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Clinical Features and Insulin Resistance in Men with a Metabolically Unhealthy Obesity Phenotype

Abstract

Purpose of the study: The aim of study was to analyze the characteristics of hormonal-metabolic parameters in men with a metabolically unhealthy obesity phenotype; identify the value of special indicators for diagnosis of insulin resistance. **Materials and methods:** The examination included 108 patients with body mass index ≥25 kg/m^2, which were hospitalized. According to the current national guidelines for the diagnosis and treatment of obesity, all examined patients were divided into 2 groups: 1 — with metabolically healthy obesity phenotype, 2 — with metabolically unhealthy obesity phenotype. The study presents the results of comparative simultaneous nonrandomized study of two groups with using of different methods of examination (anthropometric indicators, laboratory tests for inspection of the hormonal profile, biochemistry parameters, and calculation of TyG index for diagnosis of insulin resistance). **Results and discussion:** The study found that patients of working age with metabolically unhealthy obesity phenotype are characterized by unfavorable anthropometric and hormonal-metabolic parameters and more severe polymorbid pathology (first of all cardiovascular diseases). The results of study revealed the value of special indicators for the diagnosis of insulin resistance (visceral obesity index >1,85; TyG >3,98; fat mass >30,1). **Conclusion:** timely detection of insulin resistance indicators has great importance and practical application due to simplicity and accessibility.

Key words: *obesity, insulin resistance, adiponectin, fat mass*

Conflict of interests

The authors declare no conflict of interests

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AF — atrial fibrillation, AI — atherogenic index, AH — arterial hypertension, ALAT — alanine aminotransferase, ASAT — aspartate aminotransferase, BMI — body mass index, BP — blood pressure, CHD — coronary heart disease, CHF — chronic heart failure, CS — cholesterol, DM — diabetes mellitus, ES — extrasystole, GIT — gastrointestinal

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tract, HC — hip circumference, HDL — high-density lipoproteins, HOMA-IR — insulin resistance index, IR — insulin resistance, LDL — low-density lipoproteins, MHP — metabolically healthy phenotype, MUP — metabolically unhealthy phenotype, NAFLD — non-alcoholic fatty liver disease, TG — triglycerides, TyG — triglycerides/glucose index, VAI — visceral adiposity index, WC– waist circumference

Introduction

Today, obesity (OB) is regarded as one of the most critical public health problems, which leads to early disability and high mortality [1, 2]. This is primarily due to the development of insulin resistance (IR), which, in turn, is the main risk factor for the development of severe hormonal and metabolic changes [3, 4]. The number of overweight and obese patients is growing steadily [5, 6, 7]; in light of this, the development and implementation of available methods for the diagnosis of the main IR parameters seem to be a significant aspect for real clinical practice.

Patients with the so-called metabolically unhealthy obese phenotype (MUP) are considered as a special group [8, 9]. In this study, we analyzed the features of hormonal and metabolic parameters in this category of patients; ROC analysis helped to determine the TyG index (logarithmic ratio of fasting triglycerides and plasma glucose), visceral adiposity index (VAI), and the percentage of adipose tissue for IR diagnosis in clinical practice.

Study Objective

To analyze clinical, hormonal and metabolic features in patients with metabolically unhealthy obese phenotype, to evaluate the possibilities of assessing insulin resistance (IR) at the primary care stage.

Materials and Methods

This study included 108 working-age men with body mass index (BMI) ≥ 25 kg/m^2, hospitalized in cardiac and therapeutic hospitals of the Federal Government Healthcare Institution "Primary Healthcare Unit of the Ministry of Internal Affairs of Russia in the Nizhny Novgorod Region". The patients were hospitalized for exacerbation of visceral diseases, annual routine medical examination, or adjustment of current treatment.

