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Original article

Metabolically healthy obesity: prevalence, phenotype characteristic, effectiveness of weight loss

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Abstract: *The goal* was to study the prevalence of metabolically healthy obesity (MHO), the features of this phenotype compared with metabolically unhealthy obesity (MUHO), and the effect of weight loss on cardiometabolic risk factors in patients with MHO.
Material and Methods — To assess the prevalence of MHO, 389 case histories of obese patients aged 18-60 were analyzed. Three types of MHO criteria were used: 1) the definitions of metabolic syndrome (MS) according to International Diabetes Federation (IDF), 2005; 2) the HOMA-IR index (<2.7); 3) Biobank Standardisation and Harmonisation for Research Excellence in the European Union (BioSHaRE-EU) criteria, 2013. The study included comparative analysis of the medical history, anthropometry, basic metabolic parameters, and adipocytokine levels in 44 patients with MHO (taking into account the MS definitions) and 33 women with MUHO initially and with a decrease in body mass (BM) by ≥5% after 6 months.
Results — The MHO prevalence was: according to the definitions of MS – 38.6%, according to HOMA-IR index – 34.5%, in BioSHaRE-EU – 9.6%. All indicators of anthropometry, carbohydrate and lipid metabolism, including the HOMA-IR index, interleukin-6, and chemerin, as well as the duration of obesity in the MHO and MUHO groups significantly differed ($p<0.05$). After 6 months, MHO-patients who lost ≥5% BM from the initial value (63.6%) showed an increase of adiponectin, a decrease in waist circumference, HOMA-IR index, C-reactive protein (CRP), retinol-binding protein 4 (RBP-4), and chemerin ($p<0.05$).
Conclusion — The MHO prevalence was maximal according to the MS definitions and minimal with BioSHaRE-EU criteria. The BM decrease in MHO is accompanied by a decrease in the content of proinflammatory adipocytokines and the HOMA-IR index, which determines the need to treat obesity regardless of the phenotype.

Keywords: metabolically healthy obesity, cardiometabolic risk, metabolic syndrome, insulin resistance, adipocytokines.

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Introduction

By 2016, more than 1.9 billion adults over the age of 18 were overweight (39% of men and 40% of women). Of these, more than 650 million were obese (about 13% of the world's adult population) [1]. Obesity is a major risk factor for Type 2 diabetes mellitus (Type 2 DM) and cardiovascular diseases (CVD). However, in a number of obese patients, the indicators of the lipid metabolism, blood pressure (BP), and carbohydrate metabolism remain unchanged. This phenotype is called metabolically healthy obesity (MHO) [2]. In most studies, the MS criteria serve as the starting point for defining MHO definitions. In this case, as a rule, the MHO group includes patients who have no more than 1 additional MS criterion besides obesity. In a number of other studies, the priority aspect is the normal insulin sensitivity of tissues [3].

In general, about 30 different definitions of MHO currently exist in clinical studies. The absence of a single standard of definitions determines the variability of data on the prevalence of this phenotype: it ranges from 6% to 60% [4]. In 2013, a group of European experts created the BioSHaRE-EU (Biobank Standardisation and Harmonisation for Research Excellence in European Union) program to standardize biomedical research databases [5]. The first scientific development of the program was the MHO project: “Healthy Obesity Project”. In this project, the metabolically healthy are obese patients (BMI of 30 kg/m^2 or more) who do not have any manifestations of MS according to the criteria of the Third national educational program on hypercholesterolemia (NCEP ATP III, USA). This study considers the nature of nutrition, physical activity, genetic features, the composition of the intestinal microflora, the structure of muscle tissue, etc. to be the potential determinants of metabolic health that determine the formation of this phenotype. Since the MHO phenotype is typical of less pronounced chronic smoldering inflammation, the study analyzes its contribution to the development of such factors as: adipocyte hypertrophy; an abundance of pro-inflammatory macrophages; excess visceral adipose tissue; ingestion of persistent organic pollutants that accumulate in adipose tissue, as well as the accumulation of chemicals related to plastic; metabolic endotoxemia caused by adverse intestinal microbiota (which in turn changes the level of endocannabinoids in the intestine and adipose tissue by regulating the levels of cannabinoid receptor agonists) [6]. Special attention

is drawn to the study of the structure and function of adipose tissue. Currently, it is established that the amount of visceral adipose tissue in MHO is significantly less than in patients with complicated obesity. Patients with MHO and complicated obesity also showed significant differences in the gene expression profile and adipose tissue proteome [7]. Patients with MHO had a more favorable profile of circulating adipocytokines [8, 9]. Currently, the issue of the need for treatment interventions aimed at reducing body mass in patients with MHO remains debatable: a significant number of authors cite data that a decrease in BM in MHO leads to an improvement in cardiometabolic risk indicators, body composition, and increased exercise tolerance [10, 11]. Other studies note that a significant reduction in cardiometabolic risk factors and an improvement in insulin sensitivity were not detected against the background of a decrease in BM [12].

The fact that, according to many researchers, MHO seems to be a temporary or transient phenotype and justifies treatment interventions to reduce BM, despite the fact that positive changes in health status in this category of patients may be much more modest than in patients with complicated obesity [13].

