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Diagnostic markers of insulin resistance to discriminate between prediabetes and diabetes in menopausal women

A.M. CYBULSKA[1], D. SCHNEIDER-MATYKA[1], S. WIEDER-HUSZLA[2], M. PANCZYK[3], A. JURCZAK[2], E. GROCHANS[1]

[1]Department of Nursing, Faculty of Health Sciences, Pomeranian Medical University in Szczecin, Szczecin, Poland
[2]Department of Clinical Nursing, Faculty of Health Sciences, Pomeranian Medical University in Szczecin, Szczecin, Poland
[3]Department of Teaching and Outcomes of Education, Faculty of Health Science, Medical University of Warsaw, Warsaw, Poland

Abstract. – OBJECTIVE: Menopause is an important transition period in a woman's reproductive life during which hormonal changes occur, resulting in an increased risk of cardiovascular disease and type 2 diabetes. In this study, we assessed the possibility of using surrogate measures of insulin resistance (IR) to predict the risk of insulin resistance in perimenopausal women.

PATIENTS AND METHODS: The study involved 252 perimenopausal women living in the West Pomeranian Voivodeship. The methods employed in this study were diagnostic survey based on the original questionnaire, anthropometric measurement, and laboratory tests performed to determine the levels of selected biochemical parameters.

RESULTS: In the entire study population, the highest area under the curve was found for the homeostasis model assessment-insulin resistance (HOMA-IR) and quantitative insulin sensitivity check index (QUICKI). Triglyceride-glucose index (TyG index) showed a higher diagnostic value as a distinction tool between prediabetes and diabetes in perimenopausal women than the other markers. HOMA-IR significantly positively correlated with fasting blood glucose (r = 0.72; *p* = 0.001), glycated hemoglobin (HbA1C, r = 0.74; *p* = 0.001), triglycerides (TG, r = 0.18; *p* < 0.005), and systolic blood pressure (SBP, r = 0.15; *p*= 0.021), and negatively with high-density lipoprotein (HDL, r = -0.28; *p* = 0.001). QUICKI negatively correlated with fasting blood (r = -0.051; *p* = 0.001), HbA1C (r = -0.51; *p* = 0.001), TG (r = -0.25; *p* = 0.001), low-density lipoprotein (LDL, r = -0.13; *p*= 0.045), and SBP (r = -0.16; *p* = 0.011), and positively with HDL (r = 0.39; *p* = 0.001).

CONCLUSIONS: Anthropometric and cardiometabolic parameters were found to significantly correlate with IR markers. HOMA-beta, the McAuley index (McA), visceral adiposity index (VAI), and lipid accumulation product (LAP) may be useful as predictors of pre-diabetes and diabetes in postmenopausal women.

Key Words:
Insulin resistance, Menopausal women, Triglyceride–glucose index, Homeostasis model as-sessment-insulin resistance, Quantitative insulin sensitivity check index.

Abbreviations

AUC, the area under the curve; BMI, the body mass index; CMD, Cardiometabolic diseases; CVD, cardiovascular disease; DLR, Diagnostic Likelihood Ratio; DPB, diastolic blood pressure; FFA, fatty acids; FSG, fasting serum glucose; HbA1C, glycated hemoglobin; HDL, high-density lipoprotein; HEC, hyperinsulinemic-euglycemic clamp; HOMA-IR, the homeostasis model assessment-insulin resistance; IDF, International Diabetes Federation; IR, Insulin resistance; LAP, lipid accumulation product; LDL, low-density lipoprotein; McA, the McAuley index; NPV, negative predictive value; OGTT, oral glucose tolerance test; PPV, positive predictive value; RR, Riva Rocci; QUICKI, quantitative insulin sensitivity check index; SPB, systolic blood pressure; T2D, type 2 diabetes; TC, total cholesterol; TG, triglycerides; TyG index, triglyceride-glucose index; VAI, visceral adiposity index; WC, waist circumference; WHtR, waist to height ratio; YI, Youden Index.

Introduction

Cardiometabolic diseases (CMD), which include type 2 diabetes (T2D) and cardiovascular disease (CVD), as well as related risk factors,

Corresponding Author: S. Wieder-Huszla, MD; e-mail: sylwia.wieder.huszla@pum.edu.pl

such as hypertension, insulin resistance, dyslipidemia, obesity, which are the main cause of morbidity and mortality among people, irrespective of their sex[1]. However, there is a significant difference in the trajectory of cardiometabolic risk between men and women over the life course. At a young age, cardiometabolic diseases are less common in women, but with increasing age, and especially after the menopause, when risk factors for cardiometabolic diseases accumulate, this difference blurs and the risk of cardiometabolic diseases in women increases[1].

Estradiol levels decline dramatically during menopause, and changes in the estrogen/androgen ratio coincide with an increased incidence of cardiovascular disease and type 2 diabetes. Therefore, many researchers suggest that decreased estradiol is the main determinant of increased risk of cardiometabolic diseases for menopausal women[2,3]. On the other hand, increased androgenicity in peri- and postmenopausal women may be associated with an unfavorable cardiovascular risk profile[4-7]. Menopause is an important transition period in a woman's reproductive life, which is associated with vascular dysfunction, elevated blood pressure, redistribution of abdominal fat, and hyperlipidemia[8,9]. Thus, changes taking place in the body of a woman after menopause substantially increase the risk of cardiovascular disease and type 2 diabetes[3].

Diabetes is a significant civilization problem, as we observe a rapid increase in the incidence and spread of type 2 diabetes all over the world. According to a study by the International Diabetes Federation (IDF), there were 451 million adults with diabetes worldwide in 2017, and it is predicted that 693 million adults will have diabetes by 2045[10]. Insulin resistance (IR) is a metabolic condition in which insulin-dependent tissues become less sensitive to insulin, which in turn leads to metabolic imbalance. The pathogenic association of IR with prediabetes and diabetes as well as with cardiovascular disease is well known[11-13].

The risk factors for diabetes include: IR, body mass index (BMI) $\geq$ 25 kg/m^2, waist circumference in women > 80 cm, sedentary lifestyle, age > 40 years, non-Caucasian origin, family history of type 2 diabetes, hypertension or cardiovascular disease, history of glucose intolerance or gestational diabetes, diagnosis of hypertension, elevated triglycerides / low HDL cholesterol or cardiovascular disease[14,15] and polycystic ovary syndrome[16].

There are many ways to determine IR, of which the hyperinsulinemic-euglycemic clamp (HEC) is currently considered the gold standard in the diagnosis of IR[17-19]. Unfortunately, it is a complicated and time-consuming method with limited application in research settings. Therefore, substitute markers such as HOMA-IR, HOMA-beta, QUICKI, TGC/HDL have been developed[20]. What is more, in recent years, many studies[20-23] have suggested that new indices, such as visceral adiposity index (VAI)[21,22] and lipid accumulation product (LAP)[23] may also be accurate markers of IR. Alternative surrogate markers for measuring IR have also been developed: the McAuley index[24] and the Disse index, which use triglycerides or fatty acids (FFA), respectively[25].

Considering that IR is a critical pathophysiological mechanism of diabetes, novel diagnostic markers of IR may be useful in identifying pre-diabetic status and diabetes. A review of the literature indicates that there is limited evidence regarding the discriminatory accuracy of surrogate diagnostic markers of IR[17-25]. To our knowledge, previous reports have not examined the discriminatory accuracy in relation to menopausal status. The aim of our study was to assess the possibility of using surrogate measures of IR (the homeostasis model assessment-insulin resistance (HOMA-IR), the quantitative insulin sensitivity check index (QUICKI), the McAuley index (McA), visceral adiposity index (VAI), lipid accumulation product (LAP), and triglyceride-glucose index) to predict the risk of insulin resistance in perimenopausal women. The influence of selected risk factors for diabetes on the above-mentioned diagnostic markers of IR (HOMA-IR, QUICKI, McA, VAI, LAP, TyG index) was also assessed.

Patients and Methods

Organization and Course of Study

The research was carried out in the West Pomeranian Voivodeship and involved women from the general population. The inclusion criteria were female sex, the age of 44-65 years, and informed written consent to participate in the study. The exclusion criteria were thyroid, neoplastic, and mental diseases, both current and history of disease.

The study was conducted in accordance with the Declaration of Helsinki after obtaining the

approval of the Bioethics Committee of the Pomeranian Medical University in Szczecin (KB-0012/181/13). This was a cross-sectional study based on non-random convenience sampling. Participants were recruited by means of information posters left in public places and advertisements in local newspapers.