All of the examined patients were divided into two groups according to the criteria set by the National Clinical Recommendations for the Diagnosis, Treatment and Prevention of Obesity and Associated Conditions [8]: group 1 — group with metabolically healthy phenotype (MHP) and group 2 — group with metabolically unhealthy phenotype (MUP). Patients with no more than one additional associated pathological condition and normal tissue sensitivity to insulin were assigned to the MHP group (metabolically healthy obesity). Individuals with metabolically healthy phenotype were identified according to the National Clinical Recommendations for the Diagnosis, Treatment and Prevention of Obesity and Associated Conditions (2017).

In this group of patients, a slight increase in visceral adiposity index (VAI) and/or fat mass was permissible.

This paper is a cross-sectional comparative non-randomized descriptive study of two groups of patients. We used methods for assessing anthropometric parameters, including the calculation of visceral adiposity index (VAI) and the percentage of adipose tissue using the Deurenberg equation [10]. Laboratory tests, i.e., CBC, blood biochemistry and hormonal tests (immunoreactive insulin and adiponectin) were also performed. A detailed assessment of insulin resistance included, in addition to conventional parameters (HOMA-IR, Caro index), the analysis of TyG index, determined by the following formula:

$$\mathbf{[TG\ (mg/dL) \times glucose\ (mg/dL)]},$$

where TG is the level of triglycerides

Statistical processing of the material was carried out using Statistica 6.0 software package and Microsoft Excel 7.0 for Windows XP with nonparametric methods; ROC analysis was also used. Statistical processing of the results was performed using nonparametric methods of variation statistics (median and percentiles) and Mann—Whitney test to compare independent samples. Statistical significance of differences was evaluated with the probability of null hypothesis less than 0.05 ($p < 0.05$).

Data in the text and tables are presented as M ± m (where M is the arithmetic mean, and m is the arithmetic mean error). The correlation of quantitative features was analyzed using correlation and regression analysis methods and supplemented by a nonparametric method, i.e., calculation of Spearman's rank correlation coefficient, which reduces the effect of random outliers. Qualitative data were compared using the chi-square test (χ^2) (depending on the number of cases of comparison — Fisher's exact test or χ^2 test with Yates's correction for continuity). Cluster analysis was used for analyzing the compound effect of factors on the quality of life of men of working age.

Results

As a result, group 1 included 45 patients, group 2 — 63 patients. Table 1 presents the clinical features of the groups.

As the table shows, the average age of patients in the groups was approximately the same, while patients with MUP were characterized by a higher BMI. This group also had a significantly higher VAI and percentage of fat mass.

Comparative analysis of the incidence and nature of associated diseases in the two groups of patients revealed a number of differences in polymorbidity parameters (Table 2).

Table 1. *Clinical characteristics of groups of patients with metabolically healthy and metabolically unhealthy obesity phenotype*

Parameter	MHP n = 45	MUP n = 63	p-value
Age, years	43.9 ± 1.1	47.2 ± 0.9	0.06
BMI, kg/m^2	29.6 ± 0.4	36.1 ± 0.8	<0.001
WC, cm	96.5 ± 1.2	117.1 ± 1.9	<0.001
HC, cm	103.1 ± 1.1	112.3 ± 1.3	<0.001
WC/HC	0.91 ± 0.006	1.04 ± 0.008	<0.001
Fat mass, %	29.2 ± 0.6	38 ± 0.9	<0.001
VAI	1.5 ± 0.1	3.1 ± 0.4	<0.001

Note: BMI — body mass index, WC — waist circumference, HC — hip circumference, VAI — visceral adiposity index, MHP — metabolically healthy phenotype, MUP — metabolically unhealthy phenotype

Table 2. *Comorbid pathology in groups of patients with a metabolically healthy and metabolically unhealthy obesity phenotype*

