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REVIEW ARTICLE

Estrogen and bones after menopause: a reappraisal of data and future perspectives

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Abstract

Menopausal hormone therapy (MHT) is effective in preventing menopause-related bone loss and decreasing vertebral, non-vertebral and hip fracture risk. MHT contains estrogens that exert both antiosteoclastic and osteoanabolic effects. These effects are dose-dependent, as even ultra-low doses preserve or increase bone mineral density. The transdermal route of administration is effective on cancellous and cortical bone, although fracture data are still lacking. Hormone replacement therapy is the treatment of choice to preserve skeletal health in women with premature ovarian insufficiency and early menopause. MHT can be considered in women aged < 60 years or within 10 years since menopause as, in this population, benefits outweigh possible risks, such as breast cancer and cardiovascular events. Despite the ensuing bone loss after MHT discontinuation, a residual antifracture effect persists. However, in women at risk of fracture, subsequent antiosteoporotic therapy may be needed, either with an antiosteoclastic or osteoanabolic agent. In any case, longitudinal data from randomized controlled trials comparing different estrogen doses and routes of administration, as well as designating the optimal treatment strategy after MHT discontinuation, are needed to elucidate these issues further.

Keywords Estrogen · Menopausal hormone therapy · Osteoporosis · Menopause · Fractures

Introduction

Transition to menopause leads to a 9–10% decrease in bone mineral density (BMD) from the first year before up to 3 years after menopause [1]. This decrease mostly involves the cancellous compartment during the first years of menopause, whereas cortical bone loss predominates after the age of 65 years [2]. Surgical menopause does not confer an additional effect on BMD decline or fracture risk compared with natural menopause [3]. Each halving of estradiol (E_2) and doubling of follicular stimulating hormone (FSH) concentrations has been associated with a 10% and 39% reduction in lumbar spine (LS) BMD, respectively [4]. The corresponding reductions in femoral neck (FN) BMD were 12% and 27%, suggesting a predictive role for FSH and E_2 in pre- or early perimenopause for identifying women at high risk for osteoporosis [4]. Moreover, a recent meta-analysis including 462,393 postmenopausal women showed that early menopause (< 45 years) is associated with a higher fracture risk compared with normal age at menopause (> 45 years) (odds ratio (OR) 1.36, 95% confidence interval (CI) 1.11–1.66) [5]. Therefore, early menopause should be considered as a secondary cause of osteoporosis in the fracture risk assessment tool (FRAX) to predict the 10-year fracture risk [6].

This review aimed to provide an overview of the pathophysiology of menopause-associated bone loss and the effect of menopausal hormone therapy (MHT) on the reduction of fracture risk. Particular focus was placed on the differential effect of MHT according to type, dose, and route of administration within this framework.

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The role of estrogens in bone metabolism

Expression of estrogen receptors in bone cells

Estrogens play a crucial role in achieving peak bone mass, accrual growth, and final height in both genders. They act through the estrogen receptor (ER) alpha (ERα) and, to a lesser extent, ER beta (ERβ) in bone lining cells (osteoclasts, osteoblasts, and osteocytes) [2, 7]. After binding to estrogens, ERs are translocated into the nucleus of the target tissues where they act as transcriptional factors. Similarly to other nuclear receptors, they consist of an amino-terminal (NTD), a DNA-binding domain (containing two zinc fingers), a carboxyl-terminal ligand-binding domain (LBD), and a hinge region [2, 7]. ERs form homodimers which bind to DNA sequences (hormone response elements—HRE). In the absence of the ligand (estrogen), they recruit cofactors which repress transcription [2, 7]. Conversely, the binding of the ligand to LBD leads to conformational changes of the ER, revealing surfaces which can bind to coactivators, such as steroid receptor coactivator 1 (SRC-1). Indeed, animal studies have shown that SRC-1 deletion leads to trabecular bone loss [8]. ERs may also act in a ligand-independent manner, this being implicated in the anabolic response of the skeleton to mechanical loading [9].

