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Postmenopausal Osteoporosis: From Mechanisms to Modern Therapies

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ABSTRACT

Background. Osteoporosis is the most common metabolic bone disease and represents a serious public health problem, particularly among postmenopausal women. It is characterized by reduced bone mineral density and bone microarchitecture disorders, leading to an increased risk of fractures, mortality, and socioeconomic burden. Estrogens play a key role in skeletal homeostasis by regulating osteoclasts, osteoblasts, and osteocytes. Advances in research have led to the development of effective pharmacological therapies targeting bone resorption and formation. In combination with supportive measures, these therapies form the basis of individualized strategies for fracture prevention and bone health maintenance in postmenopausal women.

Aim. The aim of this study is to review the role of estrogen deficiency in the pathogenesis of postmenopausal osteoporosis and to evaluate current pharmacologic treatment options, with a particular focus on their mechanisms of action, effects on bone remodeling, and efficacy in reducing fracture risk.

Material and methods. We conducted a review of the literature from 2015-2025 available in the PubMed database, using the keywords “postmenopausal osteoporosis” “postmenopausal osteoporosis treatment” and “osteoporosis hormones”

Results. A range of effective pharmacologic therapies is available to reduce fracture risk. Antiresorptive agents such as bisphosphonates and denosumab are central to treatment, while hormone replacement therapy and selective estrogen receptor modulators may benefit selected patients. Osteoanabolic agents are particularly valuable for individuals at high fracture risk. Calcium and vitamin D provide supportive benefits when deficiency is present.

Conclusions. Personalized, long-term therapeutic strategies such using osteoanabolic agents and antiresorptive agents as are critical to preserving bone health and optimizing treatment results in postmenopausal women.

Keywords: postmenopausal osteoporosis, postmenopausal osteoporosis treatment, osteoporosis hormones

Introduction

Osteoporosis is a metabolic bone disease manifested by low bone mineral density and impaired bone structure, leading to decreased bone strength and an elevated risk of fractures [1]. Osteoporosis is the most widespread metabolic bone disease, and its main consequence is osteoporotic fractures, which significantly increase premature mortality, disability, economic burden and also lower quality of life [2,3]. Osteoporotic fractures most frequently occur in the hip, spine, and distal forearm [4]. Postmenopausal osteoporosis is a result of estrogen insufficiency, leading to greater differentiation and activation of osteoclasts, accelerated bone resorption exceeding bone formation, and rapid bone loss, particularly in the years immediately before and after menopause [5]. For women with osteoporosis and/or other risk factors for fractures, such as advanced age, smoking, metabolic diseases, side effects of medications, and previous fractures, the main goal of treatment is to minimize the risk of new fractures. This is achieved through a combination of strategies to prevent falls, drug therapy to increase bone density, and other nonpharmacologic measures [6,7].

The importance of estrogens

Estrogens refer to a class of hormones that consists of estrone, estradiol, and estriol. The majority of estrogens are secreted by the ovaries, but there are also smaller amounts produced by other tissues such as adipose tissue, the adrenal glands, the pancreas, and the brain. Estrogens are crucial for the development of female sexual characteristics and reproductive function, and they also play a role in maintaining bone health, proper brain function, and the regulation of inflammatory processes. Estradiol is the main and most active estrogen; it can be converted to estrone, and both estrone and estradiol have the potential to be turned into estriol. Premenopausal women have high levels of estradiol, but this decreases with age. After menopause, estrone takes over as the main estrogen. Estrogen binds to three main estrogen receptors: the estrogen receptor alpha, the estrogen receptor beta, which are located in the cell nucleus, and the G protein-coupled estrogen receptor, which is located on the cell membrane. Nuclear receptors regulate gene expression through two mechanisms. The first is the direct genomic pathway, in which estrogen-receptor complexes bind directly to specific DNA sequences known as estrogen response elements. The second mechanism is the indirect genomic pathway, in which estrogen-receptor complexes influence other transcription factors that do not themselves bind directly to DNA. In contrast, the non-genomic pathway involves rapid signaling that begins at the cell membrane, primarily through the estrogen receptor coupled to a G protein. This signaling activates cascades of protein kinases that ultimately influence gene expression. [7]

