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REVIEW ARTICLE

Hormonal-metabolic trajectory of menopausal transition in a normoglycemic cohort of women with different blood pressure levels

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ABSTRACT

Introduction. The gradual clustering of cardio-metabolic factors in women depending on age and decline of ovarian function justifies attention to the phenotype of the formation of the metabolic syndrome during the menopausal transition depending on the presence of hypertension without dysglycemia.

Aim. To evaluate the association of indicators of the functional state of the pituitary-ovarian axis with markers of metabolic syndrome (MetS) and parameters of insulin resistance (IR) in a cohort of normoglycemic women aged 35-59 years with different levels of blood pressure.

Patients and methods. In a cohort of women 35–59 years old without dysglycemia (n = 88), 58 women had hypertension, 30 were normotensive. It was determined: body mass index (BMI), waist circumference (WC), levels of blood pressure, triglycerides (TG), HDL-C, insulin, follicle-stimulating hormone (FSH) and estradiol, fasting glucose (FG); TyG and HOMA2-IR indices. Using SPSS (version 17) assessed the median (25; 75%); intergroup differences using the Mann-Whitney test; correlation analyzes: Spearman (R) and partial correlation (R_{pc}) to level out the influence of age.

Results. In the general cohort of women, the influence of postmenopausal duration, FSH and estradiol levels on MetS and TyG parameters depended on age, except for the correlation of postmenopausal duration with FG (R_{pc} = 0.313; p = 0.004). The range of associations of MetS markers with each other and TyG in the group of patients with hypertension is similar to those in the general cohort of women. In both cohorts, the interrelations between FG, WC, insulin and TyG remained relevant with partial correlation. The Index TyG, associated with HOMA2-IR (R=0.600; p<0.001; R_{pc}=0.426; p<0.001), had a greater range of connections with MetS components, as well as with FSH (R=0.312; p=0.017; R_{pc} =0.286; p=0.030) and estradiol (R= -0.393; p=0.002; R_{pc} = -0.376; p=0.004) in the presence of hypertension.

Conclusion. The influence of indicators of the functional state of the pituitary-ovarian axis on MetS and TyG markers was revealed, along with a spectrum of associations of parameters and factors in the formation of menopausal MetS with IR indices, especially TyG. Correlation relations between FG with postmenopausal duration and MetS components, as well as estradiol in case of hypertension, reflect a high risk of progression to dysglycemia.

Keywords: metabolic syndrome, menopausal transition, hypertension, insulin resistance, TyG index, HOMA2 family indices, fasting glycemia, follicle-stimulating hormone, estradiol.

Introduction

There is no doubt that postmenopause is associated with an increase in the prevalence of metabolic syndrome (MetS).[1-3] The incidence of MetS has been shown to gradually increase from 6 years before to 6 years after last spontaneous menstruation, independent of age and other known cardiovascular disease (CVD) risk factors.[4]

Metabolic syndrome is a cluster of the main risk factors for CVD and type 2 diabetes: proatherogenic dyslipidemia, hypertension, dysglycemia and abdominal obesity (AO). When each factor acts independently, together they synergistically double the risk of developing CVD, causing a 1.5-fold increase in all-cause mortality.[5] One of the main links in pathogenesis that accelerates this pathway is insulin resistance (IR), with gender and ethnic characteristics[6], defining different trajectories of cardiometabolic risk (CMR) in men and women.[7] The reasons for the differences in all key components of MetS and vascular remodeling may be related to the influence of peripheral sex hormones and pituitary gonadotropins.[7-12]

The presence of a unique additional risk factor for women, menopause, defines the MetS menopausal phenotype; the trajectory of its formation is closely related to changes in the functional state of the pituitary-ovarian axis. This area of scientific research has been actively developing in recent years, not limiting itself to stating only postmenopausal changes. The statement on behalf of the American Heart Association is the first to include menopausal transition (MT) as a sex-specific event influencing future cardiometabolic health.[13] It is during the MT period that dramatic endocrine and metabolic changes occur in a woman's life, the pathophysiological basis of which is largely unclear. Premenopause can occur 5-10 years before menopause, the physiological age range of which is defined as 45-55 years.[2] The average time to menopause is 51 years, with significant individual differences ranging from 40 to 60 years.[14] That is, in a population, MT can cover a large age range.

Metabolic syndrome cluster, which includes a combination of three or more components, suggests the presence of different phenotypes. One of the first variants of MS described the hypertriglyceridemic waist phenotype: increased waist circumference (WC) in combination with a triglyceride (TG) level >1.77 mmol/l, regarded as an integrative mirror of the cluster symptoms.[15] In this case, the main component of the cluster is considered to be hypertension[16]; it is closely pathophysiologically linked to MetS through insulin resistance and obesity and serves as a leading factor in CMR.[17] An updated version of the hypothesis is presented that IR and compensatory hyperinsulinemia are the primary mediators of elevated blood pressure (BP) in MetS and obesity.[18]

Hypertension at all stages of women's lives is characterized by specific characteristics of risk factors associated with menopause and its hormonal levels.[19] Sex differences in blood pressure trajectories begin early and persist with age, setting the stage for CVD.[20] A consensus document from European cardiologists, gynecologists and endocrinologists noted that decreases in estrogen levels after menopause are associated with changes in vascular function, regulation of the renin-angiotensin-aldosterone system (RAAS) and

sympathetic nervous system (SNS), decreased nitric oxide-dependent vasodilation and increased inflammation.[14] In this case, chronic inflammation and oxidative stress increase IR.

