

THE RELATIONSHIP BETWEEN MENOPAUSE AND BONE HEALTH

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Abstract

The paper describes menopausal events and their impact on bone health. Physiological events in the menopausal period as well as the pathophysiological basis for the occurrence of osteoporosis were considered. Postmenopausal women are at high risk for osteoporosis and bone fractures. The genesis of this problem lies in two factors - aging and loss of gonadal function, or their combination. Senile osteoporosis is associated with the aging process of the organism, and postmenopausal osteoporosis is primarily a consequence of estrogen deficiency. Osteoporosis is the main cause of bone fractures in the elderly population. Numerous markers of bone formation and breakdown have been described as biochemical markers of osteoporosis. For diagnostic purposes, double X-ray absorptiometry of the hip and spine is used, which is the gold standard in the diagnosis of osteoporosis. Alternatively, quantitative ultrasonography can be performed, which is a good method, but the measurements are not sufficiently precise as in other imaging techniques. An overview of the therapeutic possibilities of measures to prevent osteoporosis in the postmenopausal period is presented.

Keywords: menopause, bone health, osteoporosis, prevention

Introduction

Bones represent living tissue that plays an essential role in maintaining the structural integrity of the human body. Various factors can affect bone health: hormonal imbalance, certain hereditary conditions, inadequate nutrition,

lack of exercise, smoking, alcohol consumption, metabolic disorders, hematologic abnormalities, kidney diseases, malignant diseases, and infections. Postmenopausal osteoporosis is associated with a lack of estrogen that occurs following the cessation of ovarian function in the years following a woman's active reproductive period. Scientific evidence indicates that the function of estrogen in the bone remodeling process is very significant, as estrogen plays a role both in bone formation and in the prevention of bone resorption.

Physiological changes during the menopausal period

Menopause is part of the general aging process that affects the female reproductive tract, after which women cease menstruation¹. The term menopause signifies a woman's final menstrual period. According to the definition, we speak of menopause if more than 12 months have passed since the last menstrual period, and signs such as vasomotor and urogenital symptoms are present. Perimenopause represents the period during which issues such as vasomotor symptoms and irregular menstrual bleeding begin, heralding the end of a woman's reproductive period². This period can begin 5 to 10 years before menopause and by definition includes the first year after menopause. Menopause typically occurs around the age of 50-51 for most women. Symptoms of the transitional period usually begin around 45.5-47.5 years of age. If menopause occurs before the age of 45, it's termed early menopause, and if it occurs before the age of 40, it's referred to as premature menopause (premature ovarian insufficiency)²⁻⁴. Factors that contribute to early onset menopause include smoking, autoimmune diseases, and genetic predisposition associated with the fragile X chromosome⁵.

Menopause occurs as a result of the decreased sensitivity of the ovaries to gonadotropin stimulation, leading to disruptions in folliculogenesis and steroidogenesis. During the perimenopausal period, menstruation becomes irregular due to anovulation or failure of follicle maturation. Clinical studies have indicated that the incidence of anovulatory cycles increases rapidly after the age of 40²⁻⁶.

The first sign of perimenopause in women who still have completely regular menstruation and ovulation is a shorter menstrual cycle. A shorter duration of the menstrual cycle occurs due to the shortening of the follicular phase of the cycle, due to the decrease in the number of functional follicles. After the age of 40, the granulosa cells produce less and less amounts of inhibin A and B, so their level at the age of

45 is about 40-50% lower than before. Parallel to that process, there is a gradual increase in the level of follicle-stimulating hormone (FSH), while the level of luteinizing hormone (LH) remains unchanged. An increased amount of FSH stimulates the follicles to growth and development, but they have regular growth in a decreasing percentage and reach maturity, but secrete increased amounts of estradiol. The more frequent anovulatory cycles are accompanied by a low level of progesterone^{6, 7}.

At the level of the adrenal cortex, in perimenopause, reduced production of dehydro-epiandrosterone (DHEA) and dehydroepiandrosterone sulfate (DHEAS) is recorded, and that concentration progressively decreases with age, actually it already starts from the age of 25, and they call it a biomarker of aging.

