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CONCISE CLINICAL REVIEW

Estrogen therapy for osteoporosis in the modern era

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Abstract

Menopause predisposes women to osteoporosis due to declining estrogen levels. This results in a decrease in bone mineral density (BMD) and an increase in fractures. Osteoporotic fractures lead to substantial morbidity and mortality, and are considered one of the largest public health priorities by the World Health Organization (WHO). It is therefore essential for menopausal women to receive appropriate guidance for the prevention and management of osteoporosis. The Women's Health Initiative (WHI) randomized controlled trial first proved hormonal therapy (HT) reduces the incidence of all osteoporosis-related fractures in postmenopausal women. However, the study concluded that the adverse effects outweighed the potential benefits on bone, leading to a significant decrease in HT use for menopausal symptoms. Additionally, HT was not used as first-line therapy for osteoporosis and fractures. Subsequent studies have challenged these initial conclusions and have shown significant efficacy of HT in various doses, durations, regimens, and routes of administration. These studies support that HT improves BMD and reduces fracture risk in women with and without osteoporosis. Furthermore, the studies suggest that low-dose and transdermal HT are less likely associated with the adverse effects of breast cancer, endometrial hyperplasia, coronary artery disease (CAD), and venous thromboembolism (VTE) previously observed in standard-dose oral HT regimens. Given the need for estrogen in menopausal women and evidence supporting the cost effectiveness, safety, and efficacy of HT, we propose that HT should be considered for the primary prevention and treatment of osteoporosis in appropriate candidates. HT should be individualized and the once "lowest dose for shortest period of time" concept should no longer be used. This review will focus on the prior and current studies for various HT formulations used for the prevention and treatment of osteoporosis, exploring the safety profile of low-dose and transdermal HT that have been shown to be safer than oral standard-dose HT.

Keywords Bone mineral density (BMD) · Hormone therapy (HT) · Menopause · Osteoporosis

Clinical relevance

Osteoporosis is a disorder that affects the integrity and strength of bones. Specifically, it results in low bone mass, microarchitectural disruption, skeletal fragility, and decreased bone strength, leading to increased risk of fracture [1]. Osteoporotic fractures lead to substantial morbidity and mortality [2]. Therefore, it is imperative to establish best practice guidelines to prevent and treat osteoporosis in postmenopausal women, the greatest affected population.

Many factors affect bone development and architecture, with endogenous estrogen being a major component in evolution of bone. Since the major cause of osteoporosis in menopause is the loss of bone due to estrogen deficiency, hormone therapy (HT) is a rational therapy to use for prevention of osteoporosis [3]. HT in the form of either combined estrogen and progesterone or estrogen alone has been shown to be effective in reducing the number of both vertebral and non-vertebral fractures in postmenopausal women [4], with efficacy equivalent to that of bisphosphonates [5–7]. The Women's Health Initiative (WHI) was the largest evidence-based long-term randomized clinical trial (RCT) in

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women aged 50 to 79 years, showing various effects of HT, including prevention of fractures at the hip, vertebrae, and other sites [8]. This was significant as the study subjects in both arms of the WHI-HT were patients not necessarily at increased risk of fracture. Thus, prior studies showing HT for prevention of bone loss and osteoporosis-related fractures were supported by the findings in the WHI-HT [8].

The primary endpoint of WHI-HT was efficacy of HT in prevention of coronary vascular events and not its effect on bone fracture risk [9]. The estrogen plus progestin (CEE + MPA) arm of the study was discontinued in 2002 after 5.6 years of follow-up due to increased risks of invasive breast cancer, coronary heart disease events, stroke, and pulmonary embolism among treated women [10, 11]. Subsequently, the estrogen (CEE) alone arm of the study was discontinued in 2004 after almost 7 years of follow-up due to increased risk of stroke in the treatment group; however, unlike combined hormone treatment with estrogen and progestin, estrogen alone did not appear to affect (either increase or decrease) heart disease or increase the risk of breast cancer. Just as the combined therapy, estrogen alone showed a reduction in the risk of hip fracture [6]. These published findings were shocking, created havoc, and resulted in a paradigm shift with women discontinuing HT around the world. Moreover, medical societies based their recommendations for treatment of osteoporosis solely on this data, dismissing the benefit of HT on bone stabilization and prevention of fracture.

