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Phenotype of perimenopausal metabolic syndrome formation with arterial hypertension in a normoglycemic cohort of women

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ABSTRACT

Introduction. Menopause as a potential risk factor for insulin resistance and associated metabolic and hemodynamic disorders determines the need to study the formation of the perimenopausal metabolic syndrome (MetS) phenotype with arterial hypertension (AH).

Objective: to assess correlations between MetS markers and characteristics of the menopausal transition with their role in hypertension based on the analysis of a perimenopausal normoglycemic cohort.

Patients and methods. Of the 88 women aged 35–59 years, 58 women had hypertension and 30 were normotensive. The following were determined: waist circumference (WC), blood pressure (BP), triglyceride (TG), HDL-C, insulin, follicle-stimulating hormone (FSH), estradiol and glucose levels, TyG, HOMA2-IR indices. The following were estimated (SPSS, version 17): median (25; 75%); intergroup differences according to the Mann-Whitney criterion; comparison of proportions according to Pearson's $\chi 2$; Spearman's correlation (R) and partial correlation (Rpc) analyses were performed to level out the influence of age; binary logistic regression was used to identify prognostic factors.

Results. The TyG index correlated age-dependently with FSH (R=0.211; p=0.048) and estradiol (R= -0.262; p=0.014), and age independently with BP, WC, and HDL-C. The associations of WC with BP that are relevant in partial correlation are the closest with TyG (R=0.526 and Rpc=0.424; p<0.001) and HOMA2-IR (R=0.507 and Rpc=0.370; p<0.001), age is dependent on HDL-C, duration of postmenopause and estradiol (R= -0.313; p=0.003). According to the stepwise multiple logistic regression analysis, with an increase in WC by 1 cm, the chance of having hypertension increases by 9%; with an increase in the TyG index by 1 conventional unit - by 16 times.

Conclusion. The ascending hormonal and metabolic trajectory of the components of metabolic syndrome in perimenopause with the central pathogenetic link of insulin resistance emphasizes the importance of factors specific to women and attention to arterial hypertension with its leading role in the cluster.

Keywords: hypertension, metabolic syndrome, perimenopause, insulin resistance, TyG index, HOMA2-IR, follicle-stimulating hormone, estradiol.

Introduction

Metabolic syndrome (MetS) is a set of metabolic disorders characterized by hypertension, abdominal obesity (AO), dyslipidemia and dysglycemia associated with the risk of type 2 diabetes mellitus (T2DM), cardiovascular diseases (CVD) and total mortality[1-2]. The diagnostic criteria of MetS are multifactorial, but not every patient with MetS has the same combination[3]. The MetS cluster, defined as a set of three or more components[3-4], suggests the presence of its different phenotypes, each of which is a cardiometabolic risk factor (CMR) with the leading role of hypertension[5]. In the evolution of diagnostic definitions and concepts of the pathophysiology of MetS[6], insulin resistance (IR) remains the central link[7-8], currently recognized as both a pathogenic cause and a predictor of hypertension[9].

In hypertension, as in many other diseases, there are sex (biological characteristic) and gender (social construct) differences that influence its pathophysiology, epidemiology and clinical management[10]. The prevalence of hypertension increases with age in both sexes, but it is lower in premenopausal women than in age-matched men, with a marked increase in postmenopausal women[11-13]. The prevalence of MetS increases in postmenopausal women to 70% compared with 14%–45% in premenopausal women[14]. The menopausal phenotype of MetS has attracted particular attention, since menopause is a potential risk factor for the development of IR regardless of age, probably due to declining estrogen levels[15]. At the same time, IR and the associated metabolic disorders: dyslipidemia, weight gain and decreased glucose tolerance, tend to increase sharply with the onset of menopause[16-17], although they start already in premenopause[12,16], emphasizing the need to study the trajectory of the menopausal transition (MT).

Insulin resistance claims to explain the close relationships of the classical components of MetS with a number of other diseases. Thus, non-alcoholic fatty liver disease (NAFLD) was included as a full member of the cluster with a proposal to use the term "metabolic-associated fatty liver disease" (MAFLD), emphasizing the bilateral associations of IR with all other parameters of MetS, including hypertension[7,18-22]. The inclusion of chronic kidney disease (CKD) in this circle of closely related chronic metabolic diseases with a strong impact on the incidence of CVD and heart failure has recently been defined as the cardiovascular-renal-metabolic syndrome[23-24].

Metabolic syndrome itself is not a disease as such, but a term that serves as a platform of risk factors for people at increased risk of a number of diseases[6], including, in addition to cardiovascular, neurodegenerative and tumor[15], due to common strong risk factors, biochemical mechanisms, similarity of progression and complications[25-26]. This polyvalence in defining quite different pathologies is explained by the distribution of insulin receptors in various organs and tissues, a wide range of its metabolic effects, as well as participation in cell division and proliferation[27]. There is no doubt that IR is not just a metabolic disorder, but a complex and multifaceted syndrome that increases the risk of cardiovascular and cerebrovascular events[28] and can affect blood pressure (BP) homeostasis[29].

Such a transformation of the concept of MetS sharply raises the issues of preventive and, accordingly, prognostic measures[6]. The leading risk factor for CVD among the components of MetS and the most modifiable is hypertension[4-5,10,30]. It is important that postmenopausal women with hypertension are at higher risk of cardiovascular events at lower threshold BP values[13].

