

Menopausal metabolic syndrome.

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Abstract: The study of aspects of menopausal metabolic syndrome is not finalized yet. Therefore, the optimization of diagnostic methods is the priority task of medicine. For the purpose of studying women's changes in metabolic indicators with arterial hypertension depending on the climacteric period and possibilities of their correction also determination of thickness of epicardial fat and detection the character of its associativity to the metabolic parameters associated with cardiovascular risk, and to the indicators of cardioremodelling 134 women in a climacteric period, at the age of $52,6 \pm 6,2$ years, with duration peri- and postmenopauses of 6,7 years were investigated. Research showed effects of antihypertension therapy with Moxonidin and Klimadinon to metabolic indicators don't depend on a menopause phase, and their application is interfaced to a reliable tendency to decrease in level of atherogene lipids of serum of blood, and also leads to improvement of vessel motive function of endothelium.

Violations of endothelium function are interfaced to deeper violations of women's lipid exchange especially in postmenopause, in this respect we consider, that application of medicines for this category of patients shouldn't be limited within 3 month course.

Keywords: Hypertension, women, Premenopausal and Postmenopausal, anti-hypotension treatment, cardiovascular risks.

Introduction. Cardiovascular disease (CVD) remains the leading cause of death for both men and women in developed countries. However, in the last decades of the last century showed a persistent tendency to reduce the incidence of CVD in men, then women, on the contrary, showed an increase in morbidity and mortality from ischemic heart disease and complications of arterial hypertension (AH).

Another 10 years ago in the journal TIME (2003, August 11, P. 45-51) published the following information: "The killer of women number 1. There is no breast cancer! The Killer of Women No. 1 is a disease of the cardiovascular system, but American researchers have shown that only one in four women understands that it is more dangerous than cancer. In 50% of cases, a woman may die from the first heart attack (in men this figure reaches 30%), and of those who survived the first attack, 38% die within the first year after a heart attack (up to 25% of men) and 46% women become disabled in heart failure due to myocardial infarction (in men this figure is 22%). The reason for this "unfair" situation in the last 30-40 years is probably that the

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CVD is considered "male diseases" and many clinical studies include mostly men, and the results on men cannot be automatically transferred to women. From this point of view, more serious epidemiological situation in terms of cardiovascular morbidity and mortality in men has led to an underestimation of the importance of this problem in women. In turn, underestimation of the whole set of cardiovascular pathology often leads to an erroneous treatment of its particular manifestation (for example, AH as an independent disease), whereas for women in menopause only a multifactorial approach to diagnosis, and further to treatment and prevention can enable full and most effective impact on basic health indicators. There is a tendency that women are less likely to undergo an in-depth examination until the established CVD is established, and they are less likely to recommend measures for secondary prevention of these disorders. Such a passive attitude towards women's health must be urgently changed.

Although CVD risk factors are similar in men and women, the significance and negative contribution of each of them to the development of these disorders have certain gender differences. It is known that along with common risk factors, women have a unique risk factor for cardiovascular diseases (CVD) - the development of estrogen deficiency in postmenopausal, which in turn disrupts normal homeostasis, fatty, carbohydrate metabolism, hemodynamic disorders and other changes that trigger a continuous cascade of cardio-metabolic syndrome.

Estrogen deficiency contributes to the development of endothelial dysfunction (DED) (Angere P 2004), increased vasoconstriction, which leads to dysregulation of the vascular tone, changes in sensitivity of peripheral tissues to insulin and the development of insulin resistance, followed by the stabilization of arterial hypertension (AH) and metabolic syndrome (MS) (OR Grigoryan 2003). Emerged against the background of hyperandrogenemia - (increasing the content of androgens in the blood) violations of water-mineral metabolism lead to a change in homeostasis and contributes to the increase in body weight due to an increase in fat depots and proliferation of adipocytes. An increase for fat is common and the development of abdominal obesity (AO) in menopause is associated with both physiological changes and lifestyle changes (Grigoryan OR, Antsiferov MB 2000). At the same time, such patients develop dyslipidemia (DL) - the triglycerides (TG) content increases, but cholesterol in high-density lipoproteins (HDL cholesterol) decreases, which along with the available END leads to atherogenesis (IE Chazova, Mychka VB 2004 .).

