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Obesity phenotypes, cardiometabolic risk, and body composition in women with rheumatoid arthritis

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The aim of the study was to assess the cardiometabolic risk and body composition characteristics in women with rheumatoid arthritis (RA).

Methods. The study included 115 women aged 61.5±10.6 years with RA of 1-3 activity levels according to DAS 28. Cardiometabolic risk was assessed while taking into account the body mass index (BMI) and metabolically healthy phenotype (MHPO) or metabolically unhealthy phenotype (MUHPO) of obesity defined by a waist-to-hip ratio measurement (WHR), serum glucose and lipid levels. Body composition was determined by X-ray absorptiometry using fat-free mass index (FFMI), fat mass index (FMI), and abdominal-to-thigh fat ratio (A/G ratio).

Results. The majority of patients had a BMI≥25 kg/m^2. 23.5 % of patients were overweight, while 42.6 % were obese with MUHPO being predominant in 66.7 % of them. With increasing BMI and WHR there was an increase in blood glucose (p=0.03), triglycerides (p=0.00), FMI (p=0.03), A/G ratio (p=0.00) and a decrease in HDL-C cholesterol (p=0.03). In addition, the higher levels of those parameters were predominantly associated with the MUHPO in both the normal BMI<25 kg/m^2 and high BMI≥25 kg/m^2 groups. Regardless of BMI, MUHPO was associated with a higher incidence of arterial hypertension (AH), carotid atherosclerosis (CAS), cardiovascular disease (CVD), and diabetes mellitus (DM). According to X-ray absorptiometry, the majority of patients, including women with BMI<25 kg/m^2, had an increased amount of adipose tissue (>32 %) and abdominal obesity (A/G ratio>1). Sarcopenia (FFMI <6.0 kg/m^2) was detected in 17 (14.8 %) and sarcopenic obesity in 5 (4.3 %) patients. Lower FFMI was associated with lower BMI, higher frequency of sarcopenia and higher VAS pain intensity.

Conclusion. Patients with RA tend to be overweight/obese with MUHPO and have high cardiometabolic risk for dyslipidemia, carbohydrate metabolic disorders, AH and AS, necessitating monitoring of WHR along with BMI. Body composition reflects increased adipose tissue in the majority patients, including the normally weighted ones. There is a trend toward the lower FFMI and the develop-

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ment of sarcopenia/sarcopenic obesity with decreasing BMI, which is associated with greater pain intensity according to VAS.

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Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease with predominanly joint involvement and systemic manifestations, characterized by high comorbidity and shortened life expectancy [1], mainly due to the development of cardiovascular (CVD) and cerebrovascular diseases. The risk of CVD mortality in RA is increased 1.5-fold [2], and the risk of CVD development is increased 2-fold, being higher than in diabetes mellitus (DM) [3]. In this context, RA is considered to be an independent cardiovascular risk factor due to an accelerated development of atherosclerosis on the background of chronic inflammation and traditional risk factors (RF). Among them, the arterial hypertension (AH) and overweight/obesity are the most common in RA, which correlates with the prevalence of these factors in the general population and increases the risk of both CVD and DM [4, 5]. At the same time, the "obesity paradox" in RA is well known: both obesity and weight loss increase patients' risk of mortality [6]. To better assess cardiometabolic risk, it is recommended to distinguish obesity phenotypes in addition to the BMI definition [7]. However, there is a lack of information in the literature regarding the characteristics and clinical significance of obesity phenotypes in RA in terms of cardiometabolic risk and body composition changes.

The aim of the study was to assess the cardiometabolic risk and body composition characteristics in women with RA.