Changes in the functional state of the pituitary-ovarian axis with hormonal fluctuations affecting insulin sensitivity are observed already in premenopause[15] and can start 5-10 years before the onset of menopause[31]. These hormonal changes are closely associated with the transformation of both metabolic and hemodynamic parameters[32]. In this context, the problem of the formation of metabolic syndrome with hypertension in

perimenopausal women deepens from early diagnosis to risk prediction, paying attention to insulin resistance as the leading pathogenetic link in metabolic and hemodynamic disorders.

In a number of MetS classifications, attempts have been made to include IR/hyperinsulinemia indicators in its definitions[2]. Simple indices are widely used as IR markers: insulin HOMA-IR and HOMA2-IR, as well as non-insulin TyG[33-36]. It is believed that the triglyceride-glucose index (TyG), obtained from the concentrations of circulating triglycerides and glucose, has become a promising tool for assessing IR, surpassing HOMA-IR in prediction accuracy[37-40].

Objective: to assess correlations between MetS markers and characteristics of the menopausal transition with their role in hypertension based on the analysis of a perimenopausal normoglycemic cohort.

Patients and methods

A single-center cross-sectional study included 88 women aged 35-59 years as part of a preventive examination: 30 were normotensive and 58 had hypertension. Exclusion criteria: carbohydrate metabolism disorders and other endocrine diseases; previously diagnosed ischemic heart disease, chronic heart failure; history of acute cardiovascular complications; rhythm and conduction disorders; menopausal hormone therapy; smoking; concomitant diseases in the acute stage.

Group 1 included 30 conditionally healthy women without hypertension, aged 43.00 (40.00; 46.25) years, without family history of CVD and dysglycemia. Group 2 included 58 women, aged 50.00 (43.75; 53.00) years, with a hypertension duration of 3.21 (1.00; 5.00) years, without regular antihypertensive therapy, and a family history of CVD of 75%. Patients with hypertension did not receive any other therapy except antihypertensive therapy. Homogeneity of the groups was achieved by following inclusion/exclusion criteria; age differences in the groups were leveled using partial correlation (correlation analysis) and by introducing age as an independent variable into the logistic regression model.

The examined women had different functional states of the ovaries: 43% were postmenopausal, the duration of postmenopause (DPM) was 1.64 (0.00; 2.00) years; in group 1, menopause was recorded in 6 (20.0%) women, in group 2 – in 32 (55.2%). It should be noted that some women were in perimenopause, including late premenopause and early postmenopause, which is characterized by an increase in FSH levels>25 mIU/L[41].

The following MetS markers were determined: waist circumference (WC); systolic (SBP) and diastolic (DBP) levels; fasting blood glucose (FG) values were estimated twice by the glucose oxidase method, with the average values included in the analysis; HDL-C and triglycerides (TG) were determined by the enzymatic calorimetric method. Insulin (INS), follicle-stimulating hormone (FSH) and estradiol (E2) levels were also measured by the enzyme immunoassay on the IMMULITE 2000XPi analyzer. The TyG index was calculated using the formula: TyG index = Ln [TG (mg/dL) x GL (mg/dL) / 2], where Ln is the logarithm, TG is fasting triglycerides, GL is fasting glycemia[42]; The HOMA2-IR index was determined using the HOMA2 calculator[33].

Statistical processing of the data was performed using SPSS software (version 17). Basic statistics were determined: median (Me), interquartile range (25; 75%). The significance of intergroup differences in values was assessed using the Mann – Whitney U test. Pearson's $\chi 2$ was used to compare proportions. Correlation analysis (Spearman's rank correlation) and binary logistic regression were used to identify dependencies and prognostic factors. Partial correlation was used to level out the influence of age. In the statistical analysis procedures, the critical significance level for rejecting the null statistical hypothesis (p) was taken to be ≤ 0.05. The statistical analysis was partially carried out within the framework of the budget topic FWNR-2024-0002.

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

Results

A comparative analysis of two groups of women (Table 1), divided based on the history of hypertension and the fact of taking antihypertensive drugs, reflects statistically significant differences in most parameters. Thus, women in group 2 were older, in addition to the BP levels that marked the group, they had higher WC, TG and FG and lower HDL-C. At the same time, WC and lipid characteristics in group 1 did not fully fit into their reference limits. FG levels in both groups were within the reference range, although in group 2 they were higher (p = 0.011), unlike women without hypertension. Insulin levels, IR indices, HOMA2-IR and non-insulin TyG, also in the presence of hypertension exceeded the corresponding ones in normotensive women (Table 1).

Table 1. Comparison of clinical, metabolic and hormonal parameters in groups of women aged 35–59 years depending on the presence of arterial hypertension, Me (25; 75%).

