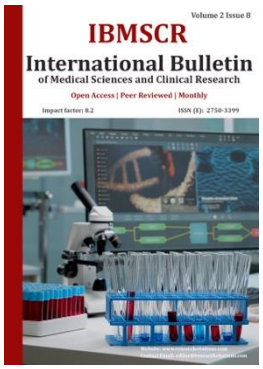

MODERN TECHNOLOGIES IN DIAGNOSIS AND TREATMENT IMMUNE-ENDOCRINE HOMEOSTASIS IN CORONARY HEART DISEASE DURING THE MENOPAUSAL PERIOD

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Annotation

According to some researchers, middle age is not just a period when women experience hot flashes and other symptoms of menopause. This is a time when their risk of cardiovascular disease increases as we see significant changes in multiple clinical measures of their physical health.

Menopause occurs, on average, at age 51. About 80% of women experience symptoms such as hot flashes, headaches, night sweats and depression. These symptoms usually last for about four years. Every tenth woman experiences menopause before the age of 45. In one in a hundred women, such changes occur before the age of 40, and in one in a thousand - before the age of 30. According to Burke A. P. et all . (2018) d hormonal imbalance in menopause determines the characteristics of its manifestation.

It has been found that early menopause can increase the risk of heart attacks. Scientists from the Erasmus University Medical Center in the Netherlands reviewed 32 studies involving a total of more than 310,000 women. The researchers compared the rates of women who experienced menopause before age 45 or older. It found that overall, women who went through menopause early were 50% more likely to suffer from coronary heart disease (CHD). They were 11% more likely to die from a heart attack and 12% more likely to die prematurely from any cause. However, early menopause had no effect on the risk of stroke.

According to the researchers, the observed connection appears to be due to the influence of the sex hormone estrogen. It has a protective effect on the heart. However, during menopause, its natural production in the body stops.

According to the study authors, estrogen plays an important role by promoting relaxation and dilation of blood vessels, which has a positive effect on blood flow. A decrease in the level of the hormone leads to the fact that, apparently, the blood vessels become stiffer, which increases the risk of a heart attack.

Thus, women who reach menopause later experience longer exposure to estrogen, which has positive effects on their hearts.

Scientists cannot yet say for sure whether hormone replacement therapy can help here. Further research is needed to draw definitive conclusions.

Introduction.

Many factors have been studied that may influence the development of coronary heart disease (CHD). One of them is menopause. Menopause occurs when the ovaries no longer respond to the control hormones released by the pituitary gland in the brain. As a result, the ovaries cannot release an egg and produce female sex hormones: estrogen and progesterone every month. It is the decrease in the level of these hormones in the bloodstream that leads to

the symptoms of menopause and causes metabolic disorders in the body. Men aged 40 years have a higher risk of developing CHD than women. But as women age, their risk increases so much that it almost becomes equal to the risk of men [1].

According to some researchers, middle age is not just a period when women experience hot flashes and other symptoms of menopause. This is a time when their risk of cardiovascular disease increases as significant changes are detected in multiple clinical measures of their physical health [2].

Menopause signals the end of a woman's reproductive life and the cessation of her menstrual cycle. This usually occurs between 49 and 52 years of age. 97% of women experience menopause by age 58. This is a natural occurrence, however, the physical and psychological changes that accompany menopause can be distressing for many women.

With the onset of menopause, there is a decline in ovarian function. The ovaries produce smaller amounts of female sex hormones, namely estrogen and progesterone. Estrogen levels gradually decline for several years after menopause. The hormonal imbalance that accompanies menopause is responsible for many of its features. [3].

According to research, the incidence of cardiovascular diseases (CVD) increases in postmenopausal women [4,5,6]. The prevalence of hot flashes and other menopausal symptoms is up to 80% in menopausal women, and the prevalence is influenced by factors such as age, ethnicity, lifestyle, education, smoking and mood [7,8]. Increasing evidence indicates that menopausal symptoms are associated with risk factors for CAD and surrogate markers of CAD and clinical manifestations of CVD [9,10].

