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Perimenopause period and menopause: cardiovascular and metabolic risks

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The number of mature and elderly women is increasing all over the world. According to the World Health Organization, in most countries of the world, the life expectancy of women after the age of 50 ranges from 27 to 32 years. Thus, approximately one third of a woman's life is lived after menopause.

Aim. To analyze and summarize scientific data on cardiovascular and metabolic risks in perimenopausal and menopausal women based on the use of scientometric databases.

Menopause should be considered as a risk factor for the development of cardiovascular diseases (CVDs), which triggers a whole cascade of pathological changes in a woman's body, including the development of arterial hypertension, dyslipidemia, abdominal obesity, insulin resistance, an increased sympathoadrenal tone, endothelial function disorders, and inflammatory vascular reactions. CVD is known to be the leading cause of death among postmenopausal women associated with the loss of estrogenic protective effect on the cardiovascular system. Women with premature menopause have a 33 % higher risk of heart failure and a 9 % higher risk of atrial fibrillation.

Metabolic syndrome is more common in postmenopausal women than in premenopausal women. It is defined as a cluster of disorders characterized by impaired glucose metabolism, high blood pressure, central obesity, low high-density lipoprotein cholesterol, high low-density lipoprotein cholesterol and triglycerides. It is the activity of low-density lipoproteins and an increase in the level of triglycerides that have serious consequences in the etiology of cardiovascular diseases and the development of atherosclerosis.

Osteoporosis ranks fourth among non-communicable diseases after CVD, cancer and diabetes. Estrogen deficiency during menopause results in increased osteoclast resorptive activity, while osteoblast function remains relatively constant, ultimately resulting in bone loss. In the first postmenopausal years, a woman can lose up to 9–35 % of bone mass, postmenopausal osteoporosis affects between one third to a half of all women.

Conclusions. Menopause is a difficult period in a woman's life, during which the risk of developing cardiovascular diseases and metabolic disorders increases, as well as almost all somatic diseases are exacerbated. Therefore, proper assessment of such risks is mandatory to improve long-term CVD outcomes. Given this, it is the interdisciplinary interaction that is central to early detection of symptoms and diagnosis of climacteric disorders for the timely prescription of treatment. Physicians working with this contingent of women should apply a comprehensive approach to health care and quality of life preservation during the menopause transition, menopause and postmenopause.

Ключові слова: період перименопаузи, менопауза, кардіоваскулярні та метаболічні ризики, серцево-судинні захворювання, метаболічний синдром, остеопороз, лікування.

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Перименопаузальний період і менопауза: кардіоваскулярні та метаболічні ризики

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У всьому світі збільшується кількість жінок зрілого та похилого віку. За даними Всесвітньої організації охорони здоров'я, у більшості країн світу тривалість життя жінок після 50 років становить від 27 до 32 років. Отже, майже третина життя жінки припадає на період після менопаузи.

Мета роботи – проаналізовано й узагальнено відомості наукової літератури, одержані в результаті пошуку в наукометричних базах даних, щодо кардіоваскулярних і метаболічних ризиків у жінок у перименопаузальному періоді та менопаузі.

Менопаузу слід вважати чинником ризику розвитку серцево-судинних захворювань, що ініціює цілий каскад патологічних змін в організмі жінки, включаючи артеріальну гіпертензію, дисліпідемію, ожиріння за абдомінальним типом, виникнення інсулінорезистентності, збільшення симпатоадреналового тонусу, порушення ендотеліальної функції, запальні судинні реакції. Як відомо, серцево-судинні захворювання є основною причиною смертності в жінок у постменопаузі, оскільки серцево-судинна система втрачає захисну дію естрогену. Жінки з передчасною менопаузою мають на 33 % вищий ризик серцевої недостатності та на 9 % більший ризик фібриляції передсердь.

Метаболічний синдром більш поширений у жінок у постменопаузі, ніж в осіб у пременопаузі. Його визначають як кластер станів, що характеризуються порушенням метаболізму глюкози, високим кров'яним тиском, центральним ожирінням, низьким рівнем холестерину ліпопротеїнів високої щільності, високим рівнем ліпопротеїнів низької щільності та тригліцеридів. Саме активність ліпопротеїнів низької щільності та підвищення рівня тригліцеридів спричиняють складні наслідки в етіології серцево-судинних захворювань, розвитку атеросклерозу.

Остеопороз посідає четверте місце серед неінфекційних захворювань після серцево-судинних захворювань, онкологічної патології та цукрового діабету. Дефіцит естрогену під час менопаузи призводить до збільшення активності резорбції остеокластів, а активність остеобластів залишається відносно постійною. Врешті це призводить до втрати кісткової тканини.