This study is part of a larger project, whose aim is to assess the health of perimenopausal women living in the West Pomeranian Voivodeship.

Research Project

The research was carried out in several stages. The methods employed in this study were: diagnostic survey, anthropometric measurement, blood pressure measurement, and laboratory tests. In the first step, we used the original questionnaire including questions regarding basic sociodemographic data (age, place of residence, employment status, education, marital status), stimulants (alcohol, tobacco) and health (menstruation, inflammation, mental and cancer diseases, menopausal status).

Anthropometric Measurements

The next step involved anthropometric measurements, such as waist circumference, weight, and height.

- Waist circumference was measured with an accuracy of 0.01 m using a flexible measuring tape (SECA). Waist circumference (WC) was measured as the horizontal distance around the abdomen at the level of the navel.
- Weight and height were assessed using a certified medical scale with an integrated SECA 711 height meter according to a standardized procedure with an accuracy of 0.1 kg and 0.1 cm, respectively. The participants stood with their back straight, heels together, barefoot in light clothing. Based on the results, the body mass index (BMI) was calculated from the formula: BMI = weight [kg] / height [m]^2. BMI (kg/m^2) was divided into categories according the Centers for Disease Control and Prevention (CDC): underweight (BMI < 18.5), normal weight (BMI = 18.5-24.9), overweight (BMI = 25.0-29.9), and obesity (BMI $\geq$ 30)[26].
- Moreover, a waist to height ratio (WHtR) was determined according to the formula: WHtR= waist circumference [cm] / height [cm]. Values of 49 or higher have been found to increase the risk of developing cardiovascular disease, diabetes, etc[27].

Blood Pressure Measurement

The Korotkov sound technique was used to measure blood pressure (BP). We ensured that the patient was in the correct position, had a period of quiet rest, used an appropriately sized cuff, and that external factors affecting blood pressure, such as smoking and taking caffeinated products prior to blood pressure measurement, were minimized[28]. We followed the recommendations of the American Heart Association[29].

Laboratory Analysis

Venous blood was then collected from each of the volunteers after an overnight fast between 7.00 and 9.30 a.m. after a 10-minute rest in a sitting position from the ulnar vein using a Vacutainer vacuum system.

The blood was collected in accordance with the binding rules and procedures for the collection, storage and transport of biological material. The determination of biochemical parameters was performed in a certified laboratory of the Pomeranian Medical University in Szczecin using standard commercial methods. We assessed the levels of: insulin, glucose, glycated hemoglobin (HbA1C), total cholesterol (TC), high-density lipoprotein (HDL) and low-density lipoprotein (LDL), and triglycerides (TG).

Diagnostic Markers of IR

According to the latest reports on the diagnosis of insulin resistance, there are two groups of IR markers, also known as surrogate diagnostic markers of IR or insulin sensitivity[30,31]:

- indices calculated from fasting plasma levels of insulin, glucose and triglycerides,
- indices calculated from plasma insulin and glucose levels obtained during 120 minutes of a normal (i.e., 75 g) oral glucose tolerance test (OGTT).

The most popular measures are HOMA-IR[32] and QUICKI[33] In our study we used:

- The Homeostasis Model Assessment-Insulin Resistance (HOMA-IR) is a validated method used to quantify IR from fasting blood glucose and insulin concentration. It was calculated from the formula[34]: HOMA-IR= Glucose [mg/dl] x Insulin [μIU/mL] / 405.
- The converse of HOMA-IR, according to the formula: 1/HOMA-IR= 1 / HOMA-IR
- HOMA-β, like HOMA-IR, determines IR based on fasting blood glucose and insulin concentrations, but is calculated from the formula[33,34]: HOMA-BETA= 360 x Insulin [μIU/mL] / Glucose [mg/dl] -63

- The McAuley index was calculated from the formula:[24] McA = exp (2.63-0.28 ln (Insulin [mU/l]) – 0.31ln (Triglycerides [mmol/l])].
- The quantitative insulin sensitivity check index (QUICKI)[33] is a marker used to assess insulin resistance. We assumed that the lower the QUICKI value, the higher the likelihood of impaired carbohydrate metabolism. QUICKI was calculated from the formula: QUICKI = 1/ (log(Insulin [μIU/mL]) + log (Glucose [mg/dl]))
- Lipid accumulation product (LAP) is a marker of visceral obesity and is based on a combination of two variables: waist circumference (WC) and fasting triglycerides (TG). LAP is widely used as a marker of metabolic disorders and a predictor of cardiovascular disease. The formula for women:[34] LAP= (waist circumference [cm] – 58) x (Triglycerides [mmol/l)].
- The TyG index was calculated from the formula[35]: TyG index= Ln (Triglycerides [mg/dl) x (Glucose [mg/dl])/2)
- The visceral adiposity index (VAI) was calculated from the formula[36]: VAI= ((waist circumference [cm]/ 36.85+ 1.89 x BMI)) x (Triglycerides [mmol/l] / 0.81) x (1.52/ HDL [mmol/l])

Division of Respondents

The study recruited 300 peri-menopausal women aged 45 to 65 years representing the general population of the West Pomeranian Voivodeship in north-western Poland. Ultimately, 252 female respondents who met all the inclusion criteria were included in the study (completion rate: 84%).

The size of the research sample was established on the basis of statistical data on the size of the population of women aged 45-64 in the West Pomeranian Voivodeship in 2020[37]. The confidence level was set at 95%, the maximum error at 7%, and the estimated fraction size at 0.5.

The respondents were divided into two groups with regard to their menopausal status defined as[38]:
- Perimenopause – the time immediately before menopause with the symptoms of the coming menopause (when endocrine, biological and clinical features of the coming menopause begin).
- Postmenopause – the last menstruation at least 12 months before the study.

The following reference values were adopted in the study according to the position of the Polish Diabetes Society of 2021[39]:
- Fasting glucose values: < 70 mg/dl – hypoglycemia; 70-99 mg/dl – normal fasting glucose; 100–125 mg/dl (5.6-6.9 mmol/dl) – impaired fasting glucose (IFG); 125 mg/dl – diabetes.
- Fasting HbA1C values: HbA1C < 6.5 mg/dl – normal value; HbA1C > 6.5 mg/dl – diabetes.

Statistical Analysis

Quantitative, nominal and ordinal variables were described using descriptive statistical methods. For quantitative variables, the following measures were determined: central tendency (mean, M) and dispersion (standard deviation, SD). For the nominal and ordinal variables, the following measures were determined: number (N) and frequency (%).

Cross-tables and Pearson's Chi-square test with odds ratio were used to assess the difference in frequency for variants of categorical variables. To assess the differences (perimenopause *vs.* postmenopause) for selected quantitative variables, Student's *t*-test with the mean difference calculated was used.

The ability of selected diagnostic markers of IR (HOMA-IR, HOMA-beta, McA, QUICKI, VAI index, TyG index, and LAP) to discriminate between prediabetes/diabetes was estimated using the receiver operating curve (ROC). The optimal cut-off for the selected markers was estimated based on the Youden index (bootstrapping). The area under the curve (AUC), sensitivity, specificity, Diagnostic Likelihood Ratio [DLR (+), DLR (-)], positive predictive value (PPV), and negative predictive value (NPV) were calculated. The discriminatory power of selected markers was compared to the reference results (HOMA-IR) with z-statistics.

The impact of diabetes risk factors on IR diagnostic markers (HOMA-IR, HOMA-beta, McA, QUICKI, VAI index, TyG index, and LAP) was calculated using Pearson's correlation coefficients (two-tailed test).

All calculations were performed with the StatisticaTM 13.3 software (TIBCO Software, Palo Alto, California, United States). For all analyses, $p < 0.05$ was considered statistically significant.

Results

Baseline Clinical Characteristics and Laboratory Results

Tables I and II shows the anthropometric and clinical characteristics of the respondents with

respect to the menopausal period. Of the 252 surveyed women, 189 (75%) had their last menstrual period at least 12 months before the study. In the entire study population, 14 people (5.5%) were diagnosed with diabetes, and the vast majority of respondents (82.5%) had fasting blood glucose values between 70-99 mg/dl. No statistically significant differences were observed in the anthropometric measurements and clinical characteristics of the respondents between the two groups.

