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Original article

Metabolically neutral obesity: terminology, prevalence, and meaning

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Abstract: Determining the leptin level in patients with abdominal obesity without signs of insulin resistance is necessary for stratifying patients into groups with normal (metabolically neutral obesity) and increased adipokine activity.
Objective — To compare the prevalence of metabolic disorders and signs of cardiovascular remodeling in young and middle-aged men with "metabolically healthy" and "metabolically neutral" obesity.
Material and methods — observational sample survey of 590 men aged 38.5±5.6 years was conducted. Average body weight was assessed on301 men (the control group). Obesity was determined in 289 patients: among them, the criteria for metabolic syndrome were diagnosed for 134 study participants, metabolically healthy obesity (MHO) was diagnosed in 155 men, and 86 patients from MHO with leptin levels <3.5 ng/ml constituted metabolically neutral obesity group. All patients were evaluated by a lipidogram, adipokine, glycemic profiles, and ultrasound examination of the heart and carotid arteries.
Results — Criteria for metabolically neutral abdominal obesity in men were determined: weight gain >30 kg/m^2 in the presence of no more than two criteria for metabolic syndrome and leptin level <3.5 ng/ml. The metabolically neutral type was characterized by a better lipid profile, which was confirmed by a lower frequency of dyslipidemia (1.7 times); the frequency of prediabetes was 7% and was half as low as in metabolically healthy obesity; atherosclerosis of the carotid arteries was 1.5 times less common in the neutral type of obesity.
Conclusion — The selection of a "metabolically neutral" type of obesity is justified since it allows us to determine the stage of the disease at which the frequency of metabolic and cardiovascular disorders is still minimal and non-drug prevention is necessary.

Keywords: metabolic syndrome, metabolically healthy obesity, metabolically neutral obesity, subclinical atherosclerosis, adipokines.

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Introduction

Obesity is an independent endocrine disease that increases the risk of developing diabetes mellitus (DM) type 2 and cardiovascular diseases (CVD) [1]. According to Rosstat data for 2018, overweight and various degrees of obesity were detected in 64.7 % of Russian men. Abdominal obesity (AO), which plays a vital role in the formation of metabolic syndrome (MS), was detected in every fourth man surveyed (ESSE-2) [1].

Currently, the scientific community is actively discussing "metabolically healthy obesity" (MHO) – an alteration of the alimentary status without hypertension and insulin resistance (IR), i.e., without MS [2, 3]. At the same time, the hormonal activity of adipocytes and initial changes in arterial vascular wall are not included in the diagnostic criteria, which may lead to underestimating the prevalence and impact of obesity.

Changes to the hormone leptin, synthesized by visceral adipocytes, are a factor in developing IR, dyslipidemia (DLP), and dysglycemia [4, 5]. Leptin has an anti-steatogenic effect and, like insulin, regulates the homeostasis of glucose and fatty acids. Weight gain is accompanied by compensatory hyperleptinemia, which prevents excessive storage of triglycerides (TG) in peripheral tissues. With leptin resistance observed in AO and fatty liver dystrophy, the concentration of free fatty acids, TG, and low-density lipoproteins (LDL) increases in blood plasma), TG is deposited in cardiac and striated myocytes, liver, and pancreas. Also, glucose metabolism is disrupted, and apoptosis of altered cells is activated. In animal models, the potentiating effect of leptin on aldosterone production, which contributes to endothelial dysfunction and cardiac fibrosis, has further been shown [6-8].

We postulate that determining the level of leptin in AO without MS would allow stratifying patients into groups with metabolically neutral obesity (MNO) and increased adipokine activity with an increased risk of developing MS in the future.

Aim: To compare the prevalence of metabolic disorders and signs of cardiovascular remodeling in young and middle-aged men with metabolically healthy and metabolically neutral types of obesity.

Material and Methods

From 2016 to 2019, a single-center, single-stage observational sample survey of 590 men aged 38.5±5.6 years was conducted. Criteria for inclusion in the study: male gender, age from 30 to 45 years, availability of voluntary informed consent. Exclusion criteria: clinical manifestations of diseases caused by atherosclerosis; significant arrhythmias and heart defects; secondary hypertension and DLP; previous associated clinical conditions; diabetes mellitus type 2; viral and toxic liver damage; positive ischemic stress test.