The goal of this study was to determine the MHO prevalence considering various definitions and to study the main features of this phenotype (the content of adipocytokines in particular), as well as to assess the impact of weight loss on cardiometabolic risk factors in patients with MHO.

Material and Methods

Study design

The first part of the work consists of a retrospective evaluation of 389 medical histories of patients aged 18 to 60 with obesity (BMI ≥30 kg/m^2) examined at the Department of Endocrinology of Sechenov University in 2003-2015. The sample included patients living in the Moscow region.

Three variants of criteria were used to identify the MHO phenotype:

1 – definitions of the IDF metabolic syndrome from 2005. In addition to the mandatory criterion – visceral obesity (waist circumference (WC) ≥94 cm for men and ≥80 cm for women) – the presence of no more than one of the following criteria: triglyceride (TG) level ≥150 mg/dL (1.69 mmol/L), or specific lipid lowering treatment; high-density lipoproteins (HDL) <40 mg/dL (1.0 mmol/L) in men and <50 mg/dL (1.3 mmol/L) in women, or specific lipid lowering treatment; systolic blood pressure (SBP) ≥130 mm Hg or diastolic blood pressure (DBP) ≥85 mm Hg, or antihypertensive therapy; increased fasting plasma glucose (FPG) ≥110 mg/dL (5.6 mmol/L)

2 - definitions based on the HOMA-IR insulin resistance index. The MHO group included patients with HOMA-IR <2.7.

3 – criteria BioSHaRE-EU of 2013. The metabolically healthy patients include obese patients who do not have any manifestations of MS according to the criteria of the Third National educational program on hypercholesterolemia (NCEP ATP III, USA), except for an WC increase in men more than 94 cm, in women – more than 80 cm [5].

A further, more detailed analysis included metabolically healthy patients considering the MS criteria. The comparison group included patients with MUHO.

The study included comparative assessment of medical histories: patient complaints, age of onset of obesity, family history for overweight or obesity and cardiovascular diseases, previously used methods to reduce BM, assessment of the structure of co-morbidities, the main indicators of anthropometry, the state of lipid and carbohydrate metabolism, and the functional state of the liver.

The second part of the work was an open prospective case-control study of 77 obese women aged 19-59 (BMI ≥30 kg/m^2). Of these, 44 were metabolically healthy, and 33 had metabolically unhealthy obesity: they were the control group. All patients filled out an informed consent form.

Initially and after 6 months, the patients were examined for anthropometry, carbohydrate and lipid metabolism, and adipocytokine levels against the background of weight loss.

Eligibility criteria

The eligibility criteria for the study were as follows: gender – female, age 18 to 60 years for the retrospective sample and 19 to 59 years for the prospective group, and the presence of obesity (BMI ≥30 kg/m^2). The non-eligibility criteria were: gender - male, age under 18 and over 60 years, BMI less than 30 kg/m^2, the presence of chronic inflammatory and infectious diseases, Type 1 diabetes, severe form of Type 2 diabetes, chronic infectious and inflammatory diseases in the acute stage, severe somatic pathology, including myocardial infarction, stroke, cancer, pregnancy, and lactation.

Study setting

The study was conducted in the Endocrinology Clinic of the University Clinical Hospital No. 2 and the Department of Endocrinology No. 1 of the Faculty of Medicine of the Federal State Autonomous Educational Institution of Higher Education Sechenov First Moscow State University of the Ministry of Health of the Russian Federation (Sechenov University).

Medical intervention

In the prospective part of the study, all patients were given recommendations for lifestyle modification concerning nutrition and physical activity. Patients with multiple ineffective attempts to reduce body mass using diet therapy in their medical history were additionally prescribed pharmacotherapy for obesity (sibutramine, orlistat). The observation lasted for 6 months. The first and control examination after 6 months included evaluation of anthropometry data: initial height, body mass, WC, hip circumference (HC), BMI (calculated as the ratio of body mass (kg) to the square of height (m^2)), and indicators of carbohydrate and lipid metabolism, liver function, and adipocytokine levels. For 6 months, one of the two subgroups of patients underwent diet therapy in combination with recommendations for increasing physical activity; the other subgroup, in addition to lifestyle modification, received pharmacotherapy of obesity using various drugs: sibutramine (Reduxin), or orlistat (Xenical).

All biochemical and hormonal studies were carried out in the Interclinical Biochemical Laboratory of the Centralized Laboratory and Diagnostic Service of the Laboratory Blood Transfusion Complex of the Federal State Autonomous Educational Institution of Higher Education. I.M. Sechenov First Moscow State University

of the Ministry of Health of the Russian Federation (Sechenov University).

The following biochemical parameters were determined from the morning portion of blood taken from the vein after an 8-hour fast: the lipid spectrum (total cholesterol, HDL, LDL, TG), alanine aminotransferase (ALT), aspartate aminotransferase (AST), glucose, C-peptide, and serum insulin. An indirect indicator of insulin resistance − the HOMA-IR index (Homeostasis Model Assesment − Insulin Resistance) was calculated using the formula fasting glucose (mmol/L) × fasting insulin (u/L)/22.5. The HOMA-IR index ≥2.7 was a criterion for the presence of insulin resistance.