У перші роки постменопаузи жінка може втратити до 9–35 % кісткової маси; постменопаузальний остеопороз уражає від третини до половини всіх жінок.

Висновки. Менопауза – складний період у житті жінки, під час якого підвищується ризик розвитку серцево-судинних захворювань і порушення обміну речовин, а також відбувається загострення майже всіх наявних соматичних захворювань. Тому правильне оцінювання таких ризиків обов'язкове для покращення віддалених результатів серцево-судинних захворювань. Зважаючи на це, актуалізується саме міждисциплінарна взаємодія, спрямована на раннє виявлення симптомів і діагностику клімактеричних розладів для своєчасного призначення лікування. Лікарям, до яких звертаються такі жінки, важливо застосовувати комплексний підхід для збереження здоров'я та якості життя пацієнток під час менопаузального переходу, менопаузи та постменопаузи.

The number of elderly people is increasing all over the world. According to the United Nations projections, their number will increase significantly from 580 million in 2005 to almost 2 billion people by 2050 [1,2]. In developed countries, the proportion of women above the age of 50 years has tripled over the past century. Most of them are mature and elderly women. In Ukraine, it is 35 % – almost one-fifth of the total country's population (National Institute for Health and Care Excellence, 2019). Past a certain age, involutional processes occur in a woman's body related to the reproductive system transition to a different functioning mode (perimenopausal transition) and come to menopause.

Clinically, menopause is diagnosed when a woman has ceased having periods for a year due to the loss of ovarian follicular activity, which usually occurs around the age of 45–55. The average age at menopause varies in different countries. In the USA, it is on average 51 years old, in European women, it is 52 years old, in Ukraine spontaneous menopause occurs at 48–49 years old.

As a rule, women live longer than men, and their average life expectancy is gradually increasing and is expected to reach 82 years in developed countries. According to the World Health Organization (WHO), in most countries of the world, the life expectancy of women after the age of 50 ranges from 27 to 32 years. Thus, women spend approximately a third of their lives after menopause. The WHO predicts that one-sixth of the world's population, namely 1.2 billion women, will be in the postmenopausal period by 2030 [3,4,5].

This period in a woman's life is associated with the development of pathological menopausal syndrome, which includes sleep / mood disturbances, vasomotor manifestations (including hot flashes and night sweats), urogenital atrophy, osteopenia and osteoporosis, mental disorders, sexual dysfunction, skin lesions, cardiovascular diseases (CVD), cancer, metabolic disorders and obesity [3]. Menopause symptoms vary and reflect a complex interaction between biological, psychological and social factors [6]. In addition, it is important to specify the stages of reproductive aging using the criteria of the Working Group and the corresponding definition of the reproductive aging stages in women (STRAW +10) [7].

Aim

To analyze and summarize scientific data on cardiovascular and metabolic risks in perimenopausal and menopausal women based on the use of scientometric databases.

Menopause should be considered as a risk factor for the development of CVD, which triggers a whole cascade of pathological changes in a woman's body, including the development of arterial hypertension, dyslipidemia, abdominal obesity, insulin resistance, increased sympathoadrenal tone, impaired endothelial function, and inflammatory vascular reactions [7,8]. As known, CVD is the main cause of mortality among women [9].

CVD usually occurs 10 years later in women than in men. Premenopausal women are thought to benefit from the protective effects of estrogen on the cardiovascular system. Cessation of menstruation and the subsequent decrease in estrogen levels may make women more vulnerable to CVD [10]. Studies conducted in recent decades have documented clear patterns of changes in sex hormones, as well as adverse alterations in lipids and lipoproteins, structural and functional indicators of vascular health, that can increase the risk of developing CVD in postmenopausal women [11]. Metabolic and clinical factors associated with menopause, such as dyslipidemia, insulin resistance, fat redistribution, and systemic hypertension contribute to an increased risk of cardiovascular aging and disease. In addition, complex interactions between oxidative stress and L-arginine and asymmetric dimethylarginine levels may influence the development of endothelial dysfunction in menopause [12]. CVD in women tends to be underdiagnosed, and women often have a lower level of risk perception. This can lead to late diagnosis and unrecognized symptoms. As soon as women experience menopause, the risk increases. Estrogen provides a protective effect, so the risk of CVD increases after menopause in most cases [13].

