Hormone Replacement Therapy in the Prevention and Management of Postmenopausal Osteoporosis

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Abstract

Osteoporosis is a major postmenopausal health concern characterized by reduced bone mineral density (BMD) and deterioration of bone microarchitecture, leading to an increased risk of fractures. Estrogen deficiency during menopause is the key factor underlying postmenopausal osteoporosis. Hormone Replacement Therapy (HRT) has demonstrated significant efficacy in preventing bone loss, improving BMD, and reducing fracture risk. However, concerns about cardiovascular events, breast cancer, thromboembolism, and other adverse effects have limited its widespread use. This review provides an updated overview of the pathophysiology of postmenopausal osteoporosis, the role of estrogen, the efficacy of HRT in fracture prevention, associated risks, alternative therapies, current global guidelines, and future perspectives. When used judiciously and tailored to the individual, HRT remains an effective option to preserve skeletal health and improve quality of life in postmenopausal women.

Keywords: Hormone Replacement Therapy (HRT), Postmenopausal women, Osteoporosis, Bone health, Estrogen therapy, Menopause, Fracture prevention, Bone mineral density (BMD), Skeletal health.

1.INTRODUCTION

Osteoporosis has evolved from being considered an inevitable consequence of aging to being recognized as a major chronic, non-communicable disease with clear diagnostic criteria, risk assessment tools, and effective treatment strategies (1,2). Several therapies are available to preserve or increase bone mineral density (BMD), with bisphosphonates often recommended for women with established osteoporosis and high fracture risk. However, much of the early evidence was based on observational studies, which are weaker compared to randomized controlled trials. Findings from the Women's Health Initiative (WHI) and subsequent analyses revealed that the benefit–risk profile of menopausal hormone therapy (MHT) depends on the timing of initiation relative to menopause (5).

Globally, osteoporosis has become a significant health concern. Vertebral and hip fractures, the most serious complications, are associated with increased morbidity and mortality. Recent large

placebo-controlled trials have demonstrated that pharmacological agents can reduce fracture risk by 30–50% (4). Nearly one in three women over the age of 50 is affected, and fracture incidence is expected to rise by 25% in the coming decade due to population aging (3).

The World Health Organization defines menopause as the permanent cessation of menstruation for 12 consecutive months. In India, the average age of menopause is 46.2 years, with 27.7% of women aged 40 years or above, underscoring the public health importance of postmenopausal bone health (9). Estrogen deficiency accelerates bone loss, particularly trabecular bone, during the menopausal transition. This link between menopause and bone fragility was first highlighted by Albright in 1947, who demonstrated that estrogen therapy helps maintain bone mass and reduce fracture risk (11).

Postmenopausal osteoporosis, often termed Type I osteoporosis, results from estrogen deficiency and may cause up to 50% trabecular bone loss. Type II, or senile osteoporosis, is age-related, affects both sexes, and is a major cause of hip fractures in the elderly (1).

2. PATHOPHYSIOLOGY OF POSTMENOPAUSAL OSTEOPOROSIS

Estrogen deficiency is the primary mechanism underlying postmenopausal osteoporosis. Reduced estrogen levels after menopause increase bone turnover, with accelerated osteoclast-mediated bone resorption and impaired osteoblast function, leading to reduced bone mineral density (BMD) and structural deterioration (1,2). Bone loss is most rapid during the first 5–7 years after menopause, with an annual decline of 1–5% in BMD (9). Collagen content, crucial for bone strength, also declines more markedly in postmenopausal women due to lack of estrogen (16). As a result, women with serum estradiol <5 pg/ml face up to an eight-fold increase in fracture risk compared to those with higher levels (16).
Osteoporosis thus reflects an imbalance in bone remodeling, where bone resorption consistently outweighs bone formation. This pathophysiological state contributes to the increased risk of vertebral, hip, and wrist fractures commonly seen in postmenopausal women (1,3).

3. ROLE OF ESTROGEN IN BONE METABOLISM

Estrogen plays a central role in bone homeostasis by promoting osteoblast activity, preventing osteocyte apoptosis, and suppressing osteoclast function. The bone-sparing effect of estrogen is mediated through multiple mechanisms, including modulation of cytokine activity, osteoclast apoptosis, and stimulation of osteoprotegerin (OPG) production (11).