The effect of estrogens on cancellous bone loss is mediated via the expression of ERα in the osteoclasts. Animal studies have demonstrated that the deletion of ERα increases the number of osteoclasts [10]. Many mechanisms linking ERα activation and suppression of osteoclastogenesis have been proposed. First, in vitro studies have revealed that ERα suppresses interleukin (IL)-6 gene expression in osteoblast lineage cells by binding to the components of the nuclear factor kappaB (NF-κB). Notably, no ER-DNA interaction is required for this function [11]. Second, the proteolytic enzyme matrix metalloproteinase-13 (MMP-13) promotes osteoclastogenesis by directly enhancing osteoclast multinucleation and bone-resorptive activity [12]. This action is independent of its enzymatic activity and is mediated by upregulation of the calcineurin-dependent 1 (NFATc1)/dendrocyte-expressed 7 transmembrane (DC-STAMP) axis. Both in vitro and animal studies have shown that silencing of MMP-13 expression in myeloma cells inhibits the development of osteolytic lesions [12]. Animal studies have also demonstrated that ERα deletion in mesenchymal/stromal cells enhances this pathway indicating its potential pathogenetic role in estrogen deficiency–related bone loss [13].

On the other hand, the binding of estrogens to ERα in osteoblasts and their pluripotent mesenchymal progenitors inhibits their apoptosis, constituting the main mechanism of cortical bone loss in states of estrogen deficiency [9]. Animal studies have shown that the protective effects of estrogens on cortical bone mass also result from non-nuclear-mediated actions of the ERα, in contrast to its binding to HRE [14, 15]. Another non-genomic cellular pathway of estrogen action is via binding to the G protein–coupled receptor (GPR)-30 (GPR30) or G protein–coupled ER (GPER), which is expressed in osteoblasts, osteocytes, and osteoclasts. GPR30 acts through second messengers, such as elevated cyclic adenosine monophosphate (cAMP) concentrations and intracellular calcium [16, 17]. There are conflicting data regarding its action. GPR30 may play a role in osteoblast differentiation, mediated by runt-related transcription factor 2 (Runx2) [18]; deletion of GPR30 in female mice results in abnormal femoral length [19].

Direct and indirect effects of estrogens on bone cells

The main direct mechanism of estrogens on osteoclasts after ERα activation is upregulated expression of the Wnt coreceptor lipoprotein receptor–related protein (LRP)-5, which increases intracellular β-catenin concentrations [20]. Another mechanism is induction of apoptosis through increased expression of the Fas ligand (FasL) gene in osteoclasts [21]. Estrogens also stimulate osteoblast differentiation (since ERα is expressed in mesenchymal osteoblast progenitors, bipotential osteoblast precursors, and mature osteoblasts) and activate Wnt signaling [9]. Another direct mechanism is inhibition of osteoblast apoptosis through decreased production of FasL [22]. Furthermore, estrogens act at the osteocyte level, since estrogen deficiency increases osteocyte apoptosis. This action may be mediated through increased expression of the protein semaphorin 3A (Sema3A) in osteocytes. Sema3A binds to its receptor in osteocytes, promotes their survival, and, thus, contributes to increased bone formation and decreased resorption [23].

However, the primary pathway through which estrogens prevent bone resorption is indirect through the osteoprotegerin (OPG)/receptor activator of NF-κB (RANK)/RANK ligand (RANKL) axis. Specifically, a variety of cells, including osteoblasts and T and B lymphocytes, produce RANKL which, in turn, binds to the RANK receptor in osteoclasts and osteoclast precursor cells, resulting in their differentiation, activation, and survival [24]. OPG is a soluble decoy receptor of RANKL which inhibits osteoclastogenesis [24]. Estrogens suppress RANKL expression through ERα in bone lining cells, thus underlining their role as a key factor in estrogen deficiency–related bone loss. Estrogens also upregulate OPG expression [25]. This mechanism accounts for the protective effect of estrogens on cortical bone. The latter effect is also mediated through non-nuclear mechanisms, such as production of cyclic nucleotides, calcium flux, and cytoplasmic kinase activation [2].

A variety of hormones, cytokines, and local growth factors mediate estrogen deficiency–induced bone loss. In particular, estrogen deficiency leads to increased interleukin (IL)-7

production in target organs, such as the thymus, spleen, and bones, and to a decreased production of transforming growth factor (TGF)-β. As a result, T cells are activated and release interferon-γ (IFN-γ), which increases antigen presentation via macrophages and major histocompatibility complex (MHC) class II [2, 26]. Activated T cells also release tumor necrosis factor-α (TNF-α), which induces osteoclast formation through RANKL [2, 26]. Apart from the latter, increased IL-7 production negatively affects osteoblastic activity [26]. Moreover, dysregulation of antioxidant mechanisms and increased production of reactive oxygen species (ROS) may account for estrogen deficiency–related bone loss, since ROS are associated with antigen presentation and the release of TNF-α and RANKL [2, 26].

