. Systemic hormone therapy may prevent bone loss in appropriately selected postmenopausal women, with formulation, route, and duration individualized according to menopausal symptoms and the benefit-risk profile (103). Stevenson *et al* (104) employed two HRT regimens. The first regimen consisted of 1 mg of 17 β -estradiol and either 5 or 10 mg of dydrogesterone administered daily for 14 consecutive days, with a 28-day cycle. The second regimen involved 2 mg of 17 β -estradiol and either 10 or 20 mg of dydrogesterone given daily for 14 consecutive days, also with a 28-day cycle. They found that, compared with baseline, HRT significantly increased total disc height in both the 1-mg E2 group (0.16 $\pm$ 0.65 cm, P=0.015) and the 2-mg E2 group (0.21 $\pm$ 0.86 cm, P=0.006). However, between-group differences were not statistically significant, and this analysis did not directly establish a reduction in fracture risk (104). Gamsjaeger *et al* (105) administered a combination of 2 mg E2 and 1 mg norethindrone acetate to postmenopausal women over a two-year period. They observed that HRT with this regimen altered osteoid composition and mineralization-related characteristics (105). The 2022 North American Menopause Society (NAMS) position statement emphasizes that the benefit-risk profile of HRT is generally more favorable in healthy women younger than 60 years or within 10 years of menopause onset (103). By contrast, initiation at an older age or more than 10 years after menopause is associated with higher absolute risks of coronary heart disease, stroke and venous thromboembolism. Risk also varies according to the route and regimen of treatment. Oral estrogen is associated with a higher risk of venous thromboembolism than transdermal estrogen, although direct comparative RCT evidence remains limited. Breast cancer risk also differs according to the type and duration of hormone therapy (106-108). Systemic HRT is generally avoided in women with estrogen-sensitive malignancies, unexplained vaginal bleeding, active liver disease, previous venous thromboembolism, or established cardiovascular disease. Therefore, treatment should be individualized according to age, time since menopause, route of administration, and baseline risk profile (103).

Recent studies continue to refine the evidence base for hormone therapy in PMO. A reanalysis of the WHI randomized trials reported fracture-risk reductions across baseline risk strata (109). Separately, a 2025 nested case-control study examined fracture risk after discontinuation of menopausal hormone therapy (110). Additionally, emerging evidence suggests that combining HRT with structured exercise can further enhance BMD (111). Contemporary analyses also highlight that the risk profile of HRT varies with formulation and route, with observational evidence suggesting lower venous thromboembolic risk with transdermal than oral estrogen (108,112). In summary, the individual benefit risk balance of HRT hinges on the type, dose and duration of HRT, along with each woman's unique characteristics. Further studies are required to investigate these variables comprehensively.

Pharmacological therapies other than menopausal hormone therapy

Bisphosphonates. Bisphosphonates, characterized by two phosphonate groups, function by inhibiting osteoclast activity and thereby reducing bone resorption, positioning them as a

Table II. Evidence types supporting hormone-related findings in postmenopausal osteoporosis.

Authors, year	Hormonal factor	Hormone-related findings	Evidence type and main limitation	(Refs.)
Khosla <i>et al</i> , 2012; Fan <i>et al</i> , 2014; Liu <i>et al</i> , 2022; Lorentzon <i>et al</i> , 2022	Estrogen/ER signaling	Estrogen deficiency contributes to remodeling imbalance; estrogen-based therapy reduces fracture risk in selected postmenopausal populations	Mechanistic evidence summarized in a review, with primary experiments in distinct human stem-cell models. Therapeutic fracture outcomes: pooled analysis of randomized trials. Clinical efficacy does not independently validate every proposed molecular pathway.	(2,53, 54,109)
Liu <i>et al</i> , 2023; Zheng <i>et al</i> , 2025; Huang <i>et al</i> , 2024 Gera <i>et al</i> , 2022	FSH/FSHR signaling	Higher FSH is associated with lower BMD in some human studies; FSH-related pathways and FSH blockade have been investigated experimentally.	Human observational associations and proteomic prediction; a small human comparison and animal and <i>in vitro</i> experiments; preclinical FSH-blocking antibody studies. A direct skeletal benefit of FSH blockade has not been established in human osteoporosis trials.	(80-82,136)
Tamma <i>et al</i> , 2009; Du <i>et al</i> , 2021; Moghazy <i>et al</i> , 2020	OT/OTR signaling	OT supports osteoblast function and has stage-dependent effects on osteoclast formation and resorption in experimental models; circulating OT is associated with skeletal measures in some populations.	Human observational studies; animal and <i>in vitro</i> studies. Human therapeutic efficacy, dosing, and long-term skeletal safety remain unestablished.	(84-86)
LeBoff <i>et al</i> , 2022; Silva <i>et al</i> , 2015; Fernandez <i>et al</i> , 2022; Abdi <i>et al</i> , 2021	PTH/PTHr1 signaling	Sustained PTH excess and intermittent PTH-receptor stimulation have different skeletal effects. Selected PTH/PTHr1 variants have been associated with BMD or osteoporosis susceptibility.	Experimental mechanisms summarized in a review; clinical trial outcomes summarized in a clinical guide; population-specific genetic association studies. Therapeutic evidence should not be conflated with evidence for individual genetic variants.	(4,16,89,90)
Xie <i>et al</i> , 2020; Chesnut <i>et al</i> , 2000	CT/CTR signaling	CT directly inhibits osteoclast-mediated resorption. Pharmacological salmon CT has shown vertebral antifracture activity, but evidence for nonvertebral or hip fracture benefit is limited.	Experimental mechanisms summarized in a review; primary randomized trial evidence for intranasal salmon CT. Drug effects do not establish that endogenous CT deficiency is a major cause of PMO.	(18,95)
Bellavia <i>et al</i> , 2024; Fleet <i>et al</i> , 2022; Chen <i>et al</i> , 2023; Mondockova <i>et al</i> , 2023	Vitamin D/VDR signaling	Vitamin D regulates calcium homeostasis; vitamin D status and selected VDR variants have been associated with skeletal outcomes.	Human observational studies; physiological and mechanistic evidence summarized in reviews; genetic association studies. Association does not establish an added antifracture benefit of supplementation in vitamin-D-replete individuals.	(17,36,96,98)

Evidence categories describe study design and are not a formal GRADE assessment. Mechanistic findings, human associations, and therapeutic trial results are presented separately because they support different levels of inference. BMD, bone mineral density; CT, calcitonin; CTR, CT receptor; ER, estrogen receptor; FSH, follicle-stimulating hormone; FSHR, FSH receptor; OT, oxytocin; OTR, OT receptor; PMO, postmenopausal osteoporosis; PTH, parathyroid hormone; PTHr1, PTH 1 receptor; VDR, vitamin D receptor; GRADE, Grading of Recommendations Assessment, Development and Evaluation.

potent class of antiresorptive agents. Following estrogen deficiency, the expression of osteoclastogenic factors increases, leading to enhanced osteoclast activity and excessive bone resorption. Bisphosphonates counteract this process by directly inhibiting osteoclast function, thereby compensating for the estrogen deficiency-induced increase in bone resorption (4). US Food and Drug Administration (FDA)-approved bisphosphonates encompass alendronate, ibandronate, risedronate and zoledronic acid (4). Nevertheless, bisphosphonates are associated with potential adverse effects such as renal impairment, gastrointestinal problems, and hypocalcemia, which restricts their application in osteoporosis treatment (113). Oral bisphosphonates should be avoided in patients with major esophageal abnormalities or those unable to remain upright after administration, while hypocalcemia should be corrected before treatment. Renal function should also be considered when selecting individual bisphosphonates (4). Rare but important adverse events include osteonecrosis of the jaw and atypical femoral fractures, which should be considered during long-term treatment and reassessment (4).

PTH and PTH-related protein analogs. Intermittent PTH receptor stimulation promotes bone formation, whereas sustained PTH elevation can favor bone resorption. Teriparatide is a PTH (1-34) analog, and abaloparatide is a PTH-related protein analog; both are used as anabolic treatments for osteoporosis (114,115). Nevertheless, these agents are associated with side effects. Common adverse effects of PTH analogs include nausea, dizziness and disturbances in calcium metabolism. An osteosarcoma signal was observed in preclinical rodent studies; however, subsequent large observational studies have not demonstrated an increased incidence of osteosarcoma in humans (116). Nevertheless, these agents should be avoided in patients at increased baseline risk of osteosarcoma, including those with Paget's disease, skeletal malignancies or bone metastases, and previous skeletal radiation exposure. Caution is also warranted in patients with active or recent urolithiasis (117).

