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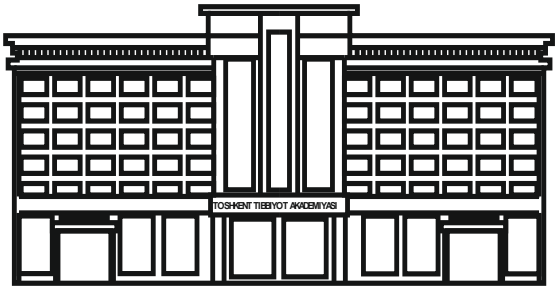

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ARTERIAL HYPERTENSION AND THE PERIMENOPAUSAL PERIOD: A CARDIOLOGIST'S VIEW

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АРТЕРИАЛЬНАЯ ГИПЕРТЕНЗИЯ И ПЕРИМЕНОПАУЗАЛЬНЫЙ ПЕРИОД: ВЗГЛЯД КАРДИОЛОГА

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ARTERIAL GIPERTENZIYA VA PERIMENOPAUZAL DAVR:KARDIOLOG NIGOHIDA

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Менопауза – один из важнейших периодов в жизни женщины, который отражает естественную утрату репродуктивных функций. Это фактор, оказывающий негативное влияние на качество жизни. Наиболее распространенные заболевания среди женщин климактерического возраста – сердечно-сосудистые. Основной симптом развития сердечно-сосудистых заболеваний – артериальная гипертензия, различные клинико-патогенетические особенности которой следует учитывать в разные периоды менопаузы.

Ключевые слова: *менопауза, метаболический синдром, сердечно-сосудистые заболевания, артериальная гипертензия.*

Klimakterik davr ayolning hayotidagi eng muhim davrlardan biri bo'lib, reproduktiv funksiyaning tabiiy yo'qolishini aks ettiradi. Gormonal o'zgarishlar va rivojlanayotgan menopauza kasalliklari ayollarning sog'lig'iga, umr ko'rish davomiyligiga va sifatiga salbiy ta'sir ko'rsatadigan omildir.Yurak-qon tomir kasalliklari menopauza yoshdagi ayollar orasida eng keng holatdir. Arterial gipertenziya yurak-qon tomir kasalliklari rivojlanishining asosiy xavf omili bo'lib, menopauzaning turli davrlarida e'tiborga olinishi kerak bo'lgan turli xil klinik va patogenetik xususiyatlarga ega.

Kalit so'zlar: *menopauza, metabolik sindrom, yurak-qon tomir kasalliklari, arterial gipertenziya.*

Arterial hypertension (AH) is the main modifiable risk factor for cardiovascular disease (CVD). With the growing obesity epidemic in developed and developing nations, the prevalence of AH is increasing and deserves a greater focus on prevention and management. AH is the main modifiable risk factor for cardiovascular disease (CVD). With in women warrants special attention due to the conditions unique to women throughout life. It is well known that conditions like pregnancy and postmenopause can be associated with AH. Other conditions unique to women including the menstrual cycle, polycystic ovarian syndrome, perimenopause, and menopause to name a few have been associated with changes in blood pressure (BP) through several hormonal pathways. This review focuses on the causes and management of AH across the lifetime of women and discusses how changes in hormones may affect the onset of AH. The menstrual cycle is one of the important indicators of women's health and its regulation polarity may vary depending on stage reproductive aging. Study Working Group stages of aging of the reproductive system women (Stages of Reproductive Aging Workshop -STRAW) distinguishes several period [19].

1. Menopausal transition is characterized by abnormal the regularity of menstrual cycles, which is a reflection of the variability of hormonal semen creation and ovulatory function [19].

2. Menopause is the permanent cessation of menstruation. This is the last independent menstruation due to age-related decrease in hormonal levels activity and "turning off" reproductive functions of the ovaries. Date of menopause is estimated retrospectively: after 12 months absence menstruation [19].