Parameter, % (individuals)	MHP, n = 45	MUP, n = 63	p, χ^2
AH stage I	40.2 (19)	14.5 (9)	p = 0.002, χ^2 = 7.31
AH stage II	48.9 (26)	48.3 (30)	p = 0.9, χ^2= 2.04
AH stage III	0	38.7 (24)	p = 0.01, χ^2= 5.8
CHD: stable angina FC I-II	0	32.8 (20)	p = 0.002, χ^2 = 8.8
Atrial fibrillation: permanent form (n = 3) paroxysmal form (n = 2)	0	8.2 (5)	p = 0.053, χ^2= 3.74
CHF stage IIA (FC I-II)	0	32.8 (20)	p = 0.002, χ^2= 8.8
NAFLD (grade 1)	10.9 (5)	25.8 (16)	p = 0.04, χ^2= 9.45
Chronic pancreatitis	17 (8)	14.7 (9)	p = 0.7, χ^2= 15.8
Chronic cholecystitis	34 (16)	42.6 (26)	p = 0.3, χ^2= 7.55
Chronic gastroduodenitis	12.8 (6)	16.4 (10)	p = 0.4, χ^2= 16
Osteoarthritis (knee/hip joints)	0	31.6 (20)	p = 0.02, χ^2= 17.5

Notes: AH — arterial hypertension, CHD — coronary heart disease, FC — functional class, AF — atrial fibrillation, CHF – chronic heart failure, NAFLD — non-alcoholic fatty liver disease

Table 3. *Blood biochemical parameters in patients with a metabolically healthy and metabolically unhealthy obesity phenotype*

Parameter	MHP, n = 45	MUP, n = 63	p-value
ASAT, U/L	26 ± 1.1	27.4 ± 2.1	0.4
ALAT, U/L	32.1 ± 2.8	44.2 ± 4.9	0.8
Total bilirubin, μmol/L	10.6 ± 1.1	12.7 ± 1.4	0.1
Urea, mmol/L	6 ± 0.3	6.6 ± 0.3	0.1
Creatinine, μmol/L	94.4 ± 2.8	96.5 ± 2.6	0.5
Glucose, mmol/L	5.2 ± 0.09	5.8 ± 0.2	0.04

Patients with MUP were characterized by a more severe cardiovascular pathology: AH stage III, presence of CHD and CHF. AH without damage to target organs and associated clinical conditions was more often observed in group 1 (MHP) ($p = 0.002$ $\chi^2 = 7.31$).

The pathology of the gastrointestinal tract (GIT) was primarily characterized by fatty liver and chronic cholecystitis. Patients with MUP more often had non-alcoholic fatty liver disease (NAFLD) of grade 1 compared to the MHP group ($p = 0.04$, $\chi^2 = 9.45$). NAFLD grade 1 is characterized by symptoms of steatohepatosis without signs of inflammation and liver fibrosis, as well as without significant increase in hepatic transaminases (alanine aminotransferase (ALAT), aspartate aminotransferase (ASAT)) [8].

A comparative analysis of laboratory biochemical parameters in the two groups of patients is presented in Table 3.

Lipid profile of patients with different phenotypes of obesity is shown in Figure 1.

Compared with the MHP group, patients with MUP demonstrated more unfavorable values of carbohydrate and lipid metabolism, which was expressed in high levels of fasting glycemia ($p = 0.04$) and triglycerides ($p < 0.001$). Patients with MHP had a higher level of high density lipoprotein cholesterol (HDL cholesterol) ($p < 0.001$). There were no statistically significant differences in other biochemical parameters.

Table 4 presents the insulin resistance parameters of the patients.