The misconception that heart disease predominantly affects men has led to gender-related risk factors being largely ignored. However, evidence is gradually accumulating that menopause before the age of 40 may increase the chance of heart disease later in life. In particular, menopause before the age of 40 is associated with an increased risk of heart failure and atrial fibrillation. A study involving more than 1.4 million women has found that the younger the age at menopause, the higher the risk of heart failure and atrial fibrillation. Women who experienced premature menopause had a 33 % higher risk of heart failure and a 9 % higher risk of atrial fibrillation [14]. Also, a link between menopausal age, heart failure and atrial fibrillation has been revealed, that may be explained by several factors, such as falling estrogen levels and changes in body fat distribution.

A correlation between menopause and CVD is quite strong. It is early menopause that is associated with an increased risk of non-fatal CVD before the age of 60. At the same time, it was not observed in women aged over 70 years. In particular, the incidence of coronary heart disease (CHD) increases dramatically after menopause. Moreover, the early onset of menopause leads to the premature development of CHD. On the other hand, women with early-onset CHD (<35 years) are more likely to experience early menopause [15]. Estrogens have a protective

effect on the development of CHD [16]. In turn, estrogen depletion leads to an increased risk of CVD, mainly through CHD, especially in cases of premature menopause. The pathophysiological basis of this atherosclerotic process is the accumulation of several risk factors, such as abdominal obesity, atherogenic dyslipidemia, insulin resistance, and arterial hypertension. The presence of vasomotor symptoms (VMS) may further increase this risk, especially in women younger than 60 years [17].

Natural and surgical premature menopause have been found to be associated with an increased incidence of combined factors (CHD, aortic stenosis, mitral regurgitation, atrial fibrillation, ischemic stroke, peripheral arterial disease, and venous thromboembolism) [18]. Of the female-specific components of atherosclerotic CVD risk assessment, pre-eclampsia and early spontaneous menopause (<40 years) have been shown to be the strongest adverse risk variables [19].

In a study focused on women at different stages of menopause to assess the association of menopause with CVD risk factors and subclinical markers of cardiometabolic disease, age at menopause and the time since menopause have been found to be risk factors, and women with metabolic syndrome had a significantly higher risk of developing CVD [20].

One of the important problems of postmenopause is lipid metabolism disorders, which leads to obesity, chronic inflammation, endothelial dysfunction, atherosclerosis development and, as a result, to an increased cardiovascular risk [21]. Changes in lipid metabolism and increased adipose tissue play a key role in the synthesis of excess fatty acids, adipocytokines, proinflammatory cytokines, and reactive oxygen species, which cause lipid peroxidation and result in the development of insulin resistance, abdominal obesity, and dyslipidemia [3]. Due to estrogen deficiency and lipid metabolism disorders, postmenopausal women have a higher risk of developing CVD. Estrogens, especially estradiol (E2), play a role in cardiovascular protection and are produced primarily in the ovaries by a process that uses low-density lipoprotein (LDL) cholesterol as a substrate. During menopause, circulating LDL cholesterol levels become excessive and cannot be used for estrogen synthesis, leading to increased blood LDL-cholesterol and CVD risk. E2 deficiency due to ovariectomy or after menopause may reduce the expression of genes required for efficient energy expenditure in the human body and genes involved in fatty acid metabolism or lipid catabolism, which may cause obesity or metabolic disorders in postmenopausal women [3].

At the time of menopausal transition, which usually lasts 2–7 years, significant changes occur in the body structure of women. The fact is that ovarian estrogens increase the accumulation of peripheral fat mainly in the subcutaneous tissue of the buttocks and thighs, while androgens, mostly bioavailable testosterone, increase the accumulation of visceral abdominal fat. Estrogen deficiency is accompanied by relative hyperandrogenism and is considered a major factor causing weight gain and body fat redistribution in postmenopausal women. Sex hormone-binding globulin levels also decrease with menopause, which increases bioavailable testosterone levels. It is known that the risk of developing abdominal obesity in postmenopausal women is almost 3 times higher than in premenopausal women. With the same values of the mean body mass index (BMI), postmenopausal women have a larger waist circumference [3]. As is known, the WHO defines obesity as BMI ≥30 kg/m^2, overweight as BMI 25.0–29.9 kg/m^2, and underweight as BMI <18.5 kg/m^2 [22]. Studies have shown that for the same testosterone levels, postmenopausal women have twice as much visceral abdominal fat and subcutaneous adipose tissue as premenopausal women. This suggests that fat redistribution can be affected by a marked decrease in estrogen levels, rather than an increase in testosterone levels [3,23].