With obesity, the deposition of adipose tissue occurs not only subcutaneously, but also around various organs, including an epicardial fat depot. Epicardial fat (EH), is hormonally active, producing biologically active substances taking part in atherogenesis. The fatty tissue of visceral localization is not just a passive energy store, but an active endocrine organ that can synthesize and secrete biologically active substances (tumor necrosis factor-, inhibitor of plasminogen activator-1,

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interleukin-6, leptin, etc.) the formation of clinically-metabolic and cardiovascular complications associated with visceral obesity [6-8]. In conditions of excessive fat deposition, with increased myocardial energy demands, epicardial fatty tissue has a significantly higher expression of adipocytokines, as well as free fatty acids.

Determination of the thickness of the ECG and identification of the nature of its conjugation with metabolic parameters associated with cardiovascular risk, and indicators of cardio remodeling in patients with excessive MT and obesity.

At the present stage, the most accurate methods of diagnosis, reflecting the number and degree of development of abdominal adipose tissue, including ectopic, are computer and nuclear magnetic resonance imaging (NMRT) [13]. In this study, the prototype was taken by A.M.Cali and S.Caprio (Ectopic fat deposition and the metabolic syndrome in obese, *Horm. Res*, Jan. 2009; 71 Suppl 1: 2-7), according to which the volume of ectopic fat detected at of magnetic resonance imaging is directly related to the amount of visceral fat, back to the amount of subcutaneous fat, and linearly correlates with insulin resistance (IR) and the risk of developing metabolic syndrome (MS). However, it should be noted that the method of diagnosing visceral fat deposition with MRI is rather expensive, time-consuming, has limited accessibility in clinical practice, it is characterized by a long time exposure and other aggravating factors. The above facts create the prerequisites for the search for new, more accessible methods for estimating the topographic quantitative content of adipose tissue in the body, primarily viscera-abdominal.

Based on the foregoing, it can be assumed that the detection of epicardial fat deposits and the determination of their thickness during echocardiography may be the most objective method of additional diagnostics of the visceral phenomenon allowing at the donor logic stage to predict the risk of the formation and progression of vascular and metabolic complications associated with the development of early cardiovascular disasters.

The purpose: to study the character of changes in metabolic parameters in women with arterial hypertension depending on the climacteric period and the possibility of their correction, as well as the determination of the thickness of the ECG and the identification of the nature of its conjugation with the metabolic parameters associated with cardiovascular risk.

Materials and methods: 134 women in menopause, aged 52.6 ± 6.2 years, with a duration of per- and postmenopausal of 6.7 years were examined. Of the surveyed women in 101 (75.4%) at the age of 52.6 ± 1.6 years, including 45 (44.6%) in premenopausal women (PreMP) and 56 (55.4%) in postmenopausal women (PostMMP), an increase in the level of blood pressure, corresponding to the values of AH I and II degrees and related to the group of low and medium risk (according to WHO / MOAG 2010) - these patients formed the main group of dynamic observation. 33 (24.6%) women aged 49.2 ± 5.3 years were included in the control

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group, including those for the periods of MP: in PrePM - 18 (age 45.1 ± 3.2 years), in PostMP - 15 (age $54,2 \pm 3,3$ years), without subjective complaints and without manifestations of AH.

The health status of the study population was assessed taking into account anamnesis, clinical examination data, anthropometric parameters, registration and evaluation of ECG, total and intracardiac hemodynamics, lipid and carbohydrate profile, gonadotropic and sex hormone levels in blood serum, and quality of life. A complex ultrasound examination of vessels was performed to determine the state of endothelial function on a high-resolution ultrasound scanner Volusion 530 DMT (Kretz-Technik, Austria). The endothelial function (EnF) was evaluated by the method of Celermajer et al., (1992) [5, 9], using a multi-frequency linear format sensor with a frequency of 5-10 MHz - a test with reactive hyperemia (cuff test).

