## BIOCHEMISTRY, BIOPHYSICS, AND MOLECULAR BIOLOGY

# Hyperleptinemia as a Marker of Various Phenotypes of Obesity and Overweight in Women with Rheumatoid Arthritis and Systemic Lupus Erythematosus

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**Abstract**—The objective of the study was to identify different phenotypes of overweight in women with systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) based on body mass index (BMI) and serum leptin levels, as well as to determine the frequencies of various metabolic disorders, hypertension, and cardiovascular complications (CVCs) in individual phenotypes. The study included 50 women with RA and 46 with SLE aged 18 to 65 years without a history of diabetes and fasting hyperglycemia. In all patients, the concentration of leptin was determined by ELISA, the concentration of insulin was determined by electrochemiluminescence analysis, and the HOMA-IR index was calculated. Hyperleptinemia was diagnosed at leptin concentrations $> 11.1$ ng/mL; insulin resistance (IR), at HOMA-IR values $\geq 2.77$. Three main phenotypes of overweight were distinguished: "classic" (BMI $\geq 25$ kg/m$^2$ + hyperleptinemia), "healthy" (BMI $\geq 25$ kg/m$^2$, without hyperleptinemia), "hidden" or "latent" (BMI $< 25$ kg/m$^2$ + hyperleptinemia), as well as "normal weight" (BMI $< 25$ kg/m$^2$, without hyperleptinemia). Patients with RA and SLE were similar in age ($p = 0.4$), disease duration ($p = 0.2$) and BMI ($p = 0.5$). Hyperleptinemia was found in 46% of women with RA and in 74% of women with SLE ($p = 0.005$), and IR was found in 10 and 22% of patients, respectively ($p = 0.2$). The "classic" phenotype of overweight was diagnosed in 30%, "healthy" in 8%, and "hidden" in 16% of cases with RA and in 44%, 0%, and 30% of cases with SLE, respectively. IR was found in 3% and hypertension in 6% of patients with "normal weight." With the "classic" phenotype, IR (29%) and hypertension (66%) were more common than with "normal weight" ($p < 0.01$ in all cases); with the "hidden" phenotype, significant differences were obtained only in hypertension frequency (45%; $p = 0.0012$), but not IR (18%). Three out of four women with a history of cardiovascular complications suffered from "classic" overweight, and one patient had a "normal weight." In women with SLE up to 65 years of age, the frequency of hyperleptinemia, but not IR, is higher than in patients with RA. In both diseases, the "classic" overweight phenotype is most common. In RA, a "hidden" phenotype was detected less often than in SLE, at the same time, a "healthy" phenotype is not characteristic of SLE. The frequency of metabolic disorders and hypertension is low with the "normal weight" and "healthy" phenotype, high with the "classic" phenotype, and intermediate with the "hidden" phenotype.

**Keywords:** rheumatoid arthritis, systemic lupus erythematosus, phenotypes, obesity, overweight, body mass index, leptin, hyperleptinemia, insulin resistance, HOMA-IR

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## INTRODUCTION

The increase in life expectancy of patients with systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA), associated with the development of new treatment regimens in recent decades, may lead to an increase in the prevalence of comorbidities such as coronary heart disease (CHD), heart failure (HF), and type 2 diabetes mellitus (DM) in middle and old age. Primary prevention of this socially significant pathology in the general population is based on timely detection and correction of reversible risk factors (dyslipidemia, obesity, arterial hypertension, and hyperglycemia). However, in immunoinflammatory rheumatic diseases (IIRDs), the significance of some of the above factors is not so clear. For example, in RA, the development of cardiovascular complications (CVCы) was associated with a decrease, but not with an increase, in the level of total cholesterol and low-density lipoproteins ("lipid paradox") [1], and mortality was associated with low body weight and weight loss ("obesity paradox") [2, 3].