Glucose, total cholesterol, HDL, LDL, TG, ALT, and AST parameters were determined using the Advia-1800 (Siemens) and Synchron CX5 and CX9 (Beckman Coulter) automatic biochemical analyzer. The level of insulin and C-peptide was measured using the Immulite 2000 (Siemens) analyzer.

High-sensitivity CRP (hs-CRP) was determined using an immunoturbidimetric method with an ADVIA 1200 biochemical analyzer with reference values of 0-5 mg/L. The remaining cytokines were determined by enzyme immunoassay (EIA): TNF-α on the alpha-TNF-EIA-BEST test system produced by Vector-Best CJSC, reference values of 0-6 pg/ml; adiponectin was tested on the Human Adiponectin ELISA test system produced by BioVendor – Laboratorni medicina a.s., reference values for women average – 13.2±6.1 ug/ml; RBP-4 was tested on the Assaay test system max retinol-binding protein 4 (RBP-4) ELISA Kit manufactured by ASSAYPRO (average reference value-27.6 ng/ml). IL-6 was measured on the Human IL-6 Platinum ELISA test system produced by eBioscence, the average reference value in serum 0-12.7 pg/ml; chemerin – on the Human Chemerin ELISA test system produced by BioVendor, reference values for women 3 to 19 years were 155.0-240.0 ng/ml, 20 to 39 years: 140.0-245.0 ng/ml, 40 to 59 years: 142.0-313.5 ng/ml, 60 to 79 years: 170.0-452.2 ng/ml.

Table 1. The structure of comorbidity and complaints in the MHO and MUHO groups (assessment of retrospective data)

	Indicator	*MHO, %*	*MUHO, %*	*p*
Comorbidity	Dyslipidemia	27.3	49.5	< 0.05
	Arterial hypertension	25	71.5	< 0.05
	Steatohepatosis	47.7	51.3	< 0.05
	Gynecological diseases	50.8	61.4	< 0.05
	Allergic reactions	42.2	38.3	< 0.05
	Disorders of carbohydrate metabolism	6.8	39.1	< 0.05
	Diseases of the joints	5.6	8.7	< 0.05
Complaints	Dyspnea	24.6	34.3	< 0.05
	Cardiac complaints	9.7	21.3	< 0.05
	Fast fatiguability	18.7	23.6	0.180
	General weakness	15.7	22.7	0.083
	Menstrual irregularities	11.9	14.4	0.284
	Back pain	13.4	13.9	0.564
	Joint pain	14.3	20.8	0.096
	Headaches	9.0	13.4	0.122
	Gastroenterological complaints	5.3	1.4	0.185

MHO, metabolically healthy obesity; MUHO, metabolically unhealthy obesity; p, statistical significance of the frequency difference.

Statistical analysis

The data obtained in the study was processed using the IBM SPSS Statistics Version 22.0 for Windows statistical software package. Mean with statistical error of the mean value (M±m), standard deviation (σ), mediana (Me) and quartile values (with data presented in the form of lower and upper quartiles) were estimated. Due to the fact that some indicators had a distribution that was markedly different from the normal, and when analyzing the dynamics, groups of less than 30 patients were compared, a nonparametric criterion was used to assess the statistical significance of intergroup differences – the coefficient of rank correlation with the group number.

To compare frequencies, the χ-square test in Fisher's exact solution was used. To evaluate the dynamics of numerical indicators, the change value was calculated as the difference Δ between the value during the last and first examination. To determine the reliability of the change, the average Δ value was compared with zero using the Student's criterion. The critical significance level for statistical hypothesis testing was assumed to be p<0.05. The sample size was not calculated beforehand.

Results

Retrospective part of the study

According to the analysis of 389 case histories of obese patients the prevalence of MHO by IDF, 2005 criteria was 38.6%, the prevalence of MHO by HOMA-IR index was 34.5%, the prevalence of MHO according to BioSHaRE-EU was 9.6%.

When analyzing anamnestic data and complaints, it was found that, despite the status of being metabolically healthy, almost 90% of patients from the MHO group were worried about being overweight. In general, the differences in the frequency of complaints between the two study groups were statistically insignificant (p>0.05), except for dyspnea and cardiac complaints (*Table* 1). Smoking in the MHO group was three times less common than in the MUHO group. Analysis of the comorbidity structure in the groups of patients with MHO and MUHO showed that dyslipidemia, hypertension, steatohepatosis, gynecological diseases, allergic reactions and disorders of carbohydrate metabolism were statistically significantly more frequent in the MUHO group. The group of patients with MUHO compared with MHO used various methods of weight loss more often. For example, diet and physical activity were used by 39.4 and 24.1% of patients respectively, orlistat – by 4.3 and 1.2%, various dietary supplements – by 2.9 and 1.2%, sibutramine – by 1.2 and 1.7% respectively; 5.2 and 5.5% of the patients did not try to reduce weight.

This work analyzed the main anthropometric and laboratory indicators in patients with MHO and MUHO. The average age of the study participants was 36.1±11.2 years in the MHO group, and 42.2±11.2 years in the MUHO group (p<0.001). Comparison of the groups showed significant differences in all the studied indicators, except for height (*Figure* 1).

The average duration of obesity at the time of the survey in the MHO and MUHO groups was 18.7±12.3 and 24.0±14.9 years respectively (p<0.001).