The main biochemical indicators in perimenopause are: increased levels of FSH and still normal levels of LH, increased concentration of estradiol, low levels of progesterone, and a decrease in the concentration of DHEA⁸.

Over time, follicles become increasingly resistant to gonadotropi stimulation, resulting in an increase in levels FSH and LH which leads to stimulation of the ovarian stroma with a subsequent increasing the level of estrone, and by decrease in the concentration of estradiol.

The most characteristic change in hormonal status in postmenopause, represents the high concentrations of gonadotropins, primarily FSH, and low concentrations of estradiol. After the end of the ovulatory function, the production of estrogen in a woman's body continues with the aromatization of androgens produced in the ovarian stroma and adrenal cortex, which are not opposed by progesterone production, so they can lead to endometrial hyperplasia and potential endometrial cancer. The main estrogen in postmenopausal women, is estrone and it is produced by the aromatization of androstenedione of non-follicular origin (production in ovarian stroma and adrenal production) that takes place in adipose tissue, muscle, liver, bone, bone marrow, fibroblasts and hair roots. The highest degree of androgen conversion in estrogen occurs in adipose tissue and that is why it is considered that obese women have less pronounced menopausal vasomotor symptoms⁷⁻⁹.

(Pre)menopausal syndrome and the effects of menopause

The typical syndrome associated with declining ovarian function includes: vasomotor disturbances, psychological issues such as behavior changes, depression, decreased concentration, insomnia, weight gain, urogenital issues, decreased libido, and changes in skin and hair. It is believed that the irregular functioning of the ovaries during perimenopause, with consequent fluctuating changes in estrogen levels, is the main cause of the onset of this syndrome, rather than just a decrease in estrogen production.

Additionally, during the premenopausal period, cycle disturbances are observed in the form of irregular bleeding, caused by anovulation, prolonged action of estrogen, inadequate function of the *corpus luteum*, and low concentrations of progesterone – thus, dysfunctional bleeding.

About 75% of women in perimenopause experience vasomotor symptoms, so-called “hot flashes”. They occur most frequently during the first two years after menopause and decrease over time. In a very small number of women, hot flashes can persist for ten years or more. They often occur during the night, resulting in disrupted sleep patterns, fatigue, and depression. Hot flashes are unpredictable, with their frequency ranging from nearly every hour to once every few days. Due to low estradiol levels, there is a disruption in hypothalamic thermoregulatory function. The consequence of a drop in central temperature is peripheral vasodilation, an increase in temperature, and sweating^{10, 11}.

The area of the external genitalia - vagina, urethra, and part of the urinary bladder - is rich in estrogen receptors. A decrease in estrogen levels leads to their atrophy. Vaginal walls become atrophic, losing elasticity, and with reduced production of vaginal secretions. The vulva undergoes atrophy due to collagen and adipose tissue loss. Estrogen deficiency also results in the fibrosis of the bladder neck, reduced collagen in the surrounding tissue, and a decrease in the number and diameter of muscle fibers in the pelvic floor. Atrophy of the genitourinary tract increases the risk of vaginal and urinary infections (such as atrophic vaginitis and atrophic cystitis) as well as traumatization. Additionally, genital tract atrophy causes painful intercourse - dyspareunia - reducing interest in sexual activity¹².

The postmenopausal uterus is reduced in size, as are the ovaries, which cannot be palpated during examination. Due to the loss of tone in the pelvic floor muscles, many postmenopausal women experience issues with the descent of genital organs.

Due to estrogen deficiency, the activity of osteoclasts and bone resorption increases while bone formation decreases. As a result, postmenopausal women are at a high risk of developing osteoporosis and fractures, which will be further discussed in the following text.

In postmenopausal women, due to the lack of estrogen and subsequently reduced synthesis of collagen and elastic fibers, the skin loses its tone, becomes dry, prone to flaking, and wrinkled. Additionally, hair in postmenopausal women tends to become dry, brittle, and thin in a large number of cases.

Postmenopausal women are at an increased risk of developing cardiovascular diseases. Estrogen is believed to reduce the risk of atherosclerosis. This is supported by the fact that cardiovascular diseases are rare until menopause, being even 6-7 times less common than in men of the same age, while after menopause, this risk becomes comparable.