Epicardial fat was assessed by echocardiography, the amount of adipose tissue behind the right ventricle was determined in the area of the atrioventricular sulcus in the two-dimensional regime. The ECG was visualized as an echo-free space, measured on the free wall of the prostate, as this area, according to clinical observation, has the maximum absolute thickness of adipose tissue (Figure 1).

The following degrees of endothelial dysfunction were determined from the values of EDVD: normal function of the endothelium of the EDVD > 10%, pathological - <10%, vasoconstriction and paradoxical vasoconstriction (<0) [5, 9].

All patients of the main group, depending on the presence of impaired endothelial function, were divided into the following groups:

- I - women in menopause with normal EnF (n = 54, 53.5%);
- II - women in menopause with impaired ENP-END, with EEVD less than 10% (n = 47; 46.5%).

All patients of the main group were assigned Climadinone ("Bionorica AG", Germany) 20 mg - 1 tablet twice a day, with a strictly time interval (12 hours), women with violations of the function of the gastrointestinal tract were recommended a syrup of 30 drops 2 times a day. Patients with EnD (group II), on the background of Climadinone as an antihypertensive drug, were administered Physiotenses ("Solvay Pharma", Germany), at a dose of 0.2 mg (1 tablet in the morning), after 1 week, if necessary, the dose was increased up to 0.4 mg. All studies were conducted in dynamics, the parameters were recorded at 3 observation points: initially, 1 month and 3 months after treatment. In the control group, the mean ELVD values corresponded to normal values ($22.6 \pm 5.3\%$).

Statistical processing of the results of the study was carried out with the help of the "Statistic 6 for WINDOWS" and "Excel 2000" application software using Student's t-test.

Results and its discussion:

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The complex of menopausal metabolic disorders included - dyslipidemia (DL), which was characterized by hypercholesterolemia (HCS), hypertriglyceridemia (HTG), decreased HDL; AO with a body mass index ≥ 26 kg / m², with a ratio of waist circumference to the hip circumference > 0.9 .

In the initial study period, the determination of parameters of carbohydrate metabolism in patients in PREM was 4.9 ± 1.5 mmol / L and 7.1 ± 1.7 mmol / L postprandial, which exceeded the values in the control group by 10.2% and 11 , 3%, respectively.

In the PostMM group, the mean values were at the subnormal level and were 5.3 ± 1.5 mmol / L fasting and 8.3 ± 1.3 mmol / L postprandial, which exceeded the control group by 16.9% and 24.1% respectively, i.e. high-normal values of the parameters of carbohydrate metabolism in women in PostMP are marked in comparison with the pre-PMP.

The results of studying the lipid profile showed a tendency to a decrease in the level of HDL cholesterol, an increase in the serum atherogenic coefficient in the whole group.

A comparative analysis of lipid metabolism indices showed that the indices of atherogenic fractions in the PostMMP group were statistically insignificantly higher than those in the PremMP group, while no such trend was observed for the values of antiatherogenic fractions.

Thus, in the PostMMP group, the mean OX values exceeded the comparison group by 8.2%, the LDL-by 7.4%, while the VLDL indicator showed a decrease trend of 5.6%. It is typical that the similar parameters of the control group were 37.7%, 24.1%, 13.5%, respectively, were lower than in the PostMAP group and 31.7%, 18.5% and 18.2%, respectively, than in the group PrePM.

The values of HDL in the PostMP group were higher by 37.5% compared to the control group, and by 18.8% in the comparison group (PremMP).

The CA in the PostMMP group exceeded the control group by 27%, and in the PreMP group by 18.2%.

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Thus, the initial phases of MP are characterized by an increase in all fractions of the lipid spectrum, including its anti-atherogenic components, while with the development of PostMP, further increase in atherogenic fractions is associated with a certain "acceleration" in the rates of increase in anti-atherogenic fractions (possibly of compensatory nature) , however, do not allow to exert sufficient influence on the atherogenic aggressiveness of blood serum, as measured by the CA.

Changes in metabolic rate (carbohydrate and lipid profile), despite initial values not exceeding the upper limits of the norm, against the background of therapy had a significant improvement trend in all analyzed parameters relative to the control period of the study, however, statistical differences with the control group were noted only in terms of OXC , VLDL and TG as in the group PremMP.