AO was assed as an increase in body mass index (BMI) >30 kg/m^2 and a waist circumference (WT) >94 cm. Metabolically healthy obesity was defined as obesity with two or fewer MS components (for example, hypertension and DLP, hypertension, and prediabetes, etc.); MS – in accordance with National recommendations (AO+hypertension and dyslipidemia and/or dysglycemia). Our scientific group proposed the metabolically neutral type of obesity, which was diagnosed in patients with MHO and leptin levels <3.5 ng/ml. This parameter was determined based on the results of the analysis of variance (It was previously evaluated the relationship of MS with the level of other adipokines – adiponectin, ghrelin, resistin, IL-6, TNF-α), and its critical value was identified based on the ROC analysis with a sensitivity of 75% and a specificity of 77% [9].

According to the BMI criterion, normal body weight was assessed in 301 men (control). AO was determined in 289 patients: among them, MS criteria were diagnosed for 134 study participants, MHO – in 155 men. To assess the feasibility of identifying the subtype of metabolically neutral obesity (MNO), 69 (44.5%) men with leptin levels greater than 3.5 ng/ml were excluded from 155 patients with MHO: a group of 86 people (55.5% of the original group) was formed. In the control groups, leptin>3.5 ng/ml was detected in 19% and in MS group, it was revealed in 74% of patients (χ^2=45.9; p<0.001).

All patients were evaluated for extended lipidogram and adipokine levels on fasting post-load glycemia during the oral glucose tolerance test (OGTT). The insulin resistance index (HOMA-IR) was determined. Changes in the heart and vascular wall were evaluated by echocardiography and ultrasound examination of the thickness of the intima-media complex of the common carotid arteries (IMT CCA).

Statistical analysis was performed using the Statistica 10.0 for Windows and IBM SPSS 20 application software package. When comparing the distributions of quantitative indicators in 4 groups, analysis of variance was used. The mean value of the trait and 95% confidence interval (M [95% CI]) were presented because some indicators had a distribution different from normal. The null hypothesis about the absence of intergroup differences was rejected at the significance level of p<0.05. We constructed contingency tables of observed and expected frequencies; the Pearson Chi-square criterion (χ^2) was used. Variance and ROC analysis were employed to develop mathematical models.

To select a group of the most informative features included in the final model, the informativeness of each in the variance one-factor analysis was evaluated, their expert assessment was made, and several models with a different set of features were tested. To more precisely solve this problem, we used ROC – analysis (receiver operating characteristic) with the construction of the corresponding curve to assess the quality of the model by dividing the two classes. The y-axis indicated the frequency of true positive results (sensitivity), and x-axis indicated the frequency of false positive results (1-specificity). In addition to the ROC curve graph, the area under the ROC curve (AUC) was used to assess the quality of the model. Depending on the AUC parameter value, the diagnostic model qualitywas considered average (0.6-0.7), good (0.7-0.8), or very good (0.8-0.9). When applying the cut-off threshold, the optimal sensitivity and specificity values were considered.

Table 1. Initial characteristics of the examined patients, M [95% – CI]

Index	*Age, years*	*BMI, kg/m^2*	*Waist circumference, cm*	*Duration of AO, years*
MNO (n=86)	37.4 [36.2-38.7]	30.1 [30-30.1]	96.2 [93.4-98.9]	4.8 [3.4-6.3]
MHO (n=155)	38.9 [38.1-39.8]	30.3 [30-30.6]	98.5 [97.4-99.6]	5.2 [4.6-5.9]
MS (n=134)	40.9 [39.9-41.8]	32.3 [31.6-32.9]	103.8 [102.4-105.3]	6.9 [6.1-7.6]
Control group (n=301)	38.3 [37.7-38.9]	24.8 [24.5-25.0]	84.4 [83.6-85.2]	0
p	$p_{MNO/MS}$<0.001	$p_{MNO/MS}$<0.001	$p_{MNO/MHO}$=0.020	$p_{MNO/MS}$<0.001
	$p_{MHO/MS}$<0.001	$p_{control/MNO}$<0.001	$p_{MNO/MS}$<0.001	$p_{MHO/MS}$<0.001
	$p_{control/MS}$<0.001	$p_{MHO/MS}$<0.001	$p_{MHO/MS}$<0.001	
		$p_{control/MS}$<0.001	$p_{control/MS}$<0.001	
		$p_{control/MHO}$<0.001	$p_{control/MHO}$<0.001	

p-values are indicated if there are statistically significant differences between groups.

