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TyG Index in Predicting Arterial Hypertension in Normoglycemic Perimenopausal Women

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ABSTRACT

Introduction. The critical role of insulin resistance (IR) in the clustering of metabolic syndrome (MetS) in association with hormonal and metabolic parameters of perimenopause determines the need to search for informative IR biomarkers in the prognosis of arterial hypertension for early prevention of cardiometabolic diseases.

Objective: to evaluate the informativeness of the surrogate marker of insulin resistance, TyG index, in predicting hypertension based on the analysis of a perimenopausal normoglycemic cohort.

Patients and methods. Of 88 normoglycemic women aged 35–59 years, 58 women had hypertension and 30 were normotensive. The following were determined: waist circumference (WC), blood pressure, triglycerides (TG), HDL-C, insulin, follicle-stimulating hormone (FSH) and estradiol, fasting glucose, TyG index. Using SPSS (version 23), we estimated the median and (25%; 75%); intergroup differences using the Mann-Whitney test; comparison of proportions using Pearson's χ^2; performed correlation analyses: Spearman's (R) and partial correlation (R_{pc}) to level out the influence of age; binary logistic regression was used to identify prognostic factors. ROC analysis was used to determine the cutoff point of the TYG indicator.

Results. The TyG index statistically significantly correlated with the spectrum of MetS and perimenopause parameters, most closely and stably with partial correlation with insulin, WC, HDL-C, duration of postmenopause, age depending on FSH. Using multiple logistic regression analysis, the following parameters were included in the model: age, insulin, WC, FSH, TyG; the TyG index statistically most significantly associated with the presence of hypertension (OR=22.089; p=0.007). Using ROC analysis, the cutoff point for TYG was determined - 8.7 conventional units with the optimal parameters of the diagnostic test (presence and absence of hypertension): AUC was 0.793 (95% CI: 0.694-0.892), p<0.0001; Se 74%, Sp 67%.

Conclusion. The surrogate indicator of insulin resistance, the TyG index, closely correlated with markers of MetS and perimenopause, being most significantly associated with the presence of hypertension. The cutoff point for TYG was 8.7 conventional units with optimal test parameters. The results of the partial correlation and the presence of age and FSH indices in the diagnostic model reflect a combination of chronological and reproductive aging in the dynamics of the menopausal transition.

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

Introduction

Perimenopause or the menopausal transition (MT) period includes dynamic changes in a woman's reproductive life with significant hormonal, metabolic and cardiovascular changes. A significant increase in cardiometabolic risk (CMR) in postmenopause draws special attention to its components: hypertension, type 2 diabetes mellitus (T2DM), abdominal obesity, dyslipidemia with their close relationship within the menopausal metabolic syndrome (MetS). [1,2] In contrast to the opinion of society, where menopause was considered a normal part of the aging process,[3] there is increasing evidence that MT is a risk factor for cardiovascular diseases (CVD), regardless of age-related changes, especially considering that the earlier the menopause, the higher the CMR.[2,4] On the one hand, perimenopause is a chaotic period associated with an increase in symptoms (hot flashes, anxiety, sleep disturbances), on the other hand - cardiovascular risk (CVR) factors due to changes in hormonal levels; these quality of life factors, like CVR risk factors, also change with age.[5] In fact, perimenopause is a natural part of reproductive aging.[5] Separation of the contribution of chronological and reproductive aging to CVR is actively debated. [6-8] Longitudinal studies of women going through menopause reflect the importance of midlife as a period of accelerated growth of CVR risk.[9]

Postmenopause is an aging process and an important period equivalent to one third of a woman's life.[6] Menopause significantly increases the risk of cardiometabolic diseases (CMD), which include T2DM and CVD in close association with MetS and are the main cause of morbidity and mortality.[10-12] MetS itself is a platform of risk factors for CVD: hypertension, insulin resistance (IR), proatherogenic dyslipidemia, abdominal obesity and dysglycemia associated with the development and progression of CVD, chronic kidney disease and type 2 diabetes, combining them into a common pathology.[13] In women, MetS is prognostically more significant for CVD due to the greater influence of the components of the syndrome compared to men.[4] Despite the accumulation of knowledge about the pathophysiological differences between the sexes in the prevalence of MetS components and the associated CMR, sex differences have been poorly studied,[14] and women are underrepresented in clinical studies.[15]

There are sex (biological characteristic) and gender (social construct) differences that influence the pathophysiology of MetS, epidemiology and clinical management of hypertension.[16] Individual components of MetS are the same in women and men, but how and when these components manifest themselves is important. Specific patterns are observed in women during premenopause and postmenopause.[4,17] That is, men and women experience different trajectories of CMR throughout life.[18] The presence of a unique additional risk factor for women, menopause, determines the menopausal phenotype of MetS. Its formation has its own trajectory, closely associated with changes in the functional state of the pituitary-ovarian axis: from premenopause to menopause and postmenopause. [19] Premenopause can occur 5-10 years before menopause, the physiological age range of which is defined as 45-55 years with an average age of 51.3 years,[20] while the CVR increases significantly at the typical age of menopause (~51 years). [21]

Menopause is a potential risk factor for the development of IR regardless of age.[22] A number of cardiometabolic perimenopausal changes do not depend on chronological aging and are largely due to reproductive aging,[7] drawing attention to the relationship between CMR and hormonal changes in the pituitary-ovarian axis during perimenopause. The main factor determining increased CMR in menopausal women was considered to be a decrease in estradiol (E2).[1,21] Insulin resistance and associated metabolic disorders: dyslipidemia, weight gain (assessed by body mass index, BMI, and waist circumference, WC) and decreased glucose tolerance tend to increase sharply with the onset of menopause. [23]