Methods

The study was conducted in the Department of Rehabilitation of Patients with Somatic Diseases of the Ivanovo State Medical University Clinic. The study included 115 women with a confirmed diagnosis of RA according to the ACR/EULAR (2010) classification criteria [1], aged 33-81 years (mean age 61.5±10.6 years), with a disease duration of 9.7±9.0 years. Early RA was diagnosed in 16 patients (13.9 %). Seropositive RA was found in 70 (60.9 %) patients with high serum rheumatoid factor (RhF) levels. The DAS-28 index was 3.91±1.04 and the visual analog scale (VAS) pain was 48.1±26.6 mm. All women received anti-inflammatory drugs at baseline, including methotrexate — 86 (74.8 %). 23 patients (20.0 %) were treated with glucocorticosteroids (GCS). Nonsteroidal anti-inflammatory drugs (NSAIDs) were taken regularly (twice a week for at least 2 months) by 51 patients (44.5 %). AH was found in 92 (80 %), carotid atherosclerosis (CAS) in 56 (48.7 %) women. CVD was present in 12 (10.4 %) patients, type 2 DM in 10 patients (8.7 %).

Inclusion criteria were: female patients with a confirmed diagnosis of RA, aged ⩾25 years. Exclusion criteria were: infectious and oncological diseases, any chronic disease in the phase of exacerbation and decompensation, pregnancy.

RA activity was assessed by the Disease Activity Score 28 (DAS-28), and the index of functional impairment according to the Health Assessment Questionnaire (HAQ-DI) was also taken into account. Office blood pressure was measured as well [8].

The obesity phenotype was determined based on the subject's body mass index (BMI) and waist-to-hip ratio (WHR). The patients were divided into two groups based on their BMI: those with a BMI below 25 kg/m² and those with a BMI above 25 kg/m². They were then classified as having a metabolically healthy phenotype (MHPO) or a metabolically unhealthy phenotype (MUHPO) based on their WHR, with a WHR of 0.85 or below indicating the former and a WHR above 0.85 indicating the latter [7].

Body composition was evaluated through X-ray dual-energy absorptiometry on a Lunar Prodigy machine (General Electric). The fat-free mass index (FFMI) was calculated as the total lean mass of the upper and

lower extremities (kg/height in m²). A value of FFMI < 6 kg/m² was considered to be indicative of sarcopenia [9]. The following ratio was employed as the fat mass index (FMI): total fat mass in kg/height in m². A fat mass ≥32 % of total mass was considered indicative of obesity. A combination of a BMI of <26 kg/m² and a fat mass content of >32 % was considered to be indicative of sarcopenic obesity. The abdominal to thigh fat ratio (A/G ratio) was also taken into account.

General clinical and laboratory examinations were performed, including the determination of C-reactive protein (CRP), total cholesterol, triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and glucose levels.

The study was conducted in accordance with the ethical standards of the Ethical Committee of Ivanovo State Medical University (protocol number 2, dated April 4, 2018). All patients provided informed consent for participation in the study.

Statistical analysis

The statistical analysis was conducted using the Statistica 10.0 software package (StatSoft, USA, 2018). The median, lower quartile, and upper quartile (Me [25;75]) were used to describe the parameters whose distribution differed from normal. The Mann-Whitney test (U-test) was used to assess the statistical significance of differences between two independent groups with respect to quantitative traits. In the case of a comparison involving three or more samples, the nonparametric ranking method, namely the Kruskal-Wallis test, was employed. Significant differences and correlations between the parameters were deemed reliable at a level of $p < 0.05$.

Results

The mean BMI values were 29.1 ± 5.5 kg/m², and the mean WHR was 0.98 ± 0.16. A total of 27 women (23.5 %) were classified as having normal body weight, while the remaining patients were were overweight or obese. Of the latter group, 39 women (33.9 %) were classified as overweight, and 49 women (42.6 %) were classified as obese. The results of the body composition analysis revealed that 17 patients (14.8 %) had a FFMI indicative of sarcopenia (≤6.0 kg/m²), while 107 patients (93.0 %) demonstrated a fat mass content exceeding 32 %. The presence of sarcopenic obesity was observed in 5 (4.3 %) patients.