Researchers from the American College of Cardiology assessed the association of sex hormone levels with CVD, coronary artery disease, and heart failure during a 12-year follow-up of 2,834 postmenopausal women free of cardiovascular disease at baseline. In this age group, more women die from CVD (41.3%) than from the next seven causes of death combined, and the risk of death from this disease is 6 times greater than from breast cancer. Recent data from the American Heart Association shows that only 46% of women are aware of this fact. Studies suggest that estrogen and progestagen therapy increases the risk of CAD in postmenopausal women, while others warn that there is no risk if women begin hormone replacement therapy immediately after menopause [11, 19].

The Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial, a prospective, randomized, double-blind, placebo-controlled study sponsored by the US National Institutes of Health, demonstrated the effects of estrogens on selected heart disease risk factors in healthy postmenopausal women. Summarizing the results of this study, we can conclude that estrogens as monotherapy or in combination with progestins have a cardioprotective effect in postmenopausal women, especially with regard to the risk of coronary artery disease [12, 20].

According to Tolstov S.N. et al. (2017) systemic metabolic changes lead to decreased levels of sex steroid binding globulin, which contributes to an increase in free androgens in the bloodstream, which themselves can reduce HDL and cause insulin resistance, hyperinsulinemia and android fat distribution. In obesity, activation of pro-inflammatory response factors is often detected, which leads to endothelial dysfunction, oxidative stress, and an inflammatory cascade of cytokines, contributing to the occurrence of atherosclerotic changes and the development of insulin resistance [13]. The listed facts determined the emergence of the term “Menopausal Metabolic Syndrome” (MMS), the components of which: dyslipoproteinemia, insulin resistance, hyperactivity of the sympathetic nervous system - are

one way or another interdependent, interconnected and become triggers for each other, creating a "vicious circle". MMC is decisive in the pathogenesis of IHD and premature vascular aging in postmenopausal women [14].

Uzbekistan is implementing large-scale measures to provide high-quality specialized cardiac care to the population and introduce high-tech treatment methods into practical healthcare. The Action Strategy of the Republic of Uzbekistan in five priority areas for 2017-2021 sets the following objectives: "improving the quality of medical care, social and medical services, ensuring a reduction in morbidity among the population and increasing life expectancy" [15, 21-25].

It has been noted that HRT does not change blood pressure in postmenopausal women with normotension [16]. The positive effect on risk factors translates into a reduction in morbidity and mortality from cardiovascular diseases. In the United States and most European countries, a significant number of postmenopausal women take hormone replacement therapy [17,18, 26-29]. However, among Russian women, awareness of HRT is extremely low, even if there are absolute indications for its use [19, 30-33].

Thus, HRT remains the first-line treatment and the most effective treatment for menopausal symptoms. A balanced clinical approach, the correct choice of dose and combination of estrogens/progestins, and, most importantly, the prescription of HRT in early postmenopause to women who need it to relieve vasomotor symptoms, is the key to the effectiveness and success of this therapy.

In this regard, the task of developing measures to prevent cardiovascular mortality and disability and their implementation in primary health care and other levels seems very relevant.

Purpose of the study : to study modern technologies in the diagnosis and treatment of immune-endocrine homeostasis in coronary heart disease in the menopausal period.

Subject and object of research. The study included 184 patients hospitalized in the Urgench branch of the Republican Specialized Scientific and Practical Center of Cardiology for the period 2016–2018. Patients with and without coronary artery disease during the perimenopause period were included. Before the start of the research, all participants gave written informed consent . Depending on age, the subjects were distributed as follows: 41-50 years – 79 patients (46±1.56); 51-60 years of age – 105 (57±2.43). The maximum number of women who were treated were patients aged 41-50 years.