Changes in the functional state of the pituitary-ovarian axis with hormonal fluctuations affecting insulin sensitivity are observed already in premenopause,[20,24] along with the transformation of closely related metabolic and hemodynamic parameters,[25] which also start in this period. [26-29] Of the components of MetS, hypertension is the leading risk factor for CVD and mortality,[30] and the most modifiable.[31-32] Its prevalence greatly affects postmenopausal women; control indicators remain suboptimal, accounting for almost 50% among middle-aged women.[2] Importantly, postmenopausal women with hypertension experience higher CVR at lower blood pressure (BP) thresholds.[33] With an average duration of 2–8 years before the last menstrual period, MT is associated with increased clinical and subclinical CVR,[7] including functional and structural indices of subclinical atherosclerosis.[34]

Dysglycemia makes a significant contribution in this direction. Prediabetes is already associated with a significant risk, presence and progression of CVD, [35-38] while the prevalence of T2DM in postmenopause was most strongly associated with BP levels,[28] and insulin resistance is the central link in pathogenesis.[38-40] There is no doubt that IR is a complex and multifaceted syndrome that increases the risk of CVD [41] and can affect BP homeostasis.[42]

To assess IR, surrogate indicators significantly associated with CVD and diabetes have been developed: the triglyceride-glucose index (TyG), the HOMA-IR index and others.[43] The TyG index is a simple, cost-effective and reliable indicator of IR. [44-45] Its potential and reliability as a prognostic biomarker of all components of the CMD and components of the MetS have been demonstrated.[46-51] The superiority of the TyG indexes over HOMA-IR in predicting hypertension has been shown,[52] with the influence of demographic characteristics: age, gender, and race.[53] The difference in the prognostic value of IR indicators depending on gender,[54] confirmed by the analysis of NHANES data on TyG among adults of different genders and ethnic groups [55] and the long-term prospective TLGS study, [56] determines the need to study proxy indicators of IR in various cohorts of individuals.

A pronounced correlation of the TyG index with the likelihood of developing hypertension in normoglycemic

patients has been revealed, [57-60] but only in rare cases was stratification by gender carried out,[61] or cohorts of postmenopausal women were studied.[61-63] We were unable to find publications on the prognostic role of TyG in relation to hypertension in perimenopausal women depending on hormonal status.

Objective: to evaluate the informativeness of the surrogate marker of insulin resistance, the TyG index, in predicting arterial hypertension in normoglycemic perimenopausal women.

Patients and Methods

A single-center cross-sectional cohort study conducted as part of a preventive outpatient examination of the population of a large city in Western Siberia (2005-2006) included 88 Caucasian women aged 35-59 years: 30 were normotensive, 58 had hypertension. Exclusion criteria: carbohydrate metabolism disorders and other endocrine diseases; previously diagnosed coronary 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) 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 the 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%); some women were in perimenopause, including late premenopause and early postmenopause, which is characterized by an increase in FSH levels > 25 mU / l.[64]

The following MetS markers were determined: WC, BMI, blood pressure levels, systolic (SBP) and diastolic (DBP); fasting glycemia (FG) values were estimated twice by the glucose oxidase method, the average values were 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 measured by enzyme immunoassay on an IMMULITE 2000XPi analyzer. The TyG index was calculated using the formula: TyG index = Ln [TG (mg/dL) x FG (mg/dL) / 2],[65] the HOMA2-IR and HOMA2-B indices were determined using the HOMA2 calculator. [66]

Statistical processing of the data was performed using SPSS software (version 23). The data were presented as median (Me) (25th; 75th percentiles) and compared using Mann-Whitney (two groups' comparisons) tests. Possible correlation between hypertension risk score and parameters were tested with Spearman's non-parametric correlation analysis and results were given as correlation coefficient (ρ). Partial correlation was used to level out the influence of age.

A receiver operating characteristic (ROC) curve analysis was applied to determine the cutoff point of the TYG indicator that could identify risk hypertension to determine the area under the curve (AUC), sensitivity (Se) and specificity (Sp). Area under curve higher than 0.75 was considered as a good discrimination. The associations between presence hypertension and clinical parameters were evaluated by logistic regression analysis, adjusted age. Two-tailed $p<0.05$ was used as the criterion for a statistically significant differences and correlations. 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. Women in group 2 were older, in addition to the BP levels that marked the group, they had higher WC, BMI, TG, FG and lower HDL-C. At the same time, anthropometric and lipid characteristics in group 1 did not fully fit into the reference limits. Glycemic 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 hypertension presence, 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
BMI, kg/m2	25,30 (22,42; 27,39)	30,60 (26,33; 34,30)	<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

Parameter	Group 1 n = 30	Group 2 n = 58	* – p 1-2
TG, mmol/l	1,75 (1,49; 2,13)	2,30 (2,00; 2,500)	<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
HOMA2-B, cu	143,24 (110,50; 168,38)	158,50 (114,60; 191,40)	NS
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)	NS

Note: p1-2–significance of differences between groups 1 и 2; NS - non-significant.

The groups did not differ statistically in the parameters of the functional state of the pituitary-ovarian axis due to the high variability of FSH and E2 levels depending on the period of MT.[19,64] Taking into account the tendency for differences between the groups in FSH levels (Table 1), the older age of women in group 2 and, accordingly, different stages of MT, the groups were compared by the FSH level>/<25 mIU/L (30% and 52% in groups 1 and 2, respectively), their statistical difference was revealed (Pearson criterion $\chi2=3.781$, $p=0.052$). 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 correlation analysis of age with MetS parameters and perimenopause in a cohort of perimenopausal women with different BP levels (n=88).

Age	Parameter									
	WC	BMI	SBP	DBP	FG	TG	HDL-C	DPM	FSH	E2
R p	0,456 <0,001	0,382 <0,001	0,374 <0,001	0,306 0,004	0,309 0,004	0,236 0,027	-0,29 0,006	0,707 <0,001	0,543 <0,001	-0,336 0,001

Note: R – Spearman's correlation coefficient.