The Discriminatory Accuracy of IR Markers (HOMA-IR, McA, QUICKI, VAI, LAP, TyG index) for Prediabetes/Diabetes

The measures of discriminatory accuracy are shown in Table III. Based on the results, in the entire study population, the highest AUC was found for HOMA-IR and QUICKI, followed by TyG index. HOMA-IR and QUICKI were characterized by the highest sensitivity (100%) and negative predictive value (NPV) (100%). The highest specificity (93.28%) and positive predictive value (PPV) (38.46%) were recorded for TyG index. The optimal cut-off values were 1.98 for VAI, 50.38 for LAP, and 123.84 for HOMA-beta. Regarding the diagnostic likelihood ratio (DLR), the highest DLR+ was recorded for TyG index (10.63), and then for HOMA-IR (6.43). DLR + > 1 indicates an increased likelihood of the disease development.

Analysis stratified by menopausal status showed that TyG index, as a marker of prediabetes/diabetes in perimenopausal women, had a higher diagnostic value than the other markers (HOMA-IR, HOMA-beta, QUICKI, VAI, LAP). In postmenopausal women, the highest AUC was observed for HOMA-IR. The best diagnostic performance of TyG index was observed in perimenopausal women and then in women under 50 years of age. The highest AUC for LAP was detected in postmenopausal women (AUC 0.722), and the lowest in women under 50 years of age: (AUC 0.356).

The Correlation of the Impact of Diabetes Risk Factors on IR Diagnostic Markers

Table IV shows the impact of selected risk factors for diabetes (WC, HC, WHtR, BMI, glucose, HbA1C, TC, TG, HDL, LDL, SPB, DBP) on the diagnostic markers of IR (HOMA-IR, McA, QUICKI, VAI, LAP, TyG index). In our study, there were significant positive correlations between HOMA-IR and fasting blood glucose (r = 0.72; p = 0.001), HbA1C (r = 0.74; p = 0.001), TG (r = 0.18; $p < 0.005$), and SBP (r = 0.15; p = 0.021), and a negative correlation between HOMA-IR and HDL (r = -0.28; p = 0.001). Additionally, negative correlations were observed between HOMA-beta and age (r = -0.14; p = 0.033), fasting blood glucose (r = -0.30; p = 0.001), HbA1C (r = -0.21; p = 0.001), and DBP (r = -0.14; p = 0.033). 1/HOMA-IR negatively correlated with fasting blood glucose (r = -0.37; p = 0.001), HbA1C (r = -0.36; p = 0.001), TG (r = -0.22; p = 0.001), LDL (r = -0.15; p = 0.018), SBP (r = -0.12; p = 0.049), and positively with HDL (r = 0.35; p = 0.001).

In our study, there were significant negative correlations between QUICKI and fasting blood glucose (r = -0.051; p = 0.001), HbA1C (r = -0.51; p = 0.001), TG (r = -0.25; p = 0.001), LDL (r = -0.13; p = 0.045), and SBP (r = -0.16; p = 0.011), and a positive correlation between QUICKI and HDL (r = 0.39; p = 0.001) (Table IV).

We observed negative correlations between McA and fasting blood glucose (r = -0.31; p = 0.001), HbA1C (r = -0.33; p = 0.001), TC (r = -0.15; p = 0.018), TG (r = -0.15; p = 0.018), LDL (r = -0.26; p = 0.001), and a positive correlation between McA and HDL (r = 0.46; p = 0.001) (Table IV).

TyG index positively correlated with fasting blood glucose (r = 0.62; p = 0.001), HbA1C (r = 0.57; p = 0.001), TC (r = 0.23; p = 0.001); TG (r = 0.69; p = 0.001), LDL (r = 0.26; p = 0.001), and SBP (r = 0.17; p = 0.009), and negatively with HDL (r = -0.38; p = 0.001) (Table IV).

In our study, LAP showed positive correlations with BMI (r = 0.15; p = 0.015), fasting blood glucose (r = 0.13; p = 0.033), TC (r = 0.30; p = 0.001), TG (r = 0.70; p = 0.001), and LDL (r = 0.23; p = 0.001), and a negative correlation with HDL (r = -0.11; p = 0.001) (Table IV).

Additionally, VAI was positively correlated with fasting blood glucose (r = 0.24; p = 0.001), HbA1C (r = 0.23; p = 0.001), TG (r = 0.77; p = 0.001), LDL (r = 0.20; p = 0.001), and negatively with BMI (r = -0.16; p = 0.009) and HDL (r = -0.50; p = 0.001) (Table IV).

Discussion

The incidence of cardiometabolic diseases is rapidly increasing worldwide, so it is important to detect IR as one of the factors playing a key role in the pathogenesis of metabolic disorders. The tests

Table I. Comparison of anthropometric and clinical characteristics with regard to menopausal status.

Variables		Perimenopause (n = 63)		Postmenopause (n = 189)		χ^2	p*	OR (95% CI)
		N	%	N	%			
Diabetes	No	61	96 .83	177	93.65	0.908	0.341	2.07 (0;45; 9.50)
	Yes	2	3.17	12	6.35			
Educational level	Elementary school or lower	11	17.46	46	24.34	1.277	0.258	0.66 (0.32; 1.37)
	Middle school or higher	52	82.54	143	75.66			
Marital status	Single	9	14.29	31	16.40	1.228	0.541	-
	Informal relationship	7	11.11	13	6.88			
	Married	47	74.60	145	76.72			
Obesity	Normal weight (BMI < 25.00)	19	30.16	50	26.46	0.601	0.741	-
	Overweight (BMI 25.00-29.99)	23	36.51	79	41.80			
	Obesity (BMI ≥ 30.00)	21	33.33	60	31.75			
Glycemia	< 70 mg/dl	2	3.17	11	5.82	2.735	0.434	-
	70-99 mg/dl	56	88.89	152	80.42			
	100-125 mg/dl	3	4.76	11	5.82			
	> 125 mg/dl	2	3.17	15	7.94			
Smoking	No	50	79.37	153	80.95	0.076	0.783	0.90 (0.44; 1.84)
	Yes	13	20.63	36	19.05			
Hypertension	No	40	63.49	103	54.50	1.557	0.212	1.45 (0.81; 2.61)
	Yes	23	36.51	86	45.50			

OR: odds ratio, CI: confidence interval. *Pearson's Chi-square test.

Table II. Comparison of anthropometric and clinical characteristics with regard to menopausal status.

	Perimenopause (n = 63)		Postmenopause (n = 189)					
	M	SD	M	SD	$t_{df = 250}$	p	MD	95% CI
Age	48.71	2.94	56.49	4.08	-13.944	< 0.001	-7.77	-8.87; -6.67
WC [cm]	88.25	13.02	89.67	12.40	-0.781	0.436	-1.43	-5.02; 2.17
Weight [kg]	76.06	17.63	74.82	13.93	0.570	0.569	1.24	-3.04; 5.52
Height [cm]	163.24	6.38	162.67	6.84	0.579	0.563	0.57	-1.36; 2.49
BMI	28.41	5.97	28.35	5.36	0.084	0.933	0.07	-1.51; 1.65
WHtR [%]	0.54	0.08	0.55	0.08	-1.000	0.318	-0.01	-0.03; 0.01
FSG [mg/dl]	91.00	37.86	93.24	34.68	-0.435	0.664	-2.25	-12.42; 7.92
HbA1C [%]	5.47	1.09	5.56	0.92	-0.619	0.536	-0.09	-0.36; 0.19
TC [mg/dl]	213.81	30.38	210.13	38.60	0.688	0.492	3.68	-6.85; 14.20
TG [mg/dl]	90.72	36.78	108.76	93.53	-1.491	0.137	-18.04	-41.86; 5.79
HDL [mg/dl]	70.49	17.38	66.76	18.89	1.383	0.168	3.73	-1.58; 9.03
LDL [mg/dl]	123.56	32.38	122.85	32.99	0.147	0.883	0.70	-8.71; 10.11
HOMA-IR	2.69	4.43	2.50	2.22	0.457	0.648	0.19	-0.64; 1.03
1/HOMA-IR	0.73	0.52	0.64	0.41	1.524	0.129	0.10	-0.03; 0.22
HOMA beta	187.37	190.98	171.48	129.98	0.740	0.460	15.89	-26.42; 58.19
McA	8.12	2.09	7.62	1.84	1.822	0.070	0.51	-0.04; 1.05
QUICKI [pt]	0.36	0.04	0.35	0.03	1.241	0.216	0.01	-0.00; 0.02
VAI	1.18	0.80	1.48	1.11	-1.969	0.050	-0.30	-0.60; 0.00
TyG	4.45	0.26	4.53	0.29	-1.834	0.068	-0.08	-0.16; 0.01
LAP	32.23	19.39	38.00	25.36	-1.653	0.100	-5.77	-12.66; 1.11

WC–waist circumference, BMI–body mass index, WHtR–waist-height ratio, FSG–fasting serum glucose, TC–total cholesterol, TG–triglyceride, HDL–high density lipoprotein, LDL–low density lipoprotein, HOMA-IR–homeostasis model assessment of insulin resistance, QUICKI–quantitative insulin sensitivity check index, VAI–visceral adiposity index, LAP–lipid accumulation product, TyG–the product of triglyceride and glucose, McA–McAuley.