Such indicators as age at the time of inclusion in the study, SBP, WC, fasting glucose, C-peptide, and TG were initially significantly lower in the MHO group (p<0.05). The level of HDL in the MHO group was statistically significantly higher than in the patients with MUHO (p=0.018).

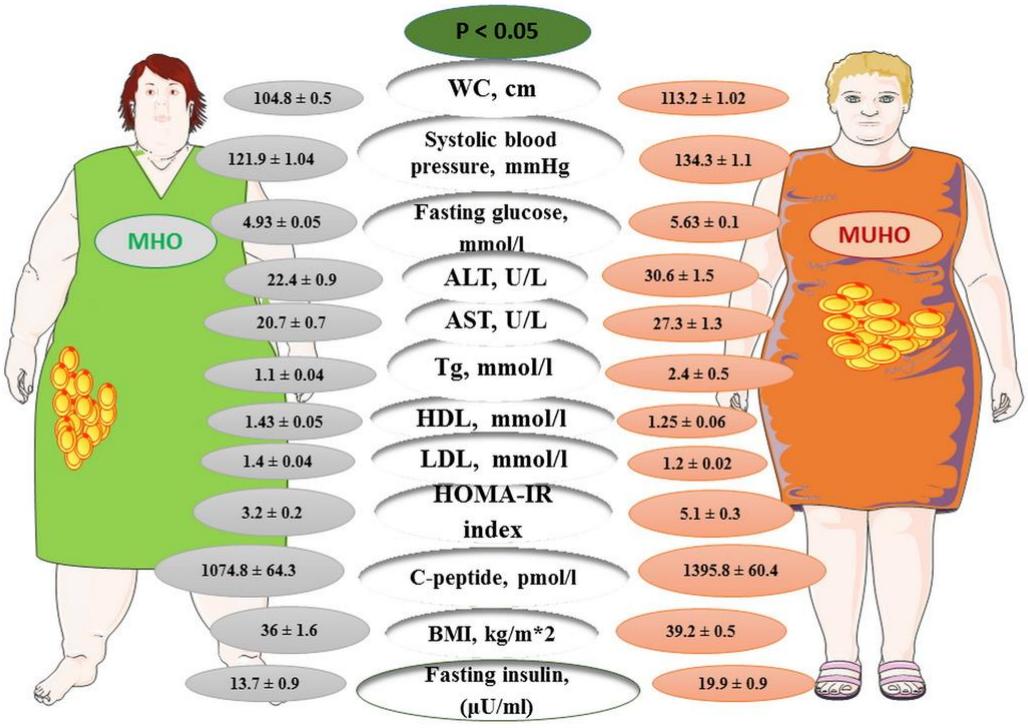

Figure 1. Comparative characteristics of the groups of patients with MHO and patients with MUHO (taking into account the criteria of IDF from 2005) (assessment of retrospective data).

MHO, metabolically healthy obesity; MUHO, metabolically unhealthy obesity, indicators are shown in the format M±m, where M is the mean value, m is the statistical error of the mean value); WC, waist circumference; SBP, systolic blood pressure; ALT, alanineaminotransferase; AST, aspartaminotransferase; TG, triglycerides; HDL, high-density lipoproteins; LDL, low-density lipoproteins; BMI, body mass index.