While the WHI is the largest RCT shedding light on HT, it was limited to the evaluation of two hormone formulations: conjugated equine estrogen (CEE) 0.625 mg/day + medroxyprogesterone acetate (MPA) 2.5 mg/day or CEE 0.625 mg/day alone. It was also limited to one dose of estrogen (CEE 0.625 mg daily) and an oral route of administration [6, 9, 12]. Furthermore, it is difficult to extrapolate the results of the WHI to the general population as the subjects were older, past the average age of menopause (mean age of 63.3 years), further away from initiation of menopause (mean length of time since menopause > 12 years), and asymptomatic women [5, 9, 12].

Given these limitations and results from subsequent studies, other governing bodies, such as the American College of Obstetricians and Gynecologists (ACOG), the International Menopause Society (IMS), the North American Menopause Society (NAMS), and others, proposed updated recommendations for HT in menopausal women. Subsequent studies evaluated different dosages and routes of estrogen therapy, including the transdermal patch and ultra-low-dose estrogens, to assess potential benefits on bone preservation while minimizing the proposed risks of HT observed in the WHI. This clinical review will summarize these studies and new recommendations for HT as a primary prevention and treatment for osteoporosis in appropriately selected postmenopausal women.

Observations

Randomized controlled trials and observational studies show that standard-dose HT, which was proposed by the manufacturer and approved by registration authorities to suit the average patient needs, reduces postmenopausal osteoporotic fractures of the hip, spine, and all non-spine fractures in women with and without osteoporosis [5, 6, 13]. In the WHI-HT, both intervention arms combined (CEE + MPA and CEE alone) showed statistically significant reduced hip fracture incidence of 33% ($p = 0.03$), with six fewer fractures per 10,000 person-years overall [13]. The 2016 IMS Recommendations on menopause hormone therapy (MHT) stated that in the age group 50–60 years or within 10 years after menopause, the benefits of MHT are most likely to outweigh any risk and can be considered as first-line therapy for fracture prevention [14]. The initiation of standard HT after the age of 60 years or more than 10 years after menopause exclusively for fracture prevention must be individualized and is not generally recommended. Conversely, the American College of Physicians (ACP) supported against HT in their clinical practice guideline for the treatment of osteoporosis in women, stating that high-quality evidence from the WHI showed that HT was associated with increased risk for venous thromboembolic (VTE), cerebrovascular events, invasive breast cancer, and node-positive tumors in one study [15].

On the other hand, the National Institute for Health and Care Excellence (NICE) proposed that the route of HT can impact the severity of adverse events, suggesting that there are alternative routes of HT that can benefit postmenopausal women [16]. Warming and colleagues, in their 2-year study comparing a combination HT transdermal patch versus a placebo among osteopenic postmenopausal women, showed that BMD measurements at the lumbar spine, hip, and total body increased by 8, 6, and 3% ($p < 0.001$) in the HT groups compared to placebo [17]. A recently published meta-analysis of nine clinical trials showed that 1–2-year use of transdermal estrogen was associated with 3.4–3.7% increase in lumbar spine BMD compared to baseline [18]. Scarbin et al. in a multicenter hospital-based case-control study showed that oral (OR [95% CI] = 3.5 [1.8–6.8]) but not transdermal estrogen (OR [95% CI] = 0.9 [0.5–1.6]) is associated with increased risk of VTE in postmenopausal women. Additionally, those who used oral therapies had an estimated VTE risk of 4.0 (95% CI 1.9–8.3) compared with women using transdermal regimens [19]. Similar results were reported elsewhere [20–23]. On the contrary, the results of the Kronos Early Estrogen Prevention Study (KEEPS), a 4-year double-blinded RCT of low-dose oral or transdermal estrogen or placebo given to healthy women ages 42 to 59 within 3 years after menopause, suggested no statistically significant differences in rates of VTE between the three groups; however, the absolute numbers of adverse events were very small in all three

treatment groups, making definitive conclusions impossible [24]. Further RCTs or population-based prospective studies are needed to corroborate these findings.