Table III. Discriminatory accuracy and cut-off values for markers of IR (HOMA-IR, QUICKI, McA, VAI, LAP, TyG).

	Sensitivity	Specificity	PPV	NPV	z	p	DLR (+)	DLR (-)	YI	Cut-offs	AUC (95% CI)
Overall											
HOMA-IR	100.0%	84.45%	27.45%	100.0%	-	-	6.43	0.00	0.84	3.081	0.955 (0.922; 0.987)
HOMA-beta	92.86%	62.87%	12.87%	99.33%	-2.259	0.024	2.50	0.11	0.56	123.84	0.838 (0.746; 0.930)
McA	100.0%	62.18%	13.46%	100.0%	3.464	0.001	2.64	0.00	0.62	7.302	0.851 (0.773; 0.929)
QUICKI	100.0%	84.45%	26.92%	100.0%	0.000	1.000	6.26	0.00	0.84	0.323	0.955 (0.922; 0.987)
VAI	64.29%	84.03%	19.15%	97.56%	-2.548	0.011	4.03	0.42	0.48	1.980	0.770 (0.634; 0.906)
TyG	71.43%	93.28%	38.46%	98.23%	-1.150	0.250	10.63	0.31	0.71	4.828	0.911 (0.833; 0.990)
LAP	64.29%	81.09%	16.67%	97.47%	-3.258	0.001	3.40	0.44	0.45	50.38	0.721 (0.581; 0.860)
Perimenopause											
HOMA-IR	100.0%	98.36%	66.67%	100.0%	-	-	61.00	0.00	0.98	12.369	0.992 (0.969; 1.000)
HOMA-beta	100.0%	93.44%	33.33%	100.0%	-1.625	0.104	15.25	0.00	0.93	55.18	0.943 (0.884; 1.000)
McA	100.0%	98.36%	66.67%	100.0%	0.707	0.480	61.0	0.00	0.98	4.49	0.984 (0.952; 1.000)
QUICKI	100.0%	98.36%	66.67%	100.0%	0.000	1.000	61.0	0.00	0.98	0.270	0.992 (0.969; 1.000)
VAI	100.0%	75.00%	11.76%	100.0%	-0.857	0.392	4.07	0.00	0.75	1.450	0.877 (0.694; 1.000)
TyG	100.0%	100.0%	100.0%	100.0%	0.707	0.480	0.00	0.00	1.00	5.348	1.000 (1.000; 1.000)
LAP	100.0%	42.62%	5.41%	100.0%	-1.242	0.214	1.74	0.00	0.42	23.668	0.672 (0.320; 1.000)
Menopause											
HOMA-IR	100.0%	83.62%	29.27%	100.0%	-	-	6.10	0.00	0.84	3.081	0.946 (0.907; 0.986)
HOMA-beta	91.67%	64.20%	14.86%	99.12%	-2.054	0.040	2.56	0.13	0.56	123.84	0.825 (0.724; 0.926)
McA	100.0%	59.89%	14.46%	100.0%	3.623	< 0.001	2.49	0.00	0.60	7.302	0.818 (0.727; 0.909)
QUICKI	100.0%	83.05%	28.57%	100.0%	0.000	1.000	5.90	0.00	0.83	0.323	0.946 (0.906; 0.986)
VAI	66.67%	81.92%	20.00%	97.32%	-2.406	0.016	3.69	0.41	0.49	1.980	0.742 (0.585; 0.899)
TyG	75.00%	90.40%	34.62%	98.16%	-1.348	0.178	7.81	0.28	0.65	4.828	0.885 (0.791; 0.980)
LAP	66.67%	79.10%	17.78%	97.22%	-2.941	0.003	3.19	0.42	0.46	50.375	0.722 (0.573; 0.872)

Continued

Table III *(Continued)*. Discriminatory accuracy and cut-off values for markers of IR (HOMA-IR, QUICKI, McA, VAI, LAP, TyG).

	Sensitivity	Specificity	PPV	NPV	z	p	DLR (+)	DLR (-)	YI	Cut-offs	AUC (95% CI)
Age≥50											
HOMA-IR	76.47%	84.46%	30.23%	97.60%	-	-	4.92	0.28	0.84	3.081	0.960 (0.926; 0.994)
HOMA-beta	92.31%	60.94%	13.79%	99.15%	-2.331	0.020	2.36	0.13	0.53	123.84	0.824 (0.722; 0.926)
McA	100.0%	61.66%	14.94%	100.0%	3.688	< 0.001	2.61	0.00	0.62	7.302	0.842 (0.759; 0.926)
QUICKI	100.0%	83.94%	29.55%	100.0%	0.000	1.000	6.23	0.00	0.84	0.323	0.960 (0.926; 0.995)
VAI	69.23%	82.90%	21.43%	97.56%	-2.433	0.015	4.05	0.37	0.52	1.980	0.772 (0.627; 0.917)
TyG	76.92%	91.19%	37.04%	98.32%	-1.429	0.153	8.73	0.25	0.68	4.828	0.903 (0.819; 0.987)
LAP	69.23%	79.79%	18.75	97.47%	-3.173	0.002	3.43	0.39	0.49	50.375	0.741 (0.604; 0.878)
Age<50											
HOMA-IR	100.0%	100.0%	100.0%	100.0%	-	-	0.00	0.00	1.00	32.394	1.000 (1.000; 1.000)
HOMA-beta	100.0%	93.33%	25.00%	100.0%	-1.773	0.076	15.00	0.00	0.93	47.621	0.933 (0.860; 1.000)
McA	100.0%	97.78%	50.00%	100.0%	0.998	0.317	45.0	0.00	0.98	4.491	0.978 (0.935; 1.00)
QUICKI	100.0%	100.0%	100.0%	100.0%	0.000	1.000	0.00	0.00	1.00	0.243	1.000 (1.000; 1.000)
VAI	100.0%	73.33%	7.69%	100.0%	-3.999	< 0.001	3.75	0.00	0.73	1.450	0.733 (0.604; 0.863)
TyG	100.0%	100.0%	100.0%	100.0%	0.000	1.000	0.00	0.00	1.00	5.348	1.000 (1.000; 1.000)
LAP	100.0%	35.56%	3.33%	100.0%	-8.930	< 0.001	1.55	0.00	0.36	23.668	0.356 (0.216; 0.495)

HOMA-IR–homeostasis model assessment of insulin resistance, QUICKI–quantitative insulin sensitivity check index, VAI–visceral adiposity index, LAP–lipid accumulation product, TyG–the product of triglyceride and glucose, McA–McAuley index, PPV–positive predictive value, NPV–negative predictive value, DLR–Diagnostic Likelihood Ratio, YI–Youden Index, AUC–the area under the curve.

Table IV. The impact of diabetes risk factors on IR diagnostic markers (HOMA-IR, HOMA-beta, 1/HOMA-IR, McA, QUICKI, VAI, LAP, TyG).