The pathogenesis of both cardiovascular diseases and carbohydrate metabolism disorders in IIRDs is based on the combined influence of autoimmune chronic inflammation, antirheumatic drugs, and con-

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ventional cardiovascular risk factors, the standard assessment of which often gives conflicting results. For example, in IIRDs, the accumulation of fat mass can be either clinically pronounced, raising no doubt about obesity upon examination, or hidden, if it is combined with sarcopenia. Conventional screening methods—determining the body mass index (BMI) and waist circumference (WC)—do not reflect the actual body composition [4−6]. For example, in RA and systemic sclerosis, the proportion of patients with excess total fat mass, according to dual-energy X-ray absorptiometry, was 71.1 and 69.6%, although only 54.4 and 50% of patients had a BMI $\geq 25$ kg/m$^2$, respectively. Pathological combined body composition, including obesity on the one hand and osteoporosis and/or sarcopenia on the other, was detected in 32.4 and 45.7% of cases, respectively [7]. In addition, anthropometric measures cannot be used to assess the existing metabolic disorders caused by excess weight, although some evidence suggests that "metabolic ill-health" in the population is associated with adverse outcomes to a greater extent than BMI [8−10].

In most cases, the term "metabolic ill-health" is understood as the presence of certain signs of metabolic syndrome and insulin resistance (IR). An increase in the level of C-reactive protein (CRP) > 3 mL/L as a marker of subclinical inflammation [10−12] is often considered as an additional criterion. However, in IIRDs, the listed parameters can be distorted due to the presence of active inflammation, autoimmune reactions, the consequences of kidney damage as part of the underlying disease, and the use of a number of antiinflammatory drugs and can quickly change in a short period of time. Giraud et al. [13] demonstrated that 16% of RA patients with normal weight, 35% with overweight, and 15% with obesity had metabolic syndrome; the body composition in non-obese patients did not differ between the metabolic health and ill-health groups.

It is necessary to search for new "early" but more stable biomarkers to identify prognostically unfavorable phenotypes of obesity, overweight, and normal weight. In this aspect, leptin, a cytokine produced by adipocytes, which is responsible for the regulation of appetite and energy metabolism, is of great interest. Currently, it is believed that it also plays an important role in metabolic dysregulation. In the general population, patients with obesity and hyperleptinemia are more likely to have IR, type 2 diabetes mellitus, hypertension, and myocardial hypertrophy [14−18]. Leptin levels directly correlate with carotid intima-media thickness and coronary artery calcification, progression of atherosclerosis, heart failure, and severe coronary artery disease [19−25]. Data on leptin levels in RA and SLE, as well as on its relationship with metabolic disorders, are contradictory [26−29].

The objective of this study was to identify different phenotypes of overweight in women with systemic lupus erythematosus and rheumatoid arthritis based on two main indices—body mass index and blood serum leptin level, as well as clarifying the frequency of various metabolic disorders, arterial hypertension, and cardiovascular complications in certain phenotypes.

## MATERIALS AND METHODS

The observational study included 96 patients: 50 women with RA and 46 women with SLE. Inclusion criteria were a definite diagnosis of RA (according to the criteria of ACR/EULAR (American College of Rheumatology/European Alliance of Associations for Rheumatology) from 2010 [30]) or SLE (according to the criteria of SLICC (Systemic Lupus International Collaborating Clinics/ACR) from 2012 [31]) and availability of informed consent. Exclusion criteria were age under 18 or over 65 years, pregnancy and lactation, history of diabetes, fasting hyperglycemia (venous blood glucose $\geq 6.1$ mmol/L), and/or taking glucose-lowering drugs at the time of examination. The characteristics of patients with RA and SLE are presented in Table 1 and Table 2, respectively.

In all patients, height and weight, waist circumference (WC) and hip circumference (HC) were measured, BMI and WC/HC ratio were calculated, and the concentrations of leptin (DBS kits (Diagnostics Biochem Canada Inc., Canada) for enzyme immunoassay), insulin (Elecsys kit for electrochemiluminescent analyzer Cobas e411 (Roche Diagnostics, United States), glucose, and total cholesterol in fasting blood serum was determined. Blood pressure (BP) was measured, taking into account the need for constant use of antihypertensive drugs (as a marker of hypertension). Information about previous cardiovascular events (myocardial infarction, operations for its revascularization, and stroke) was collected. The HOMA-IR index was calculated using the formula: glucose (mmol/L) × insulin (µU/mL) /22.5 [32]. Hyperleptinemia was diagnosed when leptin concentration was >11.1 ng/mL, IR was diagnosed when HOMA-IR values were $\geq 2.77$.

Three main phenotypes of overweight were distinguished:

1) "classic" (BMI $\geq$ 25 kg/m$^2$ + hyperleptinemia);

2) "healthy" (BMI $\geq$ 25 kg/m$^2$, no hyperleptinemia);

3) "hidden," or "latent" (BMI < 25 kg/m$^2$ + hyperleptinemia).