The interrelation between hypertension and dysglycemia during MT is of particular interest. The prevalence of diabetes in postmenopausal women increases significantly compared to premenopausal women and is most strongly associated with blood pressure levels.[21] At the same time, the influence of hypertension depending on age on the occurrence and severity of MetS and other CVD risk factors in menopausal transition has been little studied.[22] The role of follicle-stimulating hormone (FSH), estradiol (E2) levels, and postmenopausal duration (PMD) in the development of MetS parameters in relation to insulin resistance remains controversial.[23]

The overall CMR of hypertension and diabetes is multiplicative[24], justifying the need to identify specific MetS variants with an emphasis on IR parameters[25] in the initial absence of dysglycemia. Research in this direction concerns the assessment of CMR in general depending on menopausal status[13,26-28], the relationship of MT characteristics with early markers of atherosclerosis[29-31], and the consequences of menopausal hormone therapy.[26,32] Only a few studies analyze the association of characteristics of the functional state of the pituitary-ovarian axis with the risk of developing CVD or MetS in postmenopause, and less often in perimenopause.[23,33] Studies of the relationship between FSH and estradiol levels and MetS components are fragmentary, have different designs and were conducted on different ethnic populations.[11,33]

We are not aware of any work assessing the relationship between MT parameters in combination with MetS markers in a normoglycemic cohort of women with different blood pressure levels using surrogate IR markers. Recently, preference has been given to non-insulin indices; the triglyceride-glucose index TyG has been identified as an alternative biomarker of IR.[34] Reliable statistical data are presented on the relationship of TyG with the development and prognosis of cardiovascular disease[35], hypertension[36], MetS[37-38], diabetes.[39]

Aim

To evaluate the association of indicators of the functional state of the pituitary-ovarian axis with markers of metabolic syndrome and parameters of insulin resistance in a cohort of normoglycemic women aged 35-59 years with different levels of blood pressure.

Patients and methods

A single-center cross-sectional cohort study included 88 Caucasian women 35-59 years old without dysglycemia as part of a preventive examination: 30 of them were normotensive, 58 had hypertension. The age range was chosen taking into account the variability in the timing of MT in the population.[2,14] Exclusion criteria: dysglycemia and other endocrine diseases; previously diagnosed coronary heart disease, chronic heart failure; indications in the anamnesis of acute CVD; rhythm and conduction disturbances; menopausal hormone therapy; concomitant diseases in the acute stage.

In addition to the general cohort of women, to analyze the associations of MetS

components with MT parameters, women were divided into two groups. 30 conditionally healthy women without hypertension at the age of 43.00 (40.00; 46.25) years without hereditary burden of CVD and dysglycemia made up group 1. Group 2 included 58 women 50.00 (43.75; 53.00) years with a duration of hypertension of 3.21 (1.00; 5.00) with irregular antihypertensive therapy. The examined women had different functional states of the ovaries: 43% were postmenopausal, the postmenopausal duration (PMD) was 1.64 (0.00; 2.00) years; moreover, in group 1, menopause was recorded in 6 (20.0%) women, in group 2 - in 32 (55.2%).

It was determined body mass index (BMI), waist circumference (WC) and blood pressure (BP) levels: systolic (SBP) and diastolic (DBP). Fasting glucose (FG) values in blood plasma were assessed twice using the glucose oxidase method, and the average values were included in the analysis; HDL-C and triglycerides (TG) were determined by an enzymatic calorimetric method, insulin (INS), follicle-stimulating hormone (FSH) and estradiol (E2) by an enzyme-linked immunosorbent method on an IMMULITE 2000XPi analyzer. HOMA2-IR and HOMA2-%B indices were calculated for insulin using HOMA2-calculator; TyG index was calculated using the formula: TyG index = Ln [TG (mg/dl) x FG (mg/dl) / 2], where Ln is the logarithm, TG is fasting triglycerides, FG is fasting glucose.[40]

Statistical data processing was performed using SPSS programs (version 13). The normality of distribution was checked using the Kolmogorov-Smirnov test. Due to the non-normal distribution of continuous indicators, the data are presented as Me (25.75%), where Me is the median, 25 and 75 are the 1st and 3rd quartiles. The significance of intergroup differences in values was assessed using the Mann–Whitney (MW) U-test. To identify dependencies, correlation (Spearman's rank correlation, R) was used. To level out the influence of age, partial correlation (R_{pc}) was used. In statistical analysis procedures, the critical significance level for rejecting the null statistical hypothesis (p) was taken equal to 0.05.

The study was carried out in compliance with the ethical principles of scientific medical research involving human participants as set out in the Declaration of Helsinki of the World Medical Association.

Results

Descriptive characteristics of the analyzed cohort are shown in Table 1. Since hypertension served as a grouping sign, a comparative analysis of two groups of women within the survey cohort was carried out: with hypertension (group 1) and normotensive (group 2) (Table 1). Significant differences in most characteristics were revealed. Women in group 2 were older; in addition to blood pressure levels, they also had higher FG, INS, anthropometric, lipid, HOMA2-IR and TyG indices. The parameters of the HOMA2-%B index were comparable. Anthropometric and lipid characteristics were not completely within their reference limits in groups 1 and 2 when using the unified MetS criteria[41], using national criteria for assessing WC (>80 cm) and BP levels (≥140/90 mmHg).[42]

Table 1. Characteristics of clinical, metabolic and hormonal parameters in the study cohort and comparative analysis in groups of women depending on the presence of arterial hypertension, **Me** (25; 75%).

Parameter	General cohort women (Groups 1+2) (n=88)	Group 1 (normotensive) n = 30	Group 2 (hypertensive) n = 58	**p** 1-2
Age, years	47.00 (42.00; 52.00)	43,00 (40,00; 46,25)	50,00 (43,75; 53,00)	0,001
BMI, kg/m^2	27.6 (25.19;32.52)	25,30 (22,42; 27,39)	30,60 (26,33; 34,30)	<0,001
WC, cm	84.50 (76.00; 92.00)	76,50 (70,25; 83,25)	89,50 (79,00; 99,00)	<0,001
SBP, mm Hg	130.00 (120.00; 150.00)	120,00 (120,00; 130,00)	142,50 (130,00; 160,00)	<0,001
DBP, mm Hg	80.00 (80.00; 90.00)	80,00 (70,00; 80,00)	90,00 (80,00; 100,00)	<0,001
HDL-C, mmol/l	09.00 (1.00; 1.00)	1.00 (1.00; 1.03)	0,92 (0,84; 1,00)	<0,001
TG, mmol/l	1.38 (1.08; 2.12)	1.75 (1.49; 2.13)	2,30 (2,00; 2,500)	<0,001
FG, mmol/l	4.00 (3.50; 4.50)	3.60 (3.40; 4.33)	4,20 (3,60; 4,70)	0,011
INS, μU/ml	6.30 (4.35; 9.18)	5.30 (3.80; 7.00)	7.30 (5.15; 12.28)	0,013
TyG, AU	8.82 (8.54; 9.01)	8.58 (8.33; 8.80)	8,93 (8,66; 9,17)	<0,001
HOMA2-%B	140.85 (113.60; 176.70)	139.50 (110.50; 168.38)	143,90 (114,60; 191,40)	0.336
HOMA2-IR	0.77 (0.57; 1.52)	0.63 (0.45; 0.87)	0.96 (0,67; 1,64)	0,001
FSH, μU/l	11.40 (6.20; 71.10)	9.10 (5.40; 49.33)	32,75 (6.85; 74.58)	0,060
E2, pg/ml	83.80 (73.40; 348.75)	131.00 (73.40; 442.75)	73,40 (73,40; 269,25)	0.171

Note: p_{1-2} – significance of differences between groups 1 и 2.