Denosumab (RANKL inhibitor). Denosumab is a monoclonal antibody that binds RANKL and prevents its interaction with RANK, thereby inhibiting osteoclast formation and activity. In postmenopausal women, reduced estrogen levels result in an increased RANKL/OPG ratio, which promotes osteoclastogenesis and enhances bone resorption. Denosumab directly targets this pathway by binding to RANKL and blocking its interaction with RANK, thereby suppressing osteoclast activation and counteracting the excessive osteoclast activity caused by estrogen deficiency (118,119). Owing to its remarkable capacity to increase BMD, it has been introduced into clinical practice. Denosumab is generally well tolerated, but hypocalcemia remains an important safety concern, particularly in patients with impaired renal function. Severe hypocalcemia is a particular concern in advanced chronic kidney disease (CKD), especially in patients receiving dialysis or with CKD-related mineral and bone disorder (120). Delayed dosing or discontinuation can result in rebound bone turnover, rapid BMD loss and multiple vertebral fractures. Therefore, denosumab should not be discontinued without subsequent antiresorptive therapy to reduce rebound fracture risk (4,121).

Raloxifene (SERM). Raloxifene, a selective ER modulator approved by FDA, is indicated for the prevention and

treatment of osteoporosis in postmenopausal women (4). Raloxifene exerts estrogen agonist effects in bone. By activating estrogen receptor-mediated signaling, it inhibits osteoclast activity, reduces bone resorption, and increases BMD, thereby correcting the bone metabolic imbalance caused by estrogen deficiency (122,123). Guidelines from the Endocrine Society recommend raloxifene for postmenopausal women at low risk of deep vein thrombosis who are unsuitable for bisphosphonates or denosumab, or those at high risk for breast cancer, to prevent vertebral fractures (115). Notably, raloxifene reduces vertebral fracture risk, while a reduction in non-vertebral fracture risk has not been demonstrated (4). However, Raloxifene has been linked to an increased risk of venous thromboembolism and possibly fatal stroke, without a corresponding increase in total stroke events (124).

Sclerostin inhibitor (romosozumab). Romosozumab is a humanized monoclonal antibody that targets sclerostin, an osteocyte-derived inhibitor of canonical Wnt/ β -catenin signaling. By neutralizing sclerostin, romosozumab relieves inhibition of LRP5/6-mediated Wnt signaling and exerts a dual effect by increasing bone formation while reducing bone resorption (4). Current guidance supports a 12-month course of romosozumab in patients at very high fracture risk, followed by antiresorptive therapy to maintain skeletal gains (4,125). Recent clinical evidence has confirmed substantial increases in BMD and reductions in fracture risk with romosozumab. However, cardiovascular safety remains an important consideration, and treatment should be individualized according to the patient's fracture and cardiovascular risk profiles (126). Under US labeling, romosozumab should not be initiated in patients with myocardial infarction or stroke within the preceding year (127).

Current therapies are not interchangeable because they address different aspects of the imbalance in bone remodeling. Bisphosphonates and denosumab primarily suppress excessive bone resorption, while PTH analogs and romosozumab offer anabolic options for patients at very high fracture risk. Decisions about HRT also depend on age, time since menopause, and systemic safety alongside skeletal benefit. Treatment selection should therefore account for fracture risk, mechanism of action, and patient-specific safety rather than efficacy alone.

Non-pharmacological treatment. Beyond the aforementioned HRT and non-HRT pharmacological treatments, non-pharmacological approaches play a crucial role in preventing and ameliorating PMO. Lifestyle measures include smoking cessation, avoidance of excessive alcohol intake, adequate nutrition, and weight-bearing, resistance, and balance exercise adapted to individual fracture risk and physical capacity (4,128). In addition to its effects on skeletal loading, regular exercise can help preserve muscle function and physical performance, which are important components of fall and fracture prevention (4). An updated systematic review and meta-analysis of 80 controlled studies involving 5,581 postmenopausal women further demonstrated beneficial effects of exercise on BMD at the lumbar spine, femoral neck and total hip (128). Besides lifestyle modifications, adequate calcium and vitamin D intake is also advantageous. Calcium and vitamin D intake should follow applicable guidance and individual assessment.

For example, the Bone Health and Osteoporosis Foundation recommends a total calcium intake of 1,200 mg/day for women aged 51 years or older and vitamin D supplementation of 800-1,000 IU/day when needed (4). Treatment of established vitamin D deficiency should be individualized rather than equated with routine maintenance supplementation. Together, these lifestyle and nutritional measures should be considered integral components of comprehensive osteoporosis management and are generally used alongside pharmacological therapy in women at elevated fracture risk (4). The representative mechanisms, clinical efficacy, and key limitations of current therapeutic strategies for PMO are summarized in Table III.

Despite their established clinical utility, current therapeutic strategies are constrained by patient-specific safety considerations, limitations of long-term treatment, discontinuation-related effects, or incomplete applicability across different risk groups. Together with increasing recognition of the broader endocrine remodeling that accompanies menopause, these limitations provide a rationale for exploring complementary strategies that target additional hormone-related pathways and mechanisms of bone loss.

Future research directions regarding treatment based on hormonal changes during post-menopause. As aforementioned, HRT is effective in preventing and alleviating PMO, but the long-term use of estrogen- and progestin-based regimens may be associated with adverse effects. This has prompted increasing interest in natural bioactive compounds as potential complementary strategies for modulating bone remodeling. Some natural bioactive compounds have been reported to exert both pro-anabolic and antiresorptive effects by supporting osteoblast function and suppressing osteoclast activity, with additional mechanisms involving estrogen-like, anti-inflammatory, antioxidant and bone signaling effects (129). Recent experimental evidence supports this dual regulatory concept. In 2024, a formononetin-derived phytoestrogen was shown to promote osteoblast formation through BMP/Smad signaling while simultaneously inhibiting RANKL-induced osteoclastogenesis through regulation of the RANK/RANKL/OPG axis *in vitro* and in an ovariectomized mouse model (130). Additionally, several ER-targeted plant-derived compounds have also shown potential osteoprotective effects. Chen *et al* (131) generated a PMO rat model through ovariectomy. Subsequently, upon administering Secoisolaricresinol diglucoside (SDG) to the rats, it was observed that SDG regulated the expression of E2 and ER. This regulation led to a reduction in injury and inflammation, and an improvement in bone formation indices (131). Hyperoside, a flavonoid constituent of *Cuscutae Semen*, has shown osteoprotective effects in OVX mice through the ER α /integrin β 3 (ITG β 3) signaling pathway (132). Siwu decoction (SWD), composed of *Rehmannia glutinosa* (Gaertn.) DC., *Angelica sinensis* (Oliv.) Diels, *Paeonia lactiflora* Pall., and *Ligusticum striatum* DC., has been investigated for its potential effects on PMO. Network pharmacology identified the ER/phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT) pathway as a potential mechanism, which was subsequently examined in both *in vivo* and *in vitro* experiments (133). Although the aforementioned specific ER-targeted plant-derived compounds are supported predominantly by preclinical evidence, the clinical evidence

is not uniform across all classes of phytoestrogens. A 2024 systematic review and meta-analysis of 63 RCTs reported that isoflavone interventions were associated with improvements in BMD at the lumbar spine, femoral neck and distal radius in postmenopausal women (134). However, these findings cannot be directly extrapolated to compounds such as SDG, hyperoside, or SWD, for which robust randomized clinical evidence and long-term safety data remain limited.

FSH-targeted approaches have been investigated experimentally, although the direct skeletal contribution of FSH in humans remains unresolved (135). In 2022, Gera *et al* (136) developed a humanized epitope specific FSH blocking antibody, designated as MS-Hu6. They reported on the efficacy of MS-Hu6 in preventing and treating osteoporosis in mice, along with safety parameters from monkey experiments. These preclinical findings support further evaluation of MS-Hu6 for the treatment of PMO. Ning *et al* (137) reported that knockdown of the long non-coding RNA designated MRF enhanced BMSC osteogenic differentiation and bone-defect repair through FSHR-associated cyclic adenosine monophosphate (cAMP)/protein kinase A (PKA)/cAMP response element-binding protein signaling. This identifies MRF as an experimental regulatory target, but it does not establish that MRF inhibition is equivalent to systemic FSH blockade or that it is an effective treatment for PMO. Although preclinical studies of the FSH-blocking antibody MS-Hu6 have shown both preventive and therapeutic effects in animal models, its translation to humans requires further investigation. Key issues, including long-term safety, immunogenicity, optimal dosing and cost-effectiveness, remain unresolved. The cited study provides preclinical evidence and does not establish antifracture efficacy or long-term safety in humans (136).