3. Perimenopause – includes the period of menopause transition +1 year after the last menstruation. Perimenopause begins with a disruption in regular period of the menstrual cycle ("menopausal phase"transition") and lasts up to 1 year after complete cessation menstruation. This phase of the reproductive stage rhenia can occur over a wide age range (from 42 to 58 years) and lasts from 4 to 8 years1 [19].

4. Postmenopause is the period of life after the last menstruation [19].

Climacteric syndrome is a complex of vegetative – vascular, mental and metabolic-endocrine disorders that occur in women against the background of fading loss (or sudden loss) of hormonal function of the eggs nicks and general aging of the body. Average age at menopause across the board world is 48.8 years (95% confidence interval 48.3-49.2) with significant fluctuations in this applicant depending on the geographical region of the pro-living conditions of women, in the Russian Federation it ranges from 49 up to 51 years old. Prevalence of menopausal symptoms ptomov is variable and depends on a number of circumstances [19].

Vasomotor symptoms often occur in late during the menopausal transition and especially expressed in perimenopause and the first years of postmenopause. Vasomotor symptoms affect up to 80% perimenopausal women [31]. Sleep disorders are common occur in 39-47% in perimenopausal women and in 35-60% are postmenopausal [33]. Among persons aged 50 years and older in the Russian Federation, osteoporosis is detected in 34% of women, and the incidence of osteopenia is 43% [1].

Features of the pathogenesis of hypertension in women during peri- and postmenopause. Hypertension in peri- and postmenopause is one of the most important but modifiable risk factors development of CVD. Its pathogenesis has its own peculiarities. Despite the versatility of endocurve shifts during reproductive aging women, individual stages of this process may differ in their duration and

accompaniment be driven by various specific symptoms and systemic disorders: endothelial dysfunction, the formation of unfavorable cardiovascular risk following the development of visceral obesity, dyslipidemia, impaired glucose tolerance, and sarcopenia, bone loss, etc. [5]. Observed in epidemiological studies increase in the frequency of hypertension in women in peri- and post- menopause is associated with hormonal changes, arising during this period and associated with loss of vasoprotective properties of estrogens, from native hyperandrogenism, low level progesterone, increased body fat mass, chronic inflammation, increased activity SNS and decreased sodium excretion [6].

Hypertension in Premenopausal Women. Obesity-Related Hypertension. The prevalence of obesity is increasing in all age groups especially in women. Center for Disease Control (CDC) data [15] indicate that the prevalence of grade II obesity (BMI 35.0-39.9) in premenopausal women aged 20-34 years old, between 2013 and 2016, was 10.7%, and that of aged between 35 and 44 years old was 11%. The prevalence of grade II obesity has doubled compared with the data 10 years prior. AH is strongly associated with being overweight and obese in women, and weight loss has been proven to reduce BP [27]. The accumulation of adipose tissue results in a cascade of events that cause obesity-related AH. The exact mechanisms are unclear, but mainly involve the development of metabolic syndrome; greater insulin resistance leading to increased sympathetic activity, renal sodium retention, and endothelial dysfunction leading to vasoconstriction [23]. A recent population-based cross-sectional study from China suggested that adverse menstrual cycle characteristics (specifically longer menstrual cycle, irregular bleeding and heavy bleeding) are associated with increased risk of AH in overweight and obese women compared with women of normal weight [37]. However, other menstrual abnormalities like dysmenorrhea and longer duration of bleeding were associated with stage II AH [37]. Bariatric surgery has a sustained antihypertensive effect [32] and could be considered in obese women with resistant AH.