The impact of estrogens on bone tissue

Bone is a dynamic tissue in which osteoblasts form new bone tissue and osteoclasts break down aging bone tissue, keeping the skeleton healthy. This continuous cycle of replacement is called bone remodeling [8]. Various hormones and local factors, including the sex hormones estrogen and progesterone, regulate the activity of both cell types [9]. Ovarian production of estrogen and progesterone drops considerably during menopause. This decrease marks menopause as an important period for changes in bone metabolism [10]. When estrogen levels drop, bone remodeling becomes unbalanced. Bone turnover increases as the cell groups involved in remodeling become more active. More osteoblasts undergo apoptosis, the time for bone formation is shortened, and fewer osteoclasts die. As a result, the bone breakdown phase lasts longer. More osteoclasts are also recruited, further increasing bone loss. Overall, bone resorption becomes greater than bone formation [7]. New bone tissue is insufficient to completely replace lost bone, leading to significant bone loss [11]. These changes lead to postmenopausal osteoporosis. Approximately 33% of women above the age of 50 suffer from osteoporotic fractures. One study found that estradiol levels <5 pg/mL were associated with a 2.5x greater risk of hip and spine fractures [12]. These findings demonstrate that estradiol levels serve as a predictor of fracture risk, impacting both longevity and overall quality of life.

Osteocytes make up about 90% of all bone cells and are lodged in a hard, mineralized bone matrix. They serve as mechanical sensors. When bone is exposed to mechanical stimulation, osteocytes transform these physical signals into chemical responses and secrete signaling particles such as bone morphogenetic proteins, prostaglandin E2, and nitric oxide. These molecules help regulate the activity of osteoblasts and osteoclasts. The primary role of osteocytes is to regulate cell survival and react to mechanical forces. Studies have shown that the estrogen receptor alpha in osteocytes decreases during estrogen deficiency, which is related to increased bone loss [7]. Estrogen deprivation also decreases fluid-induced calcium signaling, compromising the mechanical responsiveness of osteocytes and disrupting their differentiation and activity [13]. Therefore, evidence suggests that osteocytes are an important target for estrogen. Further confirmation comes from studies conducted on mice after removal of the ovaries, which showed that osteocytes have an impaired ability to activate the Wnt and beta-catenin signaling pathway during mechanical loading in the absence of estrogen. This indicates the key role of estrogen in maintaining normal mechanosensitivity of osteocytes [14].

Pharmacotherapy

Pharmacologic treatment of osteoporosis involves drugs that are broadly divided into two main classes: agents that inhibit bone resorption and agents that promote bone formation. Medications commonly used to treat postmenopausal osteoporosis include hormone replacement therapy and estrogen receptor modulators, bisphosphonates, denosumab, parathyroid hormone analogues, vitamin D, and calcium [11]

Bisphosphonates

Bisphosphonates reduce osteoclast activity by inhibiting the enzyme farnesyl pyrophosphate synthase, which prevents the prenylation of small GTP-binding proteins. As a consequence, the cytoskeleton of osteoclasts is disrupted, the ruffled border of the cell membrane is lost [15], and vesicular transport is impaired. Exposure to bisphosphonates accelerates the process of osteoclast apoptosis. During bone resorption, mature osteoclasts absorb bisphosphonates, which bind strongly to bone minerals. They can remain attached to the bone matrix for many years; those with higher mineral affinity, such as zoledronic acid and alendronate, show longer persistence in the skeleton [16]. Therefore, even after discontinuation of treatment, previously bound bisphosphonates continue to exert residual pharmacological effects for many years. This persistent effect differs from that of other antiresorptive drugs, such as denosumab, estrogen therapy, raloxifene, and calcitonin, whose benefits rapidly disappear after discontinuation of treatment [17]. According to a systematic review encompassing 24 studies, bisphosphonate therapy resulted in lower rates of vertebral fractures than placebo (5.9% compared with 10.3%), and it likewise decreased the incidence of non-vertebral fractures (6.0% compared with 9.6%) [18]. Bisphosphonates are available in a variety of ways, including oral meds taken weekly or monthly, and IV meds given every three months or yearly. Because oral bisphosphonates don't get absorbed well, it's super important to follow the instructions for taking them. Patients should take the medication with water while sitting upright, at least 30 minutes before eating or taking other medications [4].

Denosumab

Denosumab, a fully human monoclonal antibody directed towards the receptor activator of nuclear factor kappa-B ligand (RANKL), acts as a powerful anti-resorptive agent, leading to profound and long-lasting inhibition of bone turnover [19]. Denosumab, administered as a 60 mg subcutaneous injection every six months, blocks osteoclast activity and reduces bone loss, effectively reducing the risk of fractures in osteoporosis. It is the first and only RANKL inhibitor approved by regulatory authorities and the first monoclonal antibody specifically approved for the treatment of postmenopausal osteoporosis [20]. Among postmenopausal