Variable	Diagnostic markers of IR															
	HOMA-IR		HOMA-beta		1/HOMA		QUICKI		McA		TyG		LAP		VAI	
	r	*p*	r	*p*	r	*p*	r	*p*	r	*p*	r	*p*	r	*p*	r	*p*
Age [years]	-0.02	0.735	-0.14	0.033	-0.05	0.468	-0.04	0.524	-0.04	0.570	0.11	0.090	0.07	0.273	0.07	0.283
WC [cm]	0.10	0.099	0.03	0.617	-0.03	0.616	-0.06	0.324	-0.05	0.430	0.00	0.992	0.01	0.888	0.03	0.628
HC [cm]	-0.03	0.594	-0.01	0.917	-0.01	0.842	0.02	0.799	-0.04	0.558	0.03	0.668	0.07	0.249	0.10	0.105
BMI [kg/m²]	0.00	0.950	0.03	0.683	0.03	0.640	0.02	0.723	0.08	0.231	-0.06	0.328	0.15	0.015	-0.16	0.009
WHtR [%]	0.11	0.070	0.03	0.583	-0.03	0.636	-0.07	0.276	-0.04	0.500	-0.01	0.929	-0.01	0.878	0.00	0.973
FSG [mg/dl]	0.72	0.001	-0.30	0.001	-0.37	0.001	-0.51	0.001	-0.31	0.001	0.62	0.001	0.13	0.033	0.24	0.001
HbA1c [%]	0.74	0.001	-0.21	0.001	-0.36	0.001	-0.51	0.001	-0.33	0.001	0.57	0.001	0.12	0.066	0.23	0.001
TC [mg/dl]	0.00	0.970	-0.05	0.389	-0.03	0.659	-0.01	0.931	-0.15	0.018	0.23	0.001	0.30	0.001	0.12	0.065
TG [mg/dl]	0.18	0.005	0.03	0.676	-0.22	0.001	-0.25	0.001	-0.51	0.001	0.69	0.001	0.70	0.001	0.77	0.001
HDL [mg/dl]	-0.28	0.001	-0.09	0.159	0.35	0.001	0.39	0.001	0.46	0.001	-0.38	0.001	-0.11	0.088	-0.50	0.001
LDL [mg/dl]	0.08	0.236	-0.02	0.757	-0.15	0.018	-0.13	0.045	-0.26	0.001	0.26	0.001	0.23	0.001	0.20	0.001
SBP [mm Hg]	0.15	0.021	-0.04	0.479	-0.12	0.049	-0.16	0.011	-0.11	0.073	0.17	0.009	0.11	0.079	0.08	0.183
DBP [mm Hg]	-0.02	0.735	-0.14	0.033	-0.05	0.468	-0.04	0.524	-0.04	0.570	0.11	0.090	0.07	0.273	0.07	0.283

WC–waist circumference, HC–hip circumference, BMI–body mass index, WHtR–waist-height ratio, FSG–fasting serum glucose, TC–total cholesterol, TG–triglyceride, HDL–high density lipoprotein, LDL–low density lipoprotein, HbA1C–glycohemoglobin, SPB–systolic blood pressure, DPB–diastolic blood pressure, HOMA-IR–homeostasis model assessment of insulin resistance, QUICKI–quantitative insulin sensitivity check index, VAI–visceral adiposity index, LAP–lipid accumulation product, TyG–the product of triglyceride and glucose, McA–McAuley index.

for reliable IR measurement are, in fact, the first step in effective preventive management of individuals at high risk of cardiovascular disease or diabetes[40]. In the loiterature was shown that there are many indicators of insulin sensitivity, which, based on simple mathematical equations using glucose and insulin values, allow the assessment of insulin resistance. It is worth noting, however, that due to different mathematical approaches, the properties of insulin sensitivity indices are not the same. Therefore, many researchers have undertaken the task of evaluating the usefulness of selected diagnostic markers of IR in selected groups of patients.

The Discriminatory Accuracy of IR Markers (HOMA-IR, McA, QUICKI, VAI, LAP, TyG index) of Prediabetes/Diabetes

A review [41] of the literature indicates that the HOMA-IR model is the most commonly used surrogate measure to assess IR and β-cell function in clinical and epidemiological studies. This is probably due to the fact that the ability of the HOMA model to predict the development of type 2 diabetes has been assessed in both cross-sectional and cohort studies. HOMA-IR has been found to be associated with type 2 diabetes in, among others, Japanese[42], Americans (of Mexican or Japanese origin)[43,44] and Italians[45].

Our study showed that in the entire study population, the highest AUC was found in HOMA-IR and QUICKI, followed by TyG index. Moreover, HOMA-IR and QUICKI had the highest sensitivity (100%) and NPV (100%). The highest specificity (93.28%) and PPV (38.46%) were reported for TyG index. In analyzes stratified by menopausal status of perimenopausal women, TyG index showed higher diagnostic values for prediabetes/diabetes than the other markers (HOMA-IR, HOMA-beta, QUICKI, VAI, LAP). In postmenopausal women, the highest AUC was observed for HOMA-IR. The best diagnostic performance of TyG index was observed in perimenopausal women, followed by women under 50 years of age.

In a study by Ahn et al[13], in the entire study population, the highest AUC was recorded for HOMA-IR, followed by TyG index and LAP. TyG index showed the highest sensitivity (0.732) and NPV (0.849). The highest specificity (0.811) and PPV (0.589) were observed for HOMA-IR. The optimal cut-off values were 1.52 for VAI, 41.30 for LAP, and 8.60 for TyG index. The highest DLR + was observed for HOMA-IR (3.283), followed by TyG index (2.142)[46].

It is worth noting that more and more studies prove that the usefulness of VAI, LAP, and TyG index as markers of prediabetes/diabetes in the European population is comparable to that of HbA1C[42]. Bermúdez et al[47] showed that the AUC values for LAP and VAI were 0.689 (0.665-0.714) and 0.645 (0.619-0.670), respectively. Both markers showed a higher risk of IR in the upper tercile in the two-dimensional analysis. Wang et al[48], on the other hand, believe that the IR markers (TyG index, VAI, LAP) are far better predictors of the type 2 diabetes risk than the TG/HDL ratio. Also, Janghorbani et al[49] and Amato et al[36] confirm that VAI is a strong predictor of diabetes. Ahn et al[13] claim that VAI shows a relatively lower discriminatory ability compared to other markers (LAP or TyG index).

LAP has been repeatedly described as a predictor of diabetes[50], metabolic syndrome[51], and cardiovascular disease[52]. It is noteworthy, however, that the effect of LAP on plasma glucose levels and the incidence of diabetes depends on age and sex, as indicated by Nyamdorj et al[52] and Bozorgmensh et al[53]. According to Anoop et al[23], the LAP index shows greater predictive accuracy for the risk of IR compared to HOMA-IR or QUICKI in non-obese, normoglycemic Asian men. Vasques et al[54] indicates that TyG index has better IR discriminatory ability than HOMA-IR.

The Impact of Diabetes Risk Factors on the Diagnostic Markers of IR

Our study demonstrated statistically significant correlations between selected risk factors for diabetes and IR diagnostic markers. We observed positive correlations between the HOMA-IR index and fasting blood glucose, HbA1C, TG, and SBP, as well as negative correlations between HOMA-beta and age, fasting blood glucose, HbA1C and DBP. The 1/HOMA-IR index negatively correlated with fasting blood glucose, HbA1C, TG, LDL, and SBP. QUICKI significantly negatively correlated with fasting blood glucose, HbA1C, TG, LDL, and SBP. Also, the McA index negatively correlated with fasting blood glucose, HbA1C, TC, TG, and LDL. TyG index positively correlated with fasting blood glucose, HbA1C, TC, TG, LDL, and SBP.

Mirmiran et al[55] showed in their study that a higher LAP index was associated with higher fasting blood glucose and IR in patients with type 2 diabetes. Central lipid accumulation was

also correlated to total cholesterol, HDL-C, and the ratio of triglycerides to HDL-C, irrespective of fasting serum glucose. Additionally, a strong correlation was observed between the levels of LAP, MDA, and hs-CRP. The study of Mirmiran et al also proved that compared to BMI, LAP showed a stronger correlation with fasting blood glucose, lipid and lipoprotein parameters and the lipid peroxidation index.

A study by Selvi et al[56] showed a significant positive correlation between TyG index and HbA1C. In Shin's study[57] waist circumference, systolic and diastolic blood pressure, total cholesterol, LDL cholesterol, triglycerides, and fasting blood glucose positively correlated with the TyG index.

In a study by Anik Ihnan et al,[58] the LAP index showed positive correlations with WHR, WC, BMI, FAI, and TC, and a negative correlation with HDL. These authors also observed that the VAI index positively correlated with WC, FAI, fasting blood glucose, and TC, and negatively with HDL.

Mirzaalian et al[59] noted significant negative correlations between QUICKI and all anthropometric indices (body weight, BMI, WC, neck circumference, WHtR, neck circumference to height ratio, waist circumference to neck circumference ratio, and neck circumference to wrist circumference ratio) after adjusting for sex. Among the cardiometabolic markers, TG levels showed a significant negative correlation with QUICKI. HOMA-IR positively correlated with the majority of anthropometric parameters (body weight, BMI, WC, neck circumference, WHtR, neck circumference to height ratio, waist circumference to neck circumference ratio, and neck circumference to wrist circumference ratio). As for the cardiometabolic indices, SBP and TG showed a positive correlation with the HOMA-IR index.