Another indirect mechanism is the process via which estrogen deficiency causes an increase in the expression of stromal-derived factor 1 (SDF1). SDF1, or C-X-C motif chemokine ligand (CXCL)12, is expressed predominantly by CXCL12-abundant reticular (CAR) cells. It promotes osteoclastogenesis in vitro and in vivo, as it recruits the hematopoietic stem cells into the bone compartment, by acting via its receptor (CXCR4). The CXCL12/CXCR4 axis also regulates osteoblast differentiation [27]. A recent study in mice demonstrated that estrogen deficiency increases SDF1 expression which, in turn, causes increased osteoclastogenesis and cortical bone loss [28].

In vitro studies have also shown that estrogen increases osteoblastic differentiation by suppressing sclerostin [29], an inhibitor of the Wnt/β-catenin pathway, which is produced by osteocytes, osteoblasts, and hypertrophic chondrocytes [30]. Sclerostin inhibits this pathway by binding to low-density lipoprotein receptor–related protein-5 (LRP-5) and LRP-6 [30]. Moreover, sclerostin fosters osteoclastic differentiation through the RANKL-OPG pathway [30]. Although the exact mechanism by which estrogen suppresses sclerostin is not known, in vitro studies in human osteoblasts have revealed that this is mediated through suppression of the bone morphogenetic protein (BMP)-2 signaling pathway, a potential inducer of sclerostin (*SOST*) gene expression [29]. Clinical studies have also demonstrated an inverse association between serum sclerostin concentrations and circulating free E_2 index [31]. Furthermore, MHT leads to a reduction in sclerostin concentrations in postmenopausal women [32].

Gene polymorphisms and estrogen deficiency–associated bone loss

Specific ER gene polymorphisms have been associated with low BMD and may be implicated in the pathogenesis of postmenopausal osteoporosis. For instance, Caucasian postmenopausal women with the ERβ *RsaI* polymorphism are at increased risk for osteoporosis, whereas the ERα *G2014A* polymorphism seems to exert a protective effect [33]. Besides ER genes, other genes have been implicated in the pathogenesis of estrogen deficiency–associated low bone mass, such as the interleukin (*IL*)-*1β*, *IL-6*, *IL-7*, *TNF-α*, *RANKL*, and *OPG* genes in bone marrow cells, T and B lymphocytes [26], macrophages, and dendritic cells, as well as the IL-1 receptor (*IL-1R*) [34] and the cathepsin K/OC-2 gene in osteoclasts [35]. Other gene targets for estrogens, which are associated with osteoblastic activity and regulated by ERs, include the retinoblastoma-binding protein 1 (*RBBP1*) [36] and the TGF-β-inducible early gene-1 (*TIEG*, a modulator of OPG) [37] genes.

The role of estrogens in bone metabolism is illustrated in Fig. 1.

Effect of menopausal hormone therapy on bone mineral density and fracture risk

Postmenopausal bone loss may be prevented by the administration of MHT through oral or transdermal routes. MHT includes estrogens, either as monotherapy in women with a history of hysterectomy or in combination with progestogens in women with an intact uterus [38].

The Women's Health Initiative study

Many observational and randomized controlled trials (RCTs) have demonstrated a beneficial effect of estrogen administration on fracture incidence reduction. One of the most influential studies on this concept is the Women's Health Initiative (WHI). It was designed to evaluate the effect of MHT on the incidence of coronary heart disease (primary outcome) and invasive breast cancer (primary adverse outcome). Secondary outcomes included the effect of MHT on the risk of stroke, pulmonary embolism, endometrial cancer, colorectal cancer, hip fractures, and death from other causes [39]. The first arm of WHI included 16,608 women (aged 50–79 years) with an intact uterus, randomized to daily administration of conjugated estrogen (CEE) 0.625 mg/day combined with medroxyprogesterone acetate (MPA) 2.5 mg/day ($n = 8506$) or placebo ($n = 8102$). The study was terminated after 5.2 years due to the positive association between MHT and increased risk of coronary heart disease, breast cancer, venous thromboembolic events (VTE), and cerebrovascular ischemia [39]. However, MHT was associated with a decreased risk of total, vertebral, and hip fractures (hazard ratio (HR) 0.76 (nominal 95% CI 0.69–0.85; adjusted 95% CI 0.63–0.92), 0.66 (nominal 95% CI 0.44–0.98; adjusted 95% CI 0.32–1.34), and 0.66 (nominal 95% CI 0.45–0.98; adjusted 95% CI 0.33–1.33), respectively). The absolute risk reduction was five hip fractures per 10,000 person-years [39]. Moreover, post hoc analyses of the WHI and ensuing studies showed that MHT is associated with decreased CVD risk if administered in women