"Normal weight" was diagnosed at BMI < 25 kg/m$^2$ in the absence of hyperleptinemia.

Statistical processing of data at all stages of the study was performed using parametric and nonparametric statistics. When comparing two independent groups for qualitative characteristics, the $\chi^2$ method was used (if necessary, with the Yates correction for

**Table 1.** Characteristics of rheumatoid arthritis patients ($n = 50$)

| Parameter | Value |
|---|---|
| Age (years), M [25th; 75th percentile] | 42 [33; 57] |
| BMI (kg/m2), Me [25th; 75th percentile] | 23.2 [20.4; 27.7] |
| WC (cm), Me [25th; 75th percentile] | 82 [71; 93] |
| WC/HC, Me [25th; 75th percentile] | 0.85 [0.79; 0.92] |
| Menopause, $n$ (%) | 22 (44) |
| RA duration (years), Me [25th; 75th percentile] | 5 [2, 11] |
| Positivity, $n$ (%): | |
| RF | 45 (90) |
| ACCP | 47 (94) |
| RA activity, $n$ (%): | |
| 1 — low (DAS28 < 3.2) | 9 (18) |
| 2 — moderate (DAS28 = 3.2–5.1) | 26 (52) |
| 3 — high (DAS28 > 5.1) | 15 (30) |
| RA radiological stage, $n$ (%): | |
| I | 3 (6) |
| II | 23 (46) |
| III | 14 (28) |
| IV | 10 (20) |
| Functional class, $n$ (%): | |
| I | 15 (30) |
| II | 22 (44) |
| III | 13 (26) |
| GC, n (%) | 18 (36) |
| GC dose (recalculated for prednisone), mg/day, Me [25th; 75th percentile] | 5 [5.0; 10.0] |
| csDMARDs, $n$ (%): | |
| methotrexate | 23 (46) |
| leflunomide | 6 (12) |
| other csDMARDs | 4 (8) |
| bDMARDs, $n$ (%): | |
| TNFα inhibitors | 2 (4) |
| rituximab | 10 (20) |

BMI—body mass index; WC—waist circumference; HC—hip circumference; RA—rheumatoid arthritis; RF—rheumatoid factor; ACCP—anti-cyclic citrullinated peptide antibodies; DAS28—Disease Activity Score 28; GC—glucocorticoids; csDMARDs—conventional synthetic disease-modifying antirheumatic drugs; bDMARDs—biological disease-modifying antirheumatic drugs; TNFα—tumor necrosis factor α.

low frequencies); for quantitative characteristics, the Mann–Whitney test was used; when comparing three groups, the Kruskal–Wallis method was used. Differences were considered statistically significant at $p < 0.05$; for multiple comparisons, taking into account the Bonferroni correction, at $p < 0.017$.

Patients with RA and SLE were comparable in age ($p = 0.4$), duration of IIRDs ($p = 0.2$), BMI ($p = 0.5$), WC ($p = 0.4$), and the proportion of participants in menopause ($p = 0.1$); however, the WC/HC ratio was higher in the SLE group ($p = 0.03$). In RA, the median leptin concentration was 10.8 [5.2; 23.1] ng/mL; in SLE, 29.6 [10.3; 75.5] ng/mL ($p < 0.0001$). In RA, hyperleptinemia was found in 23 (46%) patients; in SLE, in 34 (74%) patients ($p = 0.005$). IR was found in 5 (10%) and 10 (22%) patients, respectively ($p = 0.2$). Insulin and HOMA-IR levels were higher in SLE than