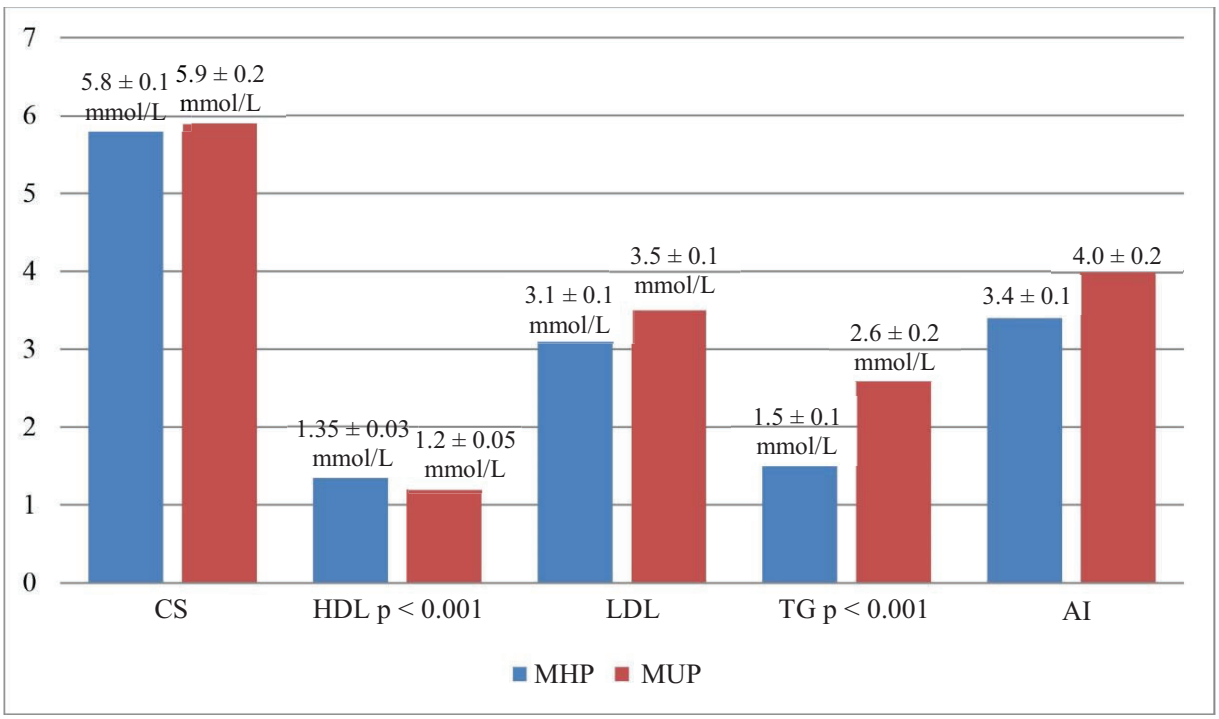

Figure 1. *Lipid profile in patients with different obesity phenotypes*

Note: CS — total cholesterol, HDL — high density lipoprotein cholesterol, LDL — low density lipoprotein cholesterol, TG — triglycerides, AI — atherogenic index

Table 4. *Indicators of insulin resistance in patients with a metabolically healthy and metabolically unhealthy obesity phenotype*

Index	Metabolically healthy phenotype, n=45	Metabolically unhealthy phenotype, n=63	P
Caro	0,85±0,11	0,39±0,05	<0,001
HOMA-IR [11]	2,32±0,26	5,99±0,7	<0,001
TyG	3,87±0,03	4,13±0,04	<0,001