Lower circulating OT concentrations have been associated with skeletal outcomes in some postmenopausal populations (85). Exogenous OT supplementation has been shown to exert anti-osteoporotic effects in OVX rats (86). A 2022 study in senescent female rats further examined the effects of OT on bone remodeling (138). Although animal studies have shown osteoprotective effects of OT, human evidence remains largely observational. A recent systematic review similarly found that intervention evidence is dominated by animal studies, whereas human studies mainly report associations between circulating OT and skeletal outcomes; clinical trials are still needed to establish therapeutic efficacy and optimal dosing (139). Well-designed, large-scale RCTs are therefore needed to clarify the appropriate dose, long-term safety, and its efficacy compared with established anti-osteoporotic treatments.

Anabolic treatment is generally followed by antiresorptive therapy to preserve skeletal gains (115). Treatment duration should follow agent-specific and jurisdiction-specific recommendations; teriparatide use beyond two years is reserved under US labeling for patients who remain at or return to high fracture risk (116). This clinical context provides the impetus for the current studies, which aim to investigate the advantages of PTH combination therapy in postmenopausal women with osteoporosis. Wei *et al* (140) reported that, following six months of treatment of patients with PMO with teriparatide alone or a combination of teriparatide and zoledronic acid, visual analogue scale (VAS) scores, along with serum levels of osteopontin (OPN) and C-terminal telopeptide of type I collagen

Table III. Therapeutic strategies for postmenopausal osteoporosis.

Therapeutic strategy	Representative agents	Main mechanism of action	Representative clinical efficacy	Key adverse effects/limitations
HRT	Estradiol; conjugated estrogens; estrogen-progestin combinations	Compensates for estrogen deficiency; activates estrogen receptor signaling in bone; suppresses osteoclast activity; reduces bone resorption and fracture risk	In a pooled analysis of the WHI hormone therapy trials, relative risks of any clinical fracture, major osteoporotic fracture, and hip fracture were reduced by 28, 40 and 34%, respectively, vs. placebo over a mean follow-up of 4.3 years (109).	Venous thromboembolism and stroke; breast cancer risk varies by regimen and duration. Selection depends on age, time since menopause, symptoms, and contraindications (103,107).
Bisphosphonates	Alendronate; risedronate; ibandronate; zoledronic acid	Inhibit osteoclast-mediated bone resorption.	The clinical guide summarizes ~50% lower spine and hip fracture incidence with alendronate over 3 years in patients with prior vertebral fracture or osteoporosis by hip BMD. Corresponding estimates for zoledronic acid are ~62-70, 41, and 21-25% lower vertebral, hip, and nonvertebral fracture incidence, respectively, over 3 years (4).	Gastrointestinal adverse effects with oral agents; renal restrictions and hypocalcemia; rare osteonecrosis of the jaw and atypical femoral fractures. Avoid oral treatment in patients with major esophageal disorders or inability to remain upright; agent-specific renal thresholds apply (4).
PTH/PTHrP analogs	Teriparatide; abaloparatide	Intermittent PTH1-receptor activation promotes osteoblast differentiation and survival and increases bone formation; suppression of sclerostin contributes to the anabolic response (114).	The clinical guide summarizes ~65-77 and 35-53% lower vertebral and nonvertebral fracture risks, respectively, with teriparatide after an average of 18 months. Abaloparatide reduced new vertebral and nonvertebral fracture risks by ~86% and 43%, respectively, vs. placebo over 18 months (4).	Nausea, dizziness, and calcium-related adverse effects; caution with active or recent urolithiasis. Avoid use in patients at increased baseline risk of osteosarcoma. A rodent osteosarcoma signal has not translated into an increased incidence in human observational studies of teriparatide (4,116).
RANKL inhibitor	Denosumab	Binds RANKL, prevents its interaction with RANK, and inhibits osteoclast formation and activity	In the FREEDOM trial, denosumab reduced new radiographic vertebral, hip, and nonvertebral fracture risks by ~68, 40 and 20%, respectively, vs. placebo over 3 years (144).	Hypocalcemia, including severe hypocalcemia in advanced chronic kidney disease; rebound bone loss and multiple vertebral fractures after delayed dosing or discontinuation. Subsequent antiresorptive

Table III. Continued.

Therapeutic strategy	Representative agents	Main mechanism of action	Representative clinical efficacy	Key adverse effects/limitations
SERM	Raloxifene	Estrogen agonist effect in bone; suppresses osteoclast activity; increases bone mineral density; reduces vertebral fracture risk	The clinical guide summarizes ~30–40% lower vertebral fracture incidence with raloxifene in patients with a prior vertebral fracture and ~55% lower incidence in those without a prior vertebral fracture. A reduction in non-vertebral fracture risk has not been demonstrated (4).	therapy is required when treatment is stopped (4,121). FDA warning for advanced kidney disease (120). Venous thromboembolism; increased fatal-stroke risk in women with coronary disease or elevated coronary risk. Contraindicated in women with a current or previous venous thromboembolism (115,124).
Sclerostin inhibitor	Romosozumab	Neutralizes sclerostin; relieves inhibition of LRP5/6-mediated Wnt/ β -catenin signaling; increases bone formation and decreases bone resorption	Reduced vertebral and clinical fracture risks by ~73% and 36%, respectively, at 12 months vs. placebo (125)	Cardiovascular risk assessment is required; under US labeling, do not initiate treatment within 1 year after myocardial infarction or stroke. Limit treatment to 12 monthly doses and follow with antiresorptive therapy (4). US prescribing information (127).
Non-pharmacological interventions	Lifestyle modification; calcium; vitamin D; exercise	Improve bone health through adequate nutrient supply and mechanical loading; support bone strength and remodeling	Supports bone health and fall prevention; a single fracture-risk reduction estimate is not applicable to this heterogeneous group (4,128).	Adjunctive care; does not replace indicated pharmacotherapy in women at high fracture risk. Avoid excessive calcium or vitamin D supplementation (4,145).

Representative agents, mechanisms of action, clinical efficacy, and adverse effects/limitations are illustrative rather than exhaustive. Clinical efficacy values represent approximate relative fracture-risk reductions reported in representative clinical trials or evidence syntheses and should not be interpreted as direct head-to-head comparisons because study populations, treatment durations, and fracture endpoints differed. HRT, hormone replacement therapy; WHI, Women's Health Initiative; BMD, bone mineral density; PTH, parathyroid hormone; PTHrP, parathyroid hormone-related protein; PTH1 receptor, parathyroid hormone 1 receptor; RANK, receptor activator of nuclear factor- κ B; RANKL, receptor activator of nuclear factor- κ B ligand; SERM, selective estrogen receptor modulator; LRP5/6, low-density lipoprotein receptor-related proteins 5 and 6; FDA, US Food and Drug Administration; US, United States.

(S-CTX), were significantly lower in the combination-treatment group compared with the teriparatide-monotherapy group (VAS: $P=0.001$; OPN: $P<0.001$; S-CTX: $P<0.001$) (140). Compared with vitamin K2 alone, combined recombinant human PTH (1-34) [rhPTH(1-34)] and vitamin K2 improved BMD and selected bone-turnover markers in a small, randomized study (141). This comparison does not establish the

additional benefit of vitamin K2 over PTH monotherapy. These results should not be interpreted as established superiority for fracture prevention without adequately powered comparative trials.

sCT, a peptide hormone, exhibits clinical efficacy in inhibiting osteoclast activity, thereby regulating bone metabolism. A meta-analysis reported changes in selected biochemical

outcomes with intranasal sCT but did not establish clear superiority for BMD outcomes or for combination treatment over conventional therapy alone (142). Furthermore, sCT is susceptible to rapid degradation, attributed to its short half-life and inherent instability. This characteristic substantially restricts its clinical utility. Zhang *et al* (143) engineered a microsphere formulation for encapsulating sCT. This innovation has achieved a decrease in the dosing frequency and an extension of the sustained-release duration, suggesting that this formulation may improve sCT delivery for PMO treatment (143). Formulation improvements do not establish superior antifracture efficacy. CT has a limited role in contemporary osteoporosis management and is generally considered only when more effective alternatives are unsuitable (115).

5. Discussion

PMO is a globally prevalent skeletal disorder with far reaching implications for women's health, intricately intertwined with the hormonal perturbations that accompany menopause. The present review has provided an in-depth exploration of the complex interplay between hormonal changes and the development of PMO, as well as the current and emerging therapeutic modalities.