Four distinct groups of patients with varying phenotypes were identified. The first group consisted of 16 patients with a BMI <25 kg/m² and MHPO. The second group included 11 patients with a BMI <25 kg/m² and MUHPO. The third group comprised 11 patients with a BMI ≥25 kg/m² and MHPO. The fourth group consisted of 77 patients with a BMI ≥25 kg/m² and MUHPO. The groups were comparable with the regard to age, duration of rheumatoid arthritis (RA), number of painful and swollen joints, methotrexate dose, HAQ-DI scores, and C-reactive protein (CRP) (Table 1).

The characteristics of the various obesity phenotypes are presented in Table 2. With the regard to cardiometabolic parameters, there were a statistically significant increase in blood glucose (p=0.03), TG (p=0.00), FMI (p=0.03), and A/G ratio (p=0.00), and a statistically significant decrease in HDL-C cholesterol (p=0.03) as BMI increased from group 1 to group 4. Furthermore, higher values were predominantly associated with the MUHPO phenotype in both the normal weight and overweight/obese categories. This is corroborated by a comparison of groups 1 and 2 of

Table 1. **Main parameters in different obesity phenotypes* in RA**

Parameters	Normal BMI, MHPO (A/G ratio≤0.85) Abs/%	BMI, MUHPO Normal (A/G ratio>0.85) Abs/%	BMI>25 kg/m², MHPO (A/G ratio≤0.85) Abs/%	BMI>25 kg/m², MUHPO (A/G ratio>0.85) Abs/%
Number, abs/%	16/13.90	11/9.57	11/9.57	77/66.96
Age, years	64 [51.5; 70]	67 [54; 75]	55 [44; 66]	63 [57; 68]
Average RA duration, yeas	6.5 [1.21; 11.75]	9 [5.5; 15]	8 [3; 13]	8 [3; 13.5]
Amount of painful joints	7 [5; 15]	10 [4; 13]	10 [6; 18]	7 [4; 11]
Amount of swollen joints	2 [0; 5]	0 [0; 3]	2 [0; 11]	1 [0; 4]
Taking methotrexate, abs/%	10/62.5	7/63.64	8/72.73	61/79.22
Methotrexate dose, mg/week	12.5 [10; 17.5]	10 [10; 12.5]	12.5 [7.5; 21.25]	12.5 [10; 17.5]
CRP, mg/l	7.56 [4.69; 10.83]	3.77 [2.16; 8.84]	5.59 [2.90; 15.79]	5.99 [2.76; 9.82]
HAQ-DI	1.06 [0.69; 1.5]	0.875 [0.375; 1.25]	1.12 [0.63; 2.25]	1.125 [0.625; 1.875]

*p>0.05 when comparing all parameters in different obesity phenotypes.

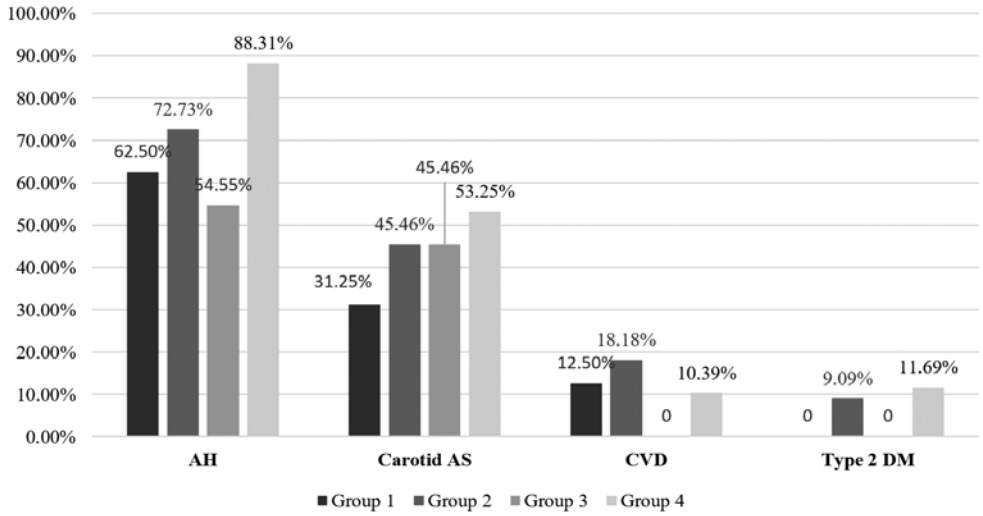

Fig. 1. Frequency of AH, carotid artery AS, CVD and type 2 DM in RA patients with different obesity phenotypes (n=115)