Taking into account the age range of women included in the cohort, when analyzing the associations of MT characteristics with MetS parameters, their dependence on age was analyzed, subdivided into completely (leveled out with partial correlation) or partially age-dependent (remained with both types of correlation analysis). In groups 1+2, a strong relationship between age and PMD (R=0.707; p<0.001) and a less strong relationship with hypertension duration (R=0.468; p<0.001) was revealed. Age had a direct effect on FSH levels (R=0.542; p<0.001) and an inverse effect on estradiol (R= -0.336; p=0.001) with a stable association of hormones with each other (R= -0.578; p<0.001; R_{pc}= -0.286; p=0.009) in and with almost the same strength in the group of patients with hypertension (R= -0.550; p<0.001; R_{pc}= -0.361; p=0.006). Positive associations of PMD with FSH in group 1+2 were stable, weakening, but persisting with partial correlation (R=0.622; p<0.001; R_{pc}= 0.273; p=0.014); negative correlations between PMD and estradiol were completely age dependent (R= -0.508; p<0.001). Moreover, in group 1, age correlated only with PMD (R=0.427; *p*=0.019); no links between age and other studied parameters were found.

Associations of lipid parameters with parameters of the functional state of the pituitary-ovarian axis in group 1+2 were completely age-dependent: direct FSH with TG, as well as estradiol with HDL-C and reverse estradiol with TG and FSH with HDL-C (Table 2). The influence of PMD, FSH and estradiol levels on MetS parameters was also completely age dependent, with the exception of the association of PMD with FG, which remained significant with partial correlation (R_{pc} = 0.313; p = 0.004). The correlation between FSH and TyG in the overall cohort of women (R=0.211; p=0.049) disappeared with partial correlation. Glycemia levels had a spectrum of associations with metabolic syndrome markers: direct associations with WC, TG and SBP, but not DBP; inverse with HDL-C, which persist even when the influence of age is leveled (Table 3). The effect of estradiol levels on the indicators of insulin (R= -0.290; p=0.006) and FG (R= -0.220; p=0.040) in groups 1+2 was completely age dependent.

Table 2. Correlations of anthropometric and metabolic parameters with characteristics of the menopausal transition when analyzed by Spearman in the general cohort of examined women

Parameter	BMI	WC	TG	HDL-C	FG
PMD	R=0.383 p<0.001	R=0.361 p=0.001	R=0.314 p=0.003	R= -0.334 0=0.002	R=0.354 p<0.001
FSH	R=0.260 p=0.014	R=0.149 p=0.166	R=0.235 p=0.028	R= -0.251 p=0.018	R=0.133 p=0.220
E2	R= -0.348 p<0.001	R= -0.313 p=0.003	R= -0.240 p=0.024	R=0.219 p=0.040	R= -0.220 p=0.040

Table 3. Correlations of anthropometric, metabolic parameters and blood pressure levels according to Spearman analysis and partial correlation in the general cohort of examined women

Parameter	BMI	WC	TG	HDL-C	SBP	DBP
FG	R=0.286; p=0.008.	R=0.444 p<0.001	R=0.337 h=0.003	R= -0.397 p<0.001	R=0.286 p=0.007	R=0.171 p=0.114
	R_{pc} =0.216 p=0.053	R_{pc}=0.349 p=0.001	R_{pc} =0.297 p=0.007	R_{pc}= -0.279 p=0.012	R_{pc}=0.219 p=0.050	R_{pc}=0.219 p=0.050
WC	R=0.840 p<0.001	N/A	R=0.392 p<0.001	R= -0.305 p=0.004	R=0.425 p<0.001	R=0.418 p<0.001
	R_{pc}=0.826 p<0.001		R_{pc}=0.343 p=0.002	R_{pc}= -0.148 p=0.187	R_{pc}=0.315 p=0.004	R_{pc}=0.332 p=0.002
HDL-C	R= -0.332 p=0.002	R= -0.397 0<0.001	R= -0.564 p<0.001	N/A	R= -0.325 p=0.002	R= -0.240 p=0.024
	R_{pc}=0.220 p=0.048	R_{pc}=-0.148 p=0.187	R_{pc}= -0.477 p<0.001		R_{pc}= -0.158 p=0.159	R_{pc}= -0.121 p=0.281
TG	R=0.406 p<0.001	R=0.392 p<0.001	N/A	R= -0.564 p<0.001	R=0.302 p=0.004	R=0.282 p=0.007
	R_{pc}=0.371 p<0.001	R_{pc}=0.343 p=0.002		R_{pc}= -0.392 p<0.001	R_{pc}=0.299 p=0.006	R_{pc}=0.304 p=0.006
BMI	N/A	R=0.840 p<0.001	R=0.406 p<0.001	R=-0.332 p=0.001	R=0.289 p=0.006	R=0.333 p=0.002
		R_{pc}=0.826 p<0.001	R_{pc}=0.371 p<0.001	R_{pc}=-0.220 p=0.048	R_{pc}=0.155 p=0.167	R_{pc}=0.175 p=0.118

Note: R- Spearman's correlation coefficient; R_{pc} - partial correlation; N/A – not applicable.

There was no effect of age on INS indicators (R=0.190; *p*=0.075) with its association with FG levels in the general cohort of women (R=0.309; p=0.004) and almost the same in the subgroup with hypertension (R=0.331; p=0.012). In the general cohort of women, INS consistently positively correlated with FG, BMI, WC and TG (Fig. 1). While maintaining the stability of the connections of the INS with FG and WC in the group of patients with hypertension (Fig.2), its associations with BMI and TG were completely age dependent. Negative associations of insulin with HDL-C in the overall cohort (Fig. 1) and in group 2 (Fig.2) with partial correlation of the association disappeared. Associations of FSH and estradiol with MetS parameters are also shown in Fig. 2.