One notable change in body composition associated with age in women is loss of lean body mass (LBM). Age-related degenerative loss of skeletal muscle (sarcopenia) occurs at a rate of 3–8 % every 10 years from the age 30 and accelerates with age. This condition is linked to an increased risk of functional disability, falls, fractures, and total mortality among the elderly [24]. Loss of LBM, or skeletal muscle, and an increase in adipose tissue cause an age-related decline in basal metabolic rate (resting energy expenditure), which is a product of energy metabolism that occurs in all human cells. It is the amount of energy (in calories) required to support biological vital functions, including body temperature regulation, muscle contraction and relaxation, respiration, blood circulation, cell growth, and brain and neuronal functions [25]. As a rule, basal metabolism accounts for about 60–75 % of daily energy expenditure and can vary widely among individuals. LBM, or skeletal muscle, which constitutes about 60–85 % of body mass, is thought to be the primary determinant of resting energy expenditure, while fat serves as a storage of excess energy. Thus, changes in body composition in women during menopause (loss of LBM) lead to a decrease in basal metabolism, the physical body of women begins to expend less energy on maintaining basic biological functions [3].

Recent studies have shown that metabolic syndrome was more common among postmenopausal women compared to those in premenopause [26]. It is defined as a cluster of conditions characterized by impaired glucose metabolism, high blood pressure, central obesity, low high-density lipoprotein (HDL) cholesterol, and high triglyceride (TG) levels. Insulin, total cholesterol, LDL- and HDL-cholesterol, and total-to-HDL cholesterol ratio are commonly altered in postmenopausal women with a 50 % risk of developing metabolic syndrome. LDL particles are the main cholesterol transporters, binding about 60 % of total serum cholesterol. Their function is not only to transport cholesterol to tissues. They are part of the plasma membrane and are converted into various metabolites, including steroid hormones. Since LDL induce vascular endothelial cell damage, high concentrations and activity of LDL have serious consequences for the etiology of cardiovascular diseases and the development of atherosclerosis [27].

HDL counteract the destructive effects of LDL. The main functions of HDL are to remove cholesterol (free cholesterol) from cells and other lipoproteins. HDL transport cholesterol accumulated in various cells and lipoproteins to the liver, from where it is excreted with bile [28]. TG is another type of fat that differs from lipoproteins in that it participates in energy metabolism. Most of the stored fat in the body is in the form of triglycerides, which are a highly concentrated form of energy and make up almost 95 % of dietary fat. An

increase in the blood level of TG is associated with CVD, type 2 diabetes mellitus (DM) and atherosclerosis [3].

As for the mechanisms of the association between hot flashes with the risk of CVD, they have not yet been fully elucidated, partly due to a limited understanding of the hot flashe physiology [29]. However, VMS may represent a new female-specific CVD risk factor that generally persists after controlling for endogenous sex hormones and traditional CVD risk factors [30]. Thus, modern studies have found that it was the severity, but not the frequency of VMS (hot flashes and night sweats), that was associated with an increased risk of CVD [31]. VMS are also a risk factor for DM, particularly for women reporting night sweats (regardless of reported hot flashes) [32]. The transition to menopause is accompanied by metabolic changes that contribute to the development of DM, especially type 2, as menopause presents an increased risk of adipose tissue accumulation in the upper body and an increased incidence of insulin resistance [33,34,35]. Since type 2 DM depends on both chronological and ovarian aging, it is quite common in postmenopausal women [36]. Similarly, DM may affect ovarian aging, potentially causing women with type 1 DM and early-onset type 2 DM to experience early menopause as compared with women without it. And an earlier age of menopause is associated with a higher risk of type 2 DM in later life [34].

Menopause is associated with numerous negative health consequences, one of which is osteoporosis (OP). The problem of OP in women is particularly relevant due to its high prevalence, serious consequences that lead to disability, a severe deterioration in the quality of life, and an increase in mortality. It is known that a femoral neck fracture often can cause death in elderly women. Scientists predict that by 2050, the number of hip fractures will increase to 1 million cases per year [4]. The significance of the OP problem in menopausal women is steadily increasing. It ranks fourth among non-infectious diseases after CVD, oncological pathology, and DM [37]. In the mechanism of this process, there is a deficiency of estrogen during menopause, which results in an increased resorption activity of osteoclasts, while the activity of osteoblasts remains relatively constant, which ultimately leads to bone tissue loss [38]. The maximum loss of bone mass occurs during the first years after menopause [39].