Our earlier analysis of the correlations between the characteristics of MetS and the levels of INS, HOMA2-IR and TyG indices served as the basis for further analysis to select TyG.[67] It showed the presence of more extensive and close relationships, and all its associations, including INS and HOMA2-IR, remained significant with partial correlation, reflecting only partial dependence on age. In contrast, INS and HOMA2-IR, when corrected for age, correlated only with WC, TG and TyG levels.[67] Of the anthropometric parameters, WC was selected taking into account its more significant associations with TyG in both types of correlation analysis, both in comparison with HOMA2-IR and with BMI (Table 3).

Table 3. Results of the correlation analysis of anthropometric parameters with insulin resistance indices in a cohort of perimenopausal women with different BP levels.

correlation coefficient	Spearman's correlation		partial correlation	
Parameter	TyG	HOMA2-IR	TyG	HOMA2-IR
WC	0,526***	0,507***	0,424***	0,370***
BMI	0,437***	0,393***	0,373***	0,292**

Note: * - significance of differences ≤0,05; ** ≤0,01; *** - ≤0,001.

The TyG index (Fig. 1) independently correlated with HDL-C, WC and INS (R=0,550; p<0,001; Rpc=0,409; p<0,001), and to a lesser extent with SBP, DBP and DPM (Fig.1). The relationships between TyG levels and FSH were age-dependent. The Spearman correlation of FSH with DPM (R=0,622; p<0,001) significantly weakened (Rpc=0,273; p<0,01) when the effect of age was leveled (Fig. 1).

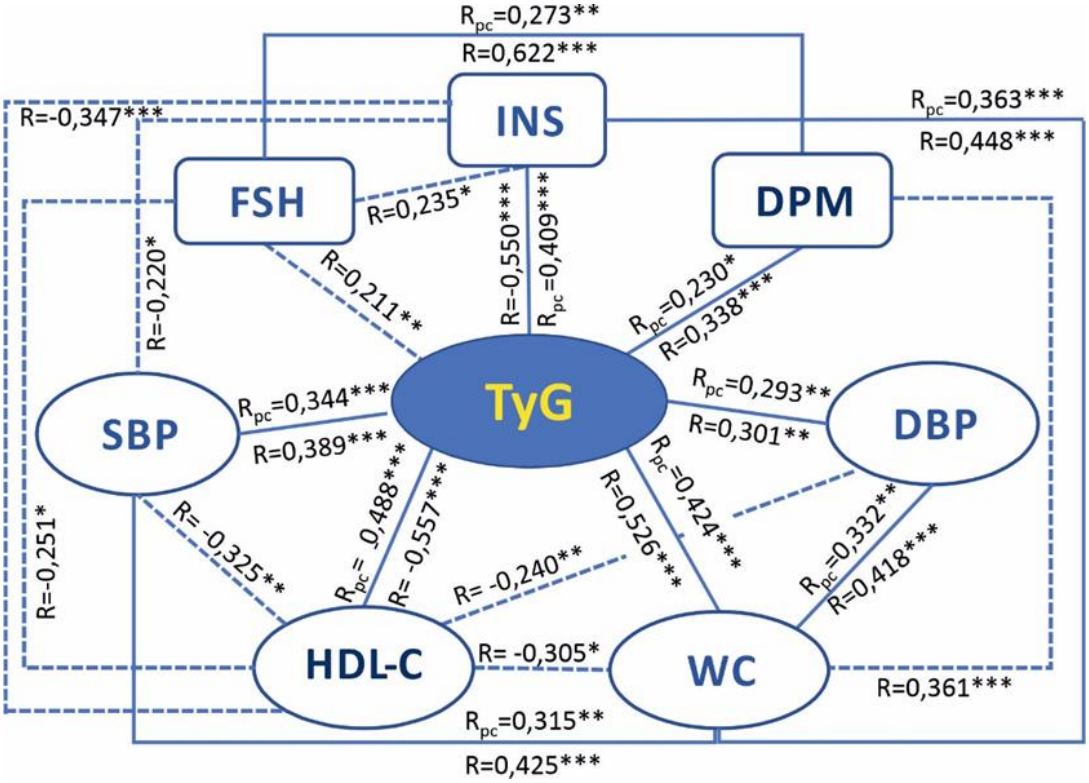

Fig.1. Associations of TyG index with markers of MetS and perimenopause in a cohort of women with different BP levels; R – Spearman's correlation coefficient (solid line); Rpc – partial correlation (dotted line); significant difference: * ≤ 0,05; ** ≤ 0,01; *** ≤ 0,001.

The correlations of WC were stable with BMI, TyG, SBP and DBP levels, and age-dependent with HDL-C and DMP. Fasting glucose, an important marker of MetS, was not included in the analysis, since it is included in the formula for calculating the TyG index. The correlations of FG with the parameters of MetS and perimenopause in comparison with TyG (Table 4) are weaker and do not correlate with DBP and FSH, however, FG is age-dependently associated with estradiol levels (Table 4).

Table 4. Results of correlation analysis of glucose levels with MetS and perimenopause parameters in a cohort of women with different BP levels (n=88).

	Parameter								
Glucose	**WC**	**SBP**	**DBP**	**INS**	**TG**	**HDL-C**	**DPM**	**FSH**	**E2**
R	0,444	0,286	0,171	0,562	0,337	-0,397	0,3543	0,133	-0,220
p	<0,001	0,007	NS	<0,001	0,001	<0,001	<0,001	NS	0,040
R_{pc}	0,349	0,219	0,156	0,440	0,297	-0,279	0,313	0,007	-0,038
p	0,004	0,050	NS	<0,001	0,007	0,012	0,004	NS	NS

Note: R – Spearman's correlation coefficient.; R_{pc} - partial correlation; p- significant NS - non-significant.

To identify associations of the studied parameters with the probability of hypertension, a univariate logistic analysis with age standardization was performed (Table 5). It included WC and HDL-C (as the main parameters of MetS) and TyG index, the logarithmic ratio [65] of two more components of MetS, reflecting the baseline insulin resistance, a key factor in many metabolic disorders. [68] Hemodynamic parameters as a characteristic of hypertension were excluded from the analysis.