Table 2. Features of the lipidogram in groups, M [95% – CI]

Index	*TC, mmol/l*	*VLDL, mmol/l*	*LDL, mmol/l*	*HDL, mmol/l*	*TG, mmol/l*
MNO (n=86)	4.7 [4.1-4.8]	0.5 [0.3-0.7]	3.3 [2.2-4.2]	1.7 [1.3-2.0]	1.2 [1.0-1.5]
MHO (n=155)	4.9 [4.7-5.1]	0.66 [0.6-0.7]	3.3 [2.9-3.6]	1.6 [1.4-1.7]	1.5 [1.2-1.8]
MS (n=134)	5.9 [5.7-6.1]	1.1 [1.0-1.2]	3.6 [3.3-3.8]	1.2 [1.1-1.3]	2.4 [2.1-2.7]
Control group(n=301)	5.1 [5.0-5.2]	0.6 [0.5-0.7]	3.2 [3.0-3.4]	1.6 [1.4-1.7]	1.3 [1.2-1.5]
p	$p_{MNO/MS}$<0.001	$p_{MNO/MS}$<0.001	$p_{Control/MS}$=0.020	$p_{MNO/MS}$<0.001	$p_{MNO/MS}$<0.001
	$p_{MHO/MS}$<0.001	$p_{MHO/MS}$<0.001		$p_{MHO/MS}$<0.001	$p_{MNO/MHO}$<0.001
	$p_{Control/MS}$<0.001	$p_{Control/MS}$<0.001		$p_{Control/MS}$<0.001	$p_{MHO/MS}$<0.001
					$p_{Control/MS}$<0.001

p-values are indicated if there are statistically significant differences between groups.

Table 3. State of carbohydrate metabolism in groups, M [95% – CI]

Index	*Fasting glucose, mmol/l*	*Glucose after 2 hours PGTT, mmol/l*	*Insulin, μIU/mL*	*HOMA-IR*
MNO (n=86)	4.9 [4.6-5.2]	5.7 [5.2-6.1]	8.6 [7.3-13.4]	2.3 [1.4-3.2]
MHO (n=155)	5.0 [4.9-5.2]	5.6 [5.3-6.0]	10.5 [11.6-16.7]	2.6 [1.6-3.6]
MS (n=134)	5.6 [5.4-5.7]	6.2 [5.8-6.6]	14.2 [5.3-15.7]	3.3 [2.6-3.9]
Control group(n=301)	5.0 [5.0-5.1]	5.6 [5.3-5.8]	7.2 [5.4-9.0]	1.6 [1.2-2.0]
p	$p_{MHO/MS}$<0.001	$p_{MHO/MS}$=0.02	$p_{Contol/MS}$<0.001	$p_{Contol/MS}$<0.001
	$p_{control/MS}$<0.001	$p_{Contol/MS}$=0.003		

p-values are indicated if there are statistically significant differences between groups

Table 4. Features of the metabolic status in various types of obesity, M [95% – CI]

index	*Adiponectin, mcg/ml*	*IL-6, pg/ml*	*Leptin, ng/ml*	*TNF-α, pg/ml*
MNO (n=86)	16.9 [10.5-21.8]	8.7 [7.3-11.0]	1.7 [1.4-2.2]	1.5 [1.0-1.8]
MHO (n=155)	18.4 [14.7-22.2]	7.5 [6.1-9.0]	2.1 [1.7-2.5]	1.4 [1.1-1.7]
MS (n=134)	23.7 [16.4-31]	10.8 [8.5-13.0]	4.4 [3.2-5.7]	2.2 [1.7-2.7]
Control group(n=301)	24.1 [19.4-28.7]	7.6 [6.5-10.7]	1.4 [1.1-1.7]	1.3 [1.1-1.6]
p		$P_{mho/ms}$=0.01	$P_{MHO/MS}$<0.001	$P_{MHO/MS}$=0.002
		$P_{control/MS}$=0.006	$P_{Contol/MS}$<0.001	$P_{control/MS}$<0.001
			$P_{Control/MHO}$=0.05	

p-values are indicated if there are statistically significant differences between groups