Premenstrual Syndrome. Clinically significant premenstrual syndrome (PMS) affects up to 15% of women and substantially interferes with quality of life. Emerging data reveal that the renin-angiotensin-aldosterone pathway that contributes to AH may also influence PMS by causing symptoms of premenstrual edema, abdominal bloating, and breast tenderness. Whether women with PMS have a higher risk of developing AH was evaluated prospectively in the Nurses' Health Study II [7]. After adjustment for age, smoking, BMI, and other risk factors, women with PMS had a hazard ratio for AH of 1.4 (95% CI 1.2, 1.6) compared with women without PMS. Among the small number of women who developed AH prior to the age of 40 years, PMS was associated with a tripling of the risk (adjusted hazard ratio 1.4; 95% CI 1.5-6.5). This risk was not modified by the use of the oral contraceptive pill (OCP) or antidepressants but seemed to be attenuated among women with high intakes of riboflavin and thiamine (p value <0.05). The study suggests PMS may be associated with future development of AH and this risk may be modifiable. The study showed that women with moderate to severe PMS had a 40% higher risk of developing AH in the following 20 years compared with women with fewer menstrual symptoms. Based on this data, regular screening for AH is warranted in women with a history of moderate to severe PMS.

Insulin resistance and hyperglycemia. Insulin resistance and hyperglycemia are associated with visceral obesity and hypertension, creating high risk of impaired glucose tolerance and type 2 diabetes in peri- and postmenopausal women [13].

Dyslipidemia. Lipid metabolism, as well as and glucose, is under the control of estrogen and testosterone, manifests itself in atherogenic types dyslipidemia: IIa, IIb and IV [29]. Given these groin dyslipidemia in the blood is significantly increased levels of total cholesterol, low lipoproteins density, apolipoprotein B and triglycerides.

Remodeling of arteries and arterioles in such patients is inextricably linked with an increase in OPSS, various development and progression of hypertension [28].

Metabolic syndrome (MS). MS is closely associated with development of visceral obesity and is its combination with hyperglycemia, insulin resistanceity, dyslipidemia and hypertension, occurring with high frequency in peri- and postmenopausal women. MS predominates in men, but in more at older ages, it is more common in women.

Factors contributing to the development of MS or its components include: increased tone of the SNS, endothelial dysfunction and vascular inflammation, characteristic peri- and postmenopause [34]. It is known that in postmenopausal women with MS and obesity response to antihypertensive therapy improves decrease in endothelial function and decrease in the severity chronic inflammation were less than in women without metabolic disorders and obesity [26]. Thus, related obesity and MS not only contribute to the development hypertension, but also reduce the effectiveness of antihypertensive therapy in postmenopausal women [18].

Hormonal Contraceptive Use. Use of estrogen-containing oral contraception is independently associated with an increased risk of ischemic stroke in women with certain medical conditions: (1) AH, (2) smokers older than 35, (3) diabetes with complications, (4) coronary artery disease, (5) history of venous thromboembolism, and (6) migraine with aura. Therefore, evidence-based guidelines from the World Health Organization and CDC recommend avoidance of the combined OCP (COC) in the presence of these medical conditions. Despite this recommendation, a recent study reported a high rate of COC use in women with a medical contraindication to estrogen use [22]. Small effects of AH can have considerable overall consequences given the large numbers of women taking the OCP. A recent meta-analysis containing 24 studies with 27,084 participants demonstrated that for every 5-year increment in oral contraceptive use, the risk of AH increased by 13% [25]. These studies highlight the need for safe and effective forms of contraception among women at increased risk for cardiovascular events. Increased BP associated with OCP use may lead to AH possibly through activation of the renin-angiotensin-aldosterone system [11]. The "traditional" vasoconstrictor ACE/AngII/Ang type I receptor pathway appears to be balanced by a vasodepressor arm of the RAAS named the ACE 2 [8]. Blood pressure is stable during the menstrual cycle possibly due to the vasodepressor arm. A recent study investigated levels of the vasoconstrictor RAAS enzymes and vasodilator ACE 2 in normal-

ly menstruating women compared with women taking the combined OCP. They found women taking OCPs have a higher Ang II/Ang ratio associated with their BP elevation, although no causal relationship could be found. This suggests OCP-mediated AH effects may be related to RAAS pathways. Giribela et al. [17] investigated the effect of a COC containing drospirenone (an anti-androgenic progestogen related to 17 alpha spironolactone that exhibits potent anti-mineralocorticoid activity) in 81 women without cardiovascular risk factors. They found that a COC containing low-dose ethinyl estradiol (20 mcg) and drosperenone did not negatively influence risk factors for cardiovascular disease. In view of the global prevalence of oral contraceptive use, careful BP monitoring of women who take oral contraceptives is important.

