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Review Article

Is there a place for menopausal hormonal therapy in the treatment of postmenopausal osteoporosis?

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Summary

Postmenopausal osteoporosis is a major problem for public health. In the past, osteoporosis was one of the primary indications for menopausal hormonal therapy (MHT), but actually it has been downgraded to second-line therapy In this review the authors would like to discuss actual data on the role of estrogen and progestins in the bone metabolism and the results of clinical studies related to MHT.

Key words: Osteoporosis; Menopause; Aging; Menopausal hormonal therapy; Fracture.

Introduction

Postmenopausal osteoporosis is a major problem for public health. It is estimated that the incidence of osteoporotic fractures is about 6,700 per 100,000 people after the age of 50 years [1]. Due to the aging of population, costs of osteoporosis treatment in Europe increases. They were estimated at 31.7 billion euro in year 2000 and are expected to double by 2050 [2]. In the past, osteoporosis was one of the primary indications for menopausal hormonal therapy (MHT), but actually mostly due to the unfavorable risk to benefit balance reported by the Women's Health Initiative (WHI) study and other clinical trials, it has been downgraded to second-line therapy [3].

In this review the authors would like to discuss actual data on the role of estrogen and progestins in the bone metabolism and the results of clinical studies related to MHT.

Estrogen and progesterone in the bone metabolism

The decrease of bone mass density (BMD) begins usually after the age of 30-40 years of life. At this time the mean speed of BMD decrease is about 1% per year. After menopause the mean speed of BMD loss is even 16% for a year [4]. The main cause of this rapid BMD loss is lack of estrogen which causes rapid loss of bone mineral density and micro-architectural deterioration leading to increased bone fragility and a higher risk of fracture.

Lack of estrogen causes direct changes on the level of bone tissue, on the level of cytokine synthesis, and on the level of receptor activator of nuclear factor kappa B ligand (RANKL).

Estrogen directly stimulate bone formation via an estrogen receptor-dependent mechanism [5]. Estrogen increase production of IGF-1 [6], and procollagen synthesis by osteoblast precursor cells [6], and increases osteoblast life span by decreasing osteoblast apoptosis [7, 8]. Estrogens also directly stimulate apoptosis of osteoclast precursor cells and inhibit the activity of mature osteoclasts [9]. Loss of these multiple estrogen-induced restraining actions on osteoclast bone resorption leads to rapid upregulation of bone loss shortly after onset of menopause.

Estrogen also influences bone metabolism through cytokine synthesis. Estrogen inhibits production of bone-resorbing cytokines such as interleukin (IL)-1, interleukin (IL)-6, tumor necrosis factor (TNF)-α, macrophage colony-stimulating factor (M-CSF), and prostaglandins [10]. Estrogen stimulates production of cytokines which inhibit bone resorption like transforming growth factor β (TGF-β) [11].

At the level of bone tissue, estrogen inhibit RANKL synthesis of by osteoclasts [12]. RANKL stimulates osteoclast recruitment and activation and inhibits osteoclast's apoptosis. Estrogen decrease osteoclast precursor differentiation by blocking RANKL/M-CSF-induced activator protein (AP)-1-dependent transcription [13, 14]. In the same time estrogen stimulate synthesis of osteoprotegerin (OPG) by osteoblasts [15]. OPG inhibits RANKL action [16]. Lack of estrogen causes increase of RANKL and decrease of OPG level what in turn causes bone resorption and osteoporosis.

Progesterone and progestins act synergistically with estrogen on the level of bone tissue. Progesterone inhibits bone resorption and increases a positive effect of estrogen action. Attention should be directed to the use of high doses

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of progestins which can interfere with normal bone metabolism through menstrual cycle inhibition.

Clinical studies

Clinical studies support the data from the studies on the estrogen action on the level of bone tissue and also reveal that MHT both increases BMD and decreases the risk of bone fractures [3].