A study by Song et al[60] conducted in a multiethnic cohort of postmenopausal women confirmed that both HOMA-IR and HOMA-B derived from basal insulin and fasting glucose levels were associated with the risk of diabetes, but these associations were independent of BMI and waist-to-hip ratio, as well as other conventional diabetes risk factors.

Even if identical clinical data (e.g., fasting blood glucose and insulin) are used in the mathematical model, in our opinion it is impossible to choose the "best" surrogate method to assess IR in perimenopausal women, since these data are highly variable. In conclusion, several surrogate markers of IR – such as HOMA-IR, TGC/HDL, QUICKI, TyG index, the McAuley index – characterized by different sensitivity and specificity have been analyzed so far[61-63]. It is worth noting that there are substantial differences in the use of widely available IR markers. Although many of them follow a mathematical formula that takes into account the same biochemical parameters (e.g., insulin and glucose levels), the effectiveness of their use in different populations varies. There are many factors to consider when choosing the right IR assessment tool. According to a literature review[64], it is worth considering the influence of racial and environmental factors on secretion capacity and insulin sensitivity. It is also worthwhile analyzing the differences in the distribution of adipose tissue by ethnic groups[65,66]. Moreover, age and sex may also play an important role in the case of the IR assessment tools[67]. Assessing the risk of IR in older patients is difficult because predictive value of traditional risk factors in seniors is lower than in middle-aged people. Some evidence suggests that obesity in the elderly may not be associated with the same risk as in younger individuals and may even be protective in some respects[68]. At the same time, weight loss that occurs with age or obesity at this age is associated with a change in the distribution of accumulated adipose tissue[46]. Moreover, the height of seniors decreases with age, and thus the BMI value in the elderly may be overestimated[69], while the WC value is higher in the elderly compared to younger people[70]. Furthermore, decreased insulin sensitivity at the cellular level is also a natural consequence of aging[46] which may, in addition to obesity, put the elderly population at greater risk of developing diabetes.

Finally, our article is an attempt to look at the various currently available methods for assessing insulin sensitivity/resistance. Assessment of insulin resistance is increasingly used in clinical situations, and this requires relatively simple markers. Surrogate markers can be a useful tool to measure IR. There are many complex, time-consuming, and invasive procedures. Simple tests involving the collection of a single fasting blood sample are also available. It is important to know advantages and limitations of each method in order to correctly interpret the data to measure insulin sensitivity, and to select the method of estimating insulin sensitivity that is best for the patient. HOMA-IR and QUICKI are examples of the best and most thoroughly validated surrogates that may allow a more physiological assessment

of glucose homeostasis. Another example is a non-invasive breath test, based on breath biomarkers of insulin resistance[71], with potential as a diagnostic tool for monitoring IR progression, but further research is needed to assess its effectiveness in patients of all ages.

Strengths and Limitations

Our study has several strengths. To our knowledge, this is the first report comparing six markers used for diagnosing prediabetes/diabetes in peri- and postmenopausal women from the European population.

Nonetheless, this study is not free from limitations. First, since it was a cross-sectional analysis, we were unable to predict prediabetes/diabetes cases among initially healthy people living in the community. Moreover, a small number of younger participants may have resulted in a low precision of discriminatory accuracy in young women. Futher research involving participants with an evenly distributed age range is needed to clarify this issue. It also seems important to conduct research taking into account various ethnic groups, as there are racial and environmental factors that may affect both insulin secretion capacity or sensitivity, as well as body fat distribution.

The gold standard for the diagnosis of IR is the euglycemic hyperinsulinemic clamp, which is not available in our study. What is more, we did not include the oral glucose tolerance test (OGTT) in our study, and thus we could not use other diagnostic markers that take this parameter into account, such as the IR index (Belfiore), two variants of the Stumvoll index (i.e., Stumvoll 0.120 and Stumvoll demographics), and the Matsuda index.

Conclusions

The present study showed that there are several diagnostic markers of IR that may be important tools in the early detection of diabetes in perimenopausal women. The IR diagnostic markers presented in this study may help diagnose prediabetes and diabetes in perimenopausal women, and thus provide an important strategy to prevent further cardiometabolic risks resulting from hormonal changes at this stage of a woman's life.

McA, VAI, and LAP are useful markers of prediabetes and diabetes in postmenopausal women, which are not inferior to HOMA-IR. An important advantage of LAP is the lower cost compared to other diagnostic markers, since we only use triglyceride and waist circumference measurement (which can be performed at minimal cost in a clinical setting) for the calculations. In the case of other markers, glucose or insulin measurements are necessary for calculations, which significantly increases the cost of the test.

Conflict of Interest

Authors' declaration of personal interests: Conceptualization, A.M.C.; D. S.-M.; methodology, A.J.; S.W-H. software, A.M.C.; validation, E.G.; M.P.; formal analysis, E.G.; M.P.; investigation, A.M.C.; resources, A.M.C.; data curation, A.M.C. writing-original draft preparation, A.M.C..; writing-review and editing, A.M.C.; E.G. visualization, A.M.C.; supervision, E.G.; D. S.-M.; S.W-H. project administration, E.G.; A.J.; funding acquisition, E.G.; A.J.

Ethics Approval

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Review Board (or Ethics Committee) of Pomeranian Medical University in Szczecin (KB-0012/181/13).

Informed Consent

All subjects were informed about the study, and all provided informed consent.

ORCID ID

A.M. Cybulska- 0000-0002-6912-287X; D. Schneider-Matyka-0000-0002-0303-9504; S. Wieder-Huszla- 0000-0002-6084-5780; M. Panczyk- 0000-0003-1830-2114; A. Jurczak-0000-0003-1935-5285; E. Grochans- 0000-0002-3679-7002.

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Authors' Contribution

Material preparation, data collection, and analysis were performed by A.M. Cybulska. Study concept and design analysis and interpretation of data A.M. Cybulska, S. Wieder-Huszla, D. Schneider-Matyka, E. Grochans; statistical analysis M. Panczyk, study supervision A. Jurczak, S. Wieder-Huszla, D. Schneider-Matyka, E. Grochans. The first draft of the manuscript was written by A.M. Cybulska and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