The studied patients were divided into five categories according to the form of the disease and type of treatment: the 1st group consisted of 38 postmenopausal patients (PMP) without IHD, the 2nd group - 42 women in the PMP with IHD, those examined in both groups were prescribed traditional therapy. Patients of the 3rd (n=40) with PMP and the 4th group (n=44) with a diagnosis of PMP + IHD received traditional pharmacotherapy in combination with the herbal preparation "Cimicifuga" (Klimadynon® BIONORICA, SE) . The 5th (control) group consisted of 20 practically healthy individuals.

A clinical and epidemiological examination of the content of estrodiol in the blood serum was carried out , estriol and estrone . Progesterone concentration has been studied as a possible marker of the risk of developing coronary artery disease. In patients to assess the role of cytokine imbalance in the destabilization of coronary artery disease in the menopausal period, the activation of pro-inflammatory reaction factors (IL1-β, IL-6, IL-17 and TNFα) was

studied before and after the administration of HRT with a drug made from herbal raw materials "Cimicifuga" produced (Klimadynon® BIONORICA , SE).

Research methods.

The hormonal status of the study patients was studied by determining the level of hormones in the blood serum. Blood was taken from the antecubital vein on an empty stomach. After centrifugation, the serum for the study was stored in the refrigerator in closed tubes at a temperature of – 10-20 ^{0} C. Determination was carried out by enzyme immunoassay using an ELISA (direct) ELISA EIA-5396 device manufactured by DRG (ZAOtekhsystems) .

With the content of estrodiol, estriol, estrone and progesterone in blood serum was determined by enzyme immunoassay on a solid-phase carrier using polyclonal antibodies. E-stradiol (estradiol) was determined using a set of diagnostic reagents for enzyme immunoassays *in vitro* , produced by DRG Instruments GMBH , Germany .

Set contents: 96-well collapsible plate (12 strips of 8 wells each, on the surface of which rabbit polyclonal antibodies to estradiol are sorbed) – 1 pc.; enzyme conjugate – estradiol, conjugated with horseradish root peroxidase, ready for use – 1 bottle; a set of reference standards – samples of human blood serum, inactivated, with an estradiol content of 0; 25; 100; 250; 500; 1000; 2000 pg/ml (conversion factor: 1 pg/ml = 3.67 pmol/l); Substrate solution with tetramethylbenzidine – 1 bottle (14 ml); stop solution - 0.5 M aqueous solution of sulfuric acid, ready for use - 1 bottle (14 ml); washing solution (concentrate ×40) – 1 bottle (30 ml). The measurement range of the method is 9.7 – 2000 pg/ml *(values according to the manufacturer's instructions)* . The coefficient of variation is 8%. Storage temperature in the manufacturer's packaging is from 2 to 8°C *(values according to the manufacturer's instructions)* , in a dry place, protected from light and a relative air humidity of 70% during the entire shelf life.

To determine the concentration of cytokines (IL-1β, IL-6, IL-17 and TNF-α) used a set of reagents from Vector-Best (Germany) for enzyme immunoassay determination of the concentration of interleukins in blood serum on a semi-automatic tablet photometer R ayto RT -2100 C with automatic plate feeding, built-in shaker and thermal printer.

The operating principle of the "ELISA- IL " kit is based on the "sandwich" version of solid-phase ELISA. Two monoclonal antibodies with different epitope specificities for IL were used . One of them is immobilized on the solid phase (inner surface of the wells), the second is conjugated with peroxidase. At the first stage of the analysis , IL contained in calibration samples and blood serum binds to antibodies immobilized on the inner surface of the wells. In the second step of the assay, the immobilized IL interacts with peroxidase. The amount of bound conjugate is directly proportional to the amount of IL in the test sample. During incubation with the substrate mixture, the solution in the wells becomes colored. The degree of coloring is directly proportional to the amount of bound labeled antibodies. After measuring the optical density of the solution in the wells, the concentration of IL in the blood serum is calculated based on the calibration curve .