Atherosclerosis progresses more rapidly in postmenopausal women, leading to a progressively increased risk of cardiovascular diseases.

Peri/postmenopausal treatment

As mentioned earlier, the decline in ovarian function leads to numerous episodes of irregular bleeding from the genital tract. Although these are most commonly dysfunctional bleeding episodes, it is necessary to exclude other organic causes of this bleeding. Only after confirming that there is no organic cause for the irregular bleeding, indicating dysfunctional bleeding, can medical treatment be initiated. For this purpose, gestagen preparations are used, typically given for about 10 days per month (usually from the 16th to the 25th day of the cycle). They are administered cyclically over a longer period and are followed by regular bleeding from the uterus. If bleeding does not occur after their administration, it indicates postmenopause as the endogenous production of estrogen has ceased. Another option for gestagen administration is the use of an intrauterine device (IUD or "coil") with the addition of gestagen (known as an intrauterine system with levonorgestrel) for therapeutic purposes, with local effects on the endometrium to control bleeding, as well as providing additional contraceptive effects.

To control the menstrual cycle in premenopausal women, contraceptive pills can be used, especially if women require contraception and there are no contraindications. It has already been mentioned that these women are at risk of unintended pregnancy, although the risk is very low. Contraceptive pills can practically be used up to the age of 50.

In the peri- and postmenopausal periods, hormone replacement therapy can be utilized. The use of hormone replacement therapy in peri- and postmenopause can be symptomatic and preventive. Symptomatic use often involves controlling vasomotor symptoms, and managing intense mood swings, fatigue, and lethargy. Estrogen therapy quickly brings these symptoms under control. Within a month, the mentioned symptoms significantly decrease, and patients experience an improvement in their quality of life. The protective effect pertains to its beneficial impact on bone mineral density and the development of atherosclerosis. A newer indication for protective use is its application in cases of high risk for developing senile dementia or Alzheimer's disease.

If women have a uterus, along with estrogen, it is necessary to administer progestin preparations to protect the endometrium. Unopposed estrogen stimulation can be a risk factor for the development of endometrial cancer. In women who have had a hysterectomy, there is no need for gestagene administration.

In women with a uterus, hormone replacement therapy can be administered either sequentially or continuously.

Sequential therapy is used in women who still have menstruation (in perimenopause) and continue to have regular monthly bleeding while using it. There are preparations available in the form of tablets or patches on the pharmaceutical market, which are used for three weeks, followed by a week-long break during which bleeding occurs. Additionally, the placement of an intrauterine system with levonorgestrel (to protect the endometrium) and the use of estrogen preparations are also options to consider.

Continuous hormone replacement therapy involves daily intake of hormone preparations and is initiated after 12 months of amenorrhea (thus in postmenopause), achieving the maintenance of endometrial atrophy, and these women do not experience bleeding. Continuous use also includes the use of tibolone - a synthetic steroid hormone that acts as an agonist on steroid receptors. Hormone replacement therapy can also be administered locally. This form of application involves the vaginal use of estrogen preparations in the form of cream or vaginal tablets, which affects vaginal mucosal atrophy¹⁴.

Contraindications for hormone replacement therapy include: vaginal bleeding of unknown cause, pregnancy, severe liver disease, episodes of venous thromboembolism, and risk of breast cancer. The most common concerns about hormone replacement therapy relate to the risk of breast cancer. However, modern perspectives indicate that the use of hormone replacement therapy slightly increases the risk of breast cancer after 5 years of use. Additionally, it has been observed that women who received hormone replacement therapy and developed breast cancer have smaller tumors, better-differentiated tumors, and negative lymph nodes at the time of diagnosis compared to women with breast cancer who did not receive hormone replacement therapy. For the initiation of hormone replacement therapy, in addition to a thorough medical history, it is necessary to conduct a breast ultrasound examination as well as mammography, along with liver function tests and coagulation parameter tests. Routine mammography is advised for all women in peri/postmenopause, starting from the age of 40, along with screening for osteoporosis. An alternative to hormone replacement therapy is the use of products containing phytoestrogens. Phytoestrogens are plant polyphenols that structurally resemble steroid hormones and exhibit similar activity to estrogens¹⁵.