Renovascular Disease (Fibromuscular Dysplasia). In 10% of patients with renovascular AH in the Western population, narrowing of the lumen is due to fibromuscular dysplasia, and not atherosclerosis. Fibromuscular dysplasia (FMD) is generally thought of as a disease that occurs in young women less than 30 years of age. The First International Consensus Report on FMD [18] estimates that 80-90% of patients with fibromuscular dysplasia (FMD) are women and the mean age at diagnosis is over 50 years. Therefore, it is suspected that age at a clinical diagnosis of FMD has been substantially delayed. In a recent study of 2420 patients with FMD, 86.2% were female [21]. FMD is a nonatherosclerotic arterial disease that is characterized by abnormal cellular proliferation and distorted architecture of the arterial wall. FMD manifests primarily as beaded (multifocal) or focal lesions in medium- or small-sized arteries, though the clinical phenotype of FMD has recently been expanded to include arterial dissection, aneurysm, and tortuosity [30].

The Effect of Hormonal Changes on Hypertension in Women. The menopause transition goes through several adaptations: normal ovarian activity, through a stage with prolonged follicular phase and no luteal activity. There is a stage with normal follicular activity and insufficient luteal phase, and finally the menopause with low estrogens and progesterone. During the transition, cycles become longer due to delayed ovulation or anovulatory cycles. As the process moves on, folliclestimulating hormone (FSH) levels are higher and inhibins are lower than in the follicular phases [20]. Once menstruation has ceased, estradiol and progesterone concentrations are low. Hormone measurements other than FSH are of little diagnostic value. The transition can take up to 4 years. Hot flushes, night sweats, and vaginal dryness are common symptoms of the menopause from estrogen withdrawal. Experimental studies in mice determined that estrogen receptors (ERs) are expressed in vascular endothelial and smooth muscle cells and estradiol can cause vasodilation by both ER-dependent and ER-independent mechanisms. Estradiol induces an increase in intracellular free calcium concentration in endothelial cells which could contribute to the increase in endothelial-derived nitric oxide (NO). Since inhibition of NO synthesis favors arterial AH, it is conceivable that estradiol protects against AH by increasing NO synthesis. Progestins inhibit the estradiol-induced synthesis of endothelium-derived NO and may contribute to the diminished vasodilator effects of estrogen observed in postmenopausal women receiving estradiol plus progestins. Additionally, estradiol activates adenyl cyclase activity and increases the synthesis of cyclic AMP, a vasodilator second messenger. Estradiol also reduces the synthesis of potent vasoconstrictors such as angiotensin II, endothelin-1, and catecholamines [14]. Experimental mouse models suggest that ovarian hormones may be responsible for lower BP in premenopausal women and for the increase in BP in postmenopausal women. A recent review by Sylvester and Brooks examined the role of T cells in immune-mediated AH in animals and discovered that premenopausal females were resistant to immune-mediated AH. This protective effect of estrogen was lost in postmenopausal animals [35].