6. ***Statistical research methods.*** The obtained information was statistically processed using a package of applied statistical programs on a Pentium-4 computer with calculations of the arithmetic mean (M), root mean square error (σ), standard error (m) and relative values (frequency, %).

The statistical significance of the obtained measurements when comparing average values was determined by Student's t test, with the calculation of the probability of error (P).

A significance level of P <0.05 was accepted as statistically significant changes. At the same time, existing guidelines for statistical processing of the results of clinical and laboratory studies were taken into account [20, 35]. During the preparation and implementation of the development, as confirmation, we adhered to the rules of evidence-based medicine given in the methodological recommendations of L.A. Ponamareva et al. [21, 34].

Results.

The average age of the examined patients was 53 ± 2.14 years. The study design consisted of 2 stages: Stage 1 - determination of the hormonal and cytokine status against the background of traditional treatment and Stage 2 - study of the hormonal and cytokine status after complex traditional treatment with the additional administration of the herbal preparation "Cosimifuga". The studied patients were divided into five categories according to the form of the disease and type of treatment: the 1st group consisted of 38 postmenopausal patients (PMP) without IHD, the 2nd group - 42 women in the PMP with IHD, those examined in both groups were prescribed traditional therapy. Patients of the 3rd group (n=40) with PMP and the 4th group (n=44) with a diagnosis of PMP + IHD received traditional pharmacotherapy with the herbal preparation “Cosimifuga” (Klimadynon® BIONORICA, SE). The 5th (control) group consisted of 20 practically healthy individuals. Proven ischemic heart disease was present in 86 (46.7%) of the examined women.

In observation groups, the spectrum of hormones estrodiol, estriol, estrone and progesterone was studied to assess their diagnostic significance in predicting the risk of developing destabilization of coronary artery disease in menopausal women with traditional treatment (Table 1) and traditional pharmacotherapy in combination with Cohosh (Table 2) .

Table 1

Concentrations of the hormones estrodiol, estriol, estrone and progesterone in postmenopausal patients without and with proven coronary artery disease against the background of traditional treatment

Groups	Estrodiol, pg/ml)	Estriol, ng/ml	Estrone, pg/ml	Progesterone, nmol/L
Control (n =20)	123.3±9.99	47.4±2.76	78.5±3.25	2.1±0.08
Group 1 (n =78) Postmenopausal without ischemic heart disease	43.8±1.36	18.6±0.79	49.4±1.35	0.7±0.03
Group 2 (n =86) Postmenopause with IHD	35.9±1.23	7.9±0.40	26.9±0.93	0.4±0.02

The results presented in Table 1 indicate that in 78 postmenopausal patients (PMP) without ischemic heart disease against the background of traditional treatment, the content of estrodiol (43.8±1.36) was statistically significantly lower than the reference values for postmenopause (2 - 21(pg/ml)) 2 times, and compared to the norm in practically healthy individuals 10 – 44 **(mcg/day) statistically significantly** decreases by 5.9 times. In patients with PMP without ischemic heart disease, the concentration of estriol was determined to be 18.6±0.79 ng/ml, which is 2 times higher than in women of group 2 (7.9±0.40 ng/ml). A

similar trend was revealed for estrone content. The lowest indicators were found for progesterone content.

The data given in table. 2 indicate that the range of hormones studied after complex traditional treatment with the addition of

Table 2

Concentrations of the hormones estrodiol, estriol, estrone and progesterone in postmenopausal patients without and with proven coronary artery disease against the background of traditional pharmacotherapy in combination with Cohosh