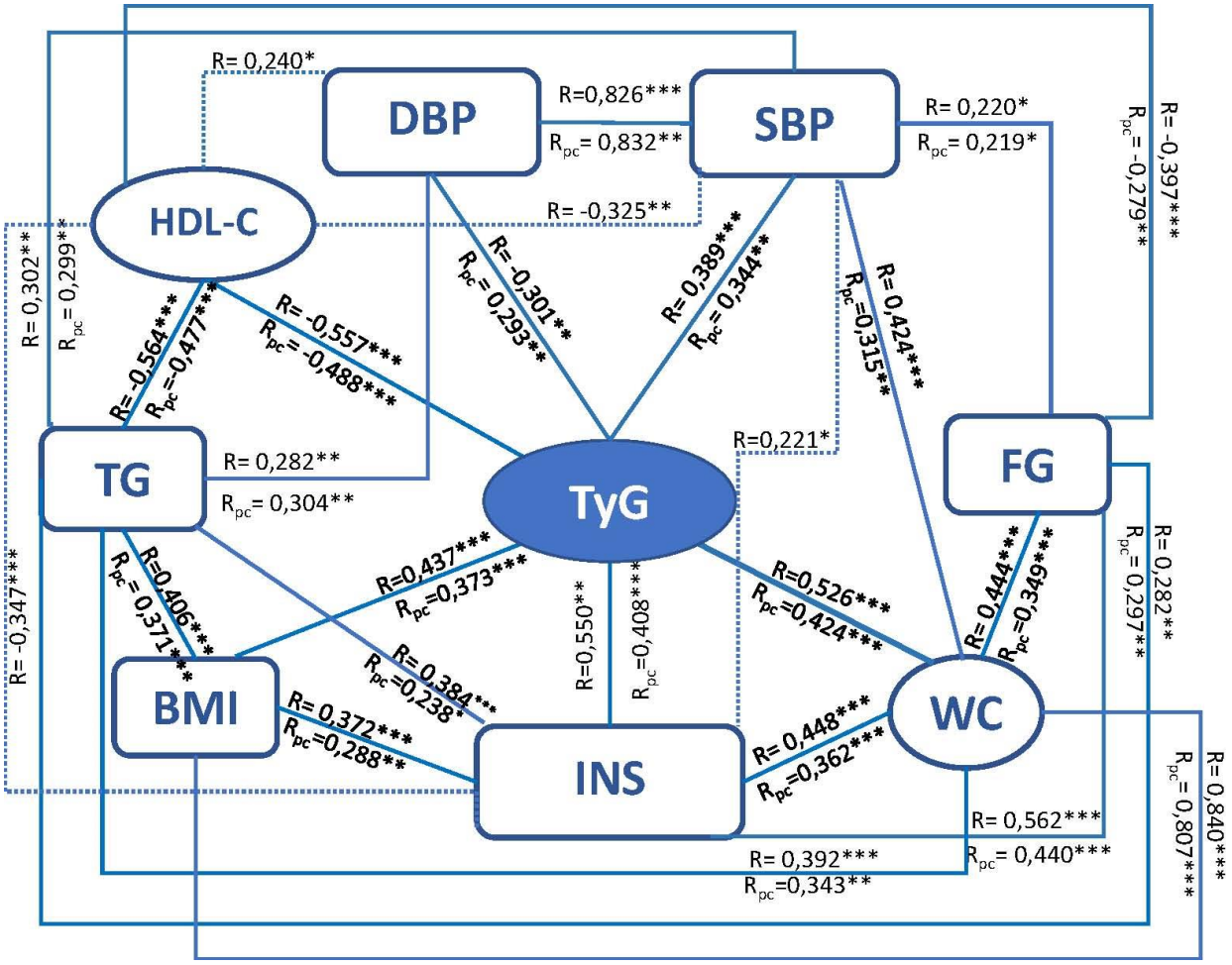

Fig. 1. Correlations between index TyG with markers and factors for the formation of menopausal metabolic syndrome in the general cohort of women without dysglycemia depending on age; R – Spearman's correlation coefficient (solid line); R_{pc} – partial correlation (dotted line); significant difference: * ≤ 0.05; ** ≤ 0.01; *** ≤ 0.001.

Indexes TyG and HOMA2-IR indices were closely positively correlated with each other (R=0.600; p<0.001; R_{pc}=0.426; p<0.001). The HOMA2-IR index, in comparison with TyG, has a smaller number of connections, somewhat lower strength and greater age dependence with anthropometric and lipid parameters. HOMA2-IR in the groups 1+2 correlated with age (R=0.257; p=0.019), postmenopausal duration (R=0.248; p=0.024) and estradiol (R= -0.255; p=0.020), as well as with BMI, TG and WC (Table 4). HOMA2-IR formed similar relationships in the group 2 with age (R=0.273; p=0.048), PMD (R=0.278; p=0.044), BMI (R=0.299; p=0.029), WC (R=0.446; p<0.001), TG levels (R=0.267; p=0.050) and E2 (R= -0.276; p=0.046). With partial correlation, HOMA2-IR retained associations in the overall cohort with WC and TG (Table 4); in group 2 only with WC (R=0.312; p=0.024). The HOMA2-IR index did not correlate with blood pressure and HDL-C levels.