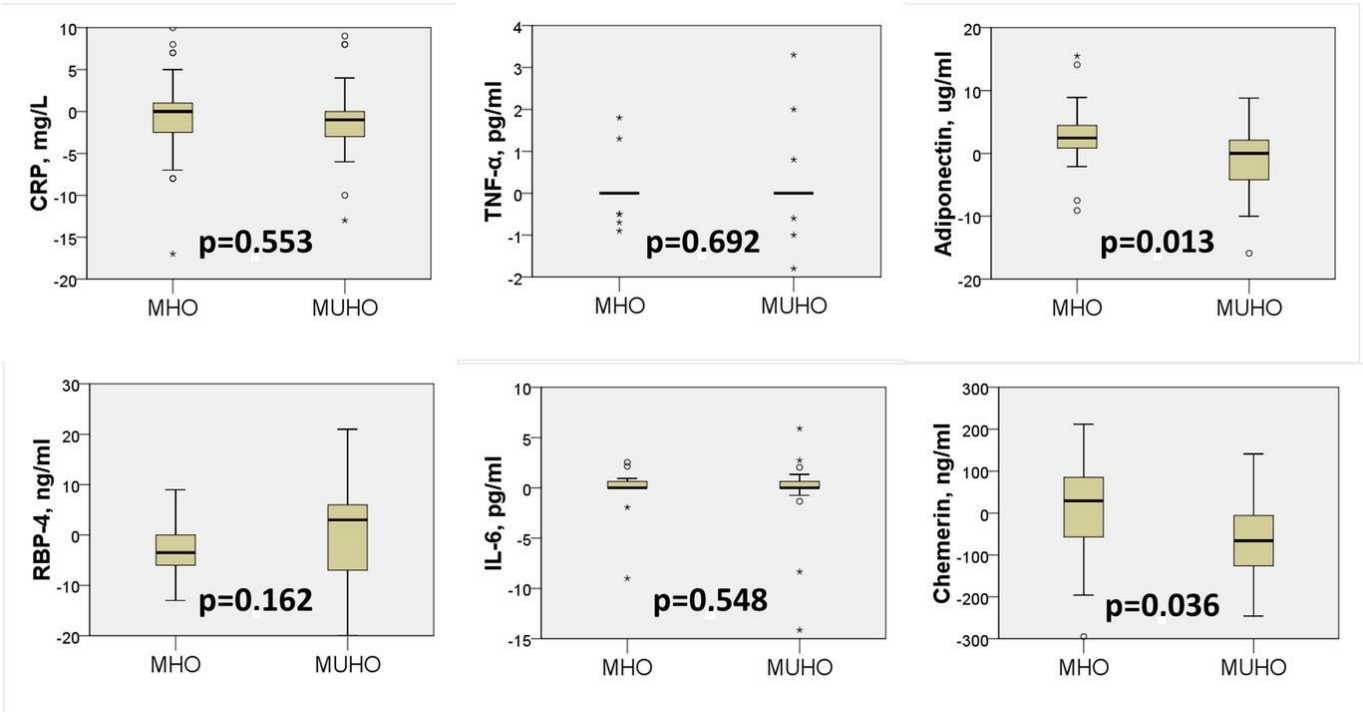

Figure 2. Dynamics of adipocytokine content against the background of clinically significant body mass decrease.

MHO, metabolically healthy obesity; MUHO, metabolically unhealthy (complicated) obesity; IL-6, interleukin-6; RPB-4, retinol-binding protein-4; CRP, C-reactive protein; TNF-α, tumor necrosis factor-α; p is a significant difference in mean ranks.

Table 2. Comparative characteristics of patients in prospective group with MHO and MUHO initially (on the first visit before weight loss)

Indicator	*MHO (n=44)*				*MUHO (n=33)*				*p*
	M±m	σ	Me	Quartiles	M±m	σ	Me	Quartiles	
Height, cm	166.41±0.71	4.7	166.0	164÷168.75	162.42±0.95	5.5	162.0	159÷165.50	<0.001
Body mass, kg	104.60±3.20	21.1	99.0	87.85÷117.40	102.50±2.50	14.2	99.3	94.20÷110.70	0.736
BMI, kg/m^2	37.89±1.18	7.8	35.4	32÷40.75	38.73±0.75	4.3	39.0	35.50÷40.60	0.083
WC, cm	106±2.20	14.3	102.5	96.25÷117	113±2.10	12.1	112.0	106.30÷117.80	0.016
HC, cm	125.20±2.10	14.2	121.0	114÷135.50	124.50±2.10	11.8	122.0	119÷129	0.907
SBP, mmHg	123.10±1.20	8.2	120.0	120÷130	130.50±2.50	14.2	130.0	120÷140	0.013
DBP, mmHg	78.90±1	6.9	80.0	71.25÷80	81.40±1.50	8.9	80.0	80÷90	0.110
Fasting glucose, mmol/L	5.04±0.07	0.5	5.1	4.62÷5.30	5.82±0.17	1.0	5.6	5.19÷6.25	<0.001
ALT, U/L	23.49±1.33	8.8	20.9	17.70÷28.25	37.39±4.47	25.7	27.0	19÷55.50	0.027
AST, U/L	21.95±0.94	6.2	22.0	18÷24	27.79±2.88	16.5	23.0	17÷32.50	0.247
Total cholesterol, mmol/L	5.14±0.15	1.0	5.1	4.52÷5.78	5.73±0.19	1.1	5.7	4.71÷6.67	0.028
TG, mmol/L	1.15±0.08	0.5	1.1	0.78÷1.49	1.94±0.17	1.0	1.7	1.42÷2.27	<0.001
HDL, mmol/L	1.43±0.05	0.3	1.4	1.30÷1.55	1.254±0.055	0.3	1.2	1.04÷1.36	0.002
LDL, mmol/L	3.25±0.14	1.0	3.2	2.77÷3.86	3.89±0.18	1.0	3.8	3.03÷4.61	0.013
Fasting insulin, μU/ml	13.60±1.52	10.1	11.2	6.95÷16.18	17.14±1.93	11.1	16.5	6.77÷23.6	0.120
HOMA-IR index	3.03±0.36	2.4	2.6	1.49÷3.49	4.43±0.56	3.2	3.9	1.91÷5.45	0.016
C-peptide, pmol/L	1132±90	573.0	998.0	755÷1320	1503±96	545.0	1424.0	1158÷1746	<0.001
hs-CRP, mg/L	3.64±0.48	3.2	2.0	1÷6	4.55±0.84	4.8	3.0	1.50÷5.50	0.520
TNF-α, pg/ml	0.54±0.03	0.2	0.5	0.50÷0.50	0.67±0.077	0.4	0.5	0.50÷0.50	0.099
Adiponectin, ug/ml	11.11±0.82	5.4	9.6	7.40÷15.18	10.15±0.86	5.0	9.4	6.55÷12.40	0.540
RBP-4, ng/ml	41.02±0.55	3.7	41.0	38.25÷43	41.15±0.72	4.1	41.0	38.50÷45	0.489
IL-6, pg/ml	0.76±0.16	1.1	0.5	0.46÷0.46	1.85±0.580	3.3	0.5	0.46÷1.50	0.035
Chemerin, ng/ml	320.10±14.50	96.4	312.5	242.50÷368.30	369.2±19.70	113.3	356.0	302÷414.50	0.032
Age, years	35.80±1.33	8.8	34.0	29÷40.75	42.55±2.05	11.8	43.0	31.50÷53	0.009
Duration of obesity, years	17.91±1.53	10.2	18.5	9÷26.75	22.58±2.60	15.0	20.0	11÷28	0.269

M, mean value; m, statistical error of the mean value; n, number of patients; p, statistical significance of mean difference, variance analysis; Me, median.