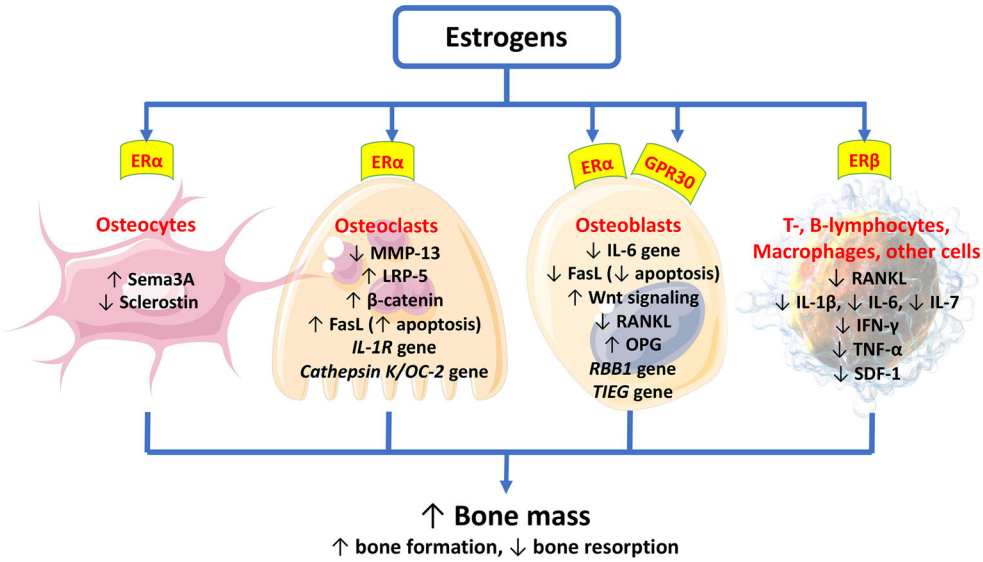

Fig. 1 Mechanisms by which estrogens increase/preserve bone mass. ERα estrogen receptor-alpha, ERβ estrogen receptor-beta, FasL Fas ligand, GPR-30 G protein–coupled receptor-30, IL-1β interleukin-1-beta, IL-1R interleukin-1 receptor, IL-6 interleukin-6, IL-7 interleukin-7, IFN-γ interferon-gamma, LRP-5 low-density lipoprotein receptor–related protein-5, MMP-13 matrix metalloproteinase-13, OPG osteoprotegerin, RANKL receptor activator of nuclear factor kappa-B ligand, RBBP1 retinoblastoma-binding protein-1, SDF1 stromal-derived factor-1, Sema3A semaphorin 3A, TIEG TGF-β-inducible early gene-1, TNF-α tumor necrosis factor-alpha, ↑ increase, ↓ decrease. Image sources (modified): osteocyte: Laboratoires Servier—Smart Servier website; images related to osteocytes (bone cells), bone structure, and bones (in French): CC BY-SA 3.0; estradiol, osteoblast, and osteoclast: Wikimedia Commons; B cell: Blausen.com staff (2014). "Medical gallery of Blausen Medical 2014". WikiJournal of Medicine 1 (2). doi: https://doi.org/10.15347/wjm/2014.010. ISSN 2002-4436

aged < 60 years or within 10 years since menopause [40]. It must also be emphasized that the MHT-associated risk of thromboembolic events depends on the route of administration, being extremely low with transdermal estrogen [38]. Concerning breast cancer, MHT was associated with an increased risk (HR 1.26, nominal 95% CI 1.00–1.59; adjusted 95% CI 0.83–1.92), although in subgroup analysis, this was evident only in women with prior use of MHT (HR 2.13, 95% CI 1.15–3.94 for < 5 years of prior use), whereas there was no increase in never-users (HR 1.06, 95% CI 0.81–1.38) [39].