Osteoporosis

Osteoporosis is a metabolic bone disorder characterized by reduced bone mass and deterioration of bone tissue microarchitecture, leading to increased bone fragility. This condition compromises overall health with physical, psychosocial, and economic consequences. It represents a chronic-progressive multifactorial condition. It is most commonly diagnosed in older Caucasian women, although it occurs in sexes, all age groups, and all races¹⁶.

Despite the fact, that osteoporosis is a disease of the older population, its significance is often overlooked when considering the health of older women. It should not be forgotten that osteopenia, a precursor to osteoporosis, is a condition resulting from menopause that can be prevented.

The reduction in bone mass occurs due to bone resorption, which is the result of accelerated bone breakdown while bone formation levels are maintained within premenopausal ranges. In postmenopause, bone resorption is about 20% faster compared to younger ages¹⁷.

The World Health Organization uses bone density, measured through DXA scans, as a criterion for bone health, expressed in terms of T-scores or Z-scores. The T-score represents bone density compared to the bone density of control subjects at their peak bone mass, while the Z-score compares the bone density of patients with individuals of similar gender and age.

The diagnostic classification recommended by the World Health Organization applies to postmenopausal women and men over 50 years old. According to this classification, osteoporosis is defined as bone mineral density equal to or less than 2.5 standard deviations below the peak bone mass. Osteopenia is defined as bone mineral density 1.0-2.49 standard deviations below the T-score¹⁸⁻²⁰.

Pathophysiological events in osteoporosis

The genesis of osteoporosis lies in the imbalance between bone resorption and formation. In physiological conditions, bone resorption and formation are balanced. Osteoporosis occurs when this balance is disrupted – either due to accelerated resorption or decreased formation. It's important to note that osteoporosis can result from reduced bone formation throughout life and failure to achieve peak bone density at younger age. The two main factors for osteoporosis are aging and loss of gonadal function. Postmenopausal osteoporosis is primarily due to estrogen deficiency, while senile osteoporosis is mainly associated with aging.

In the aging process, after the age of 30, bone resorption surpasses bone formation, which can later lead to osteopenia/osteoporosis. Women lose about 40% of cortical bone, while men lose about 15-20%. Additionally, women experience a loss of about 50% of trabecular bone, while men have a loss of about 25-30%. Age-related bone loss is characterized by decreased osteoblast supply relative to demand, whereas bone loss in postmenopause is characterized by increased osteoclast activity²¹.

Estrogen deficiency - Causes a decrease in bone density in women as well as in men because osteoblasts, osteoclasts, and osteocytes have estrogen receptors. On the other hand, estrogen indirectly affects bone through cytokines

and growth factors. In conditions of estrogen deficiency, T cells accelerate the recruitment of osteoclasts, inhibit their differentiation, and influence the prolongation of their lifespan through interleukin 1, interleukin 6, and tumor necrosis factor-alpha. Additionally, T cells cause premature apoptosis of osteoblasts through interleukin 7. In conditions of estrogen deficiency, bones are more sensitive to the effects of parathyroid hormone.

Calcium deficiency - Calcium, vitamin D, and parathyroid hormone maintain bone homeostasis. If the diet is low in calcium or if there is reduced calcium absorption due to aging or the presence of certain diseases, secondary hyperparathyroidism may occur, leading to increased calcium absorption from the bones and reduced calcium excretion through the kidneys.

Vitamin D deficiency - Vitamin D controls the concentration of calcium and phosphate, which are necessary for healthy bones and teeth. Besides maintaining bone density, this important biogenic element is believed to play a role in preventing cardiovascular, inflammatory, and malignant diseases. There are two ways to obtain vitamin D - through synthesis in the skin and dietary intake. We intake vitamin D2, through food (ergocalciferol), which is of plant origin, and vitamin D3 (cholecalciferol), which is of animal origin. However, the main source of vitamin D is the synthesis of vitamin D3 in the skin under the influence of UVB rays. The primary function of vitamin D is to regulate calcium absorption from the intestine and stimulate calcium resorption from bones to maintain serum calcium levels. In conditions of vitamin D deficiency, calcium absorption from the intestine decreases, and the production of osteoclasts increases, which mobilize calcium from bones. Due to inadequate intake, vitamin D interacts with receptors on osteoblasts, leading to increased osteoclast formation²².

