MENOPAUSAL HORMONE REPLACEMENT THERAPY IN PREVENTION MENOPAUSAL THERAPY

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Summary: Postmenopausal women suffer hip fractures caused by osteoporosis that develops primarily as a consequence of the low estrogen levels of menopause. Calcium supplementation, although probably important before menopause, cannot stop bone loss alone in the perimenopausal and postmenopausal phases. Estrogen replacement therapy remains the treatment of choice. As little as 0.625 mg of conjugated estrogens can inhibit bone loss. Oral contraceptives also have a beneficial effect on bone density. Although fluoride therapy can increase bone mass, objectionable side effects rule out its use.

Key words: estrogen replacement therapy, menopause, osteoporosis.

Purpose of Review

The goal of the review is to assess the appropriateness of menopausal hormone therapy (MHT) for the primary prevention of bone loss in women at elevated risk in the early years after menopause.

Summary

MHT should be considered in women with premature estrogen deficiency and increased risk of bone loss and osteoporotic fractures. However, MHT use for the prevention of bone loss in woman among 40-50 years old .

Inroduction

Osteoporosis is a common disease characterized by low bone mass, microarchitectural disruption, increased skeletal fragility, decreased bone strength associated with increased fracture risk, and mortality associated with fractures [1]. Due to changes in population demography, the annual number of fragility fractures will rise from 3.5 million in 2010 to 4.5 million in 2025 in the EU [2]. Therapies that are effective in osteoporotic women at high risk of fracture are available. However, to significantly impact total fracture numbers, effective options are needed to prevent

early accelerated bone loss in women in the first years after menopause and to delay the necessity of antiresorptive therapies in postmenopausal women as they age. Estrogen deficiency is the major cause of the early postmenopausal increase in bone resorption, bone loss and osteoporosis [3]. Randomized clinical studies have demonstrated that estrogen alone, or combined with progestin to protect the uterus from cancer, reduces the risk of osteoporosis-related fractures. There are currently no clinical guidelines for the management of bone loss in early postmenopausal women. The magnitude of bone remodeling and early bone loss depend on several important genetic factors and bone health characteristics of the women, such as recurrent cycle/ovulatory disturbances; overall nutrition; body mass index; protein, calcium, and vitamin D intakes; physical activity; adequacy of sleep; the psychosocial environment; and cognitive dietary restraint, modulate the bone tissue sensitivity to estrogen deficiency.

Alternative dosages and routes of MHT have been shown to be efficacious even at low doses. Oral micronized 17β-estradiol at a dose of 0.25 mg/day for 3 years in postmenopausal women resulted in significant increases in hip, spine, and total BMD compared with the placebo. This treatment reduced biochemical markers of bone turnover to a degree comparable with an estrogen dose of 1.0 mg/day. The side effect profile of the drug was similar to that of the placebo [8]. The addition of progestogen to estrogen did not interfere with this benefit.

The effect of low-dose estrogen therapy via the transdermal route on bone preservation has been well documented [1]. A double-blind, placebo-controlled study was performed in 355 nonosteoporotic postmenopausal women who had hysterectomies with or without oophorectomy. At 2 years, compared with the baseline values, lumbar spine BMD declined by 0.59% in the placebo group, but it increased by 1.65%, 4.08%, and 4.82% in the estradiol 0.025, 0.05, and 0.075 mg/day groups, respectively [3]. Administration of 0.050 mg/day or 0.025 mg/day transdermal estradiol resulted in a reduction in bone turnover markers to a similar degree [9]. Transdermal administration of 0.014 mg/day estradiol was associated with a significant increase in lumbar spine BMD and in total hip BMD compared with the placebo group [10]. A 2-year transdermal administration of estradiol and levonorgestrel resulted in significant increases in the lumbar spine, hip, and total body BMD, in the hormone groups compared with the placebo group [1]. All bone markers were significantly reduced in the hormone groups compared with the placebo group [2]. According to a meta-analysis of nine clinical trials, lumbar spine

BMD increased significantly by 3.4% and 3.7% after one and 2 years of transdermal estrogen therapy, respectively, compared with the baseline values [2].

Bone Effects of Estrogen Deficiency

After menopause, bone homeostasis is dysregulated by hormonal deficiency, leading to enhanced bone resorption and, consequently, increased bone formation. However, the rate of formation is not able to keep up with the rate of resorption, resulting in net bone loss [3]. Estrogen deficiency plays a specific role in the subclinical inflammatory bone-microenvironment state that is accompanied by an increase in oxidative stress and the generation of advanced glycation end products [3].