Table 3. The difference in the studied indicators in the MHO and MUHO groups in patients after ≥5% weight loss over 6 months

Показатель Δ	*МЗО (n=28)*		*MHO (n=21)*		*p*
	M±m	p_1	M±m	p_2	
WC, cm	-8.55±1.00	<0.001	-9.82±1.12	<0.001	0.453
HC, cm	-7.66±0.90	<0.001	-7.68±0.93	<0.001	0.943
BMI, kg/m^2	-4.82±0.88	<0.001	-3.76±0.32	<0.001	0.675
SBP, mmHg	-4.38±1.53	0.010	-9.09±5.05	0.090	0.431
DBP, mmHg	-1.03±1.25	0.420	-1.59±2.67	0.560	0.589
Fasting glucose, mmol/L	-0.05±0.16	0.770	-0.49±0.23	0.050	0.094
ALT, U/L	-0.78±2.18	0.720	-4.54±4.15	0.290	0.943
AST, U/L	-1.78±1.45	0.230	-4.12±2.35	0.110	0.935
Total cholesterol, mmol/L	-0.03±0.20	0.890	-0.57±0.23	0.020	0.157
TG, mmol/L	0.18±0.19	0.330	-0.32±0.25	0.230	0.021
HDL, mmol/L	0.07±0.05	0.220	0.01±0.06	0.910	0.806
LDL, mmol/L	-0.23±0.19	0.240	-0.76±0.21	<0.001	0.120
Fasting insulin, μU / ml	-5.17±2.52	0.012	-3.39±2.62	0.210	0.573
HOMA-IR index	-1.13±0.55	0.016	-1.21±0.77	0.130	0.266
C-peptide, pmol/L	-183.29±124.89	0.150	-96.46±160.23	0.560	0.771
CRP, mg/L	-1.72±0.43	<0.001	-3.96±1.01	<0.001	0.443
TNF-α, pg/ml	-0.11±0.14	0.440	-0.03±0.14	0.850	0.835
Adiponectin, ug/ml	4.55±0.83	<0.001	1.97±0.81	0.020	0.018
RBP-4, ng/ml	-2.97±1.00	0.010	0.19±2.01	0.790	0.133
IL-6, pg/ml	-0.14±0.14	0.320	-1.56±0.74	0.060	0.531
Chemerin, ng/ml	-45.68±17.06	0.010	-59.57±20.39	<0.001	0.048

M, mean value of the ratio; m, statistical error of the mean value; Δ, dynamics of each indicator at the third examination (the difference between the value at the third examination and the initial value); p, statistical significance of differences between the mean value of Δ from zero; n, number of patients.

Prospective part of the study

In the prospective part of the study, the initial characteristics of the studied groups are presented in *Table* 2.

Initially, neither the mean values nor the distributions of BMI, fasting insulin, hs-CRP, TNF-α, adiponectin, and RBP-4 were statistically significantly different in the two groups. Statistically significant differences in the MHO and MUHO groups were observed in the indicators of the HOMA-IR index – 3,03±0,36 and 4,43±0,56 (p=0.016), ALT – 23,49 and 37,39 U/l (p=0.027), IL-6 – 0,76±0,16 and 1,85±0,58 pg/ml (p=0.035), chemerin – 320,1±14,5 and 369,2±19,7 ng/ml (p=0.032), age at the beginning of the study – 35,80±1,33 and 42,55±2,05 years (p=0.009). After 6 months in the MHO group, a decrease in BM by 5% or more was observed in 28 people (63.6%), in the MUHO group – in 21 patients (63.6%). The difference between the studied indicators: the outcome and dynamics (Δ) are shown in *Table* 3.

In *Table* 3, p1 and p2 are the reliability of the difference between the mean value of the change from zero in the two groups, p is the reliability of the differences when comparing the first and second groups. Due to the small size of the groups, the values of p1 and p2 are indicative.

At the same time, when comparing the values in the MLO and INR groups in *Tables* 2 and 3, the analysis of rank correlations of indicators with the group number is used, that is, an exact nonparametric criterion, the correctness of which does not depend on the nature of the distributions of the studied values or on the number of observations.

The MHO group showed a statistically significant ($p<0.05$) decrease in BMI, WC, HC, SBP, fasting insulin, HOMA-IR index, hs-CRP, RBP-4, and chemerin, as well as a statistically significant increase in adiponectin levels against the background of a decrease in BM by ≥5%. The MUHO group showed a statistically significant decrease in BMI, WC, HC, fasting glucose, total cholesterol, LDL, hs-CRP and chemerin (for IL-6 p=0,060), as well as a statistically significant increase in adiponectin levels against a decrease in BM by ≥5%. All patients who received various medications for the treatment of obesity (sibutramine: n=8, orlistat: n=5) were grouped into a single subgroup "Lifestyle modification + pharmacotherapy", hereinafter – "Pharmacotherapy" (n=13). There were no statistically significant differences in changes in BM, WC and HC indicators at the second examination in the subgroups "Lifestyle modification" and "Pharmacotherapy (sibutramine, orlistat)" in either the MHO or the MUHO group.