The second arm of WHI included 10,739 women (aged 50–79 years) with a history of hysterectomy, who were allocated to conjugated equine estrogen (CEE) monotherapy (0.625 mg/day; $n = 5310$) or placebo ($n = 5429$) [41]. Except for a small increase in the risk of VTE and stroke, there was no effect on CVD risk. Notably, the risk for invasive breast cancer was marginally lower in the CEE compared with the placebo group (HR 0.77, nominal 95% CI 0.59–1.01, adjusted 95% CI 0.57–1.06). In alignment with the first arm, CEE administration was associated with a decreased risk of vertebral (HR 0.62, nominal 95% CI 0.42–0.93, adjusted 95% CI 0.34–1.13), hip (HR 0.61, nominal 95% CI 0.41–0.91, adjusted 95% CI 0.33–1.11), and total fractures (HR 0.70, nominal 95% CI 0.63–0.79, adjusted 95% CI 0.59–0.83). The absolute risk reduction with MHT was six hip fractures per 10,000 person-years [41]. A combined analysis of the MHT and the Dietary Modification WHI trials demonstrated an interaction between MHT and calcium and vitamin D supplementation; MHT was more efficacious in preventing hip fractures when it was coadministered with 1000 mg elemental calcium and 400 IU vitamin D, compared with MHT monotherapy [42].

The results of the WHI are not representative of the population of peri- or postmenopausal women in need of MHT. One of the main criticisms of this study is the fact that the population of WHI consisted of asymptomatic women with a mean age of 63.3 years in whom MHT was initiated much later (> 12 years) compared with the mean age of menopause onset (51 years). However, the WHI trial demonstrated that the antifracture efficacy of MHT was independent of age, baseline BMD, or other risk factors for fractures [43]. A more recent and comprehensive meta-analysis, published in 2016 ($n = 28$ studies), which included the WHI studies, showed a reduced risk for total (relative risk (RR) 0.74, 95% CI 0.69–0.80), hip (RR 0.72, 95% CI 0.53–0.98), and vertebral fractures (RR 0.63, 95% CI 0.44–0.91) with the use of MHT [44]. The total antifracture efficacy was evident for women aged both < 60 years (RR 0.55, 95% CI 0.44–0.68) and > 60 years (RR 0.77, 95% CI 0.71–0.84), although it was lower in the former group ($p = 0.003$) [44].

The effect of the route of estrogen administration

The route of MHT administration affects the incidence of adverse events, such as venous thromboembolism (VTE). The transdermal appliance of E_2 has not been associated with an increase in VTE events compared with oral estrogens,

making this route of administration suitable for women with cardiovascular risk factors [40].

A meta-analysis of nine RCTs and non-RCTs showed a mean increase in LS BMD of 3.4% (95% CI 1.7–5.1) and 3.7% (95% CI 1.7–5.7) after 1 and 2 years of transdermal estrogen administration, respectively [45]. Data from the RCTs ($n = 6$) revealed an increase of 4.0–6.6% in LS, following a 2-year administration of the conventional transdermal estrogen dose (50 μg/day). Interestingly, an increase in LS (2.6%) was also evident with the very low dose (14 μg/day) (data from one RTC). This study also showed a slight increase (0.6%) in total hip (TH) BMD. Another RCT, which used 25 mg of E_2 subcutaneously as an implant, demonstrated a 5.4% increase in LS, 6% in TH, and 3.7% in FN [45]. Another prospective study (not included in the meta-analysis) in postmenopausal women with osteopenia showed significant increases of 8%, 6%, and 3% in LS, FN, and TH BMD, respectively, after a 2-year administration of transdermal 17β-E_2 at a conventional dose in combination with levonorgestrel (30–40 μg/day) and calcium (500 mg/day) [46].

However, few comparative studies exist in postmenopausal women regarding the effect of different routes of estrogen administration on bone metabolism, BMD, and fracture risk. In one of them, no difference was observed in BMD between oral and transdermal estrogen administration [47]. On the other hand, in another comparative non-RCT, CEE increased LS BMD to a greater extent compared with transdermal E_2. However, no difference was demonstrated between the two routes in terms of hip BMD after 3 years of administration [48]. Comparative studies have also been conducted in patients with Turner's syndrome. A systematic review and meta-analysis, including four RCTs and non-RCTs, showed a greater increase in BMD with transdermal compared with oral estrogen administration (mean difference in *Z*-score − 0.07, 95% CI − 0.13–0.02). However, none of the included studies provided data regarding fracture risk [49].