Overall, current evidence supports estrogen deficiency as a central, but not isolated, endocrine event in PMO. Ovarian aging is accompanied by broader hormonal remodeling involving FSH, the PTH-vitamin D axis, OT and CT, and these changes converge on shared regulatory systems including the basic multicellular unit, osteoimmune signaling, calcium homeostasis, and the gut-bone axis. This network-based perspective helps explain why postmenopausal bone loss cannot be fully attributed to a single hormone or signaling pathway. However, the maturity of evidence differs substantially among these components. While several endocrine relationships are well established, the direct skeletal contributions of FSH, OT, CT, and specific gut microbial signals remain incompletely validated in humans. A key unresolved question is therefore how to distinguish endocrine changes that are associated with bone loss from those that have a causal role in skeletal deterioration. Future studies should place greater emphasis on longitudinal human data and interventional validation of these pathways.

In the realm of therapeutic strategies, HRT has been a cornerstone in the management of PMO. It has demonstrated efficacy in preventing and ameliorating osteoporosis by replenishing estrogen levels. However, the use of HRT is marred by concerns over an increased risk of cardiovascular disease and breast cancer. This risk benefit ratio is a critical consideration in clinical decision making. Future research should focus on identifying reliable biomarkers that can accurately predict an individual woman's risk of developing these adverse events with HRT. This could enable the selection of women who are more likely to benefit from HRT while minimizing potential risks. Established tissue-selective estrogen complexes combine estrogen with a SERM; their suitability still depends on the treatment indication and individual risk profile (103).

Pharmacological therapies other than HRT, including bisphosphonates, PTH analogs, denosumab, raloxifene, and the sclerostin inhibitor romosozumab, each have their own unique advantages and limitations. Bisphosphonates, potent inhibitors

of osteoclast activity, are associated with potential adverse effects such as renal impairment, gastrointestinal disturbances, and osteonecrosis of the jaw. PTH analogs, while effective in stimulating osteogenesis, carry the risk of side effects such as leg cramps, nausea, dizziness, and an increased risk of kidney stones. An osteosarcoma signal was also observed in preclinical studies (116). Denosumab, a monoclonal antibody targeting RANKL, has shown remarkable efficacy in increasing BMD, but its use is complicated by a risk of vertebral fractures upon discontinuation. Raloxifene, a selective ER modulator, is effective in reducing the risk of vertebral fractures but has limited efficacy in preventing non-vertebral fractures. Romosozumab provides a distinct osteoanabolic strategy by targeting osteocyte-derived sclerostin, although its use requires careful consideration of cardiovascular risk. These limitations highlight the need for continuous innovation in drug development. For instance, the development of novel drug delivery systems, such as nanoparticle-based carriers or targeted drug-delivery platforms, could potentially mitigate the adverse effects of these drugs by enhancing their specificity and reducing off-target effects.

Non-pharmacological treatments, such as lifestyle modifications (including smoking cessation, avoidance of excessive alcohol intake and regular exercise) and calcium and vitamin D supplementation, are integral components of osteoporosis management. However, the optimal combination and dosage of these interventions for individual patients remain ill-defined. Future research should aim to develop personalized non-pharmacological treatment plans that consider a patient's age, menopausal status, genetic background, lifestyle factors and comorbidities.

The emerging potential therapies, including plant extracts, FSH-blockade therapy, OT-related interventions, PTH combination therapy and modified sCT therapy, are supported by varying levels of preclinical and clinical evidence. Taken together, these approaches span different stages of translational development. The aforementioned specific plant-derived compounds, together with FSH blockade and OT-related approaches, remain predominantly supported by preclinical evidence. OT supplementation has shown osteoprotective effects in animal models; however, whether these findings can be translated into effective therapies for PMO requires further clinical validation. By contrast, PTH-based combination therapy has begun to accumulate clinical evidence, whereas modified sCT has mainly been explored through formulation-based optimization. This heterogeneity in evidence maturity indicates that future studies should be tailored to the specific stage of each approach, with greater emphasis on human validation, long-term safety, comparative efficacy and appropriate patient selection.

Future studies should move beyond single-factor models toward experimentally testable designs. Factorial animal models combining estrogen withdrawal with controlled perturbation of FSH and the PTH-vitamin D axis could help distinguish independent from interactive endocrine effects on bone remodeling. For the gut-bone axis, candidate strains should be tested in germ-free or antibiotic-depleted models using defined colonization, rescue experiments and metabolic profiling to establish causality. Clinical studies should stratify perimenopausal and older postmenopausal women,

given their distinct endocrine profiles, fracture risks and comorbidity burdens. For FSH- and OT-targeted therapies, dose-response relationships, pharmacokinetics, pharmacodynamics, and long-term safety should be established before large efficacy trials; immunogenicity is an additional concern for antibody-based FSH blockade.