Autoimmune Disorders: Hypothyroidism, SLE, DM. Optimal BP control is favored in patients with chronic conditions such as type 1 diabetes, systemic lupus erythematosus (SLE), and hypothyroidism to reduce risk of CVD. Hypothyroidism which is 5-8 times more common in women than men is associated with increasing peripheral resistance which can lead to diastolic hypertension. SLE, also more common in women, especially of childbearing age, can lead to AH secondary to renal manifestations of lupus. The presence of diabetes eliminates any gender advantage that premenopausal women may have at risk for cardiovascular disease. Diabetes is characterized by systemic and vascular inflammation and endothelial dysfunction. These mechanisms may link type 1 diabetes to increased pulse pressure. Inflammatory markers such as cell adhesion molecules (CAMs) and C-reactive protein (CRP) have been proposed as possible determinants of arterial stiffness/pulse pressure and hypertension. A recent study [16] investigating inflammatory markers (CRP, soluble intracellular CAM[sICAM-1], soluble vascular CAM [sVCAM-1], and soluble E-selectin [sE-selectin]) in patients with type 1 diabetes over 20 years found that higher levels of sICAM and sVAM-1 at baseline and during follow-up predicted the prevalence and incidence of AH. No differences in gender were noted. Increased expression of non-coding RNAs and micro-RNAs triggers pathways that mediate endothelial dysfunction and subsequent atherosclerosis and are also involved in the pathogenesis of AH in diabetes [38].

Antihypertensive therapy in women during peri- and postmenopause. The general strategy for treating hypertension is reducing the risk of developing CVD and its complications with use of non-drug and medicinal precise methods [36]. Non-drug methods interventions include lifestyle modification women during peri- and postmenopause with the aim of prevention of CVD and type 2 diabetes. For this purpose not we bypass a multidisciplinary approach involving medical specialists, nutritionists, sports trainers, psychologists. Thus, according to Finnish research guidelines for diabetes prevention (Finnish Diabetes Prevention Study) and the Prospective Prevention Program diabetes prevention (Diabetes Prevention Program), these goals can be achieved. It has been shown that lifestyle modification, which includes normalization of body weight, increase in physical activity, normalization of sleep, smoking cessation and alcohol abuse, antiatherogenic, low-calorie and low-

salt diet, promotes prevention or later development hypertension and type 2 diabetes [24]. Normalization of body weight in women with abdominal obesity in the peri- and postmenopause helps improve endothelial function, and regular aerobic physical ski training (30-40 min 4 times a week) reduces increase the incidence of adverse cardiovascular events events by 50%. Non-drug methods of influencing additional are treated with pharmacotherapy. Number of appointments antihypertensive drugs depends on both the use the normal level of blood pressure and the degree of cardiovascular risk. Therapy for hypertension can only be recommended for patients for patients blood pressure <150/90 mm Hg. and low CV risk [34]. Combination therapy is recommended for hypertension ≥150/90 mm Hg To optimize antihypertensive therapy and increasing patient adherence .It is advisable to use drugs that provide requiring 24-hour blood pressure control with a single dose. This means that the drugs must be metabolically neutral and provide organ protection [10]. Currently, for the treatment of hypertension it is recommended. There are 5 main classes of antihypertensive drugs drugs: ACE inhibitors (ACE inhibitors), re-blockers angiotensin II receptor type 1 (ARB), diuretics (thiazide and thiazide-like), slow-release blockers calcium channels, β-blockers [3]. Considering the high activity of the RAAS and SNS in women in peri- and postmenopause, to slow down the on the progression of target organ damage. ACEIs and ARBs are recommended ACEI helps reduce the likelihood of developing cardiovascular disease complications if present high and very high cardiovascular risk not only in patients current with AG. Clinical effectiveness of ACE inhibitors on throughout the cardiovascular continuum explained by their ability to modulate the activity of the RAAS, one of the components of the RAAS is ACE localized directly on membranes endothelial cells of small arteries and arterioles. Therefore, the use of ACE inhibitors for the correction endothelial dysfunction promotes recovery renewing the structure and function of the arterial endothelium, that in peri- and postmenopausal patients is pathogenetically justified. However, due to with an increase in peri- and postmenopausal renin-independent forms of hypertension, the effectiveness of ACE inhibitors in them lower than in other categories of patients [9]. Need to also pay attention to what is undesirable a phenomenon such as cough while taking ACE inhibitors with pain cervical disease is more common in women than in men. Selection of antihypertensive therapy in women during the period of peri- and postmenopause, it is significantly more complicated eliminate changes in carbohydrate and lipid metabolism, change in the vegetative background, since the ongoing. Therapy should not aggravate existing disorders metabolism. Sympathicotonia is a condition in which the choice of therapy can be made in favor of reason for the use of β-blockers, but their negative limited effect on glucose and lipid metabolism specifies the purpose of this group of drugs [4]. However, the prescription of β-blockers most justified in patients with hypertension in the presence of a defined transferred indications (angina pectoris, transferred myocardial infarction, chronic heart failure and right ventricular arrhythmias) [3]. Diuretics (thiazide and thiazide-like) still remain the basis of antihypertensive therapy with high clinical effectiveness, preventing cardiovascular complications and mortality [2]. It is diuretics that should perform to be used as drugs of choice, often as part of combination therapy for the treatment of hypertension in different periods of decline in women's reproductive function. However, in women with hypertension when using diuretics more often than in men. Therefore, women in the period of peri- and postmenopause, the basis of the combination prescribed therapy if necessary; the treatment should be an ACE inhibitor or an ARB. Wherein, taking into account clinical and pathogenetic features hypertension in such patients, a combination of ACE inhibitors is preferred carefully supplement with diuretics (during the peri- and postmenopause) [12]. Taking into account the peculiarities of the pathogenesis of hypertension in women in peri- and postmenopause, it is necessary to search for an alternative combinations of pharmacotherapy for hypertension in women in the menopause. Based on this attention should be paid to selective agonists I1-imidazoline receptors.