Table 5. Ultrasound structure of the heart and functional state of the vascular wall in groups, M [95% – CI]

index	LAVI, ml/m^2	LVMMI, g/m^2	Ejection fraction, %	IMT CCA, mm
MNO (n=86)	30.5 [18.8-42.2]	98.4 [82.6-114.3]	62.7 [57-68.3]	0.69 [0.64-0.74]
MHO (n=155)	33.6 [30.6-36.7]	102.8 [98.8-106.9]	63.8 [62.4-65.2]	0.74 [0.7-0.78]
MS (n=134)	34.8 [32.4-37.1]	108.2 [104.5-111.9]	65.5 [64.4-66.7]	0.93 [0.84-1.0]
Control group (n=301)	26.8 [25.6-28]	94.5 [92.5-97.5]	63.8 [62.6-64.9]	0.72 [0.68-0.75]
p	$p_{MNO/MHO}$=0.01	$p_{MNO/MHO}$=0.02	$p_{Control/MS}$=0.03	$p_{MNO/MHO}$=0.01
	$p_{MNO/MS}$<0.001	$pM_{NO/MS}$<0.001		$p_{MNO/MS}$=0.006
	$p_{Control/MS}$<0.001	$p_{MHOI/MS}$=0.05		$p_{MHOI/MS}$<0.001
	$p_{Control/MHO}$<0.001	$p_{Control/MS}$<0.001		$p_{Control/MS}$<0.001
		$p_{Control/MHO}$=0.002		

p-values are indicated if there are statistically significant differences between groups

Results

Brief anthropometric data on the groups of examined patients are presented in *Table* 1. Patients with MS were slightly older than men in the control group, MNO and MHO (p<0.001). The same group had higher BMI and WC values and a longer history of obesity (p<0.01). The MNO and MHO groups were comparable in these indicators (p>0.05), except WC (p=0.02); they did not differ in age from the control group (p>0.05).

The analysis of biochemical parameters characterizing patients' lipid, carbohydrate, and adipokine status in the MHO, MS, and control groups are summarized in *Tables* 2-4. Significant atherogenic changes in the lipid spectrum, characterized by an increase in total cholesterol (TC), LDL, and TG, were detected in patients of the MS group when compared with controls and groups of men with MNO and MHO. The most optimal lipidogram parameters were recorded in patients of the MNO group (*Table* 2). Patients with IR had higher values of fasting glycemia after the glucose tolerance test and immunoreactive insulin and HOMA index (*Table* 3). Groups with different metabolic types of obesity without IR did not differ in these indicators. Prognostically unfavorable changes in the adipokine profile were determined in MS (*Table* 4). Most of the metabolic parameters in the MNO group were comparable with the control; the leptin level was significantly higher in men with IR and MHO.

All examined patients underwent ultrasound examination of the heart with the determination of the left atrial volume index (LAVI), left ventricular myocardium mass index (LVMMI), assessment of LV systolic function, and carotid artery endothelium thickness (*table* 5). when analyzing the echocardiography data, we did not detect structural and functional heart disorders in men with MNO, while against the background of MHO, left atrium dilation (p=0.01) and large values of LVMMI were determined (p=0.02). Patients with MNO were characterized by a smaller thickness of the CCA endothelium (p=0.01). Against the background of AO, the groups of MHO and MS compared to the control showed left atrium dilation and an increase in LVMMI, indicating the beginning of LV remodeling. In patients with MS, the IMT index exceeded the average age standard (0.9 mm), indicating thickening of the endothelial complex, which, in turn, indicated probable atherosclerosis of the carotid arteries (*Table* 5).

The resulting data on the frequency of disorders of carbohydrate and lipid metabolism and changes in the heart and carotid arteries in the groups of examined patients are shown in *Figure* 1. In the group of patients with MS, prediabetes, left ventricular hypertrophy (LVH), and atherosclerotic changes in CCA were more often diagnosed. The prevalence of metabolic and cardiovascular disorders in the MHO and control groups was comparable (p>0.05). In patients with MNO, the prevalence of DLP was 1.7 times, and prediabetes was two times lower (p=0.05) than in men with MHO. In the metabolically neutral type of AO, the frequency of CCA atherosclerosis was 1.5 times lower than in the MHO. LVH in groups without IR was found with a comparable frequency, significantly more often against the background of MS (p<0.001) (*Figure* 1).