**Table 2.** Characteristics of systemic lupus erythematosus ($n = 46$)

| Parameter | Value |
|---|:---:|
| Age (years), Me [25th; 75th percentile] | 40 [31; 48] |
| BMI (kg/m$^2$), Me [25th; 75th percentile] | 24.3 [21.1; 27.2] |
| WC (cm), Me [25th; 75th percentile] | 85 [77; 93] |
| WC/HC, Me [25th; 75th percentile] | 0.91 [0.85; 0.94] |
| Menopause, $n$ (%) | 13 (28) |
| SLE duration (years), Me [25th; 75th percentile] | 3.0 [0.9; 9.0] |
| SLE presentations, $n$ (%) | |
| cutaneous manifestations | 15 (33) |
| alopecia | 5 (11) |
| oral ulcers | 2 (4) |
| arthritis | 13 (28) |
| serositis | 3 (7) |
| nephritis | 4 (9) |
| neuropsychiatric disorders | 0 |
| hematological disorders | 16 (35) |
| positive direct Coombs test | 3 (7) |
| Immunological disorders, $n$ (%) | |
| ANA (+) | 41 (89) |
| elevated anti-ds-DNA | 28 (61) |
| elevated anti-Sm | 1 (2) |
| elevated aPL | 10 (22) |
| hypocomplementemia | 27 (59) |
| SLE activity, $n$ (%) | |
| low (SLEDAI-2K = 1−5) | 2 (4) |
| moderate (SLEDAI-2K = 6−10) | 17 (37) |
| high (SLEDAI-2K ≥ 11) | 19 (41) |
| remission (SLEDAI-2K = 0) | 8 (17) |
| SLEDAI-2K (score), Me [25th; 75th percentile] | 5 [2, 8] |
| Damage index SLICC (points), Me [25th; 75th percentile] | 1 [0; 2] |
| Treatment: | |
| GC, $n$ (%) | 38 (83) |
| GC dose (recalculated for prednisone), mg/day, Me [25th; 75th percentile] | 10 [7.5; 10] |
| GC duration (years), Me [25th; 75th percentile] | 3 [1, 9] |
| Hydroxychloroquine, $n$ (%) | 35 (76) |
| Immunosuppressants, $n$ (%) | 10 (22) |
| Biological agents (rituximab, belimumab), $n$ (%) | 5 (11) |

BMI—body mass index; WC—waist circumference; HC—hip circumference; SLE—systemic lupus erythematosus; ANA—antinuclear antibodies; anti-ds-DNA—anti-double-stranded (native) deoxyribonucleic acid antibodies; anti-Sm—anti-Smith antigen antibodies; aPL—anti-phospholipid antibodies; SLEDAI-2K—SystemicLupus Erythematosus Disease Activity Index 2000; SLICC—Systemic Lupus International Collaborating Clinics; GC—glucocorticoids.

in RA (8.26 [2.89, 12.05] vs. 5.32 [3.85, 7.72] ng/mL ($p = 0.0007$) and 1.90 [1.23; 2.52] versus 1.18 [0.88; 1.78] ($p = 0.001$), respectively). Concentrations of glucose ($p = 0.3$) and total cholesterol ($p = 0.6$) did not differ.

The distribution of overweight phenotypes was as follows: in RA, the "classic" phenotype was diagnosed in 15 (30%), "healthy" in 4 (8%), and "hidden" in 8 (16%) patients; in SLE, in 20 (44%), 0 (0%), and 14
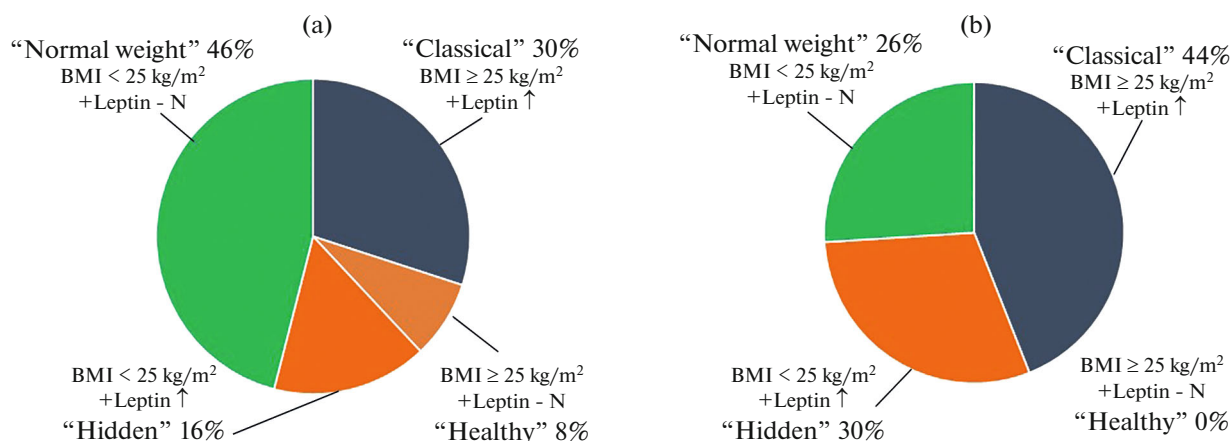
**Fig. 1.** Frequency of overweight phenotypes in patients with rheumatoid arthritis (a) and systemic lupus erythematosus (b). BMI—body mass index, N—normal values.