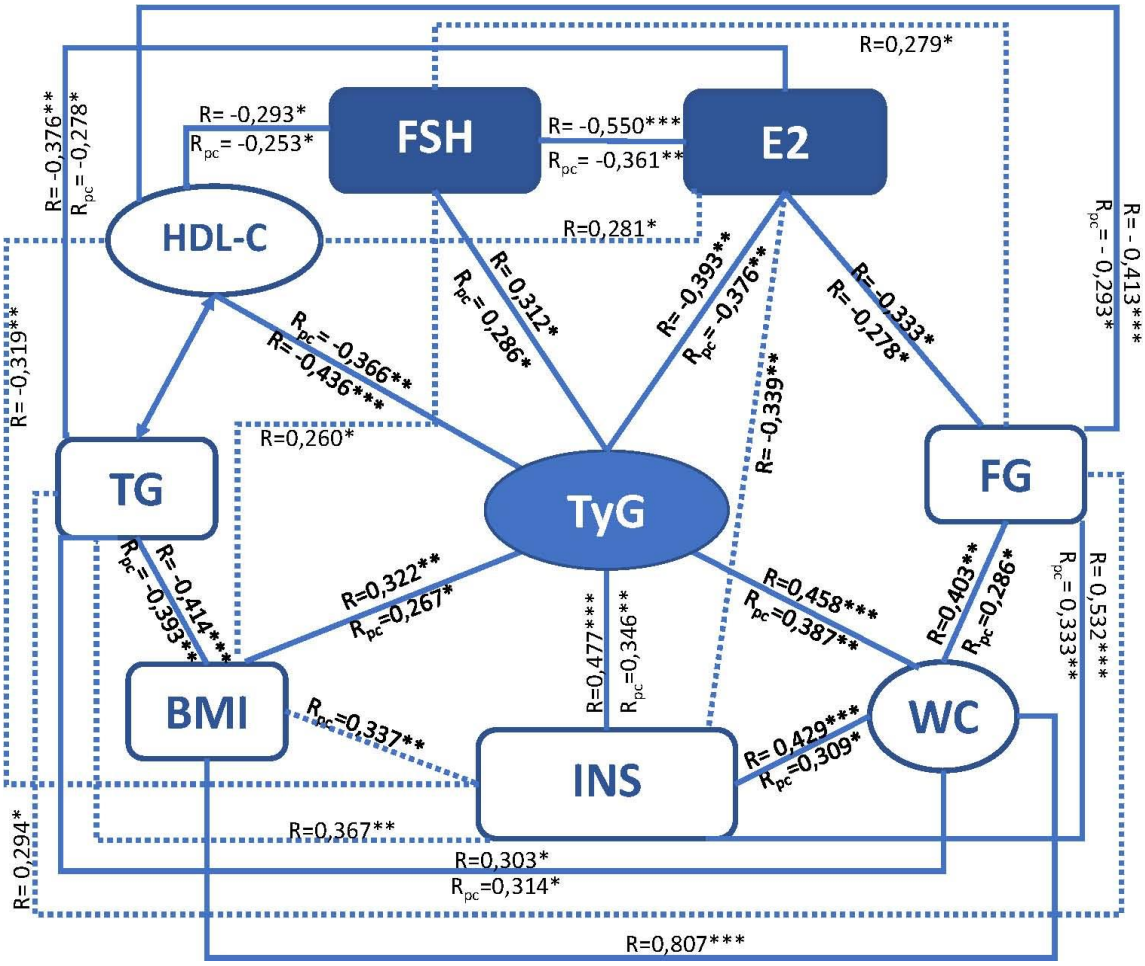

Fig. 2. Correlations between index TyG with markers and factors for the formation of menopausal metabolic syndrome in a cohort of women with arterial hypertension without dysglycemia depending on age; R – Spearman's correlation coefficient (solid line); R_{pc} – partial correlation (dotted line); significant difference: * ≤ 0.05; ** ≤ 0.01; *** ≤ 0.001.

Table 4. Correlations of anthropometric, lipid parameters and blood pressure levels with insulin, TyG and HOMA2-IR in the general cohort of examined women.

Analysis option	Spearman correlation (R)			Partial correlation (R_{pc})		
Parameter	INS	TyG	HOMA2-IR	INS	TyG	HOMA2-IR
BMI	R=0.372 p<0.001	R=0.437 p<0.001	R=0.393 p<0.001	R_{pc}=0.288 p=0.009	R_{pc} =0.373 p<0.001	R_{pc}=0.292 p=0.008
WC	R=0.448 p<0.001	R=0.526 p<0.001	R=0.507 p<0.001	R_{pc}=0.363 p<0.001	R_{pc}=0.424 p<0.001	R_{pc}=0.370
TG	R=0.384 p<0.001	R_{pc}=0.837 p<0.001	R=0.355 p<0.001	R_{pc}=0.238 p=0.001	R_{pc}=0.853 p<0.001	R_{pc}=0.249 p=0.001

Analysis option	Spearman correlation (R)			Partial correlation (R_{pc})		
HDL-C	R= -0.347 p<0.001	R=-0.567 p<0.001	R=-0.339 p=0.002	R_{pc}=-0.102 p=0.087	R_{pc}=-0.488 p<0.001	R_{pc}=-0.202 p=0.070
SBP	R=0.221 p=0.039	R=0.389 p<0.001	R=0.310 p=0.004	R_{pc}=0.054 p=0.635	R_{pc}=0.344 p=0.002	R_{pc}=0.059 p=0.597
DBP	R=0.192 p=0.074	R=0.301 p=0.004	R=0.269 p=0.014	R_{pc}=0.036 p=0.750	R_{pc}=0.293 p=0.008	R_{pc}=0.041 p=0.717

Index TyG was consistently, and only partially age dependent, associated with INS, HDL-C, BMI and WC indicators, as well as with SBP and DBP levels (Fig.1). In group 2, the TyG index, while maintaining the significant associations with anthropometric and lipid parameters, loses them with blood pressure levels, while simultaneously acquiring associations with FSH and E2 levels (Fig.2), stable with partial correlation. In group 2, TyG had significant associations with FSH (R=0.211; p=0.049), and E2 levels with TyG (R= -0.262; p=0.014) and HOMA2-IR (R= 0.255; p=0.020) only completely age dependent. TyG associations with age were also identified in the overall cohort of women (R=0.320; p=0.002) and in the group with hypertension (R=0.271; p=0.039).

The spectrum of associations of MetS markers between themselves and TyG in group 2 (Fig. 2) is generally similar to those in groups 1+2 (Fig.1), differing only in the strength of the connections and the degree of dependence on age. Indicators of the functional state of the pituitary-ovarian axis also correlated with a number of MetS markers only in group 2 (Fig. 2): estradiol is stable with FG and TG; age is dependent on insulin levels; FSH is stable with HDL-C and age depending on BMI.