In the group of premalignment in patients without end-treatment with climadinone therapy, the fasting blood sugar level was 10.4% lower than baseline, while the decrease in postprandial glucose level was 12.7%.

There is a reliable dynamics of lipid metabolism indicators: thus, there is a decrease in the level of atherogenic fractions - OX, LDL, VLDL and calculated on their basis SC by 15.8%; 19.2%; 33.3% and 29%, respectively (p <0.001), a significant increase in the anti-atherogenic fraction of HDL is also detected by 33.3% (p <0.001).

In the PostMMP group, with initially high-normal fasting glucose values, these indicators decreased by 13.5%, and postprandial glycaemia decreased by 18.3% (p

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<0.001). There is a significant dynamics of lipid metabolism - a decrease in the level of OX by 18.2%; LDL cholesterol by 22.2%, VLDLP by 36.4%, accompanied by a 22.2% increase in HDL and a decrease in the degree of atherogenicity of the serum assessed by CA, by 35.1% (all $p < 0.001$). There was a significant increase in the ED of the brachial artery in group II in women in PostMMP from 7.6 ± 1.5 to 10.3 ± 1.5 ($p = 0.001$), i.e. in 1.4 times (Table No. 2) and the tendency to increase in the PremVE EECD from $10.7 \pm 1.4\%$ to $13.2 \pm 2.8\%$ ($p = 0.08$). After treatment, endothelial dysfunction was preserved only in 7 (8.14%) in 2 in PremMP and 5 in PostMP. The effect of CI in the course of therapy on the parameters of vasomotor function is statistically significant in the patients in the PreMP in terms of the main indices: Dmax, EDVD, V0, Vmax (the diameter of the brachial artery after decompression by 4.7%, improvement of the vasomotor function, 38,6%, with increased linear velocity of blood flow V0 and Vmax of the brachial artery in response to reactive hyperemia by 5.6% and 8.2%, respectively). However, the growth parameters of V%, TKIMosa and D0 are preserved without dynamic changes. In patients with PostMP, where the initial EnF values were slightly decreased, the use of the drug allowed to achieve statistically significant changes only with respect to the increase in the rates of V0, V%, which were 0.6% and 65.4%, respectively, whereas the dynamics of the ELVD and diastolic diameter of the brachial artery before and after decompression of the cuff is unreliable.

In all the examined women, epicardial fat deposits with a thickness of 8.28 ± 1.1 (3.9 ± 0.5) mm were detected in the ECHO-CG in the anterior wall of the right ventricle. Regardless of the degree of obesity in the main group, direct, reliable correlations of the mean force between the thickness of the epicardial and BMI fat layers ($r = 0.65$, $p = 0.001$), the percentage of excess body weight ($r = 0.64$, $p = 0.001$) and high - with an index of RT / OB ($r = 0.78$, $p = 0.001$). The correlations obtained may indicate the conjugate thickness of the epicardial fat layer, not only with the severity of obesity, but also with the visceral nature of the fat deposition.

Based on the results obtained, it can be assumed that in conditions of excessive fat deposition, the thickness of the epicardial fat layer is directly associated not only with the severity of obesity (BMI, kg / m²) and its visceralization (OT value), but also with carbohydrate metabolism (level of blood glucose) and the main atherogenic fractions of the lipid spectrum of the blood (TG and LDL cholesterol), which, according to modern concepts, can directly affect the heart muscle, leading to its remodeling and violation of contractility.

In addition, direct correlation relationships between the thickness of epicardial fat with the left ventricular mass index (LVMI) and the ECHO-CG parameters reflecting the processes of cardiovascular remodeling were established in the patients examined (regardless of the type of fat release): the final systolic size of the left ventricle (LV) ($r = 0.55$, $p = 0.001$); the final diastolic LV size ($r = 0.57$, $p = 0.001$);

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end systolic LV volume ($r = 0.62$, $p = 0.001$); end diastolic LV volume ($r = 0.48$, $p = 0.001$) and right ventricle diameter ($r = 0.42$, $p = 0.003$).