Biochemical markers of bone metabolism - We distinguish markers of bone formation and markers of bone resorption. Markers of bone formation include: total and bone-specific alkaline phosphatase (serum), osteocalcin (serum), C- and N-terminal propeptides of type 1 procollagen, PICP, PINP (serum), and other non-collagenous bone proteins. Markers of bone resorption include: tartrate-resistant acid phosphatase (plasma), calcium (urine), hydroxyproline (urine), pyridinium crosslinks (urine), collagen type 1 telopeptide beta crosslaps (urine, serum), C-terminal telopeptide of type 1 collagen (ICTP - serum), NTX (urine). The bone turnover index represents the relative value of the osteocalcin and crosslaps ratio (osteocalcin/crosslaps x 1,000). The bone turnover index examines the degree of deviation from the ratio of physiological bone remodeling processes (bone formation and bone resorption) from the ideal equilibrium state. The value of the index in a healthy population is around 90²³.

Risk factors and complications of osteoporosis

Risk factors for osteoporosis include: female gender, age 50 and older, caucasian, genetic predisposition, low height, malnutrition, physical inactivity, late menarche, early menopause, conditions of estrogen and androgen deficiency, alcohol consumption, smoking cigarettes, calcium-poor diet, and the use of certain medications (steroids, insulin, anticonvulsants, chemotherapeutics, heparin).

Osteoporosis is the leading cause of bone fractures in the elderly population and the primary cause of all fractures (over 80% of cases of all fractures in individuals over 50 years old). If complete healing is not achieved, chronic painful conditions, limited mobility, and in some cases even death (fractures of the vertebrae and hips) can occur²⁴.

Diagnosis of osteoporosis

Bone densitometry measures the difference in the absorption of gamma or X-rays, ultrasound, or laser in bones and soft tissue. It provides the opportunity to measure bone mineral content (g) and indirectly measure bone density (g/cm³).

Dual-energy X-ray absorptiometry (DXA) is a widely used method that offers exceptional resolution and precision. The scanning process is brief, meaning whole-body mineral content measurement is fast, reliable, safe, and highly reproducible, thereby reducing issues with superimposition with surrounding soft tissues. The apparatus utilizes X-rays as an energy source. DXA measurements of the hip and spine represent a widespread standard in osteoporosis diagnosis. Measurement via DXA and laser absorptiometry (Dual-energy X-ray Laser, DXL) of the calcaneus bone serves as an alternative to DXA. This technique was developed to avoid measurement errors associated with surrounding soft tissue during DXA.

Quantitative Computed Tomography (QCT) measures thin cross-sectional slices. With the aid of computer analysis, bone mineral density is measured, and the density of trabecular and cortical bone is particularly assessed.

Quantitative Ultrasonography (QUS) is a method of bone densitometry measured by ultrasound. Its advantage lies in avoiding radiation, and the apparatus is easily portable. However, measurements are not as precise as with other imaging techniques^{25, 26}.

Treatment of osteoporosis

Contemporary pharmacological treatment for osteoporosis includes the use of bisphosphonates (alendronate, etidronate, ibandronate, risedronate, zoledronic acid), Selective Estrogen Receptor Modulators (SERMs)

(raloxifene, lasofoxifene, arzoxifene), calcium and vitamin D supplements, the application of monoclonal antibodies, and hormone therapy (phytoestrogens, estrogens, testosterone)²⁷⁻³⁰.

Preventive measures

Lifestyle changes and non-pharmacological measures are crucial for maintaining healthy bones. Physical activity, adequate calcium and vitamin D-rich diet, avoiding smoking, and limiting alcohol consumption are of immense importance for individuals of all ages, especially in older age. Implementing these measures yields positive outcomes even in patients with established osteoporosis, leading to increased bone strength and reduced risk of fractures.

The goals of preventive strategies include optimizing the development of the skeletal system and achieving peak bone mass during skeletal maturity, preventing secondary causes of bone loss, preserving the structural integrity of bones, and preventing fractures.