3.1 Estrogen Inhibits IL-1 and Tumor Necrosis Factor (TNF) Production

Interleukin-1 (IL-1) and tumor necrosis factor (TNF) are potent inducers of bone resorption and inhibitors of bone formation. In estrogen-deficient states, IL-1 and TNF levels rise, stimulating osteoclast differentiation and activity through upregulation of IL-6, macrophage colony-stimulating factor (M-CSF), and granulocyte M-CSF (11). Clinical studies have shown

that osteoporotic women exhibit higher IL-1 activity compared with healthy controls, confirming the central role of estrogen in regulating inflammatory mediators of bone loss (11). By suppressing IL-1 and TNF, estrogen prevents excessive osteoclastogenesis and protects against bone resorption.

3.2 Estrogen indirectly suppresses il-6

IL-6 is a critical mediator of osteoclastogenesis. It promotes differentiation of osteoclast precursors into mature osteoclasts and prolongs their survival (11). In postmenopausal women, IL-6 levels are markedly elevated, which has been linked with higher fracture risk (11). Estrogen does not directly suppress IL-6 but exerts control indirectly by inhibiting IL-1 and TNF, which are upstream stimulators of IL-6 production (11). This regulatory effect reduces osteoclast recruitment and bone resorption. In experimental models, estrogen supplementation lowers IL-6 expression, supporting its role in protecting against osteoporosis.

3.3 Estrogen Directly Induces Mature Osteoclast Apoptosis

Apoptosis is an essential mechanism to regulate osteoclast lifespan. Estrogen directly induces apoptosis of mature osteoclasts through activation of the Fas/Fas ligand system, which has been demonstrated in murine, avian, and human-derived osteoclasts (11). In states of estrogen deficiency, this pathway is downregulated, resulting in prolonged osteoclast survival and excessive bone resorption. Additionally, estrogen modulates TGF-β1 signaling, which further contributes to osteoclast apoptosis and turnover control (11). Clinical studies demonstrate that restoration of estrogen reverses this imbalance, leading to reduced osteoclast numbers and improved bone turnover markers.

3.4 Estrogen Stimulates Osteoprotegerin (OPG)

Osteoprotegerin (OPG) is a soluble glycoprotein that acts as a decoy receptor for RANKL, preventing it from binding to RANK on osteoclast precursors. This inhibition blocks osteoclast differentiation and activity, maintaining bone homeostasis (9,11). Estrogen significantly upregulates OPG production in osteoblasts and stromal cells, thereby reducing RANKL-mediated signaling and bone resorption. In estrogen deficiency, OPG levels fall, allowing unopposed RANKL activity and unchecked osteoclastogenesis. Experimental studies administering recombinant OPG in animal models of bone loss showed marked reduction in osteoclast numbers and protection against bone resorption (9). Thus, estrogen’s ability to stimulate OPG expression is one of the strongest mechanisms by which it preserves skeletal integrity.

4. CLINICAL EFFICACY OF HORMONE REPLACEMENT THERAPY (HRT)

4.1 Prevention of Postmenopausal Bone Loss

HRT plays a critical role in maintaining bone mineral density (BMD) during the early postmenopausal years. BMD typically increases within the first year of therapy, followed by a

smaller gain in the second year and stabilization thereafter as long as treatment continues (6,7). The protective effect is most pronounced at trabecular-rich sites such as the lumbar spine, although benefits are also observed at the femoral neck (6). Estrogen therapy exerts a dose-dependent influence on both BMD and bone turnover. While low-dose regimens are associated with a higher rate of non-responders compared with standard daily doses (0.625 mg conjugated equine estrogen, 2 mg 17β-estradiol, or 50 mg transdermal estradiol), the majority of women on even low-dose therapy achieve meaningful protection against early postmenopausal bone loss (3,6,7).