References

1) Benjamin EJ, Muntner P, Alonso A, Bittencourt MS, Callaway CW, Carson AP, Chamberlain AM, Chang AR, Cheng S, Das SR, Delling FN, Djousse L, Elkind MSV, Ferguson JF, Fornage M, Jordan LC, Khan SS, Kissela BM, Knutson KL, Kwan TW, Lackland DT, Lewis TT, Lichtman JH, Longenecker CT, Loop MS, Lutsey PL, Martin SS, Matsushita K, Moran AE, Mussolino ME, O'Flaherty M, Pandey A, Perak AM, Rosamond WD, Roth GA, Sampson UKA, Satou GM, Schroeder EB, Shah SH, Spartano NL, Stokes A, Tirschwell DL, Tsao CW, Turakhia MP, VanWagner LB, Wilkins JT, Wong SS, Virani SS; American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee. Heart Disease and Stroke Statistics-2019 Update: A Report From the American Heart Association. Circ Res 2019; 139: e56-e528.
2) Ober C, Loisel DA, Gilad Y. Sex-specific genetic architecture of human disease. Nat Rev Genet 2008; 9: 911-922.
3) Rossouw JE. Hormones, genetic factors, and gender differences in cardiovascular disease. Cardiovasc Res 2002; 53: 550-557.
4) Lambrinoudaki I, Christodoulakos G, Rizos D, Economou E, Argeitis J, Vlachou S, Creatsa M, Kouskouni E, Botsis D. Endogenous sex hormones and risk factors for atherosclerosis in healthy Greek postmenopausal women. Eur J Endocrinol 2006; 154: 907-916.
5) Haffner SM, Newcomb PA, Marcus PM, Klein BE, Klein R. Relation of sex hormones and dehydroepiandrosterone sulfate (DHEA-SO4) to cardiovascular risk factors in postmenopausal women. Am J Epidemiol 1995; 142: 925-934.
6) Golden SH, Dobs AS, Vaidya D, Szklo M, Gapstur S, Kopp P, Liu K, Ouyang P. Endogenous sex hormones and glucose tolerance status in postmenopausal women. J Clin Endocrinol Metab 2007; 92: 1289-1295.
7) Roa-Díaz ZM, Raguindin PF, Bano A, Laine JE, Muka T, Glisic M. Menopause and cardiometabolic diseases: What we (don't) know and why it matters. Maturitas 2021; 152: 48-56.
8) Cybulska AM, Skonieczna-Żydecka K, Drozd A, Rachubińska K, Pawlik J, Stachowska E, Jurczak A, Grochans E. Fatty Acid Profile of Postmenopausal Women Receiving, and Not Receiving, Hormone Replacement Therapy. Int J Environ Res Public Health 2019; 16: 4273.
9) Zimny M, Starczewska M, Szkup M, Cybulska A, Grochans E. Body Composition and Biological Functioning in Polish Perimenopausal Women with Type 2 Diabetes. Int J Environ Res Public Health 2021; 18: 11422.
10) Cho NH, Shaw JE, Karuranga S, Huang Y, da Rocha Fernandes JD, Ohlrogge A, Malanda B. IDF Diabetes Atlas: Global estimates of diabetes prevalence for 2017 and projections for 2045. Diabetes Res Clin Pract 2018; 138: 271-281.
11) DeFronzo RA, Ferrannini E. Insulin resistance. A multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia, and atherosclerotic cardiovascular disease. Diabetes Care 1991; 14: 173-194.
12) Paneni F, Costantino S, Cosentino F. Insulin Resistance, Diabetes, and Cardiovascular Risk. Curr Atheroscler Rep 2014; 16: 419.
13) Ahn N, Baumeister SE, Amann U, Rathamnn W, Peters A, Huth C, Thorand B, Meisinger Ch. Visceral adiposity index (VAI), lipid accumulation product (LAP), and product of triglycerides and glucose (TyG) to discriminate prediabetes and diabetes. Sci Rep 2019; 9: 9693.
14) La Sala L, Pontiroli AE. Prevention of Diabetes and Cardiovascular Disease in Obesity. Int J Mol Sci 2020; 21: 8178.
15) Yoshida Y, Chen Z, Baudier RL, Krousel-Wood M, Anderson AH, Fonseca VA, Mauvais-Jarvis F. Early Menopause and Cardiovascular Disease Risk in Women with or Without Type 2 Diabetes: A Pooled Analysis of 9,374 Postmenopausal Women. Diabetes Care 2021; 44: 2564-2572.
16) Zhu T, Cui J, Goodarzi MO. Polycystic Ovary Syndrome and Risk of Type 2 Diabetes, Coronary Heart Disease, and Stroke. Diabetes 2021; 70: 627-637.
17) Harris MI, Eastman RC. Early detection of undiagnosed diabetes mellitus: a US perspective. Diabetes Metab Res Rev 2000; 16: 230-236.
18) DeFronzo RA, Tobin JD, Andres R. Glucose clamp technique: a method for quantifying insulin secretion and resistance. Am J Physiol 1979; 237: E214-E223.
19) Lewanczuk RZ, Paty BW, Toth EL. Comparison of the [13C] glucose breath test to the hyperinsulinemic-euglycemic clampwhen determining insulin resistance. Diabetes Care 2004; 27: 441-447.
20) Tuomilehto J, Lindström J, Eriksson JG, Valle TT, Hämäläinen H, Ilanne-Parikka P, Keinänen-Kiukaanniemi S, Laakso M, Louheranta A, Rastas M, Salminen V, Uusitupa M. Finnish Diabetes Prevention Study Group. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. N Engl J Med 2001; 344: 1343-1350.
21) Ji B, Qu H, Wang H, Wei H, Deng H. Association Between the Visceral Adiposity Index and Homeostatic Model Assessment of Insulin Resistance in Participants With Normal Waist Circumference. Angiology 2017; 68: 716-721.
22) Oh JY, Sung YA, Lee HJ. The visceral adiposity index as a predictor of insulin resistance in young women with polycystic ovary syndrome. Obesity (Silver Spring) 2013; 21: 1690-1694.
23) Anoop SS, Dasgupta R, Rebekah G, Jose A, Inbakumari MP, Finney G, Thomas N. Lipid accumulation product (LAP) as a potential index to predict risk of insulin resistance in young, non-obese Asian Indian males from Southern India: observations from hyperinsulinemic-euglycemic clamp studies. BMJ Open Diabetes Res Care 2021; 9: e002414.

24) McAuley KA, Williams SM, Mann JI, Walker RJ, Lewis-Barned NJ, Temple LA, Duncan AW. Diagnosing insulin resistance in the general population. Diabetes Care 2001; 24: 460-464.

25) Disse E, Bastard JP, Bonnet F, Maitrepierre C, Peyrat J, Louche-Pelissier C, Laville M. A lipid-parameter-based index for estimating insulin sensitivity and identifying insulin resistance in a healthy population. Diabetes Metab 2008; 34: 457-463.

26) World Health Organization, BMI classification. Global Database on body mass index. Switzerland (WHO, 2006). Available at: http://www.assessmentpsychology.com/icbmi.htm.

27) World Health Organization, Waist circumference and waist-hip ratio: report of a WHO expert consultation. Available at: https://www.who.int/publications/i/item/9789241501491.

28) TRUE Consortium Recommended Standards for Assessing Blood Pressure in Human Research Where Blood Pressure or Hypertension Is a Major Focus. Kidney Int Rep 2017; 2: 733-738.

29) Unger T, Borghi C, Charchar F, Khan NA, Poulter NR, Prabhakaran D, Ramirez A, Schlaich M, Stergiou GS, Tomaszewski M, Wainford RD, Williams B, Schutte AE. 2020 International Society of Hypertension Global Hypertension Practice Guidelines. Hypertension 2020; 75:1334-1357.

30) Mahajan R. Insulin Resistance: Quest for Surrogate Markers. Int J Appl Basic Med Res 2017; 7:149.

31) Khan SH, Khan AN, Chaudhry N, Anwar R, Fazal N, Tariq M. Comparison of various steady state surrogate insulin resistance indices in diagnosing metabolic syndrome. Diabetol Metab Syndr 2019; 11: 44.

32) Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985; 28: 412-419.

33) Katz A, Nambi SS, Mather K, Baron AD, Follmann DA, Sullivan G, Quon MJ. Quantitative insulin sensitivity check index: a simple, accurate method for assessing insulin sensitivity in humans. J Clin Endocrinol Metab 2000; 85: 2402-2410.

34) Hong KW, Chung M, Cho SB. Meta-analysis of genome-wide association study of homeostasis model assessment ß cell function and insulin resistance in an East Asian population and the European results. Mol Genet Genomics 2014; 289: 1247-1255.

35) Alizargar J, Hsieh NC, Wu SV. The correct formula to calculate triglyceride-glucose index (TyG). J Pediatr Endocrinol Metab 2020; 33: 945-946.

36) Amato MC, Giordano C, Pitrone M, Galluzzo A. Cut-off points of the visceral adiposity index (VAI) identifying a visceral adipose dysfunction associated with cardiometabolic risk in a Caucasian Sicilian population. Lipids Health Dis, 2011; 10: 183.

37) Statistical Yearbook. Zachodniopomorskie Voivodship 2020. Statistical Office in Szczecin; Szczecin, Poland: 2020.

38) McKinlay SM, Brambilla DJ, Posner JG. The normal menopause transition. Am J Hum Biol 1992; 4: 37-46.

39) Araszkiewicz A, Bandurska-Stankiewicz E, Budzyński A, Cyganek K, Cypryk K, Czech A, Czupryniak L, Drzewoski J, Dzida G, Dziedzic T, Franek E, Gajewska D, Gawrecki A, Górska M, Grzeszczak W, Gumprecht J, Idzior-Waluś B, Jarosz-Chobot P, Kalarus Z, Karczewska-Kupczewska M, Klupa T, Koblik T, Kokoszka A, Korzon-Burakowska A, Kowalska I, Krętowski A, Majkowska L, Małecki M, Mamcarz A, Mirkiewicz-Sieradzka B, Młynarski W, Moczulski D, Myśliwiec M, Narkiewicz K, Noczyńska A, Rymaszewska J, Sieradzki J, Skupień J, Solnica B, Strączkowski M, Strojek K, Szadkowska A, Szelachowska M, Szypowska A, Uruska A, Wender-Ożegowska E, Wierusz-Wysocka B, Witek P, Wolnik B, Wyleżoł M, Wylęgała E, Zozulińska-Ziółkiewicz D. Zalecenia kliniczne dotyczące postępowania u chorych na cukrzycę 2016. Stanowisko Polskiego Towarzystwa Diabetologicznego. Diabetologia Kliniczn 2016; 5, A1-A76.