Balanced and healthy nutrition ensures adequate intake of calcium and vitamin D. Malnutrition, anorexia, and excessive aerobic activity in young women lead to delayed menarche and lower bone mass compared to peers. A similar situation is observed in adults undergoing restrictive diets and surgical weight loss methods. A balanced intake of protein (the recommendation is that daily intake should be 0.8 g/kg of body weight) helps minimize bone loss even in patients with established osteoporosis³¹.

The fundamental aspect of osteoporosis prevention and treatment is calcium. For women over 50 years of age, the recommended daily calcium intake is 1.200 mg (through diet and supplementation, if conducted). In situations where dietary intake does not provide sufficient calcium, calcium supplementation is necessary. Data show that the daily dietary intake for most patients is up to 600 mg, which is only half of the required daily dose. If supplementation is used, for optimal absorption, the calcium dose should not exceed 500 mg per dose. It has been proven that calcium supplementation increases bone mineral density, but there is no scientific evidence that its use alone, without simultaneous vitamin D supplementation, reduces the risk of fractures. Calcium supplementation is safe for users. The risk of nephrolithiasis (kidney stone formation) in patients on supplementation is minimally higher compared to the general population (the risk of nephrolithiasis in patients on supplementation is 2.5%, while in the general population, this risk is 2.1%)³².

Calcium supplementation should be accompanied by vitamin D. Many, otherwise healthy individuals have significantly lower serum levels of 25(OH)D compared to the optimum level. This is primarily due to inadequate dietary intake because vitamin D is not widely available in foods. It is found in fish oil, cereals, and bread. According to the

recommendations of the National Academy of Sciences, 400 IU of vitamin D per day is required for healthy younger individuals. For individuals over 50 years of age, the recommendations are 800 to 1,000 IU per day. Some experts even recommend significantly higher doses, up to 2,000 IU per day. Current recommendations for minimum levels of 25(OH)D are 30-32 ng/mL, while the upper limits are up to 60 ng/mL. Meta-analytical studies indicate that supplementation with vitamin D at doses of 700-800 IU per day reduces the risk of fractures in postmenopausal women. For patients with severe vitamin D deficiency, vitamin D supplementation can go up to 2,000 IU or more per day³³.

Increased alcohol consumption has a negative effect on bone health, as it increases the risk of fractures. The way alcohol affects bones is complex, multifactorial, and increases the risk of falls, calcium deficiency, and chronic liver overload. Also, it is not recommended to consume more than 1-2 cups of coffee per day because some studies have indicated a positive association between caffeine and the risk of fractures, most likely due to reduced calcium intake.

Cigarette smoking significantly affects bone health. The exact mechanism of action is not fully understood, but it

is believed to influence through increased metabolism of estrogen and direct action of cadmium on bone metabolism.

Regular physical activity, such as daily walks lasting 30 minutes and exercises for about 10 minutes several times a week, contributes to maintaining a healthy skeletal system. Research indicates that muscle strength in younger women positively correlates with bone density. However, physical activity in older individuals should be individually tailored according to age and the patient's overall condition.

Furthermore, education on fall prevention and consequent fractures is also recommended³⁴.

It is important to note that phytoestrogens also represent an option for osteoporosis prevention in women. Phytoestrogens are believed to influence bone health. Soy isoflavones, functionally similar to 17-beta-estradiol, exhibit activity on osteoblasts and osteoclasts through genomic and non-genomic mechanisms and have a favorable effect on bone mineral density and mechanical strength in postmenopausal women, contributing to bone formation by acting through estrogen receptors on the cell surface³⁵.

Conclusion

Postmenopausal osteoporosis is a silent but progressive disease that is highly prevalent worldwide. It represents a chronic condition that is asymptomatic, and its progression is slow. Numerous studies on this issue have identified etiopathogenetic factors and mechanisms of onset along with documented risk factors. Without proper and timely diagnosis and treatment, postmenopausal osteoporosis can lead to a significant decline in quality of life. Efforts need to be made to educate postmenopausal women about necessary lifestyle modifications even during the perimenopausal period to prevent this disorder.

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