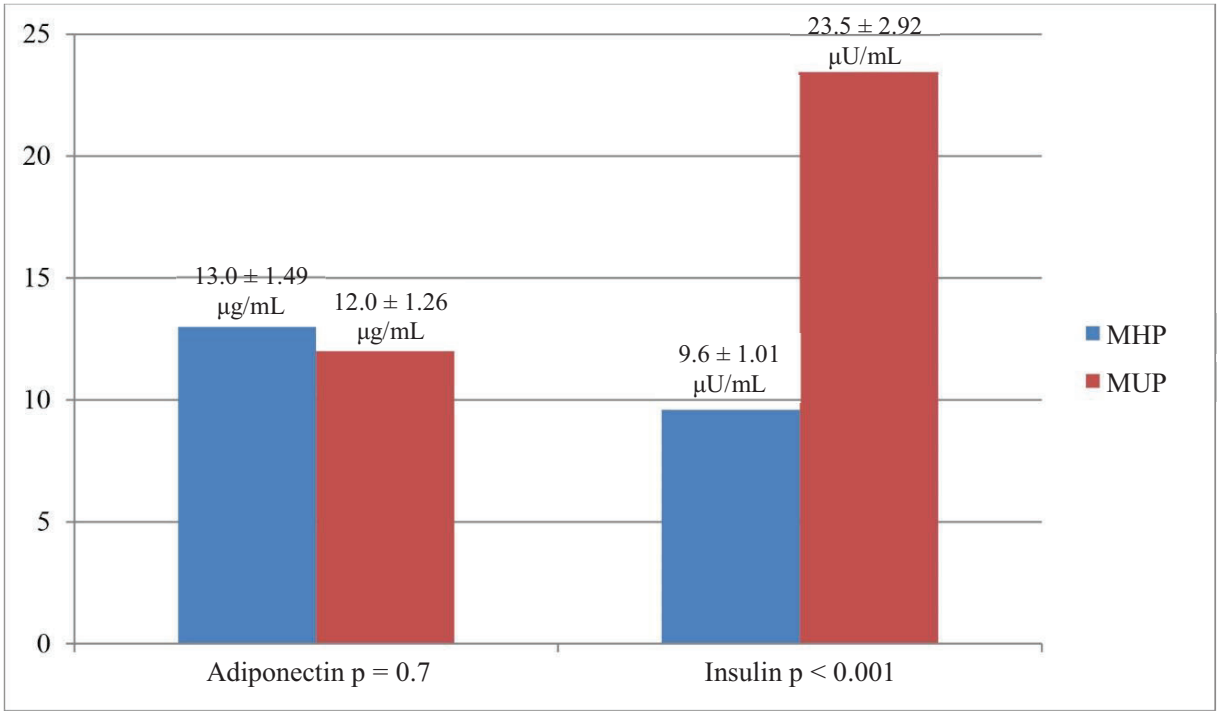

Figure 2. *Hormonal parameters in patients with metabolically healthy (MHP) and metabolically unhealthy obese phenotype (MUP)*

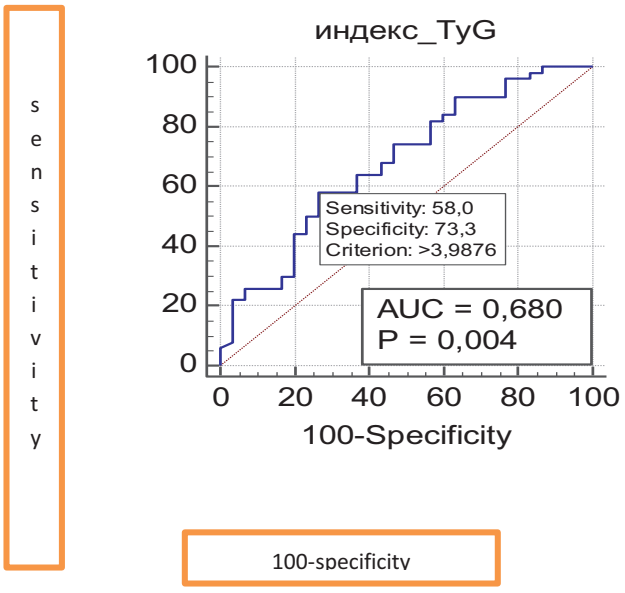

Figure 3. *Determining TyG index for IR diagnosis in men of working age*

Hormonal parameters in patients with different obesity phenotypes are presented in Figure 2.

As can be seen from results, patients with MUP showed more unfavorable values of hormonal profile expressed as hyperinsulinemia with signs of IR ($p < 0.001$). TyG index (logarithmic ratio of fasting plasma triglycerides and glucose) seems to be particularly significant; it allows detecting IR [12] and is considered a predictor of type 2 diabetes mellitus (2 type DM). Calculation of the TyG index can be simple and cost-effective at the primary health care stage since it requires just the determination of blood glucose and triglycerides, without assessing insulinemia. Analysis of the significance of the TyG index for IR diagnosis was performed using ROC analysis (Figure 3).