Table 5. Results of univariate logistic regression analysis *

Parameter	**Statistical parameters**						
	B	**Sig.**	**Exp(B)**	**95,0% C.I. for EXP(B)**		**Se**	**Sp**
				Lower	**Upper**		
WC	0,093	**0,001**	**1,097**	1,038	1,160	84,5	53,3
TyG	3,409	0,001	30,246	4,409	207,484	86,2	53,3
HDL-C	-11,427	**0,003**	**0,001**	0,0001	0,021	84,5	40,0

* Models are standardized by age

Next, a multiple logistic regression analysis was performed, which additionally included two parameters, INS and FSH, taking into account their statistical significance (Table 1), as well as a close relationship with the menopausal transition (FSH as an early responding hormone of changes in the functional state of the pituitary-ovarian axis in perimenopause [41]). When including these parameters in model (1), WC (OR = 1.093; p = 0.013) and HDL-C (OR = 0.001; p = 0.023) were statistically significantly associated with the presence of hypertension. The sensitivity of model (1) was 87.9%; specificity 60.0% (Table 6).

Table 6. Results of multiple logistic regression analysis (model 1).

Parameter	Statistical parameters				
	B	Sig.	Exp(B)	95,0% C.I. for EXP(B)	
				Lower	Upper
Age	0,088	0,172	1,092	0,962	1,240
INS	-0,057	0,284	0,944	0,851	1,049
WC	0,089	**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, OR – odds ratio, CI – 95% confidence interval for OR; Se=87,9%; Sp=60,0%.

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 (Table 7).

Table 7. Results of multiple logistic regression analysis (model 2).

Parameter	Statistical parameters				
	B	Sig.	Exp(B)	95,0% C.I. for EXP(B)	
				Lower	Upper
Age	0,079	0,203	1,082	0,958	1,221
INS	-0,028	0,607	0,972	0,873	1,082
WC	0,101	**0,003**	**1,106**	1,034	1,184
FSH	-0,004	0,677	0,996	0,978	1,014
HDL-C	-12,205	**0,004**	**0,001**	0,0001	0,023

Note: B – regression coefficient, OR – odds ratio, CI – 95% confidence interval for OR; Se=84,5%; Sp=60,0%.

When including TYG and excluding HDL-C (model 3), the sensitivity of the model remains 87.9%, the specificity increases compared to models (1) and (2) and is 63.3%, which serves as the basis for considering model 3 as the working model for further analysis (Table 8). There is a need to identify the cutoff point for the TyG index in this cohort of women, taking into account ethnic and gender characteristics in numerous studies of the prognostic role of TyG.[52-53]

Table 8. Results of multiple logistic regression analysis (model 3).

Parameter	Statistical parameters				
	B	Sig.	Exp(B)	95,0% C.I. for EXP(B)	
				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, OR – odds ratio, CI – 95% confidence interval for OR; Se=87,9%; Sp=63,3%.

Using ROC analysis (Fig. 2), a cutoff point was determined for the TYG indicator – 8.7 conventional units, at which the ratio of sensitivity and specificity of the diagnostic test (the presence and absence of hypertension) was optimal. The area under the curve (AUC) was 0.793 (95% CI: 0.694-0.892), p <0.0001; sensitivity (Se) 74%, specificity (Sp) 67%, which indicates good quality of the diagnostic test.

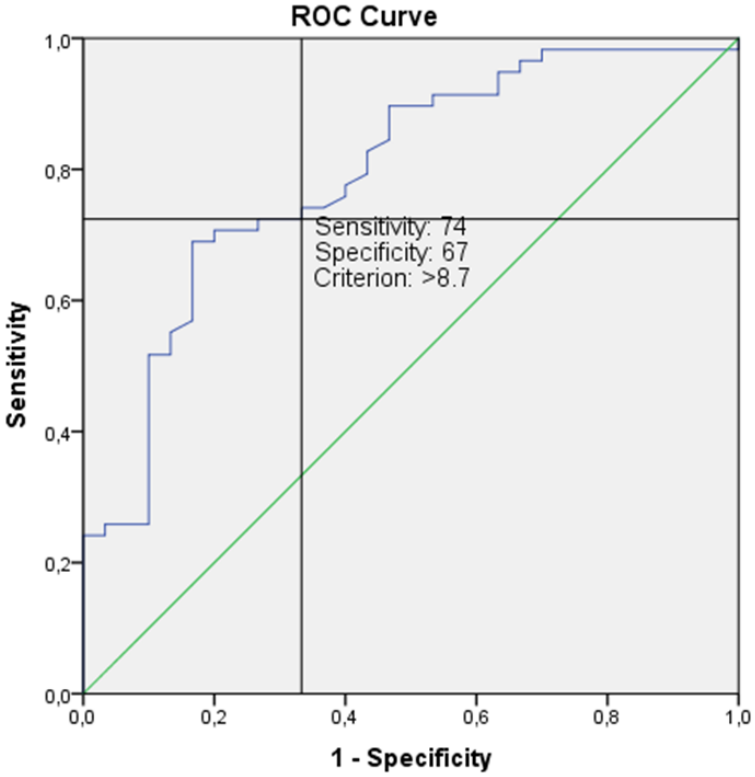

Fig.2. ROC curve of diagnostic ability of TYG indicator for predicting the presence of hypertension in normoglycemic perimenopausal women.

Discussion

In the studied cohort of perimenopausal women, age significantly correlated with all parameters of MetS and perimenopause (Table 2), most strongly with hormonal characteristics of the pituitary-ovarian axis and DPM, drawing attention to the characteristics of reproductive health and the timing of menopause. Without going into detail in the discussion of the features of chronological and biological age,[69,70] we note that human aging beyond the reproductive age (after menopause in women) can proceed in several directions: evolutionarily neutral, with acceleration, or favor a slow program.[71] When developing a comprehensive identification of phenotypic age as a marker of biological aging, a variety of data were introduced through integration, hypertension and obesity were included from clinical data, lipid and carbohydrate characteristics from biochemical data,[72] that is, MetS markers. Our study is consistent with a similar strategy.