Parameter	Group 1 (n=30)	Group 2 (n=58)	* – p 1-2
Age, years	43,00 (40,00; 46,25)	50,00 (43,75; 53,00)	0,001
WC, cm	76,50 (70,25; 83,25)	89,50 (79,00; 99,00)	<0,001
SBP, mm Hg	120,00 (120,00; 130,00)	142,50 (130,00; 160,00)	<0,001
DBP, mm Hg	80,00 (70,00; 80,00)	90,00 (80,00; 100,00)	<0,001
HDL-C, mmol/l	1,00 (1,00; 1,03)	0,92 (0,84; 1,00)	<0,001
TG, mmol/l	1,75 (1,49; 2,13)	2,30 (2,00; 2,50)	<0,001
FG, mmol/l	3,60 (3,40; 4,33)	4,20 (3,60; 4,70)	0,011
INS, μU/ml	5,30 (3,80; 7,00)	7,30 (5,15; 12,28)	0,013
HOMA2-IR, cu	0.63 (0.45; 0.87)	0.96 (0,67; 1,64)	0,001
TyG, cu	8,58 (8.33; 8,80)	8,93 (8,66; 9,17)	<0,001
FSH, IU/l	9,10 (5,40; 49,33)	32,75 (6,85; 74,58)	0,066
E2, pg/ml	280,76 (73,40; 442,75)	73,40 (73,40; 269,25)	>0,05

Note: p1-2 – significance of differences between groups 1 and 2.

The groups did not differ statistically in the parameters of the functional state of the pituitary-ovarian axis, which can be explained by the high variability of FSH and E2 levels depending on the period of MT[41,43]. We note some tendency towards differences between the groups in FSH levels (Table 1). Taking into account the older age of women in group 2 and, accordingly, different stages of the perimenopausal continuum, when comparing the groups by the FSH level>/<25 mIU/L (30% and 52% in groups 1 and 2, respectively), a statistical difference was revealed (Pearson criterion $\chi 2=3.781$, p=0.052). It should be noted that age correlated with all parameters of MetS and perimenopause (Table 2), especially closely with FSH and DPM, which served as an additional basis, in addition to the statistical difference in this indicator between the groups depending on the presence of hypertension (Table 1), for conducting a partial correlation in order to level out the influence of age.

Table 2. Results of the correlation analysis of age with parameters of MetS and perimenopause in a cohort of perimenopausal women with different levels of blood pressure (n=88)

Age	Parameters								
	WC	SBP	DBP	FG	TG	HDL-C	DPM	FSH	E2
R	0,456	0,374	0,306	0,309	0,236	-0,29	0,707	0,543	-0,336
p	<0,001	<0,001	0,004	0,004	0,027	0,006	<0,001	<0,001	0,001

Note: R – Spearman's correlation coefficient.

The correlation links analysis of the MetS characteristics with insulin levels, the HOMA2-IR index calculated on its basis, and the non-insulin TyG index (Fig. 1) showed the presence of more extensive and close links specifically for TyG. All of its associations, including INS and HOMA2-IR, remained significant even with partial correlation, reflecting only a partial dependence on age. On the contrary, insulin and HOMA2-IR, when leveling out the influence of age, correlated only with WC, TG and TyG levels (Fig. 1). Fasting glucose, an important marker of MetS, was not included in the analysis, since it is included in the calculation formulas for both IR indices.

The TyG index showed statistically significant associations with SBP and DBP levels (Fig. 1) both in the Spearman analysis (R) and taking into account the differences between the groups by age (partial correlation, R_{pc}). The correlation analysis in the group of perimenopausal patients with hypertension (group 2), which we conducted earlier[43], demonstrated the relationships of the TyG index with the parameters of the functional state of the pituitary-ovarian axis: positive with FSH (R=0.312; R_{pc} =0.286; p<0.05) and negative with E2 (R= -0.333; R_{pc} = -0.278; p<0.05). In the analyzed group of women with different BP levels (groups 1+2), we also note the presence of age-dependent relationships with FSH with INS, but not HOMA2-IR, as well as with TyG (Fig. 1).

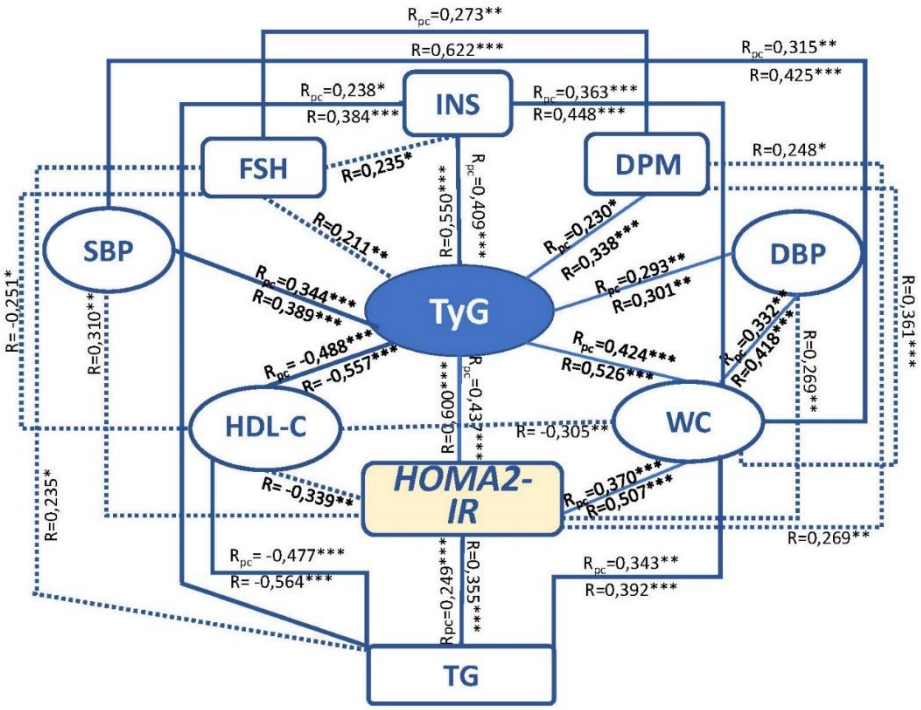

Fig.1. Associations of TyG and HOMA2-IR indices with markers of MetS and perimenopause in a cohort of women with different BP levels; R – Spearman's correlation coefficient (solid line); Rpc – partial correlation (dotted line); significant difference: * ≤ 0.05; ** ≤ 0.01; *** ≤ 0.001.