40) Ginsberg HN. Insulin resistance and cardiovascular disease. J Clin Invest 2000; 106: 453-458.

41) Hanley AJ, Williams K, Gonzalez C, D'Agostino RB Jr, Wagenknecht LE, Stern MP, Haffner SM. Prediction of type 2 diabetes using simple measures of insulin resistance: combined results from the San Antonio Heart Study, the Mexico City Diabetes Study, and the Insulin Resistance Atherosclerosis Study. Diabetes 2003; 52: 463-469.

42) Matsumoto K, Miyake S, Yano M, Ueki Y, Yamaguchi Y, Akazawa S, Tominaga Y. Glucose tolerance, insulin secretion, and insulin sensitivity in nonobese and obese Japanese subjects. Diabetes Care 1997; 20: 1562-1568.

43) Haffner SM, Miettinen H, Stern MP. The homeostasis model in the San Antonio Heart Study. Diabetes Care 1998; 20: 1087-1092.

44) Hayashi T, Boyko EJ, Leonetti DL, McNeely MJ, Newell-Morris L, Kahn SE, Fujimoto WY. Visceral adiposity and the risk of impaired glucose tolerance: a prospective study among Japanese Americans. Diabetes Care 2003; 26: 650-655.

45) Bonora E, Kiechl S, Willeit J, Oberhollenzer F, Egger G, Meigs JB, Bonadonna RC, Muggeo M, Bruneck study. Population-based incidence rates and risk factors for type 2 diabetes in white individuals: the Bruneck study. Diabetes 2004; 53: 1782-1789.

46) Kyrou I, Tsigos C. Obesity in the Elderly Diabetic Patient. Diabetes Care 2009; 32: S403-S409.

47) Bermúdez V, Salazar J, Fuenmayor J, Nava M, Ortega Á, Duran P, Rojas M, Añez R, Rivas-Montenegro A, Angarita L, Chacín M, Cano C, Velasco M, Rojas J. Lipid Accumulation Product Is More Related to Insulin Resistance than the Visceral Adiposity Index in the Maracaibo City Population, Venezuela. J Obes 2021; 2021: 5514901.

48) Wang B, Zhang M, Liu Y, Sun X, Zhang L, Wang C, Li L, Ren Y, Han C, Zhao Y, Zhou J, Pang C, Yin L, Feng T, Zhao J, Hu D. Utility of three novel insulin resistance-related lipid indices for predicting type 2 diabetes mellitus among people with normal fasting glucose in rural China. J Diabetes 2018; 10: 641-652.

49) Janghorbani M, Amini M. The Visceral Adiposity Index in Comparison with Easily Measurable Anthropometric Markers Did Not Improve Prediction of Diabetes. Can J Diabetes 2016; 40: 393-398.

50) Wakabayashi I, Daimon T. A strong association between lipid accumulation product and diabetes mellitus in Japanese women and men. J Atheroscler Thromb 2014; 21: 282-288.

51) Xiang S, Hua F, Chen L, Tang Y, Jiang X, Liu Z. Lipid accumulation product is related to metabolic syndrome in women with polycystic ovary syndrome. Exp Clin Endocrinol Diabetes 2013; 121: 115-118.

52) Decoda Study Group, Nyamdorj R, Qiao Q, Lam TH, Tuomilehto J, Ho SY, Pitkäniemi J, Nakagami T, Mohan V, Janus ED, Ferreira SR. BMI compared with central obesity indicators in relation to diabetes and hypertension in Asians. Obesity (Silver Spring) 2008; 16: 1622-1635.

53) Bozorgmanesh M, Hadaegh F, Azizi F. Diabetes prediction, lipid accumulation product, and adiposity measures; 6-year follow-up: Tehran lipid and glucose study. Lipids Health Dis 2010; 9: 45.

54) Vasques ACJ, FS, da Saúde de Oliveira M, JRM, A, JC, MA, MJA, B. TyG index performs better than HOMA in a Brazilian population: a hyperglycemic clamp validated study. Diabetes Res Clin Pract 2011; 93: e98-e100.

55) Mirmiran P, Bahadoran Z, Azizi F. Lipid accumulation product is associated with insulin resistance, lipid peroxidation, and systemic inflammation in type 2 diabetic patients. Endocrinol Metab (Seoul) 2014; 29: 443-449.

56) Selvi NMK, Nandhini S, Sakthivadivel V, Lokesh S, Srinivasan AR, Sumathi S. Association of Triglyceride-Glucose Index (TyG index) with HbA1c and Insulin Resistance in Type 2 Diabetes Mellitus. Maedica (Bucur) 2021; 16: 375-381.

57) Shin KA. Triglyceride and Glucose (TyG) Index is a Clinical Surrogate Marker for the Diagnosis of Metabolic Syndrome. Biomed Sci Letters 2017; 23: 348-354.

58) Anik Ilhan G, Yildizhan B, Pekin T. The impact of lipid accumulation product (LAP) and visceral adiposity index (VAI) on clinical, hormonal and metabolic parameters in lean women with polycystic ovary syndrome. Gynecol Endocrinol 2019; 35: 233-236.

59) Mirzaalian Y, Nourian M, Gholamalizadeh M, Doaei S, Hatami M, Hassanzadeh A, Askari G, Farahi R. The association of quantitative insulin sensitivity indices (HOMA-IR and QUICKI) with anthropometric and cardiometabolic indicators in adolescents. Arch Med Sci Atheroscler Dis 2019; 4: e32-e37.

60) Song Y, Manson JE, Tinker L, Howard BV, Kuller LH, Nathan L, Rifai N, Liu S. Insulin sensitivity and insulin secretion determined by homeostasis model assessment and risk of diabetes in a multiethnic cohort of women: the Women's Health Initiative Observational Study. Diabetes Care 2007; 30: 1747-1752.

61) Bastard JP, Lavoie ME, Messier V, Prud'homme D, Rabasa-Lhoret R. Evaluation of two new surrogate indices including parameters not using insulin to assess insulin sensitivity/resistance in non-diabetic postmenopausal women: a MONET group study. Diabetes Metab 2012; 38: 258-263.

62) Singh B, Saxena A. Surrogate markers of insulin resistance: a review. World J Diabetes 2010; 1: 36-47.

63) Simental-Mendía LE, Rodríguez-Morán M, Guerrero-Romero F. The product of fasting glucose and triglycerides as surrogate for identifying insulin resistance in apparently healthy subjects. Metab Syndr Relat Disord 2008; 6: 299-304.

64) Gower BA, Fernández JR, Beasley TM, Shriver MD, Goran MI. Using genetic admixture to explain racial differences in insulin-related phenotypes. Diabetes 2003; 52: 1047-1051.

65) Khoo CM, Sairazi S, Taslim S, Gardner D, Wu Y, Lee J, van Dam RM, Shyong Tai E. Ethnicity modifies the relationships of insulin resistance, inflammation, and adiponectin with obesity in a multiethnic Asian population. Diabetes Care 2011; 34: 1120-1126.

66) Araneta MR, Barrett-Connor E. Ethnic differences in visceral adipose tissue and type 2 diabetes: Filipino, African-American, and white women. Obes Res 2005; 13: 1458-1465.

67) Lemieux S. Contribution of visceral obesity to the insulin resistance syndrome. Can J Appl Physiol 2001; 26: 273-290.

68) Zamboni M, Mazzali G, Zoico E, Harris TB, Meigs JB, Di Francesco V, Fantin F, Bissoli L, Bosello O. Health consequences of obesity in the elderly: a review of four unresolved questions. Int J Obes (Lond) 2005; 29: 1011-1029.

69) Snijder MB, van Dam RM, Visser M, Seidell JC. What aspects of body fat are particularly hazardous and how do we measure them? Int J Epidemiol 2006; 35: 83-92.

70) Han TS, McNeill G, Seidell JC, Lean ME. Predicting intra-abdominal fatness from anthropometric measures: the influence of stature. Int J Obes Relat Metab Disord 1997; 21: 587-593.

71) Khan MS, Cuda S, Karere GM, Cox LA, Bishop AC. Breath biomarkers of insulin resistance in pre-diabetic Hispanic adolescents with obesity. Sci Rep 2022; 12: 339.