Given the prevalence of traditional CVD risk factors (family history, smoking, hypertension, overweight, dyslipidemia, T2DM) in old age, it is important to consider specific factors associated with changes in sex hormones during previous life, which affect CMR at any age, in middle-aged or young women.[73] An association between menopause and an increased risk of CVD is noted in early menopause (<45 years), which is traditionally explained by the loss of the protective effect of endogenous estrogens.[34,74,75]

Significant multidirectional associations of FSH and E2 with age reflect changes in the functional state of the pituitary-ovarian axis during MT (Table 2); the absolute value of the direct association of age with FSH was stronger in contrast to the association with E2, which is consistent with the dynamics of estradiol and FSH levels according to the stages of reproductive aging.[9] In contrast to the wide fluctuations in estradiol at the onset of menopause to consistently low levels in postmenopause, FSH levels rise steadily beginning in premenopause.[76-78] By this point in life, the follicles are virtually exhausted and cannot synthesize sufficient estrogens to reverse the effects on the hypothalamus and pituitary gland. As a result, excess gonadotropins are continually secreted, further accelerating follicular depletion until menopause.[79]

Initiation and progression of MetS parameters in women, closely related to both chronological and reproductive aging,[2,73,75,80] often secondary to menopause, are closely linked by insulin resistance. Clinically, IR is also manifested by metabolic consequences: hyperglycemia, hypertension, dyslipidemia, accumulation of visceral adipose tissue (VAT) and endothelial dysfunction (ED),[8,53] which contribute to accelerated CVR. The simplest indicator for clinical alertness regarding insulin resistance is WC, a MetS marker reflecting the accumulation of VAT. We chose WC taking into account its more significant correlations with TyG in comparison with HOMA2-IR and with BMI (Table 3). Reflecting disturbances in the biological response to insulin stimulation,[81] primarily in target tissues, liver, muscle, and adipose tissue,[53] insulin resistance plays a key role in the development and progression of many CMDs,[82] which is explained by the wide range of metabolic effects of insulin in various organs and tissues.[83]

The need for a quantitative assessment of IR has determined the development of a large number of

surrogate indices, starting with HOMA-IR. Surrogate IR indices tested using the euglycemic test were initially used to assess dysglycemia and later began to be used to predict CVD. It is believed that the non-insulin TyG index, reflecting not only glucose metabolism but also aspects of lipid metabolism that are not covered by HOMA-IR, is superior to it in predictive accuracy. [55]

Glucose and lipid metabolism disorders, in particular elevated TG and FG levels, are known risk factors for hypertension and also reflect the IR status in the liver and adipocytes.[84] A meta-analysis of twenty observational studies (n= 451 455) demonstrated the reliability of the TyG as a prognostic marker of MACE in patients with hypertension [52], with the highest risk noted in young adults with hypertension, especially in women.[63] Since the TyG index is based on TG and FG parameters, its level may theoretically depend on dyslipidemia and the patient's diabetic status.[65] The possibility of using the index in the population regardless of age, diabetes status and gender has been confirmed.[52]

The TyG index, in the absence of associations with E2, correlated age-dependently with FSH levels (Fig. 1). Our earlier correlation analysis in a group of perimenopausal patients with hypertension (group 2) revealed positive TyG relationships with FSH (R=0.312; p<0.02; Rpc =0.286; p=0.030) and negative relationships with E2 (R= -0.393; p<0.01; Rpc = -0.376; p=0.004).[19] The relationship between FSH and TyG (more stable in the subgroup of women with hypertension), in combination with the staging of MT according to STRAW+10, [9] determines the interest in the role of FSH during perimenopause. Evidence is accumulating of extragonadal functions of FSH after detection of expression of its receptors on blood vessels, adipose tissue, liver, osteoclasts, neurons of the hippocampus and cortex.[85,86] 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". [87,88]

The correlations of the TyG index with the DPM in both types of correlation analysis (Fig. 1) reflect the relationship of IR with the chronological and reproductive. [7] The triangle of correlations TyG-DPM -FSH-TyG (Fig. 1), where age is a dependent relationship of TyG with FSH, in contrast to this relationship in the subgroup of patients with hypertension, which is significant even when the influence of age is leveled,[19] possibly reflects accelerated aging in hypertension. [33,89-91] This assumption also takes into account the influence of age on the relationship of TyG with BP levels, that is, through the mechanisms of IR [92] with hypertension playing the leading role in this tandem, returning us to the peculiarities of reproductive aging of women.

The risk of developing MetS increases with years after menopause, but the full impact of DPM remains unclear. [20] It was DPM that was found to be the most important risk factor for MetS when it lasted more than 5 years [93]; the cited study did not analyze the indices of the functional state of the pituitary-ovarian axis. The effect of DPM on TyG is weaker than the associations of the IR index with the MetS markers, WC, and HDL-C (Fig. 1), drawing attention to the possibility of using these indices in the prognosis of hypertension. The observed associations with WC reflect key metabolic changes in perimenopause: the accumulation of VAT and IR, which together contribute to a marked increase in the risk of MetS and CVD.[94-97] The obesity phenotype is fundamentally important in terms of CMR; WC serves as a simple marker of abdominal obesity.[98-100] Although the increase in VAT during MT is well documented, the underlying causes and mechanisms have not been studied in detail.[101] Hormonal changes including hypoestrogenemia, hypergonadotropinemia, relative hyperandrogenemia, growth hormone deficiency, leptin resistance and chronic stress affecting the hypothalamic-pituitary-adrenal axis have been implicated in the initiation of perimenopausal obesity .[99] Changes in CMR factors occur during MT, which is divided into two subcategories: perimenopause (early and late) and postmenopausal years. [102] In women, CMR is influenced by other reproductive factors: age of menarche,[103] gestational diabetes and hypertension, [25,75] PCOS, premature ovarian failure,[25,75] determining the complexity of the problem.