The effect of estrogen dose

The effect of estrogen on bone mass seems to be dose-dependent, although limited comparative data exist to date. In a 2-year RCT, 1 mg/day of oral E_2 ($n = 157$) resulted in a greater increase in LS BMD (mean change from baseline 10.2 ± 6.0%) compared with the dose of 0.5 mg/day (mean change from baseline 8.0 ± 5.0%). This beneficial effect was evident after the first 6 months of therapy [50]. In an open-label study in young non-obese postmenopausal women, 1 mg/day of oral E_2 plus 0.5 mg/day of norethisterone acetate produced a significant increase both at LS (5.2 ± 0.7%) and FN BMD (2.8 ± 0.4%) after 24 months. The corresponding increases with 0.5 mg/day E_2 plus 0.25 mg/day of norethisterone acetate were 2.0 ± 0.3% and 1.8 ± 0.3%, significantly higher compared with calcium 1000 mg/day, which could not prevent menopause-related bone loss [51]. Higher estrogen doses are required in women with premature ovarian insufficiency (POI) or premature menopause [52]. Other studies reported that the difference in BMD according to the dose administered (i.e., CEE 0.6 mg/day vs. 0.3 mg/day) was evident only in LS, which is probably attributable to the fact that cancellous bone is more metabolically active compared with cortical bone [53]. However, a pooled analysis of data from the Million Women Study ($n = 138{,}737$ postmenopausal women) did not show a differential effect on fracture risk according to estrogen dose (either CEE, oral, or transdermal E_2) [54]. In the same context, an RCT comparing different doses of 17β-E_2 (1 and 2 mg/day) combined with gestodene 25 and 50 μg/day, respectively, either continuously or sequentially, significantly increased BMD in LS, FN, and forearm compared with placebo in a dose-dependent manner. In particular, the respective percentage changes in LS BMD after 3 years with 2 mg 17β-E_2/25 μg gestodene sequentially, 2 mg 17β-E_2/50 μg gestodene sequentially, 1 mg 17β-E_2/25 μg gestodene sequentially, 1 mg 17β-E_2/25 μg gestodene continuously, and placebo were as follows: 7.41 ± 0.72%, 8.53 ± 0.90%, 6.67 ± 0.88%, 4.44 ± 0.59%, and − 2.03 ± 0.64%. The effect of 2 mg/day 17β-E_2 on LS and FN, which is the standard dose of estrogen administered to women < 45 years, was greater than that of the 1-mg/day dose [55].

Even low estrogen doses may lead to an increase in BMD, in both the LS and hip [56]. In the Health, Osteoporosis, Progestin, Estrogen (HOPE) study, CEE, administered at doses of 0.3 or 0.45 mg/day (either as monotherapy or with MPA 1.5 mg/day), prevented bone loss in LS and TH and decreased bone remodeling during the early postmenopausal period [53]. This bone-protective effect seems to be enhanced when estrogens are coadministered with calcium and vitamin D (3.5% increase in BMD at 3.5 years, reaching up to 5.2% in patients, with > 90% compliance) [57]. Concerning 17β-E_2, ultra-low dose (0.25 mg/day) decreased bone turnover to a comparable level as did low dose (1 mg/day) and with a safety profile similar to that of placebo [58]. Moreover, this beneficial effect has also been demonstrated with transdermal estrogen (25 μg/day resulted in a similar decrease in bone turnover compared with 50 μg/day) [59].

The effect of progestogen on bone metabolism

Coadministration of estrogen with progesterone is thought to enhance the beneficial effect of estrogens in the bones. This effect is achieved through the agonistic effect of progesterone (P_4) on the progesterone receptor in osteoblasts, which promotes their maturation from stem cells and their differentiation into cell types, which, in turn, promotes the formation of bone matrix through alkaline phosphatase production [60]. A meta-analysis of five RCTs showed that coadministration of CEE (0.625 mg/day) with MPA (2.5 mg/day) increased LS

BMD by 0.68% per year (95% CI 0.38–0.97%) compared with CEE monotherapy in postmenopausal women during the first 5 years of menopause. However, this difference was not significant as concerns the dose of 0.3 mg/day or cyclic MPA administration. Moreover, no difference was observed for hip BMD [61]. However, in the Million Women Study, a prospective cohort study, fracture risk did not vary according to whether estrogens were administered either as monotherapy (RR 0.64, 95% CI 0.58–0.71) or in combination with a progestogen (RR 0.58, 95% CI 0.53–0.64) ($p = 0.19$). Of note, the type of progestogen also did not alter the results [54].