Based on the above data, 6 parameters were selected as independent variables for inclusion in the binary logistic regression model: age, WC, HDL-C, TyG index, insulin levels (as the initial parameter for calculating HOMA2-IR), and FSH levels. Hemodynamic parameters as a characteristic of hypertension and FG levels used to calculate the IR indices, HOMA2-IR, and TyG, were excluded from the analysis. Given the perimenopausal nature of the overall cohort of women, we also included FSH levels with a cutoff value of >25 IU/l, as the earliest responsive hormone in changes in the functional state of the pituitary-ovarian axis, characterizing perimenopause[41]. As a result of multiple binary logistic regression analysis, when including the above parameters in the equation, WC (OR=1.093; p=0.013) and HDL-C (OR=0.001; p=0.023) are statistically significantly associated with the presence of hypertension. The sensitivity of model (1) is 87.9%; specificity is 60.0% (Table 3).

Table 3. Results of multiple binary logistic regression (model 1).

Parameters	Statistical parameters				
	B	Sig.	OR	95,0% C.I. for OR	
				Lower	Upper
Age	0,088	0,172	1,092	0,962	1,240
INS	0,089	0,284	0,944	0,851	1,049
WC	-0,057	0,013	1,093	1,019	1.171
FSH	-0,004	0,673	0,996	0,977	1.015
TyG	1,859	0,139	6,416	0,547	75,199
HDL-C	-10,173	0,023	0,001	0,0001	0,247

Note: B – regression coefficient, Sig – statistical significance, OR – odds ratio, CI – 95% confidence interval for OR.

When excluding TYG from the logistic regression model (1), the sensitivity and specificity of model (2) were 84.5% and 60%, respectively, which, when compared with model (1), with similar specificity, is characterized by a decrease in sensitivity. At the same time, when including TYG and excluding HDL-C, the sensitivity of model (3) remains 87.9%, and the specificity increases compared to models (1) and (2) and is 63.3%, which serves as a basis for considering model 3 as a working model for further analysis (Table 4).

Table 4. Results of multiple binary logistic regression (model 3).

Parameters	Statistical parameters				
	B	Sig.	OR	95,0% C.I. for OR	
				Lower	Upper
Age	0,084	0,169	1,087	0,965	1,225
INS	-0,041	0,389	0,960	0,873	1,054
WC	0,075	0,021	1,078	1,011	1,150
FSH	-0,001	0,925	0,999	0,982	1,017
TyG	3,095	0,007	22,089	2,346	207,995

Note: B – regression coefficient, Sig – statistical significance, OR – odds ratio, CI – 95% confidence interval for OR.

As a result of stepwise multiple binary logistic regression analysis, the WC and TyG indicators were selected from model 3 (Table 5): with an increase WC by 1 cm, the chance of having hypertension increases by 9%; with an increase the TyG index by 1 conventional unit - by 16 times.

Table 5. Results of stepwise multiple binary logistic regression

Parameters	Statistical parameters			
	Sig.	OR	95,0% C.I. for OR	
			Lower	Upper
Step 1 WC, by 1 cm	<0,001	1,116	1,057	1,177
Step 2 WC, by 1 cm TyG, be 1 cu	0,005 0,006	1,087 16,377	1,025 2,200	1,153 121,916

Note: Sig – statistical significance, OR – odds ratio, CI – 95% confidence interval for OR.

Discussion

The age range of the analyzed cohort of women was chosen taking into account the characteristics of perimenopause. Hormonal factors play an important role in gender differences associated not only with the anatomical distribution of adipose tissue but also with various aspects of metabolic disorders; a protective role is traditionally attributed to endogenous estrogens[15]. The trajectories of E2 and FSH levels during the menopausal transition (MT) are not homogeneous among the population of women, being influenced by ethnicity and body mass index[44-45], environmental characteristics[46], as well as polymorphism of estrogen genes[47]. The absence of a statistical difference between the groups in E2 levels with a tendency towards the same for FSH (Table 1), as well as a sharp decrease in the strength of the association of FSH and E2 in the studied cohort of women with partial correlation (R_{pc}= -0.287; p=0.009) in contrast to the Spearman analysis (R= -0.578; p<0.001) may reflect the difference in the trajectories of these hormones in different periods of MT under the influence of the indicated features[44-47].

Inclusion of DPM in the correlation analysis revealed its stable associations in the conditions of Spearman analysis and partial correlation with FSH (Fig. 1), while the negative correlation of E2 with DPM was completely age-dependent (R = -0.508; p < 0.001). Despite conflicting data on the change in E2 levels during perimenopause: from a continuous decrease during MT to fluctuating secretion patterns without differences in early and late perimenopause[48], our data from a cross-sectional study reflect the formation of severe estrogen deficiency in late postmenopause. The risk of developing MetS increases with years after menopause, but the full impact of DPM remains unclear[31]. It was DPM that turned out to be the most important risk factor for MetS according to the results of a cross-sectional study in Turkey, while the risk increased with its duration of more than 5 years[12]; the cited work did not analyze the functional state of the pituitary-ovarian axis.