Initially, the accumulation VAT was mainly associated with the decline in estrogens.[100,104-105] Although E2 concentrations are lower in early postmenopause compared to premenopause, the patterns of E2 decline and FSH increase in perimenopause are heterogeneous.[102,106] Consistent with the concept of an “atypical pituitary hormone–target tissue axis”,[87,88] the presence of FSH receptors in VAT reflects the involvement of FSH in postmenopausal visceral obesity and may contribute to a proinflammatory environment [20,107-108]; chronic inflammation is an important marker of aging.[109]

Since the decrease in E2 values and the increase in FSH levels during MT have a significant overlap period, and ovarian hormones significantly affect FSH levels, further clinical studies are needed to determine the role of FSH in this process: primary or secondary.[108] We did not find any direct associations of WC with FSH levels, but WC consistently correlates with TyG, which interacts with gonadotropin levels in an age-dependent manner (R=0.211; p=0.049), similar to the nature of the relationship between WC and DPM (R=0.361; p<0.001) (Fig. 1). At the same time, DPM correlates with FSH, maintaining the effect of age. The data obtained return to the problem of chronological and reproductive aging, touching upon the situation with increased accumulation of VAT in perimenopause. The fully age-dependent correlation of DPM with WC (Fig. 1) is consistent with the view that the main factor determining weight gain is not menopause, but age, but hormonal changes in WC significantly contribute to the increase in VAT associated with IR.[98] In the studied cohort, WC forms a complex of relationships with the characteristics of MetS and DPM, the closest with TyG. Thus, both aging and hormonal influences, as well as lifestyle factors: alcohol consumption, physical exercise and diet, have a complex effect on the distribution of adipose tissue and its health.[96]

Increasing evidence points to the critical role of IR in the transition from the physiological state of decreased

insulin sensitivity to individual CMDs and cardiometabolic multimorbidity,[12] closely associated with atherosclerosis. The main factor in the formation and progression of atherosclerotic plaques and cardiac dysfunction is lipid imbalance[110]; its unfavorable change is observed already within one year after the last menstruation.[111] Dyslipidemia, a key feature of MetS, characterized by elevated TG and reduced HDL-C levels, plays a decisive role in the progression of the cluster,[112] with a close association of hypertriglyceridemia with IR.[113]

In abdominal obesity, adiponectin and related biomarkers may contribute to sex-specific CMD factors. Statistically significant sex differences in HDL-C, TG, FG, insulin, HOMA-IR and adiponectin levels were demonstrated.[96] In the studied cohort of women, HDL-C levels, differing depending on the presence of hypertension (Table 1), closely correlated with TyG after age adjustment; the relationships between HDL-C and FSH, BP, INS and WC were completely age-dependent (Fig. 1).

Protective markers, HDL-C and percentage of lean body mass, are closely associated with MetS.[114] It is believed that a decrease in cardiovascular protective HDL-C indicates menopause as an independent risk factor for atherosclerosis.[115] A potential marker of coronary atherosclerosis is coronary artery calcification.[116] The cardioprotective significance of HDL-C may vary depending on the stage of MT or estradiol level and depends on HDL subclasses (small and large molecules), the level of which changes at different periods of perimenopause,[117] complicating the prognostic interpretation of their conventional analysis.[116] It was reported that insulin resistance values were no longer associated with CVD risk after adjustment for LDL-C in postmenopausal women without diabetes,[118] but HOMA-IR was used as an IR marker. It is suggested that the FSH-metabolic circuit in menopause may include dyslipidemia.[119] However, these studies are fragmentary and contradictory, revealing closer but opposite associations of FSH with LDL-C and less close associations of gonadotropin with HDL-C and TG.[120,121]

In a study of the temporal relationship between blood lipids and IR in a longitudinal cohort of perimenopausal women, bidirectional relationships were observed between insulin resistance, TG, and HDL-C.[97] These results allowed the authors, without denying dyslipidemia as a recognized risk factor for IR and diabetes, to suggest that insulin resistance may be the cause of lipid disorders; while VAT in perimenopause may contribute to the development of DLP and IR. Functional changes in the phenotype of adipose tissue with the accumulation of VAT are noted with aging,[122] confirming the close relationship between chronological and reproductive aging in women. In the studied cohort, it is WC that more closely correlates with the TyG index (Table 3), reflecting the close relationship between IR and VAT. In women, it is TG that serves as one of the most important risk factors for T2DM.[4] However, in a study of the frequency of MetS and its prognostic factors in peri- and postmenopausal women according to the NCEP-ATP III criteria, the predominant marker was OT with a lower expression of TG.[123]

Of particular interest is FG, an age-dependent indicator (Table 2) that correlates with the range of parameters studied (Table 4) in the absence of relationships between age and INS ($R=0.191$; $p>0.05$). Women in the study cohort had reference levels of FG, without changes in the insulin secretory capacity of β-cells assessed by HOMA2-B (Table 1), which excluded dysglycemia at the time of examination. However, some increase in the levels of INS, WC and IR indices in women with hypertension and dyslipidemia (Table 1) reflects a further risk of dysglycemia. This is evidenced by multiple correlations of FG with the MetS and MT parameters (Table 4). Note that insulin correlates positively and age-dependently with SBP and FSH levels, negatively with HDL-C levels with a more stable relationship with WC (Fig. 1). Along with the gradual increase in IR against the background of obesity, the decrease in insulin secretion contributes to the vulnerability of glucose metabolism,[124] with the contribution of DPM to this process, as well as subclinical coronary atherosclerosis.[125] Key factors in this direction also include age, body mass index and hypertension; as a result, dysglycemia, in fact, completes the formation of "full" MetS.[126]

A longitudinal nationwide Korean study found an increased odds of sequentially acquiring abnormal FG over 8 years in pre- and postmenopause, with a more consistent association in premenopause.[127] The stronger association between obesity and T2DM in premenopause is explained by the postmenopausal synthesis of estrogens in adipose tissue via androgen aromatization, which may have a protective effect against diabetes mellitus.[128] A compelling systematic review suggests an indirect association of FSH levels with abnormal FG in postmenopausal women.[129] The statistically significant positive correlations of FG with DPM and negative correlations with E2, with its characteristic decrease in the late stage of MT and no association with FSH (Table 4), are also logically consistent with a higher probability of dysglycemia in the late phase of perimenopause.