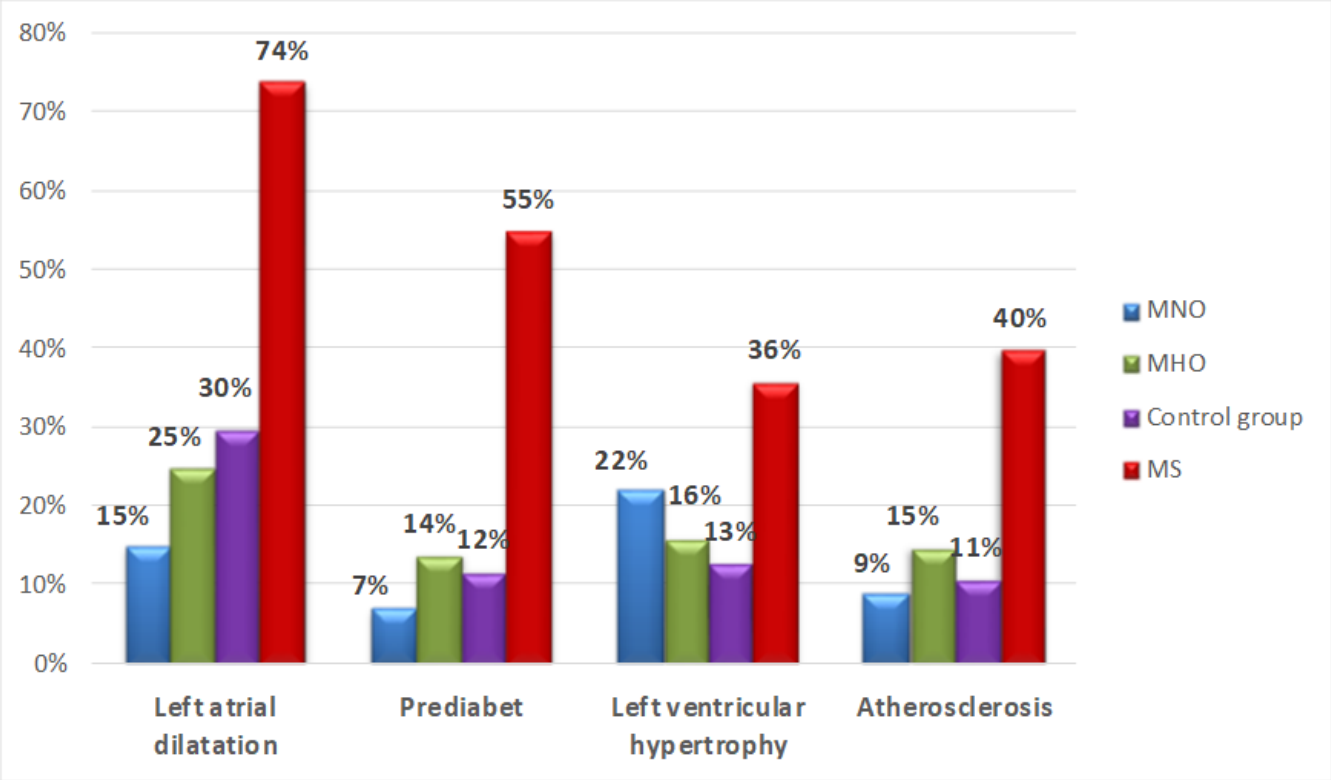

Figure 1. Frequency of changes in metabolism and cardiovascular system in groups.