4.2 Anti-Fracture Efficacy of HRT

Beyond preserving bone mass, HRT significantly reduces fracture incidence. Clinical trials and meta-analyses consistently report a ~40% reduction in vertebral fractures, ~30% reduction in hip fractures, and a 20–30% reduction in all osteoporotic fractures compared with calcium and vitamin D alone (5,6,7). The fracture-preventive effect appears greater when therapy is initiated before the age of 60. Data from the Women's Health Initiative (WHI) demonstrated that MHT prevented approximately 5 hip fractures, 18 wrist fractures, and 47 total fragility fractures per 10,000 women annually (5). Importantly, this benefit was consistent across subgroups, irrespective of age, baseline BMD, BMI, smoking status, or family history of fracture (6). At present, HRT remains the only anti-osteoporotic therapy with proven efficacy in reducing fracture risk in newly menopausal women with low to moderate risk profiles (2,5,7).

5. Management of Postmenopausal Osteoporosis

Based on the risk level, a number of drugs are now available ranging from calcium and vitamin D supplementation right up to bisphosphonates and denosumab and up to anabolic therapy in the form of teriparatide or romosozumab. With these in mind it should be advised that the selection of the 1st line of treatment should be undertaken as part of an overall long-term plan. This stance must now be reviewed, particularly in early postmenopausal women. Subsequent re-analyses of the WHI and further trials have indeed challenged the initial conclusions of the WHI and it is clear that the individual benefit-risk balance of MHT is very dependent on the type, doses and duration of MHT regimens as well as the individual risk profile in each woman (3).

The cost-effectiveness of MHT has also been explored for treatment of menopausal symptoms as well as for prevention of fracture in asymptomatic women but who are at high risk for a fragility fracture. Zethraeus et al. included the new efficacy and side effect data from WHI in an individual state transition model of 50- to 60-year-old symptomatic women from a societal perspective in Sweden. The findings illustrated that MHT was cost-effective relative to no treatment for most subgroups of hysterectomized women. However, for women retaining an intact uterus with no previous fracture, the evidence regarding cost-effectiveness was less decisive. In this study, fracture risk was the most salient determinant of the cost-effectiveness results. Therefore, when fracture risk was used instead of menopausal symptoms, MHT use was cost-effective in hysterectomized women regardless of previous fracture status.

Conversely, among women with an intact uterus, opposed MHT was cost-effective in those with a previous vertebral fracture but not otherwise. In total then, these findings are in support of the use of MHT for menopausal symptom prevention but not obviously in favour of a role in preventing fractures, especially in the low fracture risk population. A further consideration is that the analyses do not control for time since menopause, which would make the cost-effectiveness better, and it is important not to simply equate cost-effectiveness with clinical appropriateness (5).

With the various pharmaceutical alternatives to choose from, ranging from calcium and vitamin D supplements to bisphosphonates and anabolic therapy, risk-based management is essential. While the FRAX® algorithm may report a lower fracture risk of fragility in the coming decade for postmenopausal women, such women can still be at a considerably increased residual lifetime risk. Therefore, MHT could be viewed as a preventive therapy in the initial stage of a more extensive treatment plan, particularly in cases where an individualized bone therapy, such as bisphosphonates, could be unsuitable (17).

Results of a number of case-controlled and cohort trials 16–18 indicate that HRT reduces the risk of hip fracture by approximately 30%, and findings of two small placebo controlled trials9,19 conducted in women with osteoporosis indicate a 50% reduction in spine fracture risk. The outcome of a meta-analysis 20 of 13 randomised placebo-controlled trials implies a reduction in vertebral fracture by 33% (95% CI 45–98), and the outcome of a meta-analysis 21 of 22 randomised trials implies a 27% (0·56–0·94, p=0·02) reduction in non-vertebral fractures on pooled analysis, with 40% reduction in hip and wrist fractures alone. The loss of fracture reduction within 5 years of stopping HRT, regardless of the duration of treatment, means that the question of the optimal duration and timing of HRT has been raised (2).

A meta-analysis of trials with the participant range between 24 and 337 established that combined MHT (mainly CEO and MPA) was more effective in affecting LS BMD compared to estrogen alone in PMW. Likewise, Ran et al. Ensured that estradiol valerate and MPA preserved or raised BMD in 96 early PMW (age 40–55 years) (10).