It should be noted that despite the extreme variability of FSH levels, their quantitative benchmarks, unlike E2, are included in the STRAW+10 staging system for reproductive aging in women: starting from the late fertile period >25 IU/l, with a tendency to increase in the early phase of the menopausal transition and maintaining high values in the late stage of MT[41]. These data are not consistent with the classical point of view explaining the mechanisms of metabolic and hemodynamic changes during MT by estrogen deficiency[49], which characterizes late postmenopause[50].

At the same time, the prognostic significance of FSH levels was revealed in women with nosologies closely associated with MetS: at the age of 35-65 years in the development of osteoporosis[51], in postmenopause with a 10-year risk of the atherosclerotic CVD[52], at the age over 55 years with NAFLD[53]. Such studies are rare and mostly concern postmenopause. However, in combination with the

dynamics of the hormone during staging of MT[41], they determine interest in the prognostic role of FSH during MT.

Evidence of extragonadal functions of FSH is accumulating after the detection of expression of its receptors on blood vessels, adipose tissue, liver, osteoclasts, hippocampal and cortical neurons[54-55]. Additional biological functions of pituitary hormones, including FSH, when they act on non-classical organs are defined by the new concept of the "atypical pituitary hormone-target tissue axis"[56-57].

Changes in the functional state of the pituitary-ovarian axis with hormonal fluctuations affecting insulin sensitivity are observed already in premenopause[15]. The menopausal transition is associated with an increase in IR in combination with MetS markers: AO, dysglycemia, dyslipidemia, NAFLD and hypertension[32]. The relationship between hypertension and IR is close and two-way[8,58-59]. At the same time, the influence of menopause per se on BP remains uncertain[32]. All this draws attention to the associations of FSH with both BP and TyG levels.

Previously, we reported a statistically significant association of the TyG index with FSH levels in a group of perimenopausal women with hypertension that persisted with partial correlation[43]. In a cohort of women with different BP levels, we found age-independent correlations of the TyG index with SBP and DBP, WC and HDL-C (Fig. 1), with FSH levels correlating with TyG (Fig. 1) in an age-dependent manner (R=0.211; p=0.048); as did E2 levels (R= -0.262; p=0.014). All this, in addition to the results of the comparative analysis (Table 1), served as the basis for including FSH levels >/<25 IU/L, taking into account the statistically significant difference between the groups in this indicator (Pearson criterion $\chi 2=3.781$, p=0.052), in the initial model (1) of multiple logistic regression analysis (Table 2). In this context, the association of DPM with insulin resistance indices seems interesting, retaining its statistical significance even when the influence of age with TyG is leveled, in contrast to the completely age-dependent association with HOMA2-IR (Fig. 1). The associations of SBP and DBP levels with TyG behaved similarly, but not with HOMA2-IR (Fig. 1). The obtained data are consistent with the opinion about menopause as an indicator of MetS in women, regardless of age[31].

However, whether BP changes in middle-aged women are driven more by chronological aging or by the transition to menopause is a matter of debate. For example, a group of women has been identified whose trajectories of SBP, pulse BP, and mean BP are consistent with the contribution of menopause[54]. On the other hand, both menopause and BP have common determinants: body mass index (BMI), diet, smoking, and socioeconomic status. The strongest doubt is whether menopause is a dependent or independent risk factor for high BP, that is, whether its effect on BP, if any, is due directly to the decline in estrogen or to other indirect factors[60].

A combination of experimental data and clinical studies suggest that cardiometabolic changes may occur during perimenopause, superimposing the effect of aging on CVD risk, which increases significantly approximately 10 years after MT[32]. The significant role of age at menopause in predicting the formation of MetS components has been emphasized[50-54]. It has been suggested that MetS accelerates the aging process, potentially contributing to the development of age-related complications. The results of a meta-analysis of nine studies (total sample size of 8606 participants) showed that MetS was negatively associated with telomere length; this association was independent of sample size, age, and gender of the participants[61].

Graphic interpretation of the results of the conducted correlation analysis (Fig.1) reflects 3 intersections of statistically significant associations for the following parameters: HDL-C, WC and TyG, with the latter being the most intense. It is the non-insulin index IR that correlates (according to Spearman and partial correlation) with all parameters included in the analysis, with the exception of FSH, with which the association is age-dependent. From

the spectrum of HOMA2-IR correlations, the relationships with the blood pressure levels, HDL-C and DPM are completely age-dependent. As a result, TyG was chosen as the IR indicator for inclusion in the regression analysis model.

As for HDL-C, the age dependence of its associations with other parameters of MetS and perimenopause, except for the relationships with TG and TyG, are quite explainable by the perimenopausal nature of the cohort of examined women. The development of dyslipidemia in perimenopause is more complex than the classical view that the main mechanism of dyslipidemia is due to E2 deficiency[49,57]. Prospective studies during MT have shown that adverse lipid changes can begin before the decline in estrogen levels in the premenopausal stage[56]. The increase in cholesterol levels begins 5 years before the last menstruation and increases significantly within 1 year after it.[62] However, the increase in gonadotropins maintains a stable serum estradiol concentration until the late period of the menopausal transition[50].