Discussion

Menopausal transition is characterized by endocrine and metabolic changes affecting body weight, adipose tissue distribution, insulin secretion and sensitivity, determining an increased risk of CVD and diabetes.[13,26,43] Research in this direction is multidirectional. The gynecological approach focuses on the association of menopausal symptom severity with diabetes and CMR factors in middle-aged women, as well as the consequences of menopausal hormone therapy.[26,32] Differences in cardiovascular risk are considered depending on the type and age of menopause[28] and the loss of ovarian function from premenopause to postmenopause with a subsequent sharp increase in incidence[43]; on the relationship between the levels of FSH and estradiol during MT with subclinical indicators of atherosclerosis (intima-media thickness). These studies also assessed the associations of FSH and E2 with selected anthropometric and lipid parameters of MetS.[29-31] At the same time, the cause of the unfavorable anthropometric, metabolic and hemodynamic changes that constitute the essence of MetS is being debated: chronological aging or menopause?[44]

In the analyzed groups of women, depending on the presence of hypertension,

the levels of FSH and E2 were comparable, which can be explained by the large variability of hormones depending on the period of MT.[45] The age range of the examined cohort of women determined the conduct of a correlation analysis of markers and development factors of menopausal MetS in a generalized matrix (groups 1+2) with an assessment of the influence of age. Associations of FSH and E2 parameters with metabolic and anthropometric parameters in the general cohort of women were completely age dependent (Table 2), disappearing with partial correlation; correlations of almost all MetS markers with each other were only partially influenced by age (Table 3). The data obtained are consistent with the view that cardiometabolic changes can manifest themselves during the period of menopausal transition, cumulative with aging, increasing its impact on the risk of CVD.[46-47]

Attempts to analyze the associations of MetS parameters depending on FSH and estradiol showed conflicting results. A cross-sectional population-based retrospective study of a Chinese population that included patients with hypertension and diabetes on various glucose-lowering therapies revealed a direct relationship between high FSH levels and MetS biomarkers in perimenopause: WC, TG and blood pressure.[48] In contrast, in an analysis of data from eight randomized, double-blind, placebo-controlled studies of healthy menopausal Korean women, FSH levels, regardless of age, estradiol, and body weight, were inversely associated with CMR factors including BMI, WC, FG, and TG levels, while being positively associated with HDL-C. Researchers have suggested that low FSH levels may be a predictor of CVD in postmenopausal women.[23] The National Health and Nutrition Examination Survey found that elevated FSH levels were associated with a reduced risk of developing MetS: higher FSH levels were associated with lower WC, TG, BP, and FG in postmenopausal women only, but not in pre- and perimenopausal women.[33] A strong association of FSH levels with MetS severity has been reported in both peri- and post-menopausal women, but not in pre-menopausal women, with a suggested dependence on ethnicity.[11]

In addition to different designs, the cohorts of women differed quantitatively, in age, in different degrees of expression of MetS parameters with extremely dynamic levels of sex steroids during MT.[30] Due to the progressive decline in ovarian reserve, FSH concentrations increase and remain high after menopause. At the same time, the level of FSH increases sharply in the late fertile period even before the decrease in estrogen. Perimenopause, the intermediate stage between premenopause and postmenopause, until the final depletion of oocytes, can last up to 10 years. In peri- and postmenopause, low estradiol levels are associated with variable increases in FSH. Although gonadotropin levels are regulated by steroid hormones via a feedback mechanism[48], FSH levels may have an effect independent of estradiol.[30] Thus, in the AGES-Reykjavik Study of Older Adults, FSH levels in women did not correlate with estradiol[49], while correlating with age.

The variability of estradiol and FSH levels in MT is not clearly defined. Results from a longitudinal observational study of SWAN in a cohort of women 42–52 years of age show that trajectories of E2 and FSH levels fall into

several distinct unique clusters that are closely associated with BMI and race/ethnicity.[50] It is likely that reproductive factors (age at menarche, number of pregnancies, miscarriages, contraceptive use) are involved in predicting the influence of postmenopausal FSH levels on MetC parameters, regardless of estradiol, obesity and other causes.[51]

Among the menopausal transition parameters, PMD draws attention as an independent factor of influence on MetS parameters: its relationship with FSH was only partially age dependent, and with E2 levels it completely lost its significance with partial correlation. The effect of PMD on lipid parameters in the general cohort of women was completely age dependent, but somewhat stronger than that of FSH and E2. A longer postmenopausal period has been shown to be associated with an atherogenic lipid profile with low levels of HDL-C[52], including independent of baseline age, with a decrease in HDL-C observed immediately after the last menstrual cycle.[53]

These data correlate with the negative association we identified of HDL-C with FSH (Table 2), an increase in which marks the onset of MT. With full age dependence in the general cohort, this relationship in the subgroup of women with hypertension was stable even with partial correlation (Fig. 2). Also, HDL-C in the general cohort (Table 2) and in the group with hypertension (Fig. 2) was age-dependently positively correlated with estradiol, the levels of which decrease later in postmenopause and secondary to FSH. The negative effect of estradiol on TG (Table 2) was enhanced and was age independent in the presence of hypertension (Fig. 2). We believe that such a trajectory of changes in the lipid profile reflects the peculiarities of the formation of dyslipidemia during MT depending on hormonal factors.[54]

In the group of patients with hypertension, attention was paid to higher levels of FG with INS with comparable indicators of the HOMA2-%B index, along with a significant increase in IR indices: insulin HOMA2-IR and non-insulin index TyG (Table 1). Clarification of FG associations during the studied period of a woman's life is of particular interest, taking into account the high risk of diabetes in postmenopause[26,55], as well as the high frequency of hypertension in women at all stages of hormonal changes.[19]

Fasting glucose levels remained associated with PMD in Spearman analysis (Table 2) and partial correlation (R_{pc} =0.313; p=0.004). Taking into account also the correlation of FG with age, the results obtained are alarming regarding the prognosis of the state of carbohydrate metabolism, focusing attention on the age of menopause. Thus, this indicator significantly correlated with the age of diagnosis of diabetes. Each increase by 1 year in age at menopause was associated with a 3% reduction in the prevalence of diabetes (95% CI: 2-5). Age at menopause was significantly correlated with age at diabetes. Each 1-year increase in age at menopause might lead to a decrease of 0.39 years in age at diabetes.[56]