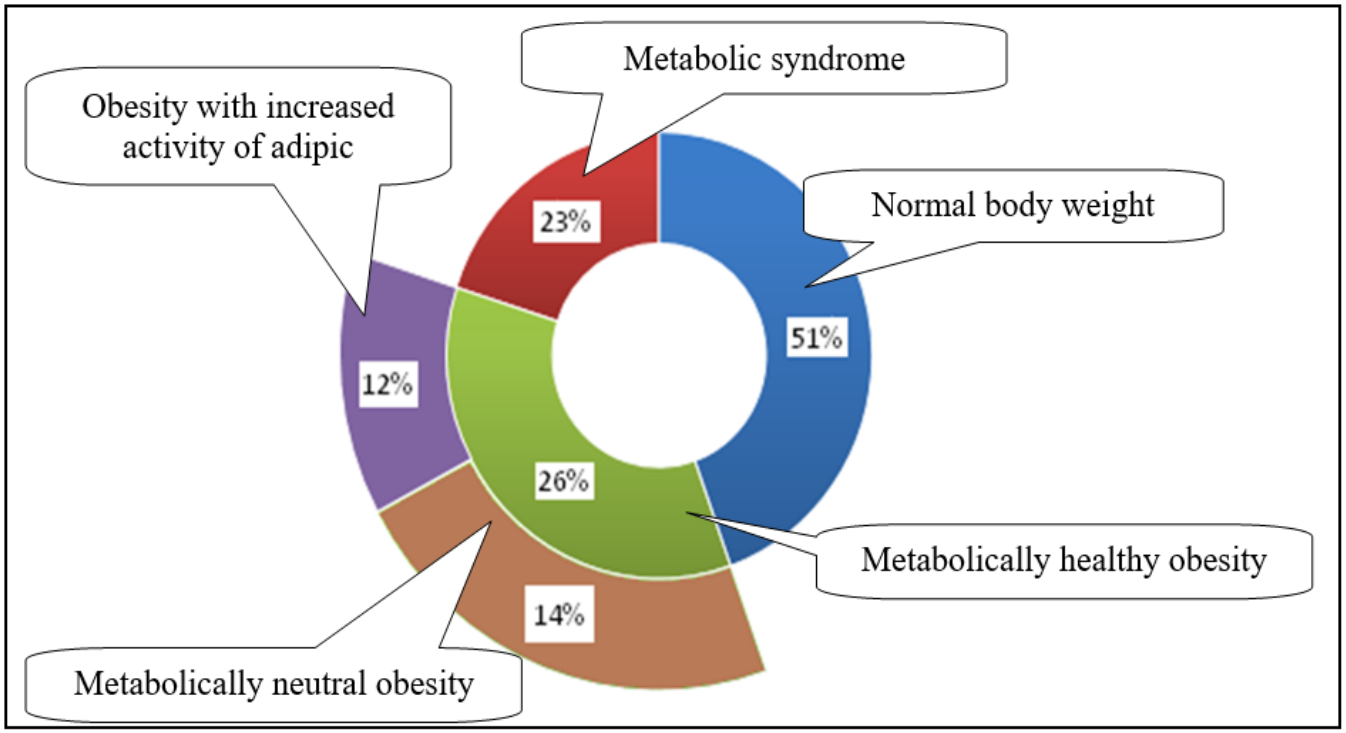

Figure 2. Prevalence of various metabolic types of abdominal obesity in the sample.

Overall, the study found that the prevalence of obesity in a specific sample was 49%. According to National Recommendations, in half of the cases, these patients were diagnosed with MS. 26% of the men in the sample fell into the category of metabolically healthy type of obesity. According to the proposed criteria, 55% of patients in this group with leptin concentrations <3.5 ng/ml were included in the metabolically neutral AO cohort (14.5% of the total sample) (*Figure* 2). Thus, it should be noted that in alimentary obesity, more than half of men (53.6%) were initially found to have AO without IR (MHO). Still, with an additional assessment of adipokine activity of adipose tissue, only 30% of the examined young people had a "neutral" metabolic profile. 23.6% of obese patients (12% of the total sample) were diagnosed with increased adipokine activity of adipose tissue (*Figure* 2).

Discussion

Our results confirm the social and medical significance of the problem of obesity. Treatment of these patients is on average 40-45% more expensive for the health system in developed countries, where 15-20% of patients require costly bariatric interventions. Patients with AO throughout their life have an increased risk of developing DM type 2, DLP, hypertension, venous thromboembolism, atrial fibrillation, obstructive sleep apnea syndrome, and dementia [10, 11]. Thus, this disease makes a significant negative contribution to the overall impact of diseases on the humanity.

In our study, the prevalence of AO was relatively high (49%) due to experimental design. According to the results of the ESSE-RF project of the Russian Federation, about 27% of men under 45 years of age showed signs of obesity; in the United States – 32.3%. Further, the frequency of AO increases with age [5].

The concept of a metabolically healthy type of obesity, i.e., AO without IR, is currently being discussed, yet clear criteria have not yet been defined. Several researchers treat MHO as obesity with two possible components of MS; according to other data, one or complete absence of MS is indicated, which is naturally reflected in the results and conclusions [12, 13].