Follicle stimulating hormone has been shown to be involved in the pathogenesis of menopause-associated dyslipidemia. Serum FSH levels positively correlate with total cholesterol, LDL-C, and the prevalence of hypercholesterolemia in women[62-63], which is logically explained by the effect of gonadotropin on non-gonadal organs[56-57], mainly through its interaction with its receptors in hepatocytes[63], taking into account the gender dimorphism of the effect of FSH on lipid metabolism in the liver, as well as through paracrine effects outside the HPG axis[57].

In the analyzed cohort of women, we included HDL-C and TG levels in the analysis as lipid markers of MetS[64]. FSH levels correlated with age-dependently with INS, TyG, HDL-C, and TG values (Fig. 1). Previously, in a subgroup of patients with hypertension, we identified only partially age-dependent associations of FSH with HDL-C (R= -0.293; p=0.026; R_{pc}= -0.253; p=0.053) and TyG (R= 0.312; p=0.017; R_{pc}= 0.286; p=0.031), while estradiol correlated with TG (R= -0.347; p=0.008; R_{pc}= -0.278; p=0.05) and TyG (R= -0.393; p=0.002; R_{pc}= -0.376; p=0.004)[43]. Estradiol levels also had age-dependent weak associations with HDL-C (R= 0.281; p=0.032), which may reflect the long-term protective effect of estrogens on this parameter during the menopausal transition[50]. Exposure to endogenous estrogen during reproductive age provides women with protection against CVD; with estrogen loss, postmenopause is associated with abdominal obesity, insulin resistance, dyslipidemia, and endothelial dysfunction[32].

In a review paper, Li Y et al. (2024) draw the attention of researchers to the concept of endocrine-associated fatty liver disease (EAFLD)[57], first proposed by Lonardo A et al.[65], in continuation of the discussion about changing the name of NAFLD to MAFLD[66], taking into account the accumulated data on the influence of various endocrine axes, including FSH-estradiol, on lipid homeostasis. It has been shown that metabolic dyslipidemia, along with smoking, obesity, hypertension and type 2 diabetes, are associated with an increased risk of NAFLD[67]. The close relationships between NAFLD and metabolic disorders allow us to consider it as a liver phenotype of MetS[68], emphasizing the systemic nature of the relationships between the components of the cluster with their integrative contribution to cardiovascular risk[20,69].

In the context of the formation of the menopausal phenotype of MetS[43], it seems important to take into account the participation of FSH in the liver control of lipid metabolism and the genesis of MAFLD with their close connection with hypertension[21]. The trajectory of this phenotype is pathogenetically associated with a change in the functional state of the pituitary-ovarian axis: from premenopause to menopause itself and postmenopause. The concept of endocrine-associated fatty liver disease, interconnected with lipid homeostasis, controlled, among other things, not only by the level of E2 with its decrease in late postmenopause, but also by FSH levels throughout

MT[50,56-57,62], clarifies the mechanisms of formation of the menopausal phenotype of MetS.

Hormonal imbalance during MT leads to distinct changes in energy expenditure and body composition[70]. At the same time, IR and associated metabolic disorders: dyslipidemia, weight gain and dysglycemia, tend to increase sharply with the onset of menopause[70-71]. In the analyzed cohort of perimenopausal women, WC, significantly and only partially age-dependently correlating with blood pressure, INS and TG levels, loses its significance with HDL-C and DPM when leveling out the influence of age; WC correlates most closely with the non-insulin triglyceride-glucose index TyG (Fig. 1). It should be noted that the associations of HDL-C turned out to be only partially age-dependent, remaining statistically significant within the partial correlation, only with TyG and TG levels, a component of the IR index calculation.

It is important that the indices used to assess IR have different information content. Thus, the advantage of the HOMA2-IR model over its predecessor HOMA-IR, which reflects only hepatic IR, is the assessment of its peripheral component[33]. TyG, reflecting the close relationships between lipid and carbohydrate metabolism within the concept of lipoglucotoxicity, better identifies IR of muscle, liver and adipose tissue, including visceral[33,72-74]. The TyG index is believed to be superior to HOMA-IR in the accuracy of MetS prediction[38]. Its strong correlation with the hyperinsulinemic-euglycemic clamp, high diagnostic sensitivity and specificity, as well as ease of clinical application justify its use as a reliable surrogate biomarker of IR[37,75-76].

One of the first MetS variants described was the hypertriglyceridemic obesity phenotype or the hypertriglyceridemic waist phenotype (HTWP), regarded as an integrative mirror of the syndrome features[77]. At the same time, the main component of the cluster is considered to be hypertension, the leading risk factor for cardiovascular mortality and morbidity[3,78]. Hypertension is pathophysiologically associated with MetS through IR and visceral obesity[59]. Moreover, abdominal obesity and menopause closely correlated with prehypertension[79]. Simultaneous associations of WC with IR indices and BP levels, closer and less age-dependent with TyG in contrast to HOMA2-IR, consistent with the HTWP phenotype[77], may reflect its participation in the formation of the hypertension phenotype in perimenopause.

The hypertriglyceridemic waist phenotype, associated to a greater extent with the female gender, since, in addition to age-related weight gain, menopause adds additional problems for women with the occurrence of significant metabolic changes and redistribution of central and visceral fat, is closely associated with hypertension[80-82]. The predominant mediating role of excess weight in the correlation of lifestyle risk factors with SBP and DBP has been shown[83]. The associations of WC with MetS markers and IR indices that we identified are consistent with the results of stepwise multiple logistic regression analysis, in the process of which, when assessing the informativeness of MetS markers in predicting hypertension in women based on the analysis of a perimenopausal cohort without dysglycemia, WC and TyG indices were selected from model 3 (Table 4).