patients with a BMI of less than 25 kg/m². Patients with a MUHPO phenotype (group 2) exhibited higher BMI (p=0.01), FMI (p=0.01), and A/G ratio (p=0.00) values. Similar trends were observed at BMI≥25 kg/m² in groups 3 and 4. A comparison of these groups revealed higher BMI (p=0.00), FMI (p=0.00), and glucose (p=0.04) and TG (p=0.01) in group 4 (MUHPO) relative to group 3 (MHPO).

The prevalence of AH, carotid artery AS, and CVD was higher in groups 2 and 4 than in groups 1 and 3, respectively. The prevalence of diabetes mellitus (DM) was observed to be 9.1 % and 11.7 %, respectively, in groups 2 and 4, which exhibited the MUHPO phenotype. In contrast, DM was not found in groups 1 and 3, which illustrated the MHPO phenotype (Figure 1).

The analysis of body composition revealed a unidirectional tendency for increases from group 1 to group 4 in both adipose tissue according to FMI (p=0.03) and A/G ratio (p=0.00) and skeletal muscle mass according to FFMI (p=0.00). The majority of patients had a high fat mass, with a percentage value of 32 % or greater. The prevalence was 62.5 % and 81.8 % in groups 1 and 2, respectively, and 100 % in groups 3 and 4. In contrast, the prevalence of sarcopenia (defined as FFMI <6 kg/m²) was significantly higher in groups 1 and 2 (56.4 % and 45.5 %, respectively) compared to groups 3 and 4 (9.1 % and 2.6 %, respectively). The diagnosis of sarcopenic obesity was made in individual cases across all groups of patients with rheumatoid arthritis (RA).

Table 2. **Main parameters of metabolic disorders and body composition in different phenotypes of obesity in RA**

	Normal BMI, MHPO (WHR ≤0,85) Group 1	Normal BMI, MUHPO (WHR>0,85) Group 2	BMI>25 kg/m², MHPO (WHR ≤0,85) Group 3	BMI>25 kg/m², MUHPO (WHR>0,85) Group 4	p
Number, abs/%	16/13.90	11/9.57	11/9.57	77/66.96	–
BMI, kg/m²	21.37[21.01;22.75]	23.53[22.23;24]	26.7 [25.7; 28.16]	31.63[27.83;33.71]	0.00
Fasting glucose, mmol/l	4.59[4.26; 4.77]	4.62[4.38; 4.83]	4.37 [4.21; 4.56]	4.88 [4.32; 5.29]	0.03
Triglycerides, mmol/l	0.85[0.73; 1.16]	1.20[0.77; 1.29]	0.90 [0.83; 1.04]	1.31 [1.04; 1.70]	0.00
HDL-C, mmol/l	1.95[1.54; 2.31]	1.72[1.59; 1.95]	1.73 [1.33; 1.91]	1.59 [1.32; 1.81]	0.03
FMI, kg/m²	7.07[5.41;7.59]	7.98[7.53;10.63	10.59[9.02;11.33]	14.37[11.96;16.08]	0.03
Fat mass >32 %, abs/%	10/62.5	9/81.8	11/100	77/100	–
A/G ratio	0.76 [0.62; 0.82]	0.97 [0.9; 1.05]	0.80 [0.75; 0.84]	1.06 [1.00; 1.13]	0.00
FFMI, kg/m²	5.92[5.62; 6.25]	6.12 [5.9; 6.45]	7 [6.38; 7.22]	7.15 [6.50; 7.59]	0.00
FFMI<6 kg/m², abs/%	9/56.3	5/45.5	1/9.1	2/2.6	–
Sarcopenic obesity abs/%	1/6.25	1/9.09	1/9.1	2/2.59	–
RhF	131.8[40.1; 232.2]	37.75 [17.75; 123.70]	59.65 [40.15; 84.0]	62.6 [18.4; 160.8]	0.35
DAS-28	3.91 [3.07; 4.98]	3.90 [3.35; 4.55]	4.90 [3.58; 5.12]	3.76 [3.13; 4.43]	0.21
Pain according to VAS, mm	58.82 [31.09; 70.59]	25.21 [4.2; 30.25]	47.9 [39.5; 62.18]	50.42 [34.45; 68.07]	0.01