- Density of bone minerals It is estimated that 70% of bone strength is accounted for by bone mineral density (BMD), which is used as a stand-in for bone strength. In previous trials, BMD was chosen as the primary outcome measure and used as a surrogate outcome for fracture. There was a distinct dose-response relationship at each site at two years when the estrogen doses were categorized as low, medium, and high doses. Bone density at 2 years was significantly different at the lumbar spine and femoral neck sites (3.9% and 2.0% for dose equivalent to 0.3 mg of conjugated estrogen, and 8.0% and 4.7% for dose equivalent to 0.9 mg). After one and two years of treatment, the meta-analysis's findings showed that HRT consistently improved bone density at both cortical and trabecular sites (8).

6.RISKS AND CONCERNS ASSOCIATED WITH MENOPAUSAL HORMONE THERAPY

Breast cancer risk:

Breast cancer risk continues to be the second worry and often the primary restriction on the use and acceptance of MHT among women. Nearly all cohort studies and the WHI have demonstrated an elevated risk of breast cancer with use of MHT. There is consistent evidence which show that the risk of breast cancer is higher with combination of estrogen þ progestogen compared with estrogen. Furthermore, the risk seems to be in relation to the type of progestogen involved. In the big cohort study E3N, neither did any increase in the risk of breast cancer occur in those women treated with a combination of E2 and natural progesterone or dydrogesterone for mean 5-year duration of treatment while the increase was significant when synthetic progestogen was added to E2. Three other European cohort studies also found a significantly reduced risk of breast cancer when E2 was prescribed together with progesterone or dydrogesterone compared to other synthetic progestogens (3).

VTE risks:

Women taking HRT, especially those with a history of venous thromboembolism or are at risk for thromboembolism, are at a higher risk of venous thromboembolism. The findings of the WHI trial also suggest an elevated risk with HRT in healthy postmenopausal women.
Since the rate of thromboembolism in healthy postmenopausal women is low, the absolute risk of venous thromboembolism with HRT is relatively low. However, the general practice is to eschew HRT in women with a thromboembolic history and employ HRT with caution in women when they are at increased risk of thromboembolism (e.g., while on prolonged immobilization).As congenital thrombophilic diseases are rare, screening for such diseases prior to prescribing HRT has not been found to be cost-effective. (13)
Risk of VTE differs based on HT formulation. Oral HT increases the risk of VTE, whereas transdermal HT does not appear to increase the risk of VTE (15).

Other risks

Data from an observational study and randomized double-blinded placebo-controlled trials have provided evidence of 1.5 to 2-fold risk of gallbladder disease with HRT. Gallbladder and biliary tract disease were secondary outcomes in the latter trials, and effects of other factors like cardiovascular disease history and dietary history on risk of gallbladder disease were not controlled.

Results from observational and case–control studies indicate a 1.5- to 2-fold elevated risk of ovarian cancer with HRT. RCTs to replicate these findings are not available, nor are contraindication evidence for the use of HRT in survivors of ovarian cancer at this point. While HRT has been found to be beneficial in some diseases, like type 2 diabetes mellitus, osteoarthritis and rheumatoid arthritis, it is not similarly found to be beneficial in others like

systemic lupus erythematosus, anti-phospholipid antibody syndrome and asthma. Once more, RCT data are unavailable, though research is ongoing to examine these matters further. (18)

CV risks:

The association between HT and CVD is multifaceted. Before the WHI, observational studies have indicated that HT use was related to reduce incidence of CVD and all-cause mortality, when comparing users and nonusers.

The WHI had sought to assess in an RCT the cardiovascular consequences of HT in women, specifically rates of CHD as a primary measure. Surprisingly, the WHI trial (of women aged 50-79 years, mean age=63) revealed an increased risk of CV events in the oCEE + MPA treatment arm in all women (CHDHR=1.29, 95%CI1.02–1.63, Stroke HR = 1.41, 95% CI 1.07-1.63) (24). From 2002, WHI analyses by age group, observational studies, and additional RCTs such as the Danish Osteoporosis Prevention Study (DOPS), KEEPS, ELITE have all proven that HT initiated in women <60 years or within 10 years of their last menstrual period (FMP) has neutral to positive impact on cardiovascular health (CVH) (18).