women with osteoporosis, ongoing denosumab therapy leads to gradual increases in bone mineral density, improvements in bone microarchitectural quality, and notable reductions in fracture risk at all major skeletal sites [21]. The study showed that denosumab steadily increased bone strength in the hip and spine at 12, 24, and 36 months. Bone biopsies taken up to 10 years confirmed normal bone structure despite strong suppression of remodeling. Bone matrix mineralization rose during the first 5 years and then settled. Denosumab also maintained bone modeling in the femur and diminished the depth of erosive lesions in the iliac crest, establishing a positive balance in each remodeling cycle. These aggregated effects improve bone microarchitecture, increase cortical bone thickness and density, and finally strengthen the bone [20]. Unlike bisphosphonates, the effects of denosumab are reversible. After withdrawal of denosumab, bone turnover increases quickly and the bone mass acquired during treatment is typically lost within 12 to 24 months [22]. There is an increased risk of vertebral fractures during the period of rapid bone loss. This should be taken into account when choosing a treatment, and lifelong denosumab therapy is commonly recommended. Nevertheless, treatment may need to be discontinued due to adverse events or because bone mineral density has increased to a level where further treatment offers no additional benefit. Patients who have a long life expectancy and who achieve bone mineral density levels in the higher range of osteopenia during denosumab treatment may also be suitable candidates for discontinuation of therapy [23].

Hormone replacement therapy

Hormone replacement therapy predominantly refers to estrogen-progestogen therapy and is administered to postmenopausal women who face a high risk of fractures, particularly among those who experience symptoms such as hot flashes and night sweats. Hormone therapy is not usually the first choice for treating osteoporosis, but postmenopausal women who use hormone replacement therapy receive additional benefits due to its positive effect on bone health. The decline in estrogen levels that takes place during menopause affects proper bone turnover. Hormone replacement therapy improves estrogen levels, helping to prevent bone loss and reduce the likelihood of osteoporosis, as well as relieving menopausal symptoms. Treatment options include estrogen alone or combinations of estrogen and progesterone, which come in several forms, such as pills, patches, and topical or vaginal preparations [4]. Results from the Women's Health Initiative study indicated that the combination of estrogen and progesterone lowers the number of hip and vertebral fractures by nearly one-third and reduces the total number of osteoporotic fractures [24]. Despite its benefits, hormone replacement therapy has the potential to increase the risk of endometrial cancer, blood clots, stroke, breast cancer, and

heart disease in some women. Due to these risks, it is not typically the first option for treating osteoporosis. Each patient should be thoroughly evaluated to determine if this therapy is appropriate [4].

Selective estrogen receptor modulators

Selective estrogen receptor modulators are a varied group of nonsteroidal molecules that influence estrogen receptors differently across tissues, acting as either agonists or antagonists [25]. By attaching to estrogen receptors in bone cells, selective estrogen receptor modulators imitate estrogen's actions, which helps limit bone loss, strengthen bone density, and lower the risk of vertebral fractures [11]. Raloxifene is the most commonly used selective estrogen receptor modulator and is prescribed to patients at high risk of fractures. These medications are primarily intended for younger postmenopausal women. Their potential to reduce the risk of breast cancer may influence patient selection, as their effects extend beyond the bones [26]. Raloxifene has been found to lower the risk of vertebral fractures but does not affect the risk of fractures at other sites. In a major trial, 5.4 percent and 6.6 percent of women taking 60 mg and 120 mg of raloxifene, respectively, experienced vertebral fractures, compared with 10.1 percent in the placebo group. The occurrence of non-vertebral fractures was similar in both groups [27]. Lasofoxifen, like other selective estrogen receptor modulators, selectively binds to human ERα and ERβ receptors with an affinity similar to estradiol [28]. It has been shown to act as a skeleton agonist and antagonist in breast and uterine tissue. Clinical trials have shown that lasofoxifen increased bone mineral density in the lower spine and reduced harmful cholesterol levels in postmenopausal women compared to placebo. Studies in rats have shown a similar cholesterol-lowering effect, suggesting possible benefits for the heart. Reported side effects include leg cramps, hot flashes, thickening of the uterine lining, uterine polyps, and yeast infections [25].

Bazedoxifene is a third-generation drug intended to act on estrogen receptors and treat postmenopausal bone density loss, causing fewer side effects than previous drugs in the same class. It can also be used in combination with conjugated equine estrogens to ease menopausal symptoms. It has been developed specifically to avoid the harmful effects on the uterus seen with older drugs. Bazedoxifene is slightly more selective for the estrogen receptor alpha than for the estrogen receptor beta. Bazedoxifene acts similarly to estrogen in the bones and in cholesterol metabolism, but blocks estrogen activity in the breast and uterus [29]. Clinical studies have shown that it increases bone mineral density at all sites measured and reduces the incidence of new spinal fractures compared to placebo. Its effect was comparable to that of raloxifene, which was used as a reference drug. In combination with conjugated estrogens,

bazedoxifene decreased the risk of endometrial thickening and greatly improved bone mineral density in the spine and hip [29]. A large five-year international study found that bazedoxifene reduced the risk of new spinal fractures at several doses and reduced the risk of non-spinal fractures by 44% at a dose of 20 mg compared with raloxifene. In women at increased risk of fractures, bazedoxifene reduced the risk of new spinal fractures by 50%. The most common side effects were hot flashes and leg cramps. Serious side effects were rare, although there was an increased risk of blood clots in the veins. Additional ultrasound and mammography studies showed no significant effect on the lining of the uterus or breast tissue [25].