This analysis showed that a TyG index higher than 3.98 suggests the presence of IR. The predictive

Table 5. *Correlative relationships of adiponectin with anthropometric, metabolic parameters and insulin resistance in patients with a metabolically unhealthy obesity phenotype*

Parameter	Index (M ± m)	Adiponectin (M ± m)	Spearman's coef.	p-value
WC/HC	1.03 ± 0.008	12.2 ± 1.2	–0.3	0.03
VAI	3.12 ± 0.34	12.2 ± 1.2	–0.3	0.01
TG (mmol/L)	2.56 ± 0.25	12.2 ± 1.2	–0.3	0.03
CS (mmol/L)	5.9 ± 0.23	12.2 ± 1.2	–0.3	0.02
LDL (mmol/L)	3.5 ± 0.18	12.2 ± 1.2	–0.3	0.04
AI	4.0 ± 0.24	12.2 ± 1.2	–0.5	<0.001
ALAT (mmol/L)	44.4 ± 4.8	12.2 ± 1.2	–0.3	0.03
TyG	4.12 ± 0.04	12.2 ± 1.2	–0.3	0.01

Note: WC/HC — ratio of waist circumference to hip circumference; VAI — visceral adiposity index, TG — triglycerides; CS — total cholesterol; LDL — low density lipoproteins cholesterol, AI — atherogenic index; ALAT — alanine aminotransferase, TyG — triglycerides/glucose index

sensitivity of the TyG index was 58% (95% CI 43.2–71.8), the specificity of this method was 73.33%, the positive likelihood ratio was 2.17, and the negative likelihood ratio was 0.57.

Today, many authors have demonstrated that the accumulation of adipose tissue around internal organs (visceral OB) plays a key role in the development of different circulatory and metabolic disorders due to the dysregulation of adipocytokine secretion, including adiponectin [13, 14]. Low adiponectin concentrations are associated with IR and 2 type DM [15].

Angioprotective and antiatherogenic properties of adiponectin are known. In patients with severe visceral OB, adiponectin synthesis decreases, causing carbohydrate and lipid metabolism disorders [16]. These relationships were observed in our study (Table 5).

In order to determine the threshold value of VAI that will indicate the presence of IR, ROC analysis was carried out; its results are presented in Figure 4.

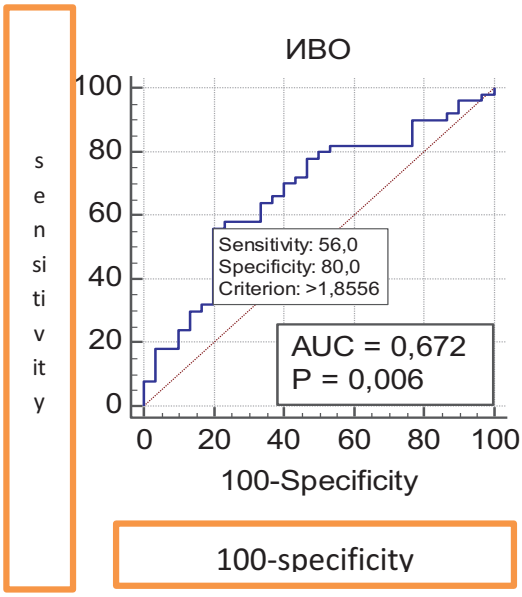

Figure 4. *Determination of VAI for predicting insulin resistance*

It was found that VAI > 1.85 is associated with the presence of IR, while VAI ≤ 1.85 is associated mostly with normal tissue sensitivity to insulin. The prognostic sensitivity of VAI was 56% (95 CI 41.3–70), specificity — 80% (95% CI 61.4–92.3), positive likelihood ratio was 2.8, and negative likelihood ratio was 0.55.