Groups	Estrodiol, pg/ml)	Estriol, ng/ml	Estrone, pg/ml	Progesterone, nmol/L
Postmenopause without ischemic heart disease, trad. treatment n =38	59.3±2.08	24.61.28±	52.5±2.05	0.9±0.04
Postmenopause without ischemic heart disease, trad. Treatment +C n =40	78.9±2.32	29.8±1.17	56.8±2.09	1.3±0.05
Postmenopause with ischemic heart disease, trad. Treatment n =42	40.5±1.81	11.6±0.58	31.3±1.36	0.6±0.04
Postmenopause with ischemic heart disease, trad. Treatment +C n =44	56.2±1.69	21.3±0.56	42.5±1.41	1.1±0.04

the drug " Cohosh" significantly increases the concentration of estrodiol, estriol, estrone and progesterone ($p < 0.05$). Research results confirm the effectiveness of timely hormone replacement therapy (HRT) in combination with the prescription of Cohosh . In our case, the benefit-risk ratio in patients taking Cohosh the benefit outweighs the risk and HRT is the gold standard for the treatment of women in primary care with coronary artery disease and improves the quality of life of this contingent of women.

Along with hormonal homeostasis, the imbalance of pro-inflammatory cytokines IL 1-β has been studied. IL -6, IL -17 and TNFα in the destabilization of coronary artery disease in menopausal patients before the prescription **of** Cohosh (Table 3 and after treatment with this drug (Table 4).

Table 3

Concentrations of proinflammatory cytokines IL 1 -β , IL -6, IL -17 and TNFα in postmenopausal patients without and with proven coronary artery disease against the background of traditional pharmacotherapy

Groups	IL - 1-β, pg/ml	IL -6, pg/ml	IL -17, pg/ml	TNFα, pg/ml .
Control (n = 20)	7.9±0.44	5.6±0.39	3.14±0.15	3.2±0.28
Group 1 (n =78) PMP without CHD	10.5±0.21	7.9±0.16	8.1±0.15	5.3±0.15
Group 2 (n =86) PCP with IHD	16.8±0.23	14.7±0.19	12.3±0.28	9.6±0.20

The determination of the concentration of IL -1-beta was based on its important role in the development of local and systemic inflammatory processes. IL -1- β increases hematopoiesis, the permeability of the vascular wall, and also triggers reactions of the inflammatory- regulatory cascade. Thus, in the group of patients with PMP without IHD, the content of IL - 1-β corresponded to 10.5±0.21 pg/ml, and in women with PMP+IHD it was set at 16.8±0.23, which exceeded the normative values by 1.32 and 2.13 times corresponding to the observation groups.

A similar trend can be seen in the amount of a marker of acute systemic inflammation - the proinflammatory cytokine IL -6 , which affects many organs and systems of the body. The biological role of IL -6 is the induction of restoration mechanisms and activation of immune defense (activation and differentiation of T cells, maturation of B cells, synthesis of C-reactive protein in the liver, enhancement of hematopoiesis). Disruption of regulatory systems, which accompanies increased production of IL -6 in patients with PMP and coronary artery disease during traditional treatment, may aggravate the damage to cardiac tissue due to an autoimmune reaction.

Interleukin-17 exhibits pronounced pro-inflammatory activity *in vitro and in vivo* , and is capable of inducing the synthesis of various inflammatory mediators, including TNF-α, IL -1, IL -6, thereby promoting the development of autoimmune pathological reactions, including the induction of inflammation in coronary artery disease. In 87 women with PMP without ischemic heart disease against the background of traditional treatment, the content was 8.1±0.15 pg/ml IL -17 exceeds control values by 2.6 times, and in the group with PMP with IHD by 3.9 times. This indicates a powerful pro-inflammatory effect and acceleration of proliferation and differentiation of mesenchymal cells.

In two observation groups, activation of interleukin-17 production increased the concentrations of extracellular protein TNFα . This biomarker is more actively produced in the group of patients with PMP + IHD (9.6±0.20 pg/ml).

Table 4 shows the results of a study of HRT using the estrogen-containing drug "Tsimitsifuga **"**. It should be noted that an imbalance of sex hormones could cause direct myocardial damage and IHD. Thus, it has been established that the purpose of "Cimicifuga **"** activates the production of pro-inflammatory interleukins. In our case , the prognosis for patients is usually favorable and a decrease in the quality of life comes to the fore, which forces them to see a doctor again and again, leading to significant economic costs and

psychological discomfort. Therefore, the study of a woman's quality of life in this period becomes particularly relevant.