A study conducted at the Ukrainian Scientific and Medical Center for Osteoporosis Problems using two-photon X-ray absorptiometry has revealed OP in 8.4 % of the total female population, 20 % of women aged 50 and older. Taking into account the fact that almost 22 million women (53.6 % of the total population of the country) were registered in Ukraine, the number of women with OP may be more than 1.8 million [40,41]. Therefore, the diagnosis of the skeleton state should be included in the plan of mandatory examination for all women in the postmenopausal period. It is desirable that all specialists who provide medical care to elderly women should be skilled at organizing examinations [42]. Bone loss in women begins at about 35–40 years of age and is 0.7–1.3 % per year. With the onset of menopause, as well as in the first 5–10 years of postmenopause, this indicator increases to 3–7 % per year. So, in the first years of postmenopause, a woman can lose up to 9–35 % of bone mass, and then the loss stabilizes again at the level of 1 % per year. At the age of 65–70 years, it makes up 0.3–0.5 %. In the postmenopausal period, OP affects from a third to a half of all women [37].

Estrogens are key regulators of bone metabolism in both women and men. In women, estrogen deficiency is one of the main causes of postmenopausal OP [43]. With the onset of menopause, bone loss occurs in two stages. The first is accelerated loss, which begins within the first three years from the moment of menopause and lasts 5–8 years (stages 0; 1st and 2nd, according to the Staging of Reproductive Aging Workshop – STRAW classification). The second is the long-term loss of bone mass, which develops slowly and lasts throughout the 2nd stage according to the STRAW [37,44,45]. The development of osteopenia and OP in menopausal women is associated with a change in the production of $1,25(OH)_2D_3$, since estrogen deficiency causes a decrease in the synthesis of the vitamin D active metabolite and reduces the intestinal calcium absorption resulting in secondary hyperparathyroidism [37,46].

The main regulator of active calcium absorption in the body is vitamin D, which is directly involved in the regulation of bone remodeling processes, intestinal calcium absorption and its renal excretion. Under physiological conditions, the level of intestinal calcium absorption does not exceed 20–30 %, and the use of vitamin D increases it to 60–80 %. In healthy adults, the processes of bone formation and resorption are balanced. In old age, due to the vitamin D insufficiency development, resorption processes increase, this balance is disturbed, and calcium removal from the bone often exceeds its intake [47,48]. Hypovitaminosis D is also associated with muscle weakness and back pain. Vitamin D deficiency is usually the result of insufficient sunlight or inadequate consumption of foods containing vitamin D (fatty fish, vegetables, cereals). Insufficiency or deficiency of this vitamin causes secondary hyperparathyroidism leading to increased bone metabolism. At the same time, sufficient levels of vitamin D help preserve muscle strength and reduce the risk of falls [46,47,48].

Vitamin D is the most well-known nutrient among a variety of micronutrients and hormones that interact to regulate the balance between blood calcium and phosphorus levels. In addition, it functions as a hormone because it is synthesized by one organ and acts on others, affecting more than 30 body tissues, including hair follicles, cells of the reproductive system, and immune cells. Studies on the role of vitamin D suggest that vitamin D deficiency can cause many diseases, including high blood pressure, cardiovascular disease, some common cancers, infections (such as tuberculosis and influenza), inflammatory conditions, autoimmune diseases (type 1 DM, rheumatoid arthritis), psoriasis, multiple sclerosis [3]. Numerous genetic, molecular, and other studies strongly indicate that vitamin D signaling has many extraskeletal effects. These include the regulation of cell proliferation, immune and muscle function, skin cell differentiation and proliferation, as well as vascular and metabolic properties. In human observational studies, low vitamin D status is associated with almost all diseases related these extraskeletal actions [46].

A correlation has been found between serum 25(OH)D levels and changes in lipid profile among postmenopausal women [49]. Numerous studies have shown that low serum vitamin D levels were associated with several metabolic

conditions such as elevated TG, low HDL cholesterol, and high blood pressure in postmenopausal women [50]. It has been revealed that vitamin D was important not only for alleviating metabolic diseases, but also for improving the quality of life in postmenopausal women [51].

Menopause is a natural and inevitable part of a woman's life, but the risk of cardiovascular disease in women increases precisely during menopause. Therefore, proper assessment of such risks is mandatory to improve long-term cardiovascular disease outcomes [52,53]. In view of the above, it is the interdisciplinary interaction aimed at early detection of symptoms and diagnosis of menopausal disorders for the timely treatment [54] that comes to the fore.

Conclusions

1. Menopause is a difficult period in a woman's life, during which the risk of developing cardiovascular diseases and metabolic disorders increases, as well as the exacerbation of almost all preexisting somatic diseases. Therefore, proper assessment of such risks is mandatory to improve long-term CVD outcomes.

2. The interdisciplinary interaction is central to early detection of symptoms and diagnosis of climacteric disorders for the timely prescription of treatment. Physicians working with this contingent of women should apply a comprehensive approach to health care and quality of life preservation during the menopause transition, menopause and postmenopause.

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