Alzheimer:

A national wide case control study done in Finland compared HT use among 84,739 postmenopausal women with and without AD diagnosis without adjusting for numerous medical confounding factors. Outcomes revealed a higher risk of 9%-17% of AD among women on either estrogen-progesterone therapy or estrogen therapy alone (OR: 1.17, 95%CI: 1.13-1.21 and OR: 1.09, 95%CI: 1.05-1.14, respectively). The research discovered that there was a higher risk of AD with 10 or more years of HT exposure, and shorter use duration was not linked to raise AD risk. Considering the observational setting of the study, as well as the lack of control for most relevant medical confounders, further data are necessary before the practice can be altered.HT has been shown to accelerate AD risk in older women or those farther from menopause onset. If started in early menopause, however, HT has a neutral effect on cognition (18).

Endometrial cancer:

Systematic review of 28 studies in 2016 reaffirmed increased risk of endometrial cancer with the use of unopposed estrogen even when use was less than five years, with risk persisting for over 10 years. The review compared formulations of combined HT and determined that continuous combined estrogen progestogen therapy is possibly protective but risk can be enhanced with present micronized progesterone use and sequential norethisterone acetate use. A non-randomized prospective study reported that women with stage I-II endometrial cancer did not have a higher risk for recurrence compared to age matched controls when treated with oCEE+MPA. This was true according to an RCT of women with early-stage disease, who had undergone hysterectomy, and was treated with estrogen therapy alone. Based on these data, HT

treatment can be considered in women with troublesome vasomotor symptoms (VMS) following early surgical menopause due to early-stage endometrial cancer (18).

OTHER THERAPIES:

Selective oestrogen receptor modulators (SERMs) and other oestrogen analogues:

SERMs are oestrogen agonists or antagonists, depending on the target tissue. Tamoxifen, previously used long-term as an adjuvant treatment for breast cancer, is an oestrogen antagonist at breast tissue but a partial agonist at bone, cholesterol metabolism, and endometrium. Tamoxifen prevents bone loss in postmenopausal women only in part, but it increases the risk of endometrial cancer, ruling out its universal use in healthy postmenopausal women.

Tibolone is a synthetic steroid that has direct and indirect action on the oestrogen, progesterone, and androgen receptors via its metabolites, but in a diverse manner based on the target tissue. Tibolone inhibits bone loss in both early and late postmenopausal women, but its influence on fracture risk remains unstudied (4).

Biphosphonates:

Bisphosphonates are stable pyrophosphate analogues with a phosphorus-carbon-phosphorus(P-C-P) bond. They are powerful anti-resorptives, suppressing the recruitment and activity of osteoclasts and inducing their apoptosis through a recently discovered molecular mechanism. The oral bioavailability of bisphosphonates is low, 1% to 3% of ingested dose, and is inhibited by food, calcium, iron, coffee, tea, and orange juice. Etidronate was the initial bisphosphonate created. Given intermittently (400 mg daily for 2 weeks, repeated at 3-month intervals)

Alendronate inhibits postmenopausal bone loss. Findings of a study in 2025 postmenopausal women with osteoporosis and at least one prevalent vertebral fracture treated with alendronate 5 mg/day for 2 years and then with 10 mg/day in a third year decreased 50% of vertebral, wrist, and hip fractures compared to placebo (4).

Calcitonin:

Calcitonin is FDA indicated for the treatment of osteoporosis in postmenopausal women who are more than five years postmenopausal when other treatment modalities are not possible. Findings for a five-year, double-blind, randomized, placebo-controlled trial of 1,255 postmenopausal women with diagnosed osteoporosis showed that 200 IU of calcitonin per day lowered the risk of new vertebral fractures by 33%.In 2013, an FDA long-term post-marketing review reported a very modest rise in cancer rates in calcitonin-treated patients and advised that health care providers evaluate the use of calcitonin for osteoporosis treatment relative to other available options (12).

PTH:

Surplus secretion and repetitive intravenous administration of PTH cause enhanced bone resorption and bone loss (4). Teriparatide, a recombinant human PTH (1–34) analogue, is the first anabolic therapy approved for osteoporosis. The AACE/ACE recommends use of teriparatide for first-time PMO treatment in individuals with a history of previous fragility fractures or with a high fracture risk and for individuals who cannot be treated orally. (12).