*p — significance of differences when comparing more than 3 samples

No definitive correlation was found between RA activity (DAS-28 and RhF) and BMI or metabolic phenotypes (see Table 2). However, there was a significant decrease in VAS pain intensity from group 1 to group 4 (p=0.01). Furthermore, when the body mass index (BMI) was less than 25 kg/m², the rheumatoid factor (RhF) was higher in group 1 (MHPO) than in group 2 (MUHPO), with a value of 131.8 [40.1; 232.2] and 37.75 [17.75; 123.70] IU, respectively (p=0,04). Furthermore, at a BMI of ≥25 kg/m², the RA activity as measured by DAS-28 was higher in group 3 (MHPO) compared to group 4 (MUHPO) (4.90 [3.58; 5.12] and 3.76 [3.13; 4.43], respectively; p=0.01).

Discussion

Obesity represents a significant RF for a number of major health concerns, including cardiovascular disease (CVD), diabetes mellitus (DM), and cancer. It is a prominent medical and social issue on a global scale. In Russia, 59.2 % of the population is overweight and 24.1 % is obese [7]. A comparable trend is evident among patients with RA, wherein individuals with an underweight status are scarce, and the majority are either overweight or obese [4]. These findings are corroborated by the results of our study, which revealed that the majority of patients were either overweight (33.9 %) or obese (42.6 %), with no underweight individuals present. Therefore, obesity was the predominant condition in our cohort of RA patients, occurring more frequently than in the general Russian population. Our data indicate that MUHPO, a marker of cardiometabolic risk due to AH, high glucose levels, hypertriglyceridemia, and reduced HDL-C cholesterol, was the predominantly observed in women with RA. Conversely, individuals with MUHPO were more likely to have AH, carotid artery AS, CVD, and type 2 DM, which was found in patients with both elevated and normal BMI.

The findings of epidemiological studies indicate that there is an increased risk of autoimmune diseases, including rheumatoid arthritis (RA), associated with obesity [10], as well as with metabolic syndrome (MS) and its components, including waist size, HDL-C, and high glucose [11]. A potential mechanism underlying the relationship between MS and RA may be CRP, which has been shown to contribute to the development of RA to a significant extent, estimated to be approximately 10 % [11]. The influence of obesity on RA activity has been the subject of considerable debate, with findings across studies being contradictory [12]. While some studies have identified a correlation between BMI and RA activity, others have not been able to confirm this association. In our study, the high prevalence of obesity was observed not only according to BMI data, but also according to the results of body composition assessment. The majority of patients exhibited a composition where the adipose tissue was predominant and an A/G ratio greater than 1, which is characteristic of abdominal obesity [13]. However, these data require cautious evaluation in this single cohort study and may be related not only to the features of RA as an underlying disease, but also to the older age of the patients and GCC intake. With regard to the relationship between obesity and its associated phenotypes and RA activity, no clear associations were identified in our cohort of patients, the majority of whom exhibited moderate disease activity. It is important to note, however, that higher RA activity was observed in patients with a BMI of less than 25 kg/m² and MHPO compared to those with a MUHPO, as indicated by separate indicators such as pain severity according to VAS, RhF, and DAS-28. This is associated with a higher incidence of sarcopenia in these patients.