In conclusion, while significant strides have been made in elucidating the influence of postmenopausal hormone level changes on osteoporosis and developing treatment strategies, numerous knowledge gaps persist. Key gaps remain in fully elucidating the molecular mechanisms linking hormonal changes to bone remodeling, integrating multi-system regulatory interactions, and establishing long-term safety and individualized treatment strategies. Future research should be directed towards a more comprehensive understanding of the underlying molecular mechanisms, the improvement of existing therapies through innovative drug design and delivery systems, and the acceleration of the translation of novel treatments from bench to bedside. This will be essential for effectively managing PMO and reducing its associated morbidity and mortality, thereby improving the quality of life for postmenopausal women worldwide.

Acknowledgements

Not applicable.

Funding

The present review was supported by the Youth Science and Technology Program of the Jiangxi Provincial Department of Science and Technology (grant no. 20252BAC200538) and the Science and Technology Program of the Jiangxi Provincial Health Commission (grant no. 202310505).

Availability of data and materials

Not applicable.

Authors' contributions

CZ conceived and designed the study. WL, ZL and PW contributed equally to this work and were primarily responsible for drafting the manuscript. JZ, HZ, YX, RY, LY and SL participated in literature collection, data organization, and manuscript preparation. WL performed the language editing of the manuscript. CZ provided important intellectual input and critical comments during manuscript preparation. CZ supervised the overall study and performed the final critical revision of the manuscript. All authors contributed to the article, read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Yao Y, Cai X, Chen Y, Zhang M and Zheng C: Estrogen deficiency-mediated osteoimmunity in postmenopausal osteoporosis. *Med Res Rev* 45: 561-575, 2025.
2. Khosla S, Oursler MJ and Monroe DG: Estrogen and the skeleton. *Trends Endocrinol Metab* 23: 576-581, 2012.
3. Kanis JA, Melton LJ III, Christiansen C, Johnston CC and Khaltaev N: The diagnosis of osteoporosis. *J Bone Miner Res* 9: 1137-1141, 1994.
4. LeBoff MS, Greenspan SL, Insogna KL, Lewiecki EM, Saag KG, Singer AJ and Siris ES: The clinician's guide to prevention and treatment of osteoporosis. *Osteoporos Int* 33: 2049-2102, 2022.
5. Noel SE, Santos MP and Wright NC: Racial and ethnic disparities in bone health and outcomes in the United States. *J Bone Miner Res* 36: 1881-1905, 2021.
6. Wang L, Yu W, Yin X, Cui L, Tang S, Jiang N, Cui L, Zhao N, Lin Q, Chen L, *et al*: Prevalence of osteoporosis and fracture in China: The China osteoporosis prevalence study. *JAMA Netw Open* 4: e2121106, 2021.
7. LeBlanc ES, Hillier TA, Pedula KL, Rizzo JH, Cawthon PM, Fink HA, Cauley JA, Bauer DC, Black DM, Cummings SR and Browner WS: Hip fracture and increased short-term but not long-term mortality in healthy older women. *Arch Intern Med* 171: 1831-1837, 2011.
8. Almeida M, Laurent MR, Dubois V, Claessens F, O'Brien CA, Bouillon R, Vanderschueren D and Manolagas SC: Estrogens and androgens in skeletal physiology and pathophysiology. *Physiol Rev* 97: 135-187, 2017.
9. Aibar-Almazán A, Voltés-Martínez A, Castellote-Caballero Y, Afanador-Restrepo DF, Carcelén-Fraile MDC and López-Ruiz E: Current status of the diagnosis and management of osteoporosis. *Int J Mol Sci* 23: 9465, 2022.
10. Wang LT, Chen LR and Chen KH: Hormone-related and drug-induced osteoporosis: A cellular and molecular overview. *Int J Mol Sci* 24: 5814, 2023.
11. Cauley JA, Robbins J, Chen Z, Cummings SR, Jackson RD, LaCroix AZ, LeBoff M, Lewis CE, McGowan J, Neuner J, *et al*: Effects of estrogen plus progestin on risk of fracture and bone mineral density: The Women's Health Initiative randomized trial. *JAMA* 290: 1729-1738, 2003.
12. Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Kooperberg C, Stefanick ML, Jackson RD, Beresford SA, Howard BV, Johnson KC, *et al*: Risks and benefits of estrogen plus progestin in healthy postmenopausal women: Principal results From the Women's Health Initiative randomized controlled trial. *JAMA* 288: 321-333, 2002.
13. Sowers MR, Greendale GA, Bondarenko I, Finkelstein JS, Cauley JA, Neer RM and Ettinger B: Endogenous hormones and bone turnover markers in pre- and perimenopausal women: SWAN. *Osteoporos Int* 14: 191-197, 2003.
14. Mattick LJ, Bea JW, Hovey KM, Wactawski-Wende J, Cauley JA, Crandall CJ, Tian L and Ochs-Balcom HM: Follicle-stimulating hormone is associated with low bone mass in postmenopausal women. *Osteoporos Int* 34: 693-701, 2023.
15. Breuil V, Trojani MC and Ez-Zoubir A: Oxytocin and bone: Review and perspectives. *Int J Mol Sci* 22: 8551, 2021.
16. Silva BC and Bilezikian JP: Parathyroid hormone: Anabolic and catabolic actions on the skeleton. *Curr Opin Pharmacol* 22: 41-50, 2015.
17. Bellavia D, Costa V, De Luca A, Maglio M, Pagani S, Fini M and Giavaresi G: Vitamin D level between calcium-phosphorus homeostasis and immune system: New perspective in osteoporosis. *Curr Osteoporos Rep* 22: 599-610, 2024.
18. Xie J, Guo J, Kanwal Z, Wu M, Lv X, Ibrahim NA, Li P, Buabeid MA, Arafa EA and Sun Q: Calcitonin and bone physiology: In vitro, in vivo, and clinical investigations. *Int J Endocrinol* 2020: 3236828, 2020.
19. Wu M, Tang W, Chen Y, Xue L, Dai J, Li Y, Zhu X, Wu C, Xiong J, Zhang J, *et al*: Spatiotemporal transcriptomic changes of human ovarian aging and the regulatory role of FOXP1. *Nat Aging* 4: 527-545, 2024.
20. Wang S, Zheng Y, Li J, Yu Y, Zhang W, Song M, Liu Z, Min Z, Hu H, Jing Y, *et al*: Single-cell transcriptomic atlas of primate ovarian aging. *Cell* 180: 585-600.e19, 2020.