Osteoanabolic agents

Parathyroid hormone is an anabolic (bone-building) drug approved for use in treating bone loss after menopause. Ongoing exposure to parathyroid hormone causes bone breakdown, as seen in hyperparathyroidism, but administering it once daily by injection has the opposite effect and stimulates the formation of new bone tissue [30]. The usual dose is 20mg administered subcutaneously daily, and treatment typically lasts up to two years. After completing therapy, patients should switch to a drug that delays bone breakdown to preserve the bone density achieved. Parathyroid hormone reduces the risk of fractures of the spine and other bones and increases bone density [4]. In two clinical trials, teriparatide (a form of parathyroid hormone) increased bone density in the lower spine more than alendronate. In one study, daily use of teriparatide increased spinal bone density by nearly 5% more than alendronate [31]. In another study of people with steroid-induced bone loss, teriparatide greatly increased bone density in the spine, hip, and femoral neck over three years more than alendronate. Teriparatide also effectively prevented spinal fractures at a higher rate than alendronate. In a study of steroid-induced bone loss, new spinal fractures occurred in 1.7% of patients taking teriparatide compared with 7.7% of patients taking alendronate. The incidence of fractures in other bones was comparable in both groups. Common side effects of parathyroid hormone include high calcium levels, headaches, nausea, and muscle cramps. It should not be used in people who already have high calcium levels or hyperparathyroidism. Animal studies have shown an increased risk of bone cancer, but this has not been observed in human studies. Caution should be exercised in people taking digoxin, as high calcium levels may increase the toxicity of digoxin [4].

Abaloparatide was developed to activate the type 1 parathyroid hormone receptor in a specific way that stimulates bone formation. Unlike parathyroid hormone, abaloparatide binds predominantly to the receptor that produces a shorter, more controlled signal within cells [32]. It is administered as an 80mcg subcutaneous injection into the abdominal area. Studies have

shown that abaloparatide decreases the risk of new vertebral and other bone fractures. In one study, the drug decreased the number of new vertebral fractures by 86% and other bone fractures by 43% compared to placebo [33]. Clinical trials in humans have shown that abaloparatide improves bone mineral density, suggesting a strong therapeutic effect. It has been found to decrease the risk of fractures of the spine, non-spine, and wrist in postmenopausal women, regardless of their prior fracture history [32].

Vitamin D and calcium

Calcium and vitamin D supplements are recommended for preventing bone loss because they may help reduce fracture risk in both elderly people living in care facilities and those living independently in the community [34]. In the case of postmenopausal osteoporosis, combining vitamin D with bisphosphonates can improve the effectiveness of therapy. Vitamin D may also enhance the sustained positive effect of bisphosphonates on bone mineral density after discontinuation of medication [35]. However, although many clinical trials have tested antiresorptive drugs in patients who were also taking calcium and vitamin D, current guidelines recommend tailoring the use of these supplements to the risk of deficiency in each patient.

Meta-analyses have shown only a small benefit from calcium and vitamin D in preventing fractures and have drawn attention to possible side effects of calcium that were previously overlooked [36]. As a consequence, the role of these supplements in the management of osteoporosis remains controversial, and evidence for their safety and efficacy in postmenopausal women receiving antiresorptive therapy remains limited [37].

Conclusions

Postmenopausal osteoporosis is a common and serious condition primarily caused by estrogen deficiency, which disrupts bone remodeling and leads to increased bone resorption, reduced bone strength, and a higher risk of fractures. Estrogens play a crucial role in maintaining skeletal integrity, particularly through their effects on osteoclasts, osteoblasts, and osteocytes, and low estradiol levels are strongly associated with fracture risk. A wide range of effective pharmacologic therapies is available to reduce fracture risk. Antiresorptive agents such as bisphosphonates and denosumab are central to treatment, while hormone replacement therapy and selective estrogen receptor modulators may benefit selected patients. Osteoanabolic agents are particularly valuable for individuals at high fracture risk. Calcium and vitamin D provide supportive benefits when deficiency is present. Overall, individualized, long-term treatment strategies are essential to preserve bone health and improve outcomes in postmenopausal women.

Disclosure

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