Khastgir *et al.* provided direct evidence that estrogen can stimulate bone formation by evaluating iliac crest bone biopsies from elderly women of mean age 65 years before and six years after percutaneous administration of high doses of estrogen [17]. They found that cancellous bone volume increased by 61%, and trabecular wall thickness by 12%. Similar results were reported by other authors [18]. Tuppurainen *et al.* revealed that five years of MHT decreased the risk of extravertebral fractures by 71% [19]. Donker *et al.* reported five years of MHT decreased a total risk of fractures by 39% [20]. A meta-analysis of 57 clinical studies revealed that MHT decreases the risk of femur fractures by 25% and vertebrae fractures by 50% [21].

Even low doses of MHT are effective at preventing the loss of bone density in spine and femur and at reducing bone turnover. The administration of calcium and vitamin D supplements facilitates the use of a lower dose of estrogen and guarantees an increase in bone mass in spine and femur similar to that observed using a standard dose [22].

The positive impact of MHT on the level of bone tissue was revealed even in the WHI study. This study provides the largest database of any osteoporosis medication in randomized controlled trials. This study showed a significant reduction in all fractures with the use of MHT [23, 24]. The use of conjugated estrogens and medroxyprogesterone acetate decreased the relative risk of femur fractures to the value of 0.66, the risk of vertebral fractures to the value of 0.66, and the risk of other osteoporotic fractures to the value of 0.77 [25].

There is a dose-response of estrogen therapy for bone protection, but even low doses of MHT are effective in preserving or improving bone density [26]. The effect of low doses on bone turnover suggests similar to higher dose effect for the prevention of fractures [27]. There are results with a ultra-low oral dose combined MHT with estradiol 0.5 mg that can alleviate subjective symptoms providing an effective protection against the postmenopausal decrease of BMD [28].

Long-term MHT use in the indication of bone preservation is considered an option for women at high risk of osteoporotic fractures, particularly when other products have been poorly tolerated, are contraindicated, or have an unfavorable risk-benefit balance [29].

The balance of benefits and risks for MHT is most favorable within the first ten years of menopause, or up to around 60 years of age [3]. During this window of opportunity, estrogen-containing hormone therapy not only relieves menopausal symptoms for women at low risk, but also may have a positive impact on women's bone health and cardiovascular risk [3].

Extending MHT use for longer intervals is considered acceptable for some women, provided that the woman is fully informed as to the potential risks and has appropriate clinical supervision [3]. This may include women at high risk of osteoporotic fracture, for whom alternate therapies are not appropriate or tolerated. This may also include women who have failed previous attempts to stop MHT and who, after discussing the pros and cons of MHT with their provider, have determined that the benefits of menopause symptom relief outweigh the risks for their particular situation [3, 30].

The importance of estrogen background in bone health is demonstrated by the rapid bone loss that occurs with use of aromatase inhibitors, such as exemestane and letrozole in treatment of postmenopausal women with estrogen receptor-positive breast cancer. These potent inhibitors of the aromatase enzyme cause marked reduction in serum estradiol levels, which leads to rapid bone loss unless treatment with antiresorptive agents is initiated prophylactically [31].

Lower peak bone density at 25–35 years of age also contributes to risk of osteoporosis and fractures later in life. Individuals with lower peak bone density for whatever cause will develop low bone density or osteoporosis sooner than those with higher peak bone density, assuming the rate of bone loss is equivalent as they age [32]. All the causes that lead to lack of estrogen before the age of 25-35 years of age. like primary (ovarian dysgenesis, premature ovarian failure) or secondary ovarian insufficiency (hypothalamic amenorrhea, hyperprolactinemia), lead to decreased bone density in future.

Prematurely menopausal women (<40 years) constitute a unique group in whom the general guidelines for use of MHT do not apply. In the absence of contraindications, MHT use until approximately the average age of natural menopause appears to be important for reducing the deleterious health consequences of early estrogen deprivation, including osteoporosis, increased risk of coronary heart disease, cognitive decline, and premature death [33].

Although MHT in not licensed anymore for the prevention of osteoporosis as a first-line treatment, MHT seems to be the only proven effective option for the primary prevention of postmenopausal osteoporosis. It is a recognized method in the prevention and treatment of osteoporosis.

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