It is the concept of MetS formation and the need for preventive measures against its progression that draw attention to the comparative prognostic value of visceral obesity and insulin resistance characteristics. WC is the best anthropometric indicator of visceral fat and a predictor of metabolic disorders such as diabetes, hypertension, and dyslipidemia[84-85], but may not differentiate between visceral and subcutaneous adipose tissue in men[86]. Quantitative imaging methods confirm that excess visceral adiposity is an independent indicator of adverse cardiovascular outcomes[19]. However, in a high-risk Iranian population that included individuals of both sexes, higher visceral adiposity index (VAI) values poorly predicted hypertension, whereas the HTGW phenotype was a stronger predictor of its occurrence[87]. In the CHARLS study (Chinese population), with equal

inclusion of men and women, the TyG index was identified as a mediator in the relationship between the visceral fat index and the incidence of hypertension[59]. It should be noted that in the conducted analysis, the strongest association with the TyG index was found specifically for WC (Fig. 1).

A significant increase in WC during MT is observed in various ethnic groups[88]. A decrease in estrogen levels, which appears to be an important trigger for these changes, is consistent with a completely age-dependent association of E2 with WC (R = -0.313; p = 0.003) in the analyzed subgroup, confirming the effect of estrogen in the postmenopausal stage of perimenopause. On the other hand, age-dependent correlations of FSH, which responds by increasing in premenopause, with TG and HDL-C (Fig. 1), but not with WC, may also reflect the influence of gonadotropin on the regulation of energy homeostasis[89]. Considering the associations of age with the parameters of MetS and the functional state of the pituitary-ovarian axis (Table 2), it seems that aging inherently increases obesity, interacting with the effects of menopause[90].

When using only BMI for anthropometric assessment during MT, it should be remembered that the opposite changes in body composition during this period with a decrease in lean mass and an increase in fat mass, lead to the fact that weight changes very little in response to menopause itself[70,91]. Although BMI closely correlates with the percentage of body fat in different populations, there are significant differences depending on gender, age, and ethnicity. It is emphasized that abdominal obesity, determined by WC, is a marker of CVD risk independent of BMI[19].

These data reflect the importance of WC assessment during MT in order to identify visceral deposition of adipose tissue. Obesity causes neurohormonal activation and activation of the renin-angiotensin-aldosterone system (RAAS) and the sympathetic nervous system (SNS), which, along with hyperleptinemia and other homeostatic deviations, contributes to sodium retention and the development of hypertension; the latter in T2DM and other conditions can lead to renal dysfunction. It should be emphasized that heart disease, stroke, and CKD are closely associated with the pathophysiological mechanisms of high BP[20]. In this regard, it is interesting that phenotype models based on WC and TG can be used as screening tools to predict the risk of CKD, with WC playing a greater role than TG[92]. In men with increasing WC values, higher fasting insulin levels were detected, but elevated TG concentrations were associated with a further increase in insulin levels[93], which coincides with the results of correlation analyses obtained in perimenopausal women both in the analyzed cohort (Fig. 1) and in the subgroup of patients with hypertension[43], reflecting the formation of insulin resistance assessed by HOMA2-IR and TyG (Fig. 1).

Thus, the characteristics of the hypertriglyceridemic waist phenomenon in the comparative analysis of subgroups of women with hypertension and normotensive women (Table 1), as well as the results of correlation and regression analyses (Fig. 1, Table 5) draw our attention to insulin resistance. Above, we recorded a greater number of statistically significant associations in TyG compared to HOMA2-IR (Fig. 1) in the analyzed cohort of perimenopausal women. To identify the prognostic capabilities of the assessed MetS markers in terms of the presence of hypertension in a cohort of perimenopausal women, 6 parameters were included in the initial model of stepwise multiple logistic regression analysis, taking into account the aim of the study and the results of the correlation analysis: age, WC, HDL-C, TyG index, insulin levels and FSH levels with a cutoff value of >25 IU/l characterizing perimenopause[41]. As a result of comparing the specificity and sensitivity of models 1-3 (Tables 3-5), the WC and TyG parameters were selected (Table 5). Thus, with an increase in WC by 1 cm, the chance of having hypertension increases by 9%; with an increase in the TyG index by 1 conventional unit - by 16 times. The diagnostic accuracy of the TyG index in determining insulin resistance as a reference method has been tested in several

studies; it also demonstrated good results in assessing IR compared to HOMA-IR in individuals with and without diabetes[37,94].

Although hypertension is a major factor in MetS, not all initial diagnoses of MetS contain hypertension as a component, and in some cases, it develops later, as the severity of the syndrome increases[3]. There is substantial evidence that IR plays a stimulatory role in the pathogenesis of cardiovascular and metabolic diseases with a high correlation between the TyG index and the occurrence of CVDwith a possible correlation between elevated TyG values and a higher risk of hypertension[39,95-97]. In a comprehensive methodologically sound review by Nayak SS et al (2024), as a result of comparing and summarizing the results of 32 meta-analyses, the TyG index showed a significant association with an increased risk of hypertension (RR = 1.52, 95% CI: 1.25–1.85) and other CVDs[98]; however, the heterogeneity and methodological quality of the included studies indicated the need to confirm these data. A meta-analysis of 7 cohort studies from the PubMed, EMBASE and Web of Science databases showed that an elevated TyG index significantly increases the risk of newly diagnosed hypertension in the general population, regardless of age, gender, BMI and ethnicity[99].