(30%), respectively (Fig. 1). In subgroups under 45 years of age with RA ($n = 30$), the "classic" phenotype was found in 4 (13%) cases, "healthy" in 3 (10%), "hidden" in 3 (10%) cases; in SLE ($n = 30$), in 10 (33%), 0 (0%), and 12 (40%) cases, respectively.

"Healthy" overweight phenotype was detected only in the patients with RA. BMI in this phenotype averaged 27.6 kg/m², median WC was 97 [87; 102] cm, and WC/HC was 0.9 [0.83; 0.99], which is higher than in the group of patients with "normal weight" ($p < 0.001$ for all parameters). Age, duration and disease activity according to DAS28 (Disease Activity Score 28), levels of inflammatory markers (erythrocyte sedimentation rate and CRP), cholesterol, glucose, HOMA-IR index, systolic and diastolic blood pressure, and frequency of use of antihypertensive drugs were comparable to those in patients with "normal weight."

Patients with "classic" and "hidden" overweight phenotypes in RA were older than those in the "normal weight" group and were more likely to be in menopause. The "hidden" phenotype was also characterized by a tendency towards longer duration of RA and more frequent use of GCs and genetically engineered biological drugs (biologics; Table 3).

In SLE, differences in three groups ("classic", "hidden" overweight phenotype, and "normal weight") were revealed not only in age, but also in the maximum dose of GCs for the entire duration of the disease, as well as a tendency towards shorter duration and greater activity of IIRDs in the last of them (Table 4).

In patients with a "healthy" overweight phenotype, there was no history of taking antihypertensive drugs or cardiovascular events. There were no differences with the subgroup with "normal weight" in the level of systolic and diastolic blood pressure, insulin concentration, total cholesterol, glucose, and HOMA-IR index. Metabolic parameters for the "classic" and "hidden" phenotypes are presented in Table 5.

The frequency of IR increased from 1 (3%) case at "normal weight" to 4 (18%) cases at "hidden" and 10 (29%) cases at the "classic" phenotype ($p = 0.009$ when compared with "normal weight"). A gradual increase in the proportion of patients receiving antihypertensive drugs was demonstrated: from 2 (6%) patients with "normal weight" to 10 (45%) patients with a "hidden" phenotype ($p = 0.0012$ when compared with "normal weight") and up to 23 (66%) patients with the "classic" phenotype ($p < 0.0001$ when compared with "normal weight"). Systolic (120 [115; 140] mm Hg) and diastolic (80 [70; 85] mm Hg) blood pressure at the "classic" phenotype turned out to be higher than at "normal weight" (110 [110; 120] mm Hg ($p = 0.001$) and 70 [65; 80] mm Hg ($p = 0.003$), respectively).

In two patients with RA and two patients with SLE, a history of one episode of cardiovascular events was registered: one had severe coronary artery disease, for which stenting of the coronary arteries was required, one had myocardial infarction, and two had acute cerebrovascular accident (ACVA). In three cases, women with CVCs had "classic" overweight phenotype, and one SLE patient with stroke had "normal weight" phenotype.

The study demonstrated that, in women under 65 years of age with SLE, despite similar BMI, levels of leptin, insulin, and the HOMA-IR index are higher, and the proportion of patients with hyperleptinemia is greater than in RA. At the same time, no statistically significant differences in the frequency of IR in RA and SLE were detected.