Compared with oral estrogen therapy (ET), transdermal ET is associated with greater reduction in sympathetic tone, little to no increases in C-reactive protein, and an overall reduced risk for atherosclerotic vascular disease [12, 25]. These differences can be explained by physiology as transdermal estrogen avoids first-pass metabolism in the liver, which permits the administration of lower doses of unmetabolized estradiol directly to the blood stream, avoiding overproduction of triglycerides. Multiple studies showed statistically significant reduction in serum triglyceride levels with the transdermal route compared to increased triglyceride levels with oral therapy [20, 26–29]. Decreased triglycerides result in decreased cardiovascular events in postmenopausal women. Additionally, because oral estrogens affect hepatic lipid metabolism and may lead to supersaturation of bile acids by cholesterol and gallstone formation, postmenopausal women taking oral ET may have increased risk of gallbladder disease, cholecystectomy, and biliary tract surgery [9]. As stated above, transdermal ET may avoid this increased risk due to absence of first-pass metabolism [9]. Furthermore, previous studies have demonstrated that transdermal estrogen decreases the incidence of coronary artery disease (CAD) by reducing systolic blood pressure and vascular resistance, while elevating cardiac stroke volume and cardiac output [18, 30, 31]. These findings suggest that transdermal estrogen not only preserves BMD, but also may serve as cardio-protection for young postmenopausal women [18]. On the other hand, it is important to understand that HT should not be solely used for either primary or secondary prevention of cardiovascular disease. This was supported by a meta-analysis by Boardman et al. which investigated the prevention of cardiovascular disease via HT in 40,410 postmenopausal women. The analysis concluded that primary or secondary prevention of cardiovascular disease events via HT has minimal benefit and can cause an increase in the risk of stroke and venous thromboembolic events [32]. They did, however, find through subgroup analysis that those who started HT less than 10 years after menopause had lower mortality and coronary heart disease [32].

In addition to differences in route of administration, ET differs in risk-benefit profile depending on the dosage of estrogen used with lower doses of estrogen still preserving BMD. Commonly used low and ultra-low doses of estrogen listed in Table 1 not only minimize the risks of ET, but also make it possible for clinicians to offer estrogen monotherapy using less often progestogen (e.g., q 6–12 month) to women with intact uterus for endometrial protection. This is of course only in the setting of careful monitoring for abnormal uterine bleeding and performing endometrial biopsy if indicated [33, 34]. Genant et al. showed in a 2-year RCT that 101 women receiving continuous unopposed oral esterified estrogens (EEs) at 0.3 mg/day had positive bone and lipid changes without inducing clinically relevant endometrial hyperplasia [35]. EEs and CEEs have been found to produce similar serum levels of estrone and estradiol [36], with less risk of VTE associated with EEs relative to CEEs [37]. Prestwood et al. showed that oral ultra-low-dose micronized 17β-estradiol at 0.25 mg/day not only reduced biochemical markers of bone turnover to a degree comparable to an estrogen dose of 1.0 mg/day, but the lower dose estrogen resulted in a side effect profile similar to that of placebo [38]. They found in a subsequent RCT that oral ultra-low-dose micronized 17β-estradiol at 0.25 mg/day for 3 years compared to placebo resulted in significant increases in hip, spine, and total BMD among postmenopausal women [39]. The effect on bone preservation with low-dose estrogen therapy has also been observed with the transdermal route. It has been observed that women given transdermal estradiol at either the conventional 0.050 mg/day dosing or the half strength dose of 0.025 mg/day resulted in a reduction in bone turnover markers to a similar degree [40].

Furthermore, lower than standard doses of estrogen therapy, regardless of route of administration, have been shown to serve the dual purpose of preserving BMD and relieving menopausal symptoms [9]. This was seen in a 12-week RCT of 324 women who received a low-dose, 7-day matrix estradiol transdermal system that delivers 0.025 mg of 17β-estradiol daily for 7 days and experienced relief in their vasomotor symptoms, namely a decrease in hot flush frequency by 84% [41]. Ettinger et al. showed that even a lower dose of transdermal estradiol at 0.014 mg/day, which is adequate for hot flash relief in some women, has beneficial skeletal benefits [42]. This was also seen in the HOPE (Health, Osteoporosis, Progestin, Estrogen) trial: a large RCT with lower doses of

Table 1 Bone-sparing doses of estrogen

	FDA-approved dose*	Commonly used low or ultra-low dose
Oral conjugated estrogens (mg/day)	0.625	0.45 or 0.3
Oral micronized 17β-estradiol (mg/day)	0.5	0.25
Oral esterified estrogens (mg/day)	0.3	–
Transdermal 17β-estradiol (μg/day)	25	14

*Source: Epocrates in athenahealth® version 16.11 (last updated on Jan 9, 2018)

CEE (0.45 and 0.3 mg/day), with or without a lower dose of MPA (1.5 mg/day). Findings showed prevention of the loss of spine and hip BMD, reduced bone turnover, improvement in vasomotor symptoms, vaginal atrophy, lipid profiles, bleeding profiles, and endometrial hyperplasia in women on HT [43–47].