21. Jin C, Wang X, Yang J, Kim S, Hudgins AD, Gamliel A, Pei M, Contreras D, Devos M, Guo Q, *et al*: Molecular and genetic insights into human ovarian aging from single-nuclei multi-omics analyses. *Nat Aging* 5: 275-290, 2025.
22. Talaulikar V: Menopause transition: Physiology and symptoms. *Best Pract Res Clin Obstet Gynaecol* 81: 3-7, 2022.
23. Guo Z and Yu Q: Role of mTOR signaling in female reproduction. *Front Endocrinol (Lausanne)* 10: 692, 2019.
24. Xu D, Song S, Wang F, Li Y, Li Z, Yao H, Zhao Y and Zhao Z: Single-cell transcriptomic atlas of goat ovarian aging. *J Anim Sci Biotechnol* 14: 151, 2023.
25. Cai H, Chang T, Li Y, Jia Y, Li H, Zhang M, Su P, Zhang L and Xiang W: Circular DDX10 is associated with ovarian function and assisted reproductive technology outcomes through modulating the proliferation and steroidogenesis of granulosa cells. *Aging (Albany NY)* 13: 9592-9612, 2021.
26. Piccinni MP, Vicenti R, Logiodice F, Fabbri R, Kullolli O, Pallecchi M, Paradisi R, Danza G, Macciocca M, Lombardelli L and Seracchioli R: Description of the follicular fluid cytokine and hormone profiles in human physiological natural cycles. *J Clin Endocrinol Metab* 106: e721-e738, 2021.
27. Sherman BM and Korenman SG: Hormonal characteristics of the human menstrual cycle throughout reproductive life. *J Clin Invest* 55: 699-706, 1975.
28. Kawakita T, Yasui T, Yoshida K, Matsui S and Iwasa T: Associations of LH and FSH with reproductive hormones depending on each stage of the menopausal transition. *BMC Womens Health* 23: 286, 2023.
29. Burger HG, Hale GE, Dennerstein L and Robertson DM: Cycle and hormone changes during perimenopause: The key role of ovarian function. *Menopause* 15: 603-612, 2008.
30. Rasul S, Mashayekhi Y, Javaid M, Merie S, Khalaf MA, Ahmed T, Haris M and Mustafa I: Hormonal changes during menopause and their impact on bone health: Insights from orthopedic and reproductive medicine. *Cureus* 17: e93224, 2025.
31. Korkmaz H, Deveci CD, Üstün Y and Pehlivanoglu B: Comparison of plasma oxytocin level in women with natural and surgical menopause. *Endocrine* 82: 209-214, 2023.
32. Liu N, Yang H, Han L and Ma M: Oxytocin in women's health and disease. *Front Endocrinol (Lausanne)* 13: 786271, 2022.
33. Eastell R, Yergey AL, Vieira NE, Cedel SL, Kumar R and Riggs BL: Interrelationship among vitamin D metabolism, true calcium absorption, parathyroid function, and age in women: Evidence of an age-related intestinal resistance to 1,25-dihydroxyvitamin D action. *J Bone Miner Res* 6: 125-132, 1991.
34. Filipović B, Ajdžanović V, Živanović J, Trifunović S, Ristić N, Milošević V and Šošić-Jurjević B: Age-related changes in calcitonin-producing thyroid C-cells of male wistar rats. *Microsc Microanal*: 1-9, 2022 (Epub ahead of print).
35. Suzuki N, Yamamoto K, Sasayama Y, Suzuki T, Kurokawa T, Kambegawa A, Srivastav AK, Hayashi S and Kikuyama S: Possible direct induction by estrogen of calcitonin secretion from ultimobranchial cells in the goldfish. *Gen Comp Endocrinol* 138: 121-127, 2004.
36. Fleet JC: Vitamin D-mediated regulation of intestinal calcium absorption. *Nutrients* 14: 3351, 2022.
37. Alinia T, Sabour S, Hashemipour M, Hovsepian S, Pour HR and Jahanfar S: Relationship between vitamin D levels and age of menopause and reproductive lifespan: Analysis based on the National health and nutrition examination survey (NHANES) 2001-2018. *Eur J Obstet Gynecol Reprod Biol* 289: 183-189, 2023.
38. Sharma M and Kalra S: Vitamin D and menopause. *J Pak Med Assoc* 74: 815-817, 2024.
39. Holick MF, Matsuoka LY and Wortsman J: Age, vitamin D, and solar ultraviolet. *Lancet* 2: 1104-1105, 1989.
40. Jo JY, Lee YJ, Seo HK, Kang MJ, Cho IA, Choi WJ, Kim SC and Cho MC: Vitamin D status and bone health in postmenopausal women working in greenhouses. *J Menopausal Med* 28: 70-77, 2022.
41. Ciarambino T, Crispino P, Minervini G and Giordano M: Vitamin D: Can gender medicine have a role? *Biomedicines* 11: 1762, 2023.
42. Ma Q, Miri Z, Haugen HJ, Moghanian A and Loca D: Significance of mechanical loading in bone fracture healing, bone regeneration, and vascularization. *J Tissue Eng* 14: 20417314231172573, 2023.
43. Kular J, Tickner J, Chim SM and Xu J: An overview of the regulation of bone remodelling at the cellular level. *Clin Biochem* 45: 863-873, 2012.
44. Huber C, Collishaw S, Mosley JR, Reeve J and Noble BS: Selective estrogen receptor modulator inhibits osteocyte apoptosis during abrupt estrogen withdrawal: Implications for bone quality maintenance. *Calcif Tissue Int* 81: 139-144, 2007.
45. Geoghegan IP, McNamara LM and Hoey DA: Estrogen withdrawal alters cytoskeletal and primary ciliary dynamics resulting in increased Hedgehog and osteoclastogenic paracrine signalling in osteocytes. *Sci Rep* 11: 9272, 2021.
46. Lewis KJ, Cabahug-Zuckerman P, Boorman-Padgett JF, Basta-Pljakic J, Louie J, Stephen S, Spray DC, Thi MM, Seref-Ferlengez Z, Majeska RJ, *et al*: Estrogen depletion on in vivo osteocyte calcium signaling responses to mechanical loading. *Bone* 152: 116072, 2021.
47. Iwamoto R, Koide M, Udagawa N and Kobayashi Y: Positive and negative regulators of sclerostin expression. *Int J Mol Sci* 23: 4895, 2022.
48. McNamara LM: Osteocytes and estrogen deficiency. *Curr Osteoporos Rep* 19: 592-603, 2021.
49. Ponzetti M and Rucci N: Osteoblast differentiation and signaling: Established concepts and emerging topics. *Int J Mol Sci* 22: 6651, 2021.
50. Naqvi SM, Panadero Pérez JA, Kumar V, Verbruggen ASK and McNamara LM: A novel 3D osteoblast and osteocyte model revealing changes in mineralization and pro-osteoclastogenic paracrine signaling during estrogen deficiency. *Front Bioeng Biotechnol* 8: 601, 2020.
51. Zuo HL, Xin H, Yan XN, Huang J, Zhang YP and Du H: 17 β -Estradiol improves osteoblastic cell function through the Sirt1/NF- κ B/MMP-8 pathway. *Climacteric* 23: 404-409, 2020.
52. Guo L, Chen K, Yuan J, Huang P, Xu X, Li C, Qian N, Qi J, Shao Z, Deng L, *et al*: Estrogen inhibits osteoclasts formation and bone resorption via microRNA-27a targeting PPAR γ and APC. *J Cell Physiol* 234: 581-594, 2018.
53. Fan JZ, Yang L, Meng GL, Lin YS, Wei BY, Fan J, Hu HM, Liu YW, Chen S, Zhang JK, *et al*: Estrogen improves the proliferation and differentiation of hBMSCs derived from postmenopausal osteoporosis through notch signaling pathway. *Mol Cell Biochem* 392: 85-93, 2014.
54. Liu Z, Lee HL, Suh JS, Deng P, Lee CR, Bezouglaia O, Mirnia M, Chen V, Zhou M, Cui ZK, *et al*: The ER α /KDM6B regulatory axis modulates osteogenic differentiation in human mesenchymal stem cells. *Bone Res* 10: 3, 2022.
55. Zhang W, Dang K, Huai Y and Qian A: Osteoimmunology: The regulatory roles of T lymphocytes in osteoporosis. *Front Endocrinol (Lausanne)* 11: 465, 2020.
56. Zhang J, Fu Q, Ren Z, Wang Y, Wang C, Shen T, Wang G and Wu L: Changes of serum cytokines-related Th1/Th2/Th17 concentration in patients with postmenopausal osteoporosis. *Gynecol Endocrinol* 31: 183-190, 2015.
57. Sang C, Zhang J, Zhang Y, Chen F, Cao X and Guo L: TNF- α promotes osteoclastogenesis through JNK signaling-dependent induction of Semaphorin3D expression in estrogen-deficiency induced osteoporosis. *J Cell Physiol* 232: 3396-3408, 2017.
58. Li CH, Ma ZZ, Jian LL, Wang XY, Sun L, Liu XY, Yao ZQ and Zhao JX: Igaratimod inhibits osteoclastogenesis by modulating the RANKL and TNF- α signaling pathways. *Int Immunopharmacol* 90: 107219, 2021.
59. Liu Z, Li C, Huang P, Hu F, Jiang M, Xu X, Li B, Deng L, Ye T and Guo L: CIRC-Hmbox1 targeting miRNA-1247-5p is involved in the regulation of bone metabolism by TNF- α in postmenopausal osteoporosis. *Front Cell Dev Biol* 8: 594785, 2020.
60. Li S, Liu G and Hu S: Osteoporosis: Interferon-gamma-mediated bone remodeling in osteoimmunology. *Front Immunol* 15: 1396122, 2024.
61. Bhadriraja H, Patel V, Singh AK, Savardekar L, Patil A, Surve S and Desai M: Increased frequency of Th17 cells and IL-17 levels are associated with low bone mineral density in postmenopausal women. *Sci Rep* 11: 16155, 2021.
62. Zhang Z, Tao Z, Zhang Z, Zhang W, Zhang X, Xu X, Gao R, Tao X and Zhou X: Single-cell transcriptomic analysis reveals AP-1 downregulation remodels bone marrow environment and contributes to osteopenia in ovariectomized mice. *J Orthop Translat* 52: 1-13, 2025.
63. Lagerquist MK, Gupta P, Sehic E, Horkeby KL, Scheffler JM, Nordqvist J, Lawenius L, Islander U, Corciulo C, Henning P, *et al*: Reduction of mature B cells and immunoglobulins results in increased trabecular bone. *JBM Plus* 6: e10670, 2022.
64. Xu Q, Li D, Chen J, Yang J, Yan J, Xia Y, Zhang F, Wang X and Cao H: Crosstalk between the gut microbiota and postmenopausal osteoporosis: Mechanisms and applications. *Int Immunopharmacol* 110: 108998, 2022.