The tendency to normalize the lipid spectrum of the blood was revealed after 3 months of therapy in the Climadinone + Physiotens group on the background of treatment, which manifested itself in a decrease in the level of total cholesterol, LDL and in the increase in HDL, whereas in the comparison group the lipid profile did not change significantly.

The level of total cholesterol, initially significantly elevated, decreased by 7.05% (from the baseline data) in patients in the PremMP, to 3.3 ± 0.29 ($p = 0.07$). The decrease by 3 months of treatment was more pronounced in women in PostMMP, with initially higher rates of total cholesterol. The dynamics of the total cholesterol index in this group was 14.04%.

Within 3 months, there were small (statistically unreliable) fluctuations in the level of TG ($p > 0.05$).

Decrease in "atherogenic" LDL on the background of Climadinone + Physiotens therapy in patients with END in the Premix for 5.5% (3.91 ± 0.21) and 2.37% (4.52 ± 0.22) in patients with EnD in PostMP.

One of the most significant indicators in the analysis of the lipid spectrum of blood against the background of the therapy is the level of HDL, as it is known that this fraction has "antiatherogenic" activity, increasing with the intake of estrogens. In our study, the treatment of Climadinon + Physiotens caused an increase in HDL by 5.5% (1.09 ± 0.03) and 13.54% (1.18 ± 0.03).

For the final evaluation of blood atherogenicity, great importance is attached not so much to the absolute values of LDL and HDL, as to their ratio, i.e. SC. This indicator allows you to judge the risk of developing atherosclerosis. The statistically significant decrease in this ratio was 15.2% in premenopausal and 28.4% in postmenopausal, which is a favorable prognostic sign. The positive dynamics of SC in patients in premenopausal (4.5%) is probably due to the timeliness of the treatment, whereas in postmenopausal women, the SC was almost unchanged (0.2%).

The analysis of endothelial function indices showed that a significant tendency towards improvement was noted against the background of complex therapy: changes in Dmax, EDVD, V0, Vmax (6.8%, 41.5%, 5.8%, 6.8 % respectively); and in PostMMP - Dmax, EDVD and V0 (0, 41.5%, 3.4%).

Complex therapy was accompanied by an improvement in the functional state of the vascular endothelium. After treatment, group II showed a significant ($p < 0.04$) increase in the percentage increase in the diameter of the brachial artery in a sample with reactive hyperemia (from 10.6 to 17.2% $p = 0.0001$) in women in PostMP, unreliable data are recorded (from 10.7 ± 2.4 to 15.1 ± 3.5 $p = 0.07$).

Thus, the direct conjugation of the thickness of epicardial fat obtained in the main group with clinical and metabolic disorders associated with visceral obesity, as

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well as with parameters of echocardiography, reflecting the processes of cardio remodeling and forming hypertrophy of the myocardium of the LV, may indicate that in women on the background of MMC the presence of fatty deposits in the epicardium, visualized by standard ECHO-CG, regardless of the severity of obesity, may be an additional objective diagnostic and a thickness of epicardial fat of more than 6 mm is a prognostic marker of a high risk of developing early cardiovascular complications.

Taking into account the bias and inadequate informative value of the determination of RT, OB / OB index (as a method of visceral fat removal) reflecting mainly the degree and amount of subcutaneous fat, the echocardiography of fat deposits in the epicardium along the anterior wall of the right ventricle is suggested as the simplest, with the ability in dynamics to estimate the amount of visceral fat, and an economically advantageous method for diagnosing pathological visceral fat release, allows conductive when epicardial fat thickness exceeding 6 mm to predict a high risk of early cardiovascular disease.

In addition, it can be noted that the effects of antihypertensive therapy with moxonidine and climadinone on metabolic parameters do not depend on the phase of menopause, and their use is associated with a reliable tendency to reduce the level of atherogenic lipids in blood serum, and also leads to an improvement in the vasomotor function of the endothelium.

The complex 12-week therapy of Climadinone and Physiotense allows to improve the indices of endothelial function, thereby providing anti-remodeling effect on the heart and blood vessels. Infringements of EnF are associated with deeper lipid metabolism disorders especially in women in PostMP, therefore we believe that the use of drugs in this category of patients should not be limited to a 3-month course.

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