Despite the decreased estrogen levels in menopausal women and the clear benefits of HT, bisphosphonates, instead of HT, are the first-line therapy for the primary prevention of osteoporosis. However, currently available RCTs on efficacy of bisphosphonates for primary prevention of osteoporosis neither showed nor had adequate power to support fracture prevention in non-osteoporotic women [48]. Indeed, only oral CEE has been shown to reduce the risk of fracture in both osteoporotic and non-osteoporotic women [2]. National Osteoporosis Foundation (NOF) guidelines [49] recommend pharmacotherapy for postmenopausal women with low bone mass (T-score between − 1.0 and − 2.5), if the Fracture Risk Assessment Tool (FRAX) calculated a 10-year probability of hip fracture (HF) reaches 3% or a 10-year probability of any major osteoporosis-related fracture (MOF) is ≥ 20%. The accuracy of FRAX using aforementioned 10-year USA treatment threshold for fracture risk prediction has been questioned by a meta-analysis of seven large population-based longitudinal cohort studies from five countries [50]. The study findings suggest that a substantial number of patients who developed fractures, especially MOF within 10 years of follow up, were missed by the baseline FRAX assessment using the 10-year intervention thresholds of 20% for MOF and 3% for HF [50]. Therefore, correctly identifying and subsequently treating those non-osteoporotic menopausal women at risk of fracture remains a challenge. Due to dual benefits of HT on bone and vasomotor symptoms (VMS), young peri- or postmenopausal women with VMS and low bone mass are the best candidates for hormone monotherapy, provided no contraindication exists. Otherwise, bisphosphonates can be combined with a selective serotonin reuptake inhibitor (SSRI) to aid in prevention of osteoporosis and treatment of VMS [51]. Selective estrogen receptor modulators (SERMs), such as raloxifene (60 mg/day), have been shown to increase BMD and reduce the risk of vertebral fractures but not non-vertebral fractures in women with osteoporosis [52]. A single oral pill of bazedoxifene/CEE (20/0.45 mg) is also available in the USA for the treatment of VMS and prevention of postmenopausal osteoporosis; however, there are no fracture data for this therapy [48]. While HT can have significant side effects, the above alternative therapies also have contraindications and side effects that maybe just as harmful. Adverse effects of raloxifene include venous thromboembolism (VTE), leg cramps, and death from stroke [1]. Side effects of bisphosphonates include osteonecrosis of the jaw, abnormal bone histology, and associations with atypical femur fractures (AFF) [1, 51, 53]. Furthermore, gastrointestinal side effects are common in that 30% of women require proton pump inhibitors (PPI), which themselves can have negative effects on bone health. PPI in observational studies have been found to decrease BMD and increase osteoporotic hip fractures after 5 years of use [51, 53]. Of interest, studies of bone histology in osteoporotic women taking transdermal estradiol for 6 years showed that estrogen correlates with continuing collagen production evidenced by increase in collagen as well as intermediate and mature collagen cross-links in cancellous and cortical bone [54–56]. A study evaluating intervertebral discs that are 100% collagen and make up one-quarter of the length of the spine showed that estrogens protect the spine by maintaining the size of the individual and total intervertebral disc space as well as the length of the spine; however, bisphosphonates do not [54, 57]. While bisphosphonates and raloxifene demonstrate fracture prevention in women with osteoporosis, there is no data regarding fracture reduction among women without osteoporosis.