When comparing the dynamics of the studied indicators in the MHO and MUHO groups, the statistically significant differences were found in the level of TG (+0.18±0.19 mmol/L vs -0.32±0.25 mmol/L, p=0,021), adiponectin (+4.55±0.83 ug/ml vs +1.97±0.81 ug/ml, p=0.018), chemerin (-45,68±17,06 ng/ml vs -59,57±20,39 ng/ml, p=0,048) respectively (*Figure* 2). There were no statistically significant differences in WC, fasting glucose, fasting insulin, HDL, HOMA-IR index, hs-CRP, TNF-α, RBP-4 and chemerin.

Using the Spearman's rank correlation coefficient in the group of patients with MUHO, we noted a positive correlation between a decrease in hs-CRP level and a decrease in C-peptide level ($r=0.446$, $p<0.05$), a negative correlation between a decrease in TNF-α and age ($r=-0.541$, $p<0.01$), negative correlation between the dynamics of the level of chemerin and BMI ($p<0.01$, $r=-0.567$), the dynamics of the level of chemerin and OT ($p<0.05$, $r=0.5$), positive – between the dynamics of the level of chemerin and TG ($p<0.05$, $r=0.43$). In the MHO and MUHO group, there was a positive correlation between a decrease in IL-6 levels and an increase in HDL cholesterol ($r=0.417$, $p<0.05$), a positive correlation between the dynamics of RBP-4 and WC ($r=0.427$, $p<0.05$). At the same time in the MUHO group there was a positive correlation between a decrease in the level of RBP-4 and a decrease in the level of insulin and the HOMA-IR index ($r=0.459$, $p<0.05$).

Undesirable effects

No undesirable effects were observed in the course of the study.

Discussion

The results of the National Health and Nutrition Examination Surveys (NHANES, USA) are an example of a clear relationship between the prevalence of MHO and its definitions. Among the 5440 participants, 31.7% of obese patients were considered to be metabolically healthy taking into account the presence of no more than one of the 6 cardiometabolic risk factors like increased blood pressure, TG levels, fasting glycemia, hs-CRP, reduced HDL, and insulin sensitivity. The stricter criteria assume the absence of all 6 factors: only 16.6% of obese patients were referred to the MHO group. In the same sample, changes in the threshold values of the HOMA-IR index from 5.1 to 2.5 led to a reduction in the number of MHO patients up to 6% [14]. The greatest prevalence of the MHO phenotype was stated taking into account the use of MS criteria according to IDF from 2005: 38.6%. A group of Russian authors (O. Rotar et al.) studied the MHO prevalence in 13 regions of Russia (Volgograd, Vologda, Voronezh, Vladivostok, Ivanovo, Kemerovo, Krasnoyarsk, Orenburg, Tomsk, Tyumen, Saint Petersburg and North Ossetia-Alania) with the participation of 1,600 people aged 25 to 65. The maximum MHO prevalence with the criteria of MS according to IDF was noted in Tyumen: it was 52.2%. The minimum was recorded in Voronezh: 25.7%, with a total prevalence of 41% and no significant gender differences [15]. In another Russian study of the researchers from Saint Petersburg, the MHO prevalence was significantly lower – only 8.7% [16]. The lower indicators were predetermined by the fact that in this study, the MHO criteria included a combination of the minimum number of manifestations of the metabolic syndrome in combination with normal tissue sensitivity to insulin.

The absence of a statistically significant difference in the frequency of complaints in the MHO and MUHO group allows concluding that there is some discrepancy between the concept of MHO in terms of the used anthropometric and laboratory criteria and the subjective feelings of the patient.

In this work, the special attention was drawn to the study of the level of adipocytokines. Adiponectin is an adipokine synthesized exclusively in adipose tissue. It has a distinct antidiabetogenic, anti-atherogenic, and anti-inflammatory effect. Adiponectin inhibits phagocytic activity and production of IL-6 and TNF-α by macrophages, and can also induce the formation of anti-inflammatory cytokines IL-10 and IL-1 by monocytes and macrophages [17]. Initially, the level of adiponectin did not differ significantly in the MHO and MUHO groups, which can be explained by a comparable BMI in these patients. Besides, against the background of a decrease in BM by ≥5% in both groups the increase in adiponectin level was statistically significant ($p<0.05$) and in the MHO group significantly higher than in the case of complicated obesity, which indicates the feasibility of reducing BM in all obese patients, regardless of the phenotype.

C-reactive protein (CRP) is synthesized mainly in the liver under the stimulating influence of IL-6 and TNF-α, as well as in adipose tissue. By stimulating the expression of adhesion molecules ICAM-1, VCAM-1 and E-selectin on the endothelial surface (which leads to binding and modification of very low-density lipoprotein cholesterol (VLDL)), CRP initiates chronic vascular inflammation and atherogenesis. One of the most important independent factors in the development of coronary heart disease is an increase in the level of CRP in blood plasma [18]. Despite the absence of a statistically significant difference in the level of CRP in the MHO and MUHO groups initially, after a BM

decrease by ≥5%, the CRP level significantly decreased in both groups.