The term *metabolically healthy* per se (metabolically healthy obese) is incorrect and an oxymoron, since it conflicts with two definitions at once. The World Health Organization defines health as a state of complete physical, mental and social well-being, and not just the absence of diseases and physical defects [14, 15]. In turn, obesity is a chronic, recurrent, multi-factorial neurobehavioral disease in which an increase in adipocyte mass in the body contributes to the dysfunction of adipose tissue and its biomechanical effects on surrounding organs and systems with the development of metabolic and psychosocial health consequences (American Society for Metabolic & Bariatric Surgery Updates to 2014-2015). In this regard, it is not clear how the term *healthy* can be logically applied to a recognized disease [16, 17].

However, using the criteria for MNO diagnosis, we diagnosed this type of obesity in 53.6% of young men with AO. According to the CARDIA study, the frequency of MNO in its participants was 47% [18], according to O. Rotar et al. – 43% of men are 25-65 years old. At the same time, the risk of cardiovascular complications in this category was 1.45 times higher than those examined with average body weight without metabolic disorders but two times lower than in patients with metabolic disorders and average body weight [19].

It has been shown that with age, as the duration of anamnesis increases, MHO in 45% of patients is transformed into MS, which makes it possible to determine this metabolic type as the initial stage of AO, which is more typical for young people [6]. Our research data confirm this observation: MHO was diagnosed in patients younger than the MS group by two years, with a BMI lower by 2 kg/m^2 and a shorter history of the disease.

When assessing lipid, carbohydrate, and adipokine metabolism, most of the indicators in the men of the MHO group corresponded to the control group data. At the same time, changes in the ratio of lipid carrier protein fractions and leptin levels were noted as possible initial manifestations of adipose tissue metabolic dysfunction. The frequency of DLP and prediabetes in MHO was comparable to the control group.

According to ultrasound examination of the heart and carotid arteries in patients with MHO, compared with the control, signs of left atrium dilatation increased LVMMI were determined, which indicated initial cardiovascular remodeling. In general, the incidence of LVH and carotid artery atherosclerosis was slightly higher in men with MHO when compared with the control group without AO.

We have evaluated the factors showing the highest correlation with the AO. According to the analysis of variance, this parameter was the level of leptin. ROC analysis was performed to determine the threshold level of leptin, which allows detecting adipocyte dysfunction. As the study group, the category of men with MS was considered as having the most unfavorable lipid, carbohydrate, and adipokine profiles. Based on the results of mathematical analysis, the leptin level was determined to be 3.5 ng/ml (sensitivity 75% and specificity 77%). A group (86 men) with a leptin level <3.5 ng/ml was formed from patients with MHO (155 people).

Thus, the proposed metabolic type of obesity – "metabolically neutral" AO in men-is an increase in body weight >30 kg/m^2 in the presence of one criterion of MS (AH/DLP/prediabetes) and a leptin level <3.5 ng/ml.

When comparing metabolic changes in MNO and MHO, it was found that the "metabolically neutral" type was characterized by a better lipid profile, which was confirmed by a lower frequency of DLP (1.7 times) in this type of AO. The frequency of prediabetes in MNO was 7% and was half as low as in MHO; CCA atherosclerosis was 1.5 times less common in MNO. The prevalence of DLP, prediabetes, and atherosclerosis in the category of "metabolically neutral" AO type was lower than the control group, which could be due to the presence in this category of the proportion of patients with metabolic disorders with normal body weight (metabolically unhealthy non-obese).

Thus, the selection of a metabolically neutral type of obesity is justified since it allows us determining the stage of the disease, at which the frequency of metabolic and cardiovascular disorders is still minimal, and non-drug prevention is necessary. Exceeding the leptin threshold >3.5 ng/ml in AO may require more aggressive lifestyle adjustments and possibly an early start of drug therapy.

Conclusion

Determining the level of leptin in alimentary obesity is a necessary diagnostic criterion that characterizes the probability of metabolic disorders and changes in the cardiovascular system.

It is advisable to use the term and criteria of the *metabolically neutral* type of obesity in medical practice, thereby allowing stratifying patients who are in need of an active prevention and treatment.

Conflict of interest

The authors declare that they have no conflicts of interest.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the Ethics Committee of the Military Medical Academy (Protocol No. 169 of 22.12.2015), by the standards of Good Clinical Practice and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

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