Conclusion

The prevalence of HTN in premenopausal and postmenopausal women is increasing. High-quality evidence to provide guidelines on optimal management is more limited in younger women. Assessing women's unique risk factors for CVD could improve medical decision-making. Future research in this area is essential and should focus on recruiting more young women in HTN clinical trials. In women, menopausal state and presence of chronic conditions should be included in the determination of CVDrisk. Thus, the period of peri- and postmenopausal is the natural period of extinction of the reproductive functions of a woman, characterized by development various clinical disorders, forming the basis for the formation of serious pathological clinical conditions - hypertension, CVD, obesity, type 2 diabetes, postmenopausal osteoporosis. May during the menopausal transition is not the only way to prevent and treat clinical conditions accompanying menopause, including CVD and its complications, which requires appropriate current therapeutic approach. Pharmacotherapy hypertension in women in this period, as one of the key risk factors for the development of CVD, complications and death hypotension, implies the use of antihypertension healthy medicines with high strong and persistent antihypertensive activity, organoprotection, metabolic neutrality and a favorable tolerability profile. Use of I1-imidazoline agonists receptors, in particular moxonidine in women, including in peri- and postmenopause, especially when presence of abdominal obesity and MS in the composition combination therapy is justified, because along with with a clear antihypertensive effect when leads to a decrease in SNS activity, correction excess body weight, insulin resistance, improving the quality of life - reducing the degree nor the severity of menopausal disorders, osteoporosis, as well as slowing down the progression destruction of target organ – heart. I1-imidazoline receptor agonists recommended in combination with other antihypertensive drugs, if the treatment is primarily classes of drugs does not lead to lower than the target blood pressure level or is poorly tolerated.

The list of references is available at the editorial office

ARTERIAL HYPERTENSION AND THE PERIMENOPAUSAL PERIOD: A CARDIOLOGIST'S VIEW

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Menopause is one of the most important periods in a woman's life and reflects the natural loss of reproductive functions. This is a factor that has a negative impact on quality. Cardiovascular disease is the most common disease among menopausal women. Arterial hypertension (AH) is the main symptom of the development of cardiovascular diseases and has various clinical and pathogenetic features that should be taken into account during different periods of menopause.

Key words: *menopause, metabolic syndrome, cardiovascular diseases, arterial hypertension.*