In the foreign and Russian literature, no information on the comparison of leptin concentrations in RA and SLE was found, although there are reports of both increased and similar levels of adipocytokine in these IIRDs compared to healthy controls [26–29]. In a number of studies, the frequency of IR in RA was greater than in SLE [33, 34], and in other studies it was

**Table 3.** Characteristics of rheumatoid arthritis patients with "classic" or "hidden" overweight phenotypes and with "normal weight"

| Parameter | Overweight phenotypes | | Normal weight ($n = 23$) | $p$ |
|---|---|---|---|---|
| | classical ($n = 15$) | hidden ($n = 8$) | | |
| Age (years), M[25th; 75th percentile] | 57 [43; 61] | 52 [42; 59] | 34 [28, 41] | $p_{k-w} = 0.0004$<br>$p_{1-2} = 0.73$<br>$p_{1-3} = 0.0003$<br>$p_{2-3} = 0.003$ |
| BMI (kg/m2), Me [25th; 75th percentile] | 29.6 [27.0; 31.1] | 23.0 [20.6; 24.2] | 20.5 [18.6; 21.7] | $p_{k-w} < 0.0001$<br>$p_{1-2} < 0.0001$<br>$p_{1-3} < 0.0001$<br>$p_{2-3} = 0.023$ |
| WC (cm), Me [25th; 75th percentile] | 97 [89; 107] | 82 [73; 87] | 71 [69; 80] | $p_{k-w} < 0.0001$<br>$p_{1-2} = 0.001$<br>$p_{1-3} < 0.0001$<br>$p_{2-3} = 0.09$ |
| WC/HC, Me [25th; 75th percentile] | 0.92 [0.86; 1.03] | 0.87 [0.83; 0.92] | 0.83 [0.78; 0.85] | $p_{k-w} = 0.0008$<br>$p_{1-2} = 0.19$<br>$p_{1-3} = 0.0002$<br>$p_{2-3} = 0.054$ |
| Menopause, $n$ (%) | 10 (67) | 6 (75%) | 4 (17%) | $p_{1-2} = 0.95$<br>$p_{1-3} = 0.006$<br>$p_{2-3} = 0.01$ |
| RA duration (years), Me [25th; 75th percentile] | 5 [3, 11] | 12 [5, 24] | 3 [1, 9] | $p_{k-w} = 0.08$<br>$p_{1-2} = 0.17$<br>$p_{1-3} = 0.25$<br>$p_{2-3} = 0.038$ |

| Parameter | Overweight phenotypes | | Normal weight ($n = 23$) | $p$ |
|---|---|---|---|---|
| | classical ($n = 15$) | hidden ($n = 8$) | | |
| DAS28, Me [25th; 75th percentile] | 4.6 [3.1; 5.1] | 4.4 [3.4; 4.9] | 4.5 [3.8; 5.5] | $p_{k-w} = 0.46$<br>$p_{1-2} = 0.97$<br>$p_{1-3} = 0.30$<br>$p_{2-3} = 0.34$ |
| CRP (mg/L), Me [25th; 75th percentile] | 3.9 [1.1; 31.6] | 7.3 [2.1; 11.7] | 10.1 [2.0; 48.5] | $p_{k-w} = 0.54$<br>$p_{1-2} = 0.83$<br>$p_{1-3} = 0.41$<br>$p_{2-3} = 0.36$ |
| GC, $n$ (%) | 5 (40) | 6 (75) | 6 (26) | $p_{1-2} = 0.14$<br>$p_{1-3} = 0.91$<br>$p_{2-3} = 0.04$ |
| GC dose (recalculated for prednisone), mg/day, Me [25th; 75th percentile] | 7.5 [5, 10] | 6.25 [5, 10] | 5 [5, 5] | $p_{k-w} = 0.57$<br>$p_{1-2} = 0.93$<br>$p_{1-3} = 0.43$<br>$p_{2-3} = 0.48$ |
| Methotrexate, $n$ (%) | 7 (47) | 4 (50) | 11 (48) | $p_{1-2} = 0.78$<br>$p_{1-3} = 0.79$<br>$p_{2-3} = 0.76$ |
| bDMARDs, $n$ (%) | 4 (27) | 4 (50) | 2 (9) | $p_{1-2} = 0.51$<br>$p_{1-3} = 0.30$<br>$p_{2-3} = 0.04$ |

$p_{k-w}$—$p$ value using the Kruskal—Wallis method for comparing three groups; $p_{1-2}$—$p$ value for comparing the "classic" phenotype and "normal weight" groups; $p_{2-3}$—$p$ value for comparing the "hidden" phenotype and "normal weight" groups; $p_{1-3}$—$p$ value for comparing the "classic" and "hidden" phenotypes; HC—hip circumference; RA—rheumatoid arthritis; DAS28—Disease Activity Score 28; CRP—C-reactive protein; GC—glucocorticoids; bDMARDs—biological disease-modifying antirheumatic drugs.

**Table 4.** Characteristics of