Insulin level is not part of the five MetS criteria, since measuring this parameter for screening is cumbersome,[130] but the patterns of its relationships with MetS markers are of interest. Associations of INS with TyG and WC, stable when corrected for age (Fig. 1), the absence of changes in HOMA2-B with a reference increase in FG, reflect the intense work of β-cells together with an increase in IR, assessed by TyG (Table 1), with only a partial influence of age (Fig. 1). An increase in INS levels in close connection with an increase in IR is at the center of a whole complex of links in the pathogenesis of MetS.[131] It is believed that an increase in TyG is associated with a violation of β-cell function independent of glucose metabolism, and the TyG index is an alternative indicator for predicting β-cell dysfunction.[132]

The TyG index forms a spectrum of significant associations with the characteristics of MetS and perimenopause (Fig. 1), the closest with INS, WC and HDL-C, maintaining with partial correlation. The presence of stable associations of TyG with SBP and DBP levels indirectly reflects the participation of insulin resistance in the formation of hypertension, and the age-dependent

relationship of the index with FSH and preserved with age-corrected DPM - a complex role in the dynamics of perimenopause. The obtained data serve as a basis for assessing the TyG index in predicting hypertension in normoglycemic women in perimenopause. The presence of hypertension served as a grouping variable, by which the examined women were divided into groups, with stable correlations of TyG with BP levels in the general correlation matrix.

To identify associations of the studied parameters (the main components of MetS) with the probability of hypertension, a univariate logistic analysis with age standardization was performed (Table 5). All three parameters were significantly associated with hypertension, however, with the same sensitivity for WC and HDL-C (84.5%), the lipid parameter had a lower specificity (40.0%), while the TyG index, with the same specificity as WC (53.3%), had a higher sensitivity (86.2%).

The multiple logistic regression analysis additionally included the INS and FSH parameters, taking into account their statistical significance (Table 1) and close relationship with MT. An additional reason for including FSH in this analysis was new data on the extragonadal effects of FSH: the effect on FG levels,[129] lipid withdrawal,[120,121,133] and accumulation of VAT.[99,133] When including the specified parameters in model (1), 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 6). 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 (Table 7). At the same time, when including TYG and excluding HDL-C (model 3), the sensitivity of the model 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 8).

Thus, this model, including OT and TyG, generally accepted markers of IR, as well as insulin (as an indicator of the compensatory function of β-cells with an increase in OT and TyG), with the inclusion of FSH (the first hormone of the pituitary-ovarian axis, the change in which marks premenopause and, accordingly, reproductive aging) and age (as an indicator of chronological aging), reflects the chance of having hypertension in a cohort of perimenopausal women. There is a need to identify a cutoff point for the TyG index, taking into account ethnic and gender characteristics in the prognostic and diagnostic role of TyG.[52,53] Using ROC analysis (Fig. 2), a cutoff point for the TYG indicator was determined - 8.7 conventional units, at which the ratio of sensitivity and specificity of the diagnostic test (the presence and absence of hypertension) turned out to be optimal. The area under the curve (AUC) was 0.793 (95% CI: 0.694-0.892), p <0.0001; sensitivity (Se) 74%, specificity (Sp) 67%, which indicates good quality of the diagnostic test.

TyG index has been identified as a reliable alternative marker of insulin resistance in CMD,[59,65,134-137] including hypertension.[59,134] The question arises about the mechanisms of the relationship between IR and hypertension. Molecular mechanisms underlying IR and CMD include metabolic flexibility, endothelial dysfunction (ED) and inflammation, coagulation disorders, and smooth muscle dysfunction.[65] Insulin resistance also strongly correlates with CVD, potentially through pathways of excessive activation of the sympathetic nervous system,[138-140] the renin-angiotensin-aldosterone system,[138,139] and increased sodium reabsorption.[52] Elevated baseline TyG levels and higher long-term trajectory have been independently associated with increased arterial stiffness.[141]

Metabolic flexibility is understood as the ability to switch between energy sources in response to changing physiological needs.[142] Traditionally, its understanding included the analysis of postprandial glucose metabolism only. The modern interpretation of metabolic flexibility includes an assessment of the interaction between glucose and TG metabolism.[143] Insulin plays a central role in coordinating metabolic flexibility, and IR can disrupt it, contributing to the development of T2DM and obesity.[144] We believe that the statistically significant age-adjusted relationships of INS with WC and TyG (Fig. 1) reflect this pathogenetic pathway, and the use of the TyG index to assess insulin resistance, although it assesses insulin sensitivity by integrating only fasting triglyceride and glucose levels,[145] acquires additional meaning.

With age, VAT, closely associated with the synthesis of proinflammatory mediators, angiogenic dysfunction, and microvascular abnormalities, may exert systemic adverse effects on the CMR and various target organs.[122] Conditions associated with high BP include ED[146] and low-grade inflammation.[147] Since VAT releases multiple proinflammatory cytokines,[122,148] it is widely believed that the initiation of pathological events associated with the development of postmenopausal obesity is directly associated with systemic inflammation.[149] Population studies have linked IR to systemic low-grade chronic inflammation,[148] which is also initiated by estrogen deficiency.[104] A compelling analysis of three cohorts: NHANES, UK Biobank and Shanghai-Pudong (n=178974) showed that inflammatory markers linked TyG index and obesity indices with adverse cardiovascular events in hypertensive patients; the authors emphasize that insulin resistance and the inflammatory pathways through which IR causes adverse clinical outcomes remain a priority for future research.[140]