65. Shieh A, Epeldegui M, Karlamangla AS and Greendale GA: Gut permeability, inflammation, and bone density across the menopause transition. *JCI Insight* 5: e134092, 2020.
66. Sprouse JC, Sampath C and Gangula PR: Supplementation of 17 β -estradiol normalizes rapid gastric emptying by restoring impaired Nrf2 and nNOS function in obesity-induced diabetic ovariectomized mice. *Antioxidants (Basel)* 9: 582, 2020.
67. Meng Q, Ma M, Zhang W, Bi Y, Cheng P, Yu X, Fu Y, Chao Y, Ji T, Li J, *et al*: The gut microbiota during the progression of atherosclerosis in the perimenopausal period shows specific compositional changes and significant correlations with circulating lipid metabolites. *Gut Microbes* 13: 1-27, 2021.
68. Chen T, Wang N, Hao Y and Fu L: Fecal microbiota transplantation from postmenopausal osteoporosis human donors accelerated bone mass loss in mice. *Front Cell Infect Microbiol* 14: 1488017, 2024.
69. Zeng HQ, Li G, Zhou KX, Li AD, Liu W and Zhang Y: Causal link between gut microbiota and osteoporosis analyzed via Mendelian randomization. *Eur Rev Med Pharmacol Sci* 28: 542-555, 2024.
70. Wei Q, Zhou Y, Hu Z, Shi Y, Ning Q, Ren K, Guo X, Zhong R, Xia Z, Yin Y, *et al*: Function-oriented mechanism discovery of coumarins from *Psoralea corylifolia* L. in the treatment of ovariectomy-induced osteoporosis based on multi-omics analysis. *J Ethnopharmacol* 329: 118130, 2024.
71. Zhang J, Zhang Q, Liu H, Liu X, Yu Y, Han D, He X, Zeng P and Wang J: Soy-whey dual-protein alleviates osteoporosis of ovariectomized rats via regulating bone fat metabolism through gut-liver-bone axis. *Nutrition* 103-104: 111723, 2022.
72. Liang Z, Hao Y, Yang L, Yuan P, Kang W, Liang T, Gu B and Dong B: The potential of *Klebsiella* and *Escherichia-Shigella* and amino acids metabolism to monitor patients with postmenopausal osteoporosis in northwest China. *BMC Microbiol* 23: 199, 2023.
73. Huang R, Liu P, Bai Y, Huang J, Pan R, Li H, Su Y, Zhou Q, Ma R, Zong S and Zeng G: Changes in the gut microbiota of osteoporosis patients based on 16S rRNA gene sequencing: A systematic review and meta-analysis. *J Zhejiang Univ Sci B* 23: 1002-1013, 2022.
74. Feng B, Lu J, Han Y, Han Y, Qiu X and Zeng Z: The role of short-chain fatty acids in the regulation of osteoporosis: New perspectives from gut microbiota to bone health: A review. *Medicine (Baltimore)* 103: e39471, 2024.
75. Tyagi AM, Yu M, Darby TM, Vaccaro C, Li JY, Owens JA, Hsu E, Adams J, Weitzmann MN, Jones RM and Pacifici R: The microbial metabolite butyrate stimulates bone formation via T regulatory cell-mediated regulation of WNT10B expression. *Immunity* 49: 1116-1131.e7, 2018.
76. Lucas S, Omata Y, Hofmann J, Böttcher M, Iljazovic A, Sarter K, Albrecht O, Schulz O, Krishnacoumar B, Krönke G, *et al*: Short-chain fatty acids regulate systemic bone mass and protect from pathological bone loss. *Nat Commun* 9: 55, 2018.
77. Li S, Wang J, Zhang Y, Wang J, Zhou T, Xie Y, Zhou Y, Tang L, Hu L, Dong Q and Sun P: Gut microbiota and short-chain fatty acids signatures in postmenopausal osteoporosis patients: A retrospective study. *Medicine (Baltimore)* 103: e40554, 2024.
78. Yuan Y, Li J, Wang K, Li J and Wei H: Meta-analysis of the effects of probiotic supplementation on bone turnover markers in middle-aged and elderly patients with osteoporosis. *Front Cell Infect Microbiol* 15: 1738378, 2026.
79. Yu J, Cao G, Yuan S, Luo C, Yu J and Cai M: Probiotic supplements and bone health in postmenopausal women: A meta-analysis of randomised controlled trials. *BMJ Open* 11: e041393, 2021.
80. Liu Z, Tong H, Su B, Yu M and Chen Y: The non-linear associations of serum follicle-stimulating hormone levels with bone mineral density and the risk of osteoporosis during menopausal transition: An analysis of national health and nutrition examination survey data. *Endocrine* 80: 212-220, 2023.
81. Zheng Y, Li J, Li Y, Wang J, Suo C, Jiang Y, Jin L, Xu K and Chen X: Plasma proteomic profiles reveal proteins and three characteristic patterns associated with osteoporosis: A prospective cohort study. *J Adv Res* 75: 491-503, 2025.
82. Huang J, Zhang Z, He P and Zhou J: Possible mechanisms underlying the regulation of postmenopausal osteoporosis by follicle-stimulating hormone. *Heliyon* 10: e35405, 2024.
83. Dunietz GL, Tittle LJ, Mumford SL, O'Brien LM, Baylin A, Schisterman EF, Chervin RD and Young LJ: Oxytocin and women's health in midlife. *J Endocrinol* 262: e230396, 2024.
84. Tamma R, Colaizzi G, Zhu LL, DiBenedetto A, Greco G, Montemurro G, Patano N, Strippoli M, Vergari R, Mancini L, *et al*: Oxytocin is an anabolic bone hormone. *Proc Natl Acad Sci USA* 106: 7149-7154, 2009.
85. Du Y, Xu C, Shi H, Jiang X, Tang W, Wu X, Chen M, Li H, Zhang X and Cheng Q: Serum concentrations of oxytocin, DHEA and follistatin are associated with osteoporosis or sarcopenia in community-dwelling postmenopausal women. *BMC Geriatr* 21: 542, 2021.
86. Moghazy H, Abdeen Mahmoud A, Elbadre H and Abdel Aziz HO: Protective effect of oxytocin against bone loss in a female rat model of osteoporosis. *Rep Biochem Mol Biol* 9: 147-155, 2020.
87. Martin TJ: Bone biology and anabolic therapies for bone: Current status and future prospects. *J Bone Metab* 21: 8-20, 2014.
88. Taipaleenmäki H, Saito H, Schröder S, Maeda M, Mettler R, Ring M, Rollmann E, Gasser A, Haasper C, Gehrke T, *et al*: Antagonizing microRNA-19a/b augments PTH anabolic action and restores bone mass in osteoporosis in mice. *EMBO Mol Med* 14: e13617, 2022.
89. Fernandez C, Tennyson J and Priscilla AS: Osteoporosis and its association with vitamin D receptor, oestrogen α receptor, parathyroid receptor and collagen type I alpha receptor gene polymorphisms with bone mineral density: A pilot study from South Indian postmenopausal women of Tamil Nadu. *Biochem Genet* 60: 2015-2036, 2022.
90. Abdi S, Almiman AA, Ansari MGA, Alnaami AM, Mohammed AK, Aljohani NJ, Alenad A, Alghamdi A, Alokail MS and Al-Daghri NM: PTHR1 genetic polymorphisms are associated with osteoporosis among postmenopausal arab women. *Biomed Res Int* 2021: 2993761, 2021.
91. Martin TJ, Robinson CJ and MacIntyre I: The mode of action of thyrocalcitonin. *Lancet* 1: 900-902, 1966.
92. Naot D and Cornish J: The role of peptides and receptors of the calcitonin family in the regulation of bone metabolism. *Bone* 43: 813-818, 2008.
93. Farley JR, Tarbaux NM, Hall SL, Linkhart TA and Baylink DJ: The anti-bone-resorptive agent calcitonin also acts in vitro to directly increase bone formation and bone cell proliferation. *Endocrinology* 123: 159-167, 1988.
94. Cornish J, Callon KE, Cooper GJ and Reid IR: Amylin stimulates osteoblast proliferation and increases mineralized bone volume in adult mice. *Biochem Biophys Res Commun* 207: 133-139, 1995.
95. Chesnut CH III, Silverman S, Andriano K, Genant H, Gimona A, Harris T, Kiel D, LeBoff M, Maricic M, Miller P, *et al*: A randomized trial of nasal spray salmon calcitonin in postmenopausal women with established osteoporosis: The prevent recurrence of osteoporotic fractures study. PROOF Study Group. *Am J Med* 109: 267-276, 2000.
96. Chen X, Shen L, Gao C, Weng R, Fan Y, Xu S, Zhang Z and Hu W: Vitamin D status and its associations with bone mineral density, bone turnover markers, and parathyroid hormone in Chinese postmenopausal women with osteopenia and osteoporosis. *Front Nutr* 10: 1307896, 2024.
97. Al-Rawaf HA, Alghadir AH and Gabr SA: Circulating MicroRNA expression, vitamin D, and hypercortisolism as predictors of osteoporosis in elderly postmenopausal women. *Dis Markers* 2021: 3719919, 2021.
98. Mondockova V, Kovacova V, Zemanova N, Babikova M, Martiniakova M, Galbavy D and Omelka R: Vitamin D receptor gene polymorphisms affect osteoporosis-related traits and response to antiresorptive therapy. *Genes (Basel)* 14: 193, 2023.
99. Santoro N and Randolph JF Jr: Reproductive hormones and the menopause transition. *Obstet Gynecol Clin North Am* 38: 455-466, 2011.
100. Gallagher JC, Riggs BL and DeLuca HF: Effect of estrogen on calcium absorption and serum vitamin D metabolites in postmenopausal osteoporosis. *J Clin Endocrinol Metab* 51: 1359-1364, 1980.
101. Gallagher JC and Sai AJ: Vitamin D insufficiency, deficiency, and bone health. *J Clin Endocrinol Metab* 95: 2630-2633, 2010.
102. Colaizzi G, Sun L, Di Benedetto A, Tamma R, Zhu LL, Cao J, Grano M, Yuen T, Colucci S, Cuscito C, *et al*: Bone marrow oxytocin mediates the anabolic action of estrogen on the skeleton. *J Biol Chem* 287: 29159-29167, 2012.
103. 'The 2022 Hormone Therapy Position Statement of The North American Menopause Society' Advisory Panel: The 2022 hormone therapy position statement of The North American menopause society. *Menopause* 29: 767-794, 2022.
104. Stevenson TEJ, Brincat MP, Pollacco J and Stevenson JC: Effect of hormone replacement therapy on intervertebral disc height. *Climacteric* 26: 110-113, 2023.
105. Gamsjaeger S, Eriksen EF and Paschalis EP: Effect of hormone replacement therapy on bone formation quality and mineralization regulation mechanisms in early postmenopausal women. *Bone Rep* 14: 101055, 2021.