Table 4

Concentrations of proinflammatory cytokines IL 1 -β , IL -6, IL -17 and TNFα in postmenopausal patients without and with proven coronary artery disease against the background of traditional pharmacotherapy in combination with Cohosh

Groups	IL - 1-β, pg/ml	IL -6, pg/ml	IL -17, pg/ml	TNFα, pg/ml .
Postmenopause without ischemic heart disease, trad. treatment (n =38)	8.4±0.35	6.2±0.23	4.9±0.27	4.2±0.20
Postmenopause without ischemic heart disease, trad. treatment +C (n =40)	8.1±0.26	5.8±0.22	4.3±0.18	3.9±0.22
Postmenopause with ischemic heart disease, trad. treatment (n =42)	13.7±0.40	12.8±0.30	9.6±0.36	7.8±0.29
Postmenopause with ischemic heart disease, trad. +C treatment (n =44)	11.2±0.36	12.3±0.24	7.5±0.39	6.5±0.25

Thus, the results of the studies made it possible to personalize menopausal hormonal therapy taking into account risk factors for the development of severe forms of coronary artery disease.

CONCLUSIONS:

1. The effectiveness of the dosage form of the drug "Cimicifuga" has been substantiated.
2. The minimum effective dosage of the estrogen-containing drug "Cimicifuga" has been selected.
3. Optimization of combination pharmacotherapy for coronary artery disease in the postmenopausal period involves studying the interaction of estrogen-containing drugs with cardiovascular drugs.
4. In the benefit-risk ratio in patients taking sex hormones for the treatment of menopausal disorders, the benefit outweighs the risk.
5. HRT is the gold standard for treatment of patients with hormonal imbalance and improves the quality of life of this group of women. To prevent the occurrence and progression of atherosclerotic changes in blood vessels, HRT using estrogen-containing

drugs is indicated. Early use of HRT prevents the risk of such serious pathologies as coronary artery disease.

6. A single determination of the levels of steroid hormones and proinflammatory cytokines in blood serum is informative only for a specific postmenopausal cycle or a given period of time.

The secretion of estrogen and progesterone by the ovaries in postmenopause practically stops. Despite this, estradiol and estrone are detected in the blood serum of all women. They are formed in peripheral tissues from androgens secreted by the adrenal glands. Most estrogens are formed from androstenedione, secreted mainly by the adrenal glands and to a lesser extent by the ovaries. This occurs predominantly in muscle and fat tissues. In this regard, with obesity, the levels of estrogen in the blood serum increase, which in the absence of progesterone increases the risk of hyperplastic processes and uterine cancer. Thin women have lower serum estrogen levels and therefore have an increased risk of osteoporosis. Clinical manifestations of menopausal syndrome are observed in obese women even with high estrogen levels.

An imbalance of sex hormones could cause direct damage to the myocardium and IHD. Thus, it has been established that the purpose of "Cimicifuga" activates the production of estrogen and pro-inflammatory interleukins. In our case, the prognosis for patients is usually favorable and a decrease in the quality of life comes to the fore, which forces them to see a doctor again and again, leading to significant economic costs and psychological discomfort. Therefore, the study of a woman's quality of life in this period becomes particularly relevant.

The results of the studies made it possible to personalize menopausal hormonal therapy taking into account risk factors for the development of severe forms of coronary artery disease:

- The effectiveness of the dosage form of the drug "Cimicifuga" has been substantiated;
- The minimum effective dosage of the estrogen-containing drug "Tsimitsifuga" has been selected;
- Combination pharmacotherapy for ischemic heart disease in the postmenopausal period has been optimized, taking into account the interaction of the estrogen-containing drug "Cosimifuga" with traditional cardiovascular drugs;

The choice of therapy must be selected taking into account the age, stage of reproductive aging and quality of life of the patients.

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