Current guidelines and recommendations:

Some global guidelines support MHT as a possible first-line treatment to preserve bone density in women on the threshold of menopause. EMAS members are in agreement that the "administration of systemic MHT has a beneficial risk–benefit profile for women younger than 60 years or within 10 years since the onset of menopause for menopausal symptoms and osteoporosis". The benefit–risk ratio is best for the treatment of prominent VMS and women under age 60, or 10 years from the onset of menopause, particularly those at risk for bone loss or fracture and with no contraindications, as is claimed by the North American Menopause Society. IMS recommendations also reflect this position.

While the American Association of Clinical Endocrinologists highlights that "MHT should be administered at the lowest dose and shortest duration needed to manage menopausal symptoms," they also stress its use for osteoporosis prevention and treatment within an overall benefit-versus-risk assessment for each patient. The US Endocrine Society refers to the absence of agreement on the efficacy of MHT in the prevention of CVD, breast cancer, or dementia but recognizes its unproven benefit in fracture prevention. The American College of Obstetricians and Gynecologists prioritizes the treatment of menopausal symptoms, supporting the use of the "lowest dosage, shortest duration" principle.

The UK's National Institute for Health and Care Excellence (NICE) advocates MHT for postmenopausal symptoms, considering the reduced risk of CVD with estrogen-alone MHT and slight or zero levels of coronary heart disease risk with combined MHT in women under 60 years old. In formulating a treatment plan, the baseline cardiovascular risk, status of breast cancer, and past history of thromboembolic disease should be taken into account. The impact of NICE guidelines in the UK and their correlate with European healthcare attitudes is an added international context. Their ongoing revisions, bringing in the most up-to-date medical science, make them a necessary resource for clinicians and patients making MHT decisions in Europe and worldwide (17).

Postmenopausal Osteoporosis (ACE/ACE 2016) For the treatment of postmenopausal osteoporosis (PMO), AACE/ACE offers evidence-based information. Ibandronate and raloxifeneare regarded as alternatives, while alendronate, risedronate, zoledronic acid, or denosumab (Prolia, Amgen) are suitable as first-line treatments for people with a moderate risk of fractures or no history of fragility fractures. Alendronate and rise-dronate are recommended as alternatives to denosumab, teriparatide (Forteo, Lilly), and zoledronic acid as first-line

treatments for patients with a history of fragility fractures or other signs of high fracture risk. Advanced age, frailty, glucocorticoids, very low T-scores, and an elevated risk of falls are all signs of high fracture risk. For those who are unable to use oral therapy, teriparatide, denosumab, or zoledronic acid should be taken into consideration. For spine-specific efficacy, ibandronate or raloxifene may be used as the first line of treatment.

ACR 2017: Osteoporosis Induced by Glucocorticoids GIO stratifies patients according to their age, fracture risk, and glucocorticoid therapy dosage and duration. Every patient beginning long-term glucocorticoid therapy needs to have their initial clinical fracture risk evaluated, and this evaluation needs to be repeated every 12 months.

• NOF 2014-PMO and Men over 50 • The NOF has created a Clinician's Guide to Osteoporosis Prevention and Treatment. The general considerations are similar to those of other well-known organizations and are included for both men and women of different ages. This guidance does not specify a preference for one therapeutic class over another or offer recommendations for initial medication therapy, despite the fact that it offers broad recommendations for diagnosis and screening. • American College of Physicians 2017—Osteoporosis and Low BMD in Women and Men (12).

Conclusion

Hormone replacement therapy (HRT) continues to hold an important role in the management of postmenopausal health concerns. It remains the most effective option for alleviating vasomotor symptoms, improving sleep, mood, and overall quality of life (19). In addition, HRT offers protection against postmenopausal bone loss and reduces the risk of osteoporotic fractures, thereby addressing one of the major long-term complications of menopause (20).

The safety and effectiveness of HRT are strongly influenced by the timing of initiation, with evidence supporting its use when started within 10 years of menopause or before the age of 60. The choice of hormone type, dosage, and route of administration further determine treatment outcomes, making individualized therapy essential (19,21). Despite concerns about cardiovascular and cancer risks, recent evidence indicates that these risks can be minimized with careful patient selection, appropriate regimen design, and regular monitoring (20,21).
Overall, when applied judiciously and tailored to the individual woman’s needs, HRT represents a valuable therapeutic approach for improving quality of life, preserving bone health, and supporting healthy aging in postmenopausal women.

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