Insulin resistance is usually considered as a decrease in sensitivity to the metabolic effects of insulin, including insulin-mediated glucose utilization. However, decreased sensitivity to the normal vascular action of insulin, especially decreased nitric oxide production, plays an additional important role in the development of CVD in IR.[150] Recent data indicate that the action of insulin extends beyond metabolic cells and also affects blood vessels, where insulin affects capillary transport,[151] focusing attention on the endothelium as a controller of subsequent insulin actions on metabolically active tissues.[152] Accordingly, IR variants are distinguished:

endothelial (vascular)[151,153,154] and metabolic (systemic),[153,154] with the former predominantly affecting vascular endothelial cells, and the latter primarily affecting peripheral cells.[154] Metabolic IR (characterized by a quantitative reduction in the action of insulin on glucose metabolism in skeletal muscle, liver, and adipose tissue) is a hallmark of diabetes, obesity, and related conditions.[153] Vascular and metabolic IR synergistically create conditions that predispose to the development of CVD. Moreover, endothelial dysfunction may precede impaired insulin-stimulated glucose uptake, making it a key factor in the development of CVD.[155]

The multifaceted relationship between IR and atherosclerosis is undeniable, with emphasis on their role as independent and interrelated factors contributing to CVR. Atherosclerosis is characterized by lipid accumulation and chronic inflammation in the arterial walls due to hypertension, dyslipidemia, and genetic predisposition, with ED being a key early event.[156] Metabolic and clinical factors secondary to menopause: dyslipidemia, IR, VAT, and hypertension contribute to accelerated CVR. Menopause is independently associated with adverse effects on functional and structural parameters of subclinical atherosclerosis,[2,34] which appears to be the end result of the interaction the factors of the CVR and their amplification during perimenopause.[8]

Postmenopausal hypertension and accelerated atherosclerosis were previously explained solely by decreased estrogen levels. Recently, the relationship between elevated FSH levels and the prevalence of extragonadal diseases has been studied within the framework of the concept of "atypical pituitary hormone-target tissue axis",[87,88] which has attracted particular attention in the development of age-related diseases in perimenopausal and postmenopausal women.[133] The increased risk of MetS in MT may be partly due to changes in FSH and luteinizing hormone (LH) levels. However, studies of this relationship at all stages of MT are fragmentary, and their results are contradictory. It is reported that high FSH levels in postmenopause favored insulin sensitivity with higher adiponectin levels and lower HOMA-IR.[157] In NHANES, elevated FSH and LH levels were associated with lower risk and severity of MetS in postmenopausal women.[158] However, in another report, elevated gonadotropin levels were associated with increased body fat mass and decreased lean mass in postmenopausal but not premenopausal women, with an emphasis on higher FSH and LH percentiles.[159] Higher FSH levels were associated with higher WC, TG, LDL-C, BP, and risk of metabolic syndrome in perimenopausal women,[20,107,108] suggesting a role for elevated FSH as a risk factor for biomarkers of perimenopausal MetS,[160] drawing attention specifically to MT. Distinct trajectories of blood pressure were reported during menopause, allowing the researchers to identify a group of women whose trajectories are consistent with the contribution of menopause.[161]

Evidence has been presented for a possible role of FSH in the pathogenesis of endothelial dysfunction and CVD in women with pathologically high plasma FSH concentrations, such as menopause.[162] This is consistent with experimental data on decreased serum adiponectin levels, thereby promoting fat accumulation[20] due to FSH receptor signaling in adipose tissue.[161] Follicle stimulating hormone levels are independently associated with adiponectin levels in postmenopause.[163] Adiponectin, a hormone secreted by adipose tissue that has insulin-sensitizing and anti-inflammatory properties with protective effects against endothelial dysfunction, provides protection against atherosclerosis via metabolic and sphingolipid changes in the endothelium.[164] The adiponectin ("rescue hormone") system is considered as the missing link between metabolic and cardiovascular diseases due to its cardioprotective, anti-inflammatory and metabolic effects, including increased insulin sensitivity.[165]

Conclusion

Early cardiovascular protection depends on the accuracy of risk prediction with insulin resistance playing a critical role, determining the importance of searching for simple, informative biomarkers of IR.[12] The TyG index is increasingly recognized for assessing IR and cardiometabolic risk in individuals without diabetes, including hypertension,[50,60,84,166] with the expectation that it will become an alternative to the clamp test.[167] The interaction of multiple risk factors in the pathogenesis of CVD suggests additional prognostic value for integrated parameters such as TyG.[52] The study of the relationship between the TyG index and hypertension is one of the most pronounced trends in recent years,[60] confirmed by current bibliographic analysis.[168] TyG associations with hypertension are multifaceted: links with prognosis, different stages and phenotypes of hypertension, their progression, could serve as a surrogate indicator for early treatment of hypertension,[169] and can also be used in the population regardless of age, diabetic status and gender.[52] Although the positive relationship between the TyG index and the development of hypertension is reasonably presented in current meta-analyses,[60,167] the gender specificity of these associations requires additional research.[167] In the existing literature, such data regarding the stages of MT are rare.[170]

Insulin resistance plays a critical role in the clustering of menopausal MetS during the transition from individual CMD to cardiometabolic multimorbidity.[12] The ability of IR to independently predict atherosclerotic plaque progression has been convincingly demonstrated, even in individuals without diabetes, acting through both traditional risk factors and direct vascular effects.[156] As menopausal transition is staged, vascular endothelial function progressively declines and the stiffness of large elastic arteries increases.[5] In fact, during MT, reproductive aging is superimposed on chronological aging with serious consequences for cardiovascular-renal-metabolic syndrome and CVD.[73,101] The understanding that perimenopause is a biopsychosocial turning point in the prevalence of CMR and CVD[171] determines the importance of studying the relationships between metabolic and hormonal parameters in perimenopausal women with age-adjusted correlations.

Conflict of interests

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.

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;
D.S. Ruyatkin - idea, concept and design of the article, collection and processing of material, analysis of the data obtained, writing the text of the article;
L.V. Shcherbakova – ideas for statistical data analysis and participation in its implementation

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