The effect of menopausal hormone therapy discontinuation on bone mass

MHT discontinuation is followed by a decrease in BMD to the same level as was observed during the first 2 years of menopause (5–6%) [1, 62]. According to the Postmenopausal Estrogen/Progestin Interventions (PEPI) Safety Follow-up Study [63], 495 postmenopausal women, having been assigned to MHT (0.625 mg/day CEE combined with different types of progestogen) for 3 years, were followed for an additional 4 years with BMD assessment. The annual rates of BMD loss (− 1.01% and − 1.04% in TH and LS, respectively) did not differ from those in women who had not received MHT. This study also supported the hypothesis that longer-term MHT (beyond 3 years) does not lead to further BMD gain [63].

In addition, conflicting data exist regarding MHT discontinuation and increased fracture risk [64]. An observational cohort study in the USA revealed that the number of postmenopausal women receiving estrogen therapy decreased from 85 to 18% during the period 2002–2007, leading to a 50% increase in hip fracture risk at the end of the second year following MHT discontinuation [64]. Nevertheless, recent data indicated that the beneficial effect of estrogen on bone microarchitecture [65], as well as its antifracture efficacy [66], may be maintained for at least 2 years following MHT discontinuation. Remarkably, post hoc analysis of the two WHI arms did not show any increased fracture risk at 5 years after MHT discontinuation compared with placebo. Conversely, a residual antifracture benefit was observed in women who received estrogen monotherapy [66]. Evidence for a long-lasting bone-protective effect after MHT discontinuation emerged from the prospective epidemiological study focusing on risk factors for osteoporosis and cardiovascular disease (the PERF study) [67]. Specifically, in 263 healthy postmenopausal women with normal BMD, in whom MHT (mostly 2 mg/day E_2) was administered for 2–3 years during the early postmenopausal period, both BMD and bone mineral content remained higher (> 5%) compared with placebo 5–15 years after MHT discontinuation. The annual rates of bone loss after MHT in forearm and LS were − 0.70% and − 0.61%, respectively, comparable with those of placebo (− 0.92% and − 0.40%). This preservation of BMD in the MHT group was also associated with a significantly reduced risk of vertebral and all osteoporotic fractures (OR 0.47, 95% CI 0.24–0.93 and 0.48, 95% CI 0.26–0.88, respectively) [67].

In cases where MHT was discontinued and the fracture risk is high, MHT should be replaced by another bone-specific treatment to achieve continuous antifracture protection [68]. The degree of fracture risk is the primary determinant of the type of treatment [69].

Recommendations

According to the international guidelines, hormone replacement therapy (HRT) is the treatment of choice to preserve skeletal health in women with POI and early menopause. MHT may be considered in peri- and postmenopausal women at risk of fracture, aged < 60 years or during the first 10 years after the menopause. In these cases, benefits from MHT outweigh possible risks, such as breast cancer or cardiovascular events. In general, MHT is contraindicated in cases at high CVD risk, assessed by the relevant calculation tools. In the case of moderate CVD risk, the transdermal route of administration is preferred [38, 52, 70–73].

Conclusions and future perspectives

Based on current evidence, MHT is effective in increasing BMD and decreasing vertebral, non-vertebral and hip fracture risk, even in women without osteoporosis. Besides POI and premature menopause, where HRT constitutes the treatment of choice, MHT can be considered in women aged < 60 years or within 10 years since menopause who are at risk of fracture.

The bone-protective effects of estrogens are dose-dependent, although limited data exist on fracture risk. Even ultra-low estrogen doses (oral or transdermal 17β-E_2 of 0.5 mg/day or 25 μg/day, respectively) are effective. Transdermal estrogens, which exert a neutral effect on VTE risk and can be prescribed to women at moderate CVD risk, have exhibited efficacy in increasing LS and hip BMD. However, studies assessing fracture risk based on the above concept are still lacking. Longitudinal data from RCTs comparing different estrogen doses and routes of administration are needed to elucidate these issues further.

Despite the ensuing bone loss after MHT discontinuation, a residual antifracture effect may persist. However, for women at risk of fracture, subsequent bone-specific therapy is needed. The type of therapy will be determined by the degree of fracture risk.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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