The DEXA body composition study represents the "gold standard" for the assessment of a patient's nutritional status, facilitating a more precise evaluation of the distribution of fat and muscle tissue. It is also capable of diagnosing sarcopenia and sarcopenic obesity. Sarcopenia is defined by quantitative and qualitative alterations in skeletal muscle tissue, which are associated with an elevated risk of falls and fractures. Furthermore, the development of sarcopenic obesity is associated with an increased risk of cardiovascular disease (CVD) and mortality. The primary diagnostic criterion for sarcopenia is the determination of fat-free mass index (FFMI) [9]. Prior research has documented alterations in body composition among individuals with RA that differentiate them from those without it. These changes include reduced muscle mass accompanied by increased adipose tissue content, which in turn increases the likelihood of developing sarcopenia and sarcopenic obesity [14]. Furthermore, our study demonstrated a relatively high prevalence of sarcopenia in women with RA (14.8 %) and sarcopenic obesity in over one-third of them (4.3 %). Concurrently, the distinctive characteristics of the nutritional status of patients with RA

manifest as increased muscle mass in conjunction with elevated BMI. Conversely, in the general population, there is a reduction in muscle tissue content with increasing obesity [7].

It is possible that alterations in body composition in RA may be attributable to chronic autoimmune inflammation and depend on the activity of RA. It is likely that decreases in BMI, fat mass, and muscle mass with may reflect higher RA activity. In general, the maintenance of fat mass and BMI in the absence of significant obesity in patients with RA may be protective and explain the "obesity paradox" described in the literature [6]. It is evident that a lower BMI is a principal predictor of sarcopenia in RA. This should be considered alongside other predictors, such as advanced age, severity of RA, presence of osteopenia or osteoporosis, and use of glucocorticoid-containing medications [15].

In our study, no patients were identified as underweight. However, it is likely that individuals with normal body weight may also require special attention in the presence of other RF of sarcopenia in RA. The development of sarcopenia has a markedly adverse impact on the prognosis of these patients, leading to frailty with a substantial decline in life quality and an elevated risk of premature mortality. Speaking of sarcopenic obesity, it was observed in one-third of patients with sarcopenia, occurring in all groups, including those with a BMI of less than 25 kg/m² in both MUHPO and MHPO cohorts. In patients with a BMI of 25 kg/m² or greater, all cases of sarcopenia were accompanied by obesity, which had a detrimental impact on prognosis.

The limitations of this study include the relatively small cohort of patients (115 women), the predominance of middle-aged and elderly women with predominantly moderate RA activity, the absence of morbid obesity, and the one-stage nature of the study without data on BMI dynamics.

Therefore, in order to assess the cardimetabolic risk in patients with RA, it is essential to consider the obesity phenotype in conjunction with BMI, and to supplement these data with the study of body composition in order to identify the presence of sarcopenia and sarcopenic obesity in groups at risk of its development.

Conclusion

Patients with RA tend to be overweight or obese with metabolic syndrome and high cardiometabolic risk for developing dyslipidemia, carbohydrate metabolism disorders, AH and AS. Regardless of BMI, MUHPO is more frequently accompanied by AH, carotid AS, CVD, and type 2 DM compared with MHPO.

An increase in adipose tissue is evident in the majority of patients, including those with a normal weight. A downward trend in FFMI and an increased prevalence of sarcopenia/sarcopenic obesity have been observed in individuals with a BMI below 25 kg/m². This is associated with a higher level of VAS pain intensity.

In patients with RA, it is reasonable to monitor both BMI and WHR to assess the cardiometabolic risk. A MUHPO at any BMI level indicates an increased risk of developing cardiovascular complications and disorders of carbohydrate metabolism. In addition to cardiometabolic risk, nutritional status should be assessed with body composition analysis to identify the presence of sarcopenia and sarcopenic obesity in groups at risk for their development.

Conflict of interests: none declared.

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