The continued effect on BMD and fracture prevention after discontinuing osteoporosis therapies remains a concern. It is suggested that there may be residual BMD and fracture benefit after discontinuation of bisphosphonate therapy, making this an appealing option [1]. On the other hand, most studies show no lasting benefit on bone after estrogen discontinuation. Bone loss following discontinuation of HT is similar to bone loss following menopause, often referred to as "catch up bone loss" [58]. However, recently published research findings from two WHI-HT trials (CEE + MPA and CEE alone) suggested no evidence for increased fracture risk 5 years after stopping HT among former HT users compared with former placebo users. The study also showed residual benefit for total fractures in former HT users from the CEE-alone trial [59]. If HT needs to be discontinued in women at high risk of fracture, the 2014 NOF guideline recommends that it should be replaced with another pharmacological agent such as bisphosphonate or denosumab for continued bone protection [60].

Conclusions

Physicians around the world reserve the use of HT to women with moderate-severe vasomotor symptoms with the concept of "lowest dose for the shortest period of time" despite the various benefits of HT, including prevention and management of osteoporosis, improved sexual function in women with vaginal atrophy, decreased cardiovascular events, improved mood, and overall improved quality of life [13]. This practice was a direct result of the initial data presented from the WHI studies. However, given the limitations of the WHI and subsequent studies showing multiple benefits of HT, it is essential to challenge biases and reservations of HT for women. More importantly, physicians should consider the role of HT with the concept of "appropriate dose, duration, regimen, and route of administration" as this can differ for each patient [13, 61].

HT has been shown to be efficacious in reducing the number of vertebral and non-vertebral fractures in postmenopausal women, with efficacy equivalent to that of bisphosphonates [5–7]. Furthermore, HT decreases the incidence of all osteoporosis-related fractures, including vertebral and hip fractures, even in women not at high risk of fracture and women not diagnosed with osteoporosis [8]. HT should be offered to menopausal woman younger than 60 years of age or within 10 years of menopause, especially those with VMS, for primary prevention and treatment of osteoporosis [3, 8, 13, 53]. Shared decision making is always recommended while counseling patients about the benefits/risks of HT.

Ultra-low dose of transdermal estradiol (14 μg per day) monotherapy for 2 years has shown a significant increase in BMD and prevention of bone loss without increased risk of endometrial hyperplasia and vaginal bleeding compared to placebo [62]; however, the prescription of low-dose estrogens in monotherapy in women with an intact uterus is not currently recommended and requires adequate surveillance in highly selected patients. Perhaps ultra-low-dose transdermal estradiol (Table 1) can be given to women aged 60 and older for the modest increases in estrogenic action to preserve skeletal integrity without significant breast effects and endometrial stimulation due to the lower progestogen dose required for endometrial protection [3]. Additionally, the use of transdermal preparations has been shown to less likely increase the risk of VTE, stroke, and CAD than oral preparations. Thus, these low-dose non-oral HT options may be considered for women with cardiovascular risk factors (e.g., diabetes, hypertension, and obesity), women of advancing age, and for those who choose extended duration use of HT for bone protection [42, 61, 63].

Learning objectives

1. To learn the emerging evidence on estrogen therapy and revisit the role of estrogen for primary prevention and treatment of osteoporosis.
2. To understand that risk profiles of estrogen therapy vary depending on formulation, dosage, duration, and route of administration.
3. To comprehend the necessity of adjusting the once "lowest dose for shortest period of time" concept to "appropriate dose, duration, regimen, and route of administration" individualized to each patient.

Clinical tips

1. Hormone therapy (HT) should be offered for the primary prevention and treatment of osteoporosis in appropriate menopausal women younger than 60 years of age or within 10 years of menopause, especially when menopausal symptoms are present.
2. Emerging evidence suggests that the once "lowest dose for shortest period of time" concept should be adjusted to "appropriate dose, duration, regimen, and route of administration" individualized to each patient
3. Transdermal and low-dose HT have shown to have a low adverse effect profile while still proving to be efficacious in increasing BMD. Lack of documented benefit of bisphosphonates for non-osteoporotic women along with unique physiologic impact and dual benefits of non-oral HT regimens, including ultra-low-dose regimens, the use of appropriate estrogen or HT regimens for the primary prevention of osteoporosis should be considered even in selected women who are not suffering from severe menopause-associated symptoms.

Compliance with ethical standards

Conflict of interest None for VL and XJ, R Kagan has received research grants and support from Therapeutics MD (paid to Sutter Health), and has served as a consultant to Amgen, Merck, and Pfizer.

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