Important information regarding the effects of MHT in the preservation of bone mass by reducing the rate of osteoclastic bone resorption and maintaining new bone formation was provided by dynamic bone histomorphometry in a randomized, double-blind, clinical prospective trial that enrolled healthy women aged 45-55 years who were treated for 2 years with either cyclic estradiol/norethisterone acetate or placebo [5]. Bone biopsies from untreated women demonstrated an increased osteoclastic erosion rate, erosion surface and erosion depth compared with women in the MHT group. In untreated women, delayed osteoclast apoptosis resulted in a longer osteoclast lifespan and increased resorptive activity and erosion depth. The bones of women taking MHT were characterized by preservation of bone balance at individual basic multicellular units (BMUs) (wall thickness-erosion depth) and no change in erosion depth or osteoclastic erosion depth. A relative osteoblastic insufficiency was present in the placebo group because osteoblastic bone formation was unable to keep up with the increase in bone resorption [5]. Accordingly, a significant decrease in osteoclast number and osteoclastic resorption rate, but not mineralizing surface or bone formation rate, was observed after 6 months of CEE treatment [5].

Both MHT and antiresorptive therapies such as aminobisphosphonates and denosumab increase BMD, reduce bone turnover and are efficacious in the treatment of postmenopausal osteoporosis [2]. A reduction in the number of remodeling sites may decrease the probability of trabecular perforation and failure and thus stabilize the trabecular network [6]. However, estrogen but not antiresorptive therapies [6], by enabling maintenance of bone formation, can adjust the physiological rate of bone remodeling, and restore quality of bone organic matrix, that affects bone micromechanical properties independently of mineralization [6]. Moreover, estrogen but not antiresorptive therapies [3] attenuate the inflammatory bone-

microenvironment and maintain the equilibrium between bone resorption and bone formation by modulating osteoblast/osteocyte and T cell regulation of osteoclasts.

Of importance are beneficial effects of MHT on connective tissue, namely, muscle and cartilage. In a meta-analysis, postmenopausal women treated with MHT had approximately 5% greater muscle strength than those not on MHT [4]. According to Collins et al. the loss of muscle strength in females resulting from estrogen deficiency appears to be associated with apoptotic pathways that contribute to the loss of muscle mass, inadequate preservation of skeletal muscle mass and reduced quality of the remaining skeletal muscle [1]. Estrogen may protect skeletal muscle against apoptosis via its effects on hydrogen peroxide-induced apoptosis and mitochondrial dysfunction [2]. On the other hand, the cross-sectional area of the skeletal muscles around the femur was lower in osteoporotic patients who underwent long-term aminobisphosphonate treatment than that of the BMD-matched control postmenopausal women [2].

A significantly lower intervertebral disc height was demonstrated in postmenopausal osteoporotic women when compared with that in untreated nonosteoporotic women who, in turn, had significantly lower disc height than premenopausal women and women taking MHT [1]. Intervertebral disc space shows a progressive decline that almost entirely occurs in the first 5–10 years after menopause [7]. Estrogen was shown to have direct chondroprotective effects and to be able counteract cartilage degradation in an in vivo model of increased cartilage turnover [7].

Safety Aspects of Menopausal Hormone Therapy

According to clinical studies [13], the individual benefit/risk balance of MHT is very dependent on the type, doses, and duration of MHT as well as the individual risk profile of each woman. These aspects are considered in the guidelines [3].

Ischemic stroke is affected differentially by the route of estrogen administration [6•] due to the hepatic first-pass effect of estrogens when administered orally. Oral but not transdermal estrogen activates the coagulation cascade and increases fibrinolytic activity and may also induce resistance to activated protein C, which has been associated with an increased VTE risk [7. 8].

Other risks associated with MHT include dementia (in women aged ≥ 60 years) [9], gallbladder disease [10], and urinary incontinence [11].

Conclusion

MHT prevents bone loss and deterioration of the bone microarchitecture [10] and decreases the incidence of osteoporosis-related fractures even in postmenopausal women not diagnosed with osteoporosis, with an efficacy similar to that of bisphosphonates. However, due to differences in the mode of action, estrogen but not antiresorptive therapies can attenuate the inflammatory bone-microenvironment and maintain the physiological equilibrium between bone resorption and bone formation. Importantly, the use of MHT for 5-10 years from the onset of menopause has potentially valuable effects on the bone for many years after MHT discontinuation [2]. Also, MHT during the early postmenopausal years effectively improveshot flashes and night sweats, and may improve other features involved in the genesis of osteoporotic vertebral fractures, namely, the quality of connective tissue.

The evidence of increased risks of breast cancer does not allow recommending MHT for the prevention of bone loss in the population, even in women younger than 60 years old or who are within 10 years of menopause onset. However, MHT should be considered in women with premature estrogen deficiency and increased risk of bone loss and osteoporotic fractures. Selective estrogen receptor modulators [13,14,15,] appear to be an available option to delay the necessity of antiresorptive therapies in postmenopausal women as they age. Clinical trials are needed to test the efficacy, safety and cost-effectiveness of other antiresorptive options in the prevention of accelerated bone loss in the early years after menopause in women with increased risk of an accelerated bone loss in order to reduce the number of future fractures associated with the changing population demography.

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