106. Vigneswaran K and Hamoda H: Hormone replacement therapy-current recommendations. *Best Pract Res Clin Obstet Gynaecol* 81: 8-21, 2022.
107. Gosset A, Pouillès JM and Trémollières F: Menopausal hormone therapy for the management of osteoporosis. *Best Pract Res Clin Endocrinol Metab* 35: 101551, 2021.
108. Weller SC, Davis JW, Porterfield L, Chen L and Wilkinson G: Hormone exposure and venous thromboembolism in commercially insured women aged 50 to 64 years. *Res Pract Thromb Haemost* 7: 100135, 2023.
109. Lorentzon M, Johansson H, Harvey NC, Liu E, Vandenput L, Crandall CJ, Cauley JA, LeBoff MS, McCloskey EV and Kanis JA: Menopausal hormone therapy reduces the risk of fracture regardless of falls risk or baseline FRAX probability-results from the women's health initiative hormone therapy trials. *Osteoporos Int* 33: 2297-2305, 2022.
110. Vinogradova Y, Iyen B, Masud T, Taylor L and Kai J: Discontinuation of menopausal hormone therapy and risk of fracture: Nested case-control studies using routinely collected primary care data. *Lancet Healthy Longev* 6: 100729, 2025.
111. Platt O, Bateman J and Bakour S: Impact of menopause hormone therapy, exercise, and their combination on bone mineral density and mental wellbeing in menopausal women: A scoping review. *Front Reprod Health* 7: 1542746, 2025.
112. Arnautu AM, Nimigeen VR, Nacea-Radu CA, Tilici DM and Paun DL: Menopausal hormone therapy-risks, benefits and emerging options: A narrative review. *Int J Mol Sci* 26: 11098, 2025.
113. Yong EL and Logan S: Menopausal osteoporosis: Screening, prevention and treatment. *Singapore Med J* 62: 159-166, 2021.
114. Leder BZ: Parathyroid hormone and parathyroid hormone-related protein analogs in osteoporosis therapy. *Curr Osteoporos Rep* 15: 110-119, 2017.
115. Eastell R, Rosen CJ, Black DM, Cheung AM, Murad MH and Shoback D: Pharmacological management of osteoporosis in postmenopausal women: An endocrine society* clinical practice guideline. *J Clin Endocrinol Metab* 104: 1595-1622, 2019.
116. Krege JH, Gilsen AW, Komacko JL and Kellier-Steele N: Teriparatide and osteosarcoma risk: History, science, elimination of boxed warning, and other label updates. *JBM Plus* 6: e10665, 2022.
117. Ayers C, Kansagara D, Lazur B, Fu R, Kwon A and Harrod C: Effectiveness and safety of treatments to prevent fractures in people with low bone mass or primary osteoporosis: A living systematic review and network meta-analysis for the american college of physicians. *Ann Intern Med* 176: 182-195, 2023.
118. Eghbali-Fatourehchi G, Khosla S, Sanyal A, Boyle WJ, Lacey DL and Riggs BL: Role of RANK ligand in mediating increased bone resorption in early postmenopausal women. *J Clin Invest* 111: 1221-1230, 2003.
119. Chen Y, Zhu J, Zhou Y, Peng J and Wang B: Efficacy and safety of denosumab in osteoporosis or low bone mineral density postmenopausal women. *Front Pharmacol* 12: 588095, 2021.
120. U.S Food and Drug Administration (FDA): FDA adds Boxed Warning for increased risk of severe hypocalcemia in patients with advanced chronic kidney disease taking osteoporosis medicine Prolia (denosumab). FDA, 2024. <https://www.fda.gov/drugs/drug-safety-communications/fda-adds-boxed-warnin-g-increased-risk-severe-hypocalcemia-patients-advanced-chronic-kidney-disease>. Accessed October 8, 2026.
121. Reid IR and Billington EO: Drug therapy for osteoporosis in older adults. *Lancet* 399: 1080-1092, 2022.
122. Ho WC, Chang CC, Wu WT, Lee RP, Yao TK, Peng CH and Yeh KT: Effect of osteoporosis treatments on osteoarthritis progression in postmenopausal women: A review of the literature. *Curr Rheumatol Rep* 26: 188-195, 2024.
123. Snyder KR, Sparano N and Malinowski JM: Raloxifene hydrochloride. *Am J Health Syst Pharm* 57: 1669-1678, 2000.
124. Lewiecki EM, Miller PD, Harris ST, Bauer DC, Davison KS, Dian L, Hanley DA, McClung MR, Yuen CK and Kendler DL: Understanding and communicating the benefits and risks of denosumab, raloxifene, and teriparatide for the treatment of osteoporosis. *J Clin Densitom* 17: 490-495, 2014.
125. Cosman F, Crittenden DB, Adachi JD, Binkley N, Czerwinski E, Ferrari S, Hofbauer LC, Lau E, Lewiecki EM, Miyauchi A, et al: Romosozumab treatment in postmenopausal women with osteoporosis. *N Engl J Med* 375: 1532-1543, 2016.
126. Wong RMY, Wong PY, Liu C, Wong HY, Fong MK, Zhang N, Cheung WH and Law SW: Treatment effects, adverse outcomes and cardiovascular safety of romosozumab-existing worldwide data: A systematic review and meta-analysis. *J Orthop Translat* 48: 107-122, 2024.
127. National Library of Medicine: EVENITY (romosozumab-aqqg) injection, solution. <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=471baba2-7154-4488-9891-0db2f46791e7>. Accessed October 8, 2026.
128. Mohebbi R, Shojaa M, Kohl M, von Stengel S, Jakob F, Kerschhan-Schindl K, Lange U, Peters S, Thomasius F, Uder M and Kemmler W: Exercise training and bone mineral density in postmenopausal women: An updated systematic review and meta-analysis of intervention studies with emphasis on potential moderators. *Osteoporos Int* 34: 1145-1178, 2023.
129. Wang T, Liu Q, Tjhiow W, Zhao J, Lu A, Zhang G, Tan RX, Zhou M, Xu J and Feng HT: Therapeutic potential and outlook of alternative medicine for osteoporosis. *Curr Drug Targets* 18: 1051-1068, 2017.
130. Yan XJ, Wang ZJ, Wang H, Wei MZ, Chen YC, Zhao YL and Luo XD: Formononetin derivative for osteoporosis by simultaneous regulating osteoblast and osteoclast. *J Nat Prod* 87: 2004-2013, 2024.
131. Chen G, Chen Y, Hong J, Gao J and Xu Z: Secoisolariciresinol diglucoside regulates estrogen receptor expression to ameliorate OVX-induced osteoporosis. *J Orthop Surg Res* 18: 792, 2023.
132. Wei Q, Ouyang M, Guo X, Fu X, Liu T, Luo Y, Tang H, Yang Y, Gao X and Mao H: Effect of hypeside on osteoporosis in ovariectomized mice through estrogen receptor α /ITG β 3 signaling pathway. *Eur J Pharmacol* 977: 176666, 2024.
133. Yang J, Cong N, Shi D, Chen S, Zhang Z and Zhao P: Siwu decoction exerts a phytoestrogenic osteoprotective effect on postmenopausal osteoporosis via the estrogen receptor/phosphatidylinositol 3-kinase/serine/threonine protein kinase pathway. *J Ethnopharmacol* 332: 118366, 2024.
134. Inpan R, Na Takuathung M, Sakuludomkan W, Dukaew N, Teekachunhatean S and Koonrunsesomboon N: Isoflavone intervention and its impact on bone mineral density in postmenopausal women: A systematic review and meta-analysis of randomized controlled trials. *Osteoporos Int* 35: 413-430, 2024.
135. Zaidi M, Yuen T and Kim SM: Pituitary crosstalk with bone, adipose tissue and brain. *Nat Rev Endocrinol* 19: 708-721, 2023.
136. Gera S, Kuo TC, Gumerova AA, Korkmaz F, Sant D, DeMambro V, Sudha K, Padilla A, Prevot G, Munitz J, et al: FSH-blocking therapeutic for osteoporosis. *Elife* 11: e78022, 2022.
137. Ning Q, Li M, Liao Z, Chen E, Liu H, Liang Y, Chen Y, Li Y and Huang L: LncRNA MRF targeting FSHR inhibits the osteogenic differentiation of BMSCs and bone defect repair through the regulation of the cAMP-PKA-CREB signaling pathway. *Stem Cell Res Ther* 16: 200, 2025.
138. Santos LFG, Fernandes-Breitenbach F, Silva RAS, Santos DR, Peres-Ueno MJ, Ervolino E, Chaves-Neto AH and Dornelles RCM: The action of oxytocin on the bone of senescent female rats. *Life Sci* 297: 120484, 2022.
139. Mohammadi SM, Karimi S, Saniee N, Kamyari N and Radmanesh E: The effect of oxytocin on osteoporosis improvement: A systematic review. *Med J Islam Repub Iran* 38: 140, 2024.
140. Wei K, Qu Y, Gao Y and Ma Y: Comparison of efficacy of teriparatide (parathyroid hormone 1-34) alone and in combination with zoledronic acid for osteoporosis in postmenopausal women. *J Coll Physicians Surg Pak* 31: 240-242, 2021.
141. Zhang Z, Xia K, Gong W, Mai R, Liu P and Lu Z: Efficacy of recombinant human parathyroid hormone 1-34 and vitamin K2 combination therapy in postmenopausal osteoporosis. *Horm Metab Res* 57: 33-38, 2025.
142. Li N, Gong YC and Chen J: A meta-analysis of the therapeutic effect of intranasal salmon calcitonin on osteoporosis. *Eur J Med Res* 26: 140, 2021.
143. Zhang X, Chen J, Cui Y, Yan G, Tang H, Man Y, Yang J, Bi Y and Teng L: A size-switchable microsphere loaded with salmon calcitonin as two-weekly dosing for osteoporosis therapy. *Eur J Pharm Biopharm* 205: 114565, 2024.
144. Cummings SR, San Martin J, McClung MR, Siris ES, Eastell R, Reid IR, Delmas P, Zoog HB, Austin M, Wang A, et al: Denosumab for prevention of fractures in postmenopausal women with osteoporosis. *N Engl J Med* 361: 756-765, 2009.
145. Burt LA, Billington EO, Rose MS, Raymond DA, Hanley DA and Boyd SK: Effect of high-dose vitamin D supplementation on volumetric bone density and bone strength: A randomized clinical trial. *JAMA* 322: 736-745, 2019.