The role of hypertriglyceridemia in dysregulation of glucose metabolism and the prognosis of diabetes is recognized, and the specific mechanisms of the relationship are being clarified. It was assumed that it was indirect through an increased level of non-esterified fatty acids, but when trying to revise the concept of lipotoxicity, it was considered

more likely that hypertriglyceridemia had a direct effect on glucose homeostasis as an early and key sign.[57] Based on prospective studies, the tandem influence of an increase in TG levels and a decrease in HDL-C in the development of dysglycemia is emphasized.[58] This is consistent with the associations we identified between FG and TG, HDL-C in the general cohort of women (Fig. 1) and the subgroup of patients with hypertension (Fig. 2). The associations between TG and HDL-C were more independent of the influence of age. It was shown that in perimenopausal women with low levels of HDL cholesterol, the risk of diabetes was 2.2 times higher than in healthy women; when analyzing the temporal relationship of TG and HDL-C with IR, the authors found bidirectionality of these relationships.[59]

Blood pressure levels contribute to this glycemic trajectory, which is reflected in stable associations of FG and SBP (Fig. 1) in the overall cohort of women. In tandem with age-related factors associated with SBP with a tendency to increase FG as PMD progresses, BP indicators correlate with WC, which was positively correlated with FG. Our data are consistent with the view that menopausal status is an independent risk predictor for increased FG and BP levels.[60] However, the relationships between CMR parameters in perimenopausal women, as well as the influence of FSH and E2 levels on them, remain the subject of research and debate. It is emphasized that in perimenopause, an increase in blood pressure can be both a direct consequence of hormonal changes in the vascular system and metabolic changes with age; moreover, SBP is the most important risk factor for aging, contributing to greater vascular and myocardial stiffness in women than in men.[14]

The effect of age on insulin secretion and insulin resistance parameters is controversial. Previously, an analysis of the European IR Study Group database revealed an independent effect of age/aging on the decrease in basal insulin release in Caucasians of any gender aged 18–85 years without diabetes.[61] Subsequently, in nondiabetic individuals participating in a general health examination program, when assessing IR using the HOMA-IR index, sex differences in the effect of aging on insulin resistance were observed in a subgroup of postmenopausal women.[62] Recently, based on experimental studies in animal models of aging, reductions in insulin levels or insulin signaling have been shown to promote longevity.[63] Insulin resistance increases with age, but centenarians generally remain normoglycemic, have lower fasting insulin levels, and have higher insulin sensitivity. It has also been shown that HOMA-IR is nonlinearly correlated not with chronological age, but with biological age.[64]

In the absence of data in our study on the direct effect of age on the levels of insulin and HOMA2-%B (Table 1), there were direct stable connections between FG and INS both in groups 1+2 (Fig.1) and in group 2 (Fig.2). Insulin levels correlated significantly positively with BMI, TG, somewhat more closely with WC and negatively with HDL-C (Table 4). These associations were completely age dependent. The complex of stable associations of INS with WC, TG, BMI and TyG identified in partial correlation in patients with hypertension in the absence of a decrease in HOMA2-%B suggests an initial decrease in the reserve capacity of β-cells. The absence of TyG

associations with HOMA2-B, in the presence of those with INS, does not refute this hypothesis, since the absence of dysglycemia reflects preserved, albeit stressed, β-cell secretory function. These data bring us back to the parallel increase in INS levels and insulin resistance in adults without dysglycemia with age, which is associated with central obesity with a subsequent risk of developing T2DM, as well as hypertension and CVD.[63]

Insulin resistance index HOMA-IR has previously been widely used as a surrogate measure of IR. Taking into account the lack of standardization of insulin levels due to the pronounced variability of their reference values, as well as the diagnostic and prognostic role of dyslipidemia in the MetS cluster, the TyG index was proposed as a surrogate characteristic of IR. It is actively used in the study of various MetS phenotypes.[39,65] Index TyG is considered to be superior to HOMA-IR for predicting MetS[37] and may be useful for identifying IR in apparently healthy individuals.[66]

Menopausal transition is associated with an increase in fat mass predominantly in the abdominal region[67-68], increased IR, dyslipidemia and endothelial dysfunction.[25,46] When analyzing the associations of MetS parameters with the HOMA2-IR and TyG indices (Table 4), closer associations and greater stability with partial correlation were found in TyG. Note that the mathematical model HOMA2-IR, unlike HOMA-IR, reflects not only hepatic insulin resistance, but also its peripheral component.[69]

It was index TyG that turned out to be at the center of the relationships between the studied MetS markers and the factors influencing its development in the general cohort of women (Fig. 1). Index TyG, unlike HOMA2-IR, in addition to stable associations with WC, BMI, HDL-C, correlated with the levels of INS, SBP and DBP (Fig.1). We regarded the correlations between TyG with TG and FG levels as not applicable, taking into account the formula for calculating the index. In addition to TyG, OT was a definite center of attraction (Fig. 1), which has significant associations with FG, TG, INS, SBP, the closest with TyG. The levels of SBP and DBP also correlated with lipid parameters, but the main association, taking into account its strength and independence of age, was the connection of all of these indicators with the TyG index.

Cardiometabolic diseases are characterized by significant sexual dimorphism[70]; may manifest during MT, increasing the impact of aging on CVD risk.[46] Menopause is a potential risk factor for the development of IR regardless of age[25], probably due to a decrease in estrogen levels.[9] Estrogens play a primary and constant regulatory role in maintaining lipid-glucose homeostasis. Loss of estrogen leads to dyslipoproteinemia, increased TG and decreased HDL-C, increased IR, and accumulation of visceral fat, which is associated with other unfavorable metabolic changes.[27,68]

The negative association of TyG with estradiol and the positive association with FSH in the group of patients with hypertension were practically independent of age (Fig. 2). The presence of more pronounced MetS components, as well as greater PMD compared to normotensive women, attracted attention to this group. Estradiol levels in the presence of hypertension correlated consistently negatively with the levels of FG, TG, and also age

dependently negatively with INS and positively with HDL-C (Fig. 2). Estradiol protects β-cell functionality by preventing their apoptosis and adapting insulin secretion to IR.[71] Impaired insulin action and/or insulin secretion contribute to the onset and maintenance of conditions such as obesity, hyperglycemia, hyperlipidemia, and hypertension.[9] Estradiol and its receptors in the hypothalamus play a key role in the development of MetS during menopause.[72]