According to clinical recommendations, there is another parameter for the diagnosis of visceral obesity — calculation of the percentage of fat mass [8, 9]. In men, this figure should not exceed 25% [8]. Fat mass of more than 25% is a marker of visceral OB, as it indicates the predominance of visceral fat over subcutaneous fat. However, a moderate increase in this value is possible for MHP obesity parameters [8]. The examined patients with MHP showed an average fat mass of 29.2 ± 0.6%, the group with MUP — 38 ± 0.9%, p < 0.001. To determine the threshold value for fat mass in men of working age and its relationship with the severity of IR, ROC analysis was performed. Results are shown in Figure 5.

It was shown that fat mass of more than 30.1% is associated with IR. The predictive sensitivity of this parameter was 84% (95% CI 64–88.5),

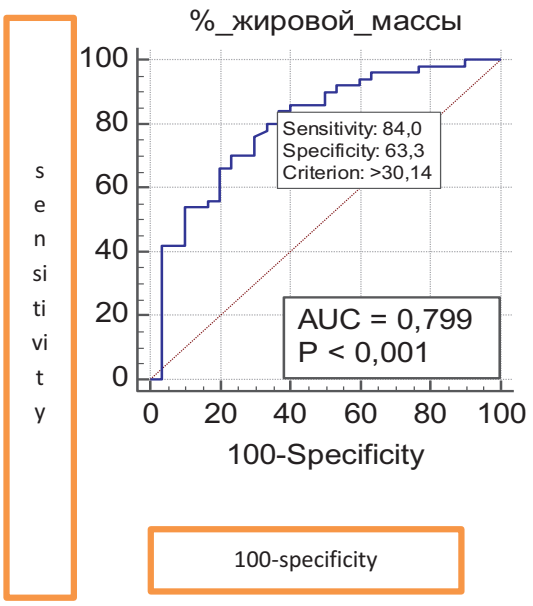

Figure 5. *Determination of the percentage of fat mass in men of working age for detecting insulin resistance*

specificity — 63.3% (95% CI 47.2–82.7), diagnostic efficacy — 73.65%, positive likelihood ratio — 2.34, negative likelihood ratio — 0.33.

This analysis can also be used in real clinical practice: calculation of fat mass percentage requires just the BMI and the age of subject.

The determination of IR factors, therefore, is an important stage in the assessment of the cardiometabolic and vascular risk in obese individuals. The development and use of examination procedures that are available in real practice for this category of patients seem to be the most significant issue. From this perspective, fat tissue percentage and VAI are parameters that are accessible at the primary health care stage and are informative in terms of assessing cardiovascular risks. This corresponds to the data obtained by other authors [17], although so far, there is no consensus on the diagnostic and prognostic significance of VAI [18].

Conclusions

1. Patients of working age with a metabolically unhealthy phenotype (MUP) of obesity are characterized by unfavorable anthropometric parameters and comorbid pathologies, primarily cardiovascular pathologies.
2. The special feature of patients with MUP is the presence of unfavorable hormonal and metabolic parameters and insulin resistance.
3. In terms of cost-effectiveness, TyG index > 3.98; VAI > 1.85 and fat mass > 30.1% are preferable as signs of insulin resistance at the primary health care stage, considering their simplicity, accessibility and no need to conduct additional (hormonal) studies.

Author Contribution:

All the authors contributed significantly to the study and the article, read and approved the final version of the article before publication.

Panova E.I. (ORCID ID: https://orcid.org/0000-0002-7220-4745): final approval of the manuscript for publication.

Pimankina M.S. (ORCID ID: https://orcid.org/0000-0002-8280-2669): substantiation and writing of the manuscript.

Karataeva O.V. (ORCID ID: https://orcid.org/0000-0002-0041-7098): collection, analysis and interpretation of data

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