Tumor necrosis factor-α (TNF-α) is a proinflammatory cytokine synthesized in monocytes and macrophages. It plays a major role in the development of inflammation and autoimmune diseases along with IL-6 [19]. The expression of TNF-α in human adipose tissue is relatively small, and it decreases as the BM decreases. An experiment on several independent animal models has indicated that treatment with anti-TNF-α antibodies reduces the severity of inflammation, fatty liver disease, and insulin resistance [20]. For TNF-α, there were no statistically significant differences between MHO and MUHO both initially and after a decrease in BM by ≥5% in each of these groups. A similar result was obtained in the work of L.M. Berstein and co-authors (2017) [21].

IL-6 can induce the synthesis of pro-inflammatory proteins in the liver like fibrinogen and CRP. Under the influence of IL-6, the expression of lipoprotein lipase in adipocytes decreases, and their absorption of free fatty acids increases; in turn, it leads to an increase in TG production. Plasma IL-6 levels negatively correlate with insulin sensitivity [18]. In terms of this study, the higher levels of IL-6 were initially observed in the MUHO group. On the background of weight loss in 6 months ≥5%, the MUHO group showed statistically significant reduction in the level of IL-6, if compared to initial values and compared with the MHO group.

Retinol-binding protein 4 (RBP-4) is secreted in adipocytes and hepatocytes and transports retinol from the liver to various tissues. Many studies have shown a relationship between the level of RBP-4 and arterial hypertension, hypertriglyceridemia and a decrease in HDL. RBP-4 disrupts the action of insulin in the muscles by reducing tyrosine phosphorylation in the receptor [17]. Apparently, the absence of a statistically significant difference in the level of RBP-4, one of the cytokines maximum related to the development of insulin resistance, in the MHO and MUHO groups is partly due to the mean value of the HOMA-IR index in both groups >2.7. After a BM decrease by ≥5% in the MHO group, the decrease in the level of RBP-4 was statistically significant ($p<0.05$) in contrast to the MUHO group ($p=0.79$), which indicates the feasibility of reducing MT in metabolically healthy patients.

One of the interesting and ambiguous adipokines, chemerin is mainly secreted by adipocytes, preadipocytes and cells of the vascular-stromal fraction of adipose tissue and is a chemoattractant for various types of immune cells. It can contribute to both the emergence of immune responses (according to most authors) and the resolution of inflammation, depending on the isomeric form. There is an indication of the antitumor effect of chemerin in the lungs, skin, reproductive system, and digestive tract [22]. According to the obtained data, the MHO group initially had significantly lower level of chemerin than that of MUHO group. After the ≥5% decrease in BM, the level of chemerin statistically significantly decreased in each group of patients with a statistically significant difference between groups.

When using the IDF criteria (2005) for referring patients to the MHO or MUHO group, the HOMA-IR index indicators corresponding to the presence of insulin resistance in both groups were found with a statistically significant difference ($p=0.031$) between them. It correlates with data from other authors who had used the same definitions of MHO [23]. This once again indicates the need to optimize and unify the criteria for MHO.

Conclusion

Thus, the maximum prevalence of MHO is observed when using the MS criteria (38.6%), the minimum – when using the BioSHaRE-EU criteria (9.6%). Due to the large variability of data on prevalence depending on the accepted criteria, it is necessary to develop common definitions of the MHO. The main indicators of anamnestic data, carbohydrate, lipid metabolism, anthropometry were statistically significantly different in the studied groups of patients. The longer existence of obesity in the MUHO group suggests that MHO is a potentially unstable phenotype and, may transform into a metabolically unhealthy one over time. A clinically significant decrease in body weight in patients with MHO compared to MUHO is accompanied by a slightly more pronounced decrease in insulin resistance and levels of a number of pro-inflammatory adipokines with an increase in the anti-inflammatory adipokine – adiponectin. This determines the need to treat obesity regardless of the phenotype.

Limitations

The study's limitations include a relatively small sample of patients receiving pharmacotherapy for obesity.

Conflict of interest

Some results of this study was presented on 3rd International Conferences on Obesity and Chronic Diseases (July 23-25, 2018, Los Angeles, United States), published as abstract in the collection of abstracts of the Conferences https://obesity.unitedscientificgroup.org/pdfs/ICOCD_Book-2018.pdf (p. 48), and published in *Almanac of Clinical Medicine*: Adipocytokine profile and effectiveness of the weight loss in patients with metabolically healthy obesity. 2018; 46(3): 212–221, https://doi.org/10.18786/2072-0505-2018-46-3-212-221.

The authors declare no obvious or potential conflict of interest related to the publication of the present article.

Ethical approval

The clinical study within the framework of the dissertation (thesis) was approved by the Interuniversity Ethics Committee under the Association of Russian Medical Pharmaceutical Universities (Minutes No. 10 of a meeting of the Interuniversity Ethics Committee under the Association of Russian Pharmaceutical Universities from 17 Nov, 2011).

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