In the absence of a correlation between E2 and WC, as a marker of excess abdominal adipose tissue, the relationship between WC and TyG was significant and stable (Fig.2). In group 2, the TyG index forms a spectrum of associations with MetS markers, as well as stable, almost age-independent associations with FSH and E2 levels. At the same time, TyG loses its connection with blood pressure levels (Fig. 2) identified in the general cohort of women (Fig. 1), possibly due to some monotony of blood pressure levels in the group against the background of antihypertensive therapy. The nature of the relationship between hypertension and IR is complex.[73] Higher TyG is positively associated with the risk of increased BP in healthy people, suggesting the index's potential as a potential predictor of hypertension.[74] Hypertension, diagnosed by BP thresholds: ACC/AHA 2017 (>130/80 mmHg) and ESC/ESH 2018 (140/90 mmHg), is associated with the occurrence of diabetes and accelerated progression of IR assessed by HOMA2-IR; the association is weaker when using the 2017 ACC/AHA criteria.[75] In this context, age-stable independent associations of SBP and DBP levels with TyG in the analyzed cohort of women with different blood pressure levels are logical.

Follicle-stimulating hormone levels are closely associated with IR, prediabetes, and diabetes in postmenopausal women with normal or abnormal fasting glycemia[8]; the nature of this relationship has not been clearly established: multidirectional correlations of FSH levels with HOMA-IR have been shown. There is a rationale for considering FSH as a protective factor against IR[76]: a higher risk of diabetes was associated with a slower increase in FSH during early perimenopause[77], with similar results in postmenopause.[51] In our cross-sectional study, in the absence of connections with HOMA2-IR, FSH levels in the general cohort were positively age-dependently correlated with TyG; in the group of patients with hypertension, age was independently positively correlated with TyG and negatively with HDL-C, while also forming positive relationships with FG and BMI, disappearing when adjusted for age (Fig. 2).

Chen Y et al show, that FSH levels affect MetS only in postmenopausal women, but not in pre- and perimenopausal women.[11] It has been suggested that estrogens protect against CMR factors before menopause, but not during or after MT. At the same time, a significant relationship was found between FSH levels and the assessment of the severity of MetS in peri- and postmenopausal women, but not in premenopausal women. We believe that the diversity of the data obtained is based on age-related individual and population variability in the timing of the menopausal transition and differences in study designs. Sex hormone trajectories and MetS incidence were not consistent across race/ethnicity subgroups during menopausal transition.[11,50] These individual trajectories correlate with subclinical CVD, suggesting that monitoring

women over time rather than assessing risk at one time is more important.[78] In relation to diabetes prognosis, sex hormones were found to be a partial mediator of the relationship between overweight/obesity and hyperglycemia, using a score combining features of several sex hormones.[79] Insulin resistance is the main mechanism of a number of pathological conditions, not only of a metabolic, but also of a systemic nature, which is mediated by visceral adipose tissue as an independent endocrine organ. Among many hormonally active molecules, adipocytes are able to synthesize angiotensin II, regulating blood pressure levels. An increase in leptin levels can activate the RAAS and the production of proinflammatory cytokines in the brain, which led to a progressive increase in blood pressure. Insulin resistance and compensatory hyperinsulinemia cause a cascade of reactions that contribute to the initiation and progression of hypertension.[80] Activation of the RAAS, together with increased SNS activity in the setting of obesity, increases renal sodium reabsorption and blood pressure. In persistent obesity, progressive metabolic abnormalities, including IR and dyslipidemia, may promsote inflammation and atherosclerosis and aggravate hypertension, creating a vicious circle.[18]

On the other hand, uncontrolled hypertension leads to a decrease in peripheral circulation, contributing to a decrease in the sensitivity of peripheral tissues to insulin and an imbalance of two signaling kinase pathways due to activation of insulin receptors: mitogen-activated protein kinase (promotes the secretion of vasoconstrictor endothelin-1) and the phosphatidylinositol 3-kinase pathway/ protein kinase B (consistent with IR, caused by glucotoxicity, lipotoxicity or inflammation, causing a decrease in NO production) – which ultimately leads to endothelial dysfunction and is characteristic of diabetes.[81] Hyperinsulinemia increases the activity of the central parts of the SNS with subsequent increased sympathetic stimulation of the heart, blood vessels and kidneys[82]; promotes activation of the RAAS and melanocortin system of the brain, which play a decisive role in the occurrence of hypertension.[18] The situation is aggravated by the loss of estrogens due to the loss of their powerful protective effect, which leads to endothelial dysfunction.[43]

Thus, insulin resistance integrates the components of the metabolic syndrome, anthropometric, metabolic and hemodynamic, under the influence of the functional state of the pituitary-ovarian axis into the trajectory of the menopausal transition, pathogenetically linking them together. The progressive nature of IR with age and the worsening of estrogen deficiency in close connection with the clustering of MetS and increasing its severity dictate the need to further clarify the connection of its components with the functional state of the pituitary-ovarian axis at all stages of menopausal transition. The association of late postmenopause with various comorbid pathologies is well documented, determining the need for early preventive measures and justifying interest in surrogate markers of insulin resistance. The recently demonstrated association of the TyG index and TyG-BMI with new-onset hypertension in women reflects the predictive capabilities of the TyG line indices for hypertension[36]. Compared with HOMA-IR, the non-insulin TyG index has been shown to better predict metabolic syndrome [37] and diabetes.[39]

Conclusion

There is no doubt about the involvement of FSH and E2 levels in the formation of MetC with their different trajectories during the menopausal transition. The complexity of the problem is due to their indirect influence through relationships with the cluster components, as well as many interfering factors. The results of the few studies so far require replication and further exploration of the potential underlying mechanism. The identified spectrum of relationships between metabolic syndrome components, as well as FSH and estradiol levels with the surrogate index of insulin resistance TyG in the presence of hypertension, emphasizes the importance of this index as a guideline in prognostic and preventive direction.

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Authorship

L.A. Ruyatkina – idea, concept and design of the study, analysis and interpretation of the data obtained, writing the text of the article, editing the text of the manuscript;

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L.V. Shcherbakova – ideas for statistical data analysis and participation in its implementation

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