A substantial body of research suggests that IR, including TyG, may contribute to the onset and progression of hypertension through its deleterious effects on vascular function and structure, including increased arterial stiffness[100-103], which is considered a risk factor for hypertension[104]. Elevated baseline TyG levels and higher long-term TyG trajectory were independently associated with increased arterial stiffness in the Hanzhong Adolescent Hypertension Cohort[105]. The onset of hypertension in hypertensive individuals may be associated with activation of the RAAS and SNS[106], similar to the effects of obesity[20], which is logical given the close association of hypertension with MetS through pathophysiology including obesity[30]. There is increasing evidence that visceral adipose tissue and TyG are independently associated with the incidence of hypertension[59].

All components of MetS contribute to autonomic dysfunction[3]. IR has been shown to be associated with low-grade systemic inflammation, which may contribute to endothelial dysfunction[9,29,107]. Insulin resistance may also affect renal sodium metabolism, stimulate SNS activity and modulate the secretion of vasoactive substances[75,108]. All of these factors are associated with the development of hypertension[98]. Moreover, the TyG index has been associated with different stages and phenotypes of hypertension, its progression, and could serve as a surrogate indicator for early treatment of hypertension[75]. The links between hypertension and MetS are multiple and complex, and they are still not fully understood[30].

Insulin resistance has sex differences because sex hormones play an important role in insulin sensitivity. Estrogen, the major female sex hormone, appears to have a protective effect on insulin sensitivity, which declines after menopause[15]. Thus, when stratified by sex, a higher TyG index was significantly associated with stage 2 hypertension in women but not in men; however, the study included women over 45 years of age, most of whom were postmenopausal[75]. The loss of estrogen with menopause in women appears to be mechanistically related to a decrease in β-adrenergic vasodilation and an increased risk of hypertension in older women. Other important factors contributing to hypertension via sympathetic mechanisms are obesity and arterial stiffness, which increase with age[109]. The role of estrogen deficiency in increased RAAS activity is discussed[60,110]. Postmenopausal E2 deficiency promotes chronic low-grade inflammation in parallel with the switch of RAAS to a proinflammatory pathway, which leads to oxidative stress and cardiovascular aging with an increased incidence of cardiac hypertrophy, hypertension, atherosclerotic CVD, arrhythmias, and heart failure[111].

Thus, insulin resistance is a multifaceted condition with complex interactions between insulin signaling pathways, metabolic disorders, autonomic

dysfunction, subcellular signaling abnormalities, RAAS activation, and inflammation[112]. In addition, IR is a time-dependent phenomenon specific to organs and tissues. Insulin resistance is involved in target organ damage through dysregulation of peripheral vascular resistance and increased BP. Persistence of IR causes metabolic disorders that determine the development of type 2 diabetes[29]. It is logical that dysglycemia in close connection with insulin resistance manifests itself in women with a higher frequency in postmenopause against the background of diagnosed hypertension[113-114]. In a prospective cohort study of patients without dysglycemia with a history of hypertension or with newly diagnosed hypertension according to both ACC/AHA (2017) and ESC/ESH (2018) criteria, it was shown for the first time that hypertension according to both criteria was associated with a more rapid increase in IR, assessed by HOMA-IR over 4.5 years, and the incidence of T2DM. These results provide evidence in support of the idea that IR is the main reason linking hypertension and T2DM[115]. Importantly, higher quartiles of all IR indices were significantly associated with an increased risk of MetS and hypertension[116].

This ascending hormonal-metabolic trajectory of CVD risk factors in women, often starting clinically with hypertension, highlights the importance of female-specific factors.[117] Sex hormones, not only estradiol, but also gonadotropins, have a major impact on the manifestation and outcome of MetS, including the inclusion of MAFLD and possibly CKD in this cluster,[57,63,118-121] closing the circle of formation of menopausal MetS at a qualitatively different level of cardiovascular-renal-metabolic syndrome.[24,122] The complex pathophysiological overlap between the components of MetS may partially explain how new antidiabetic drugs exhibit pleiotropic effects[30].

Conclusion

Thus, metabolic syndrome is a heterogeneous entity with age- and sex-specific variations in cluster components, which may have important implications for interpreting the association between metabolic syndrome and cardiovascular risk over the lifespan. El Khoudary SR et al (2020), on behalf of the American Heart Association, for the first time include the menopausal transition as a sex-specific event that profoundly impacts future cardiometabolic health and highlight the significance of the menopausal transition as a time of CVD risk acceleration, emphasizing the importance of monitoring women's health in midlife.[123] Careful identification of gender-specific risk factors is vital to fully understand the cardiovascular and cardiometabolic diseases that increasingly affect women.[2] In this context, early detection and dynamic monitoring of IR using the non-insulin TyG index is becoming increasingly important, taking into account the spectrum of its associations with metabolic, hemodynamic and hormonal parameters with the definition of cut-off points for identifying different MetS phenotypes.[35,124-125] An elevated TyG index at baseline and long-term trajectories of the TyG index may provide insight into the prevention of hypertension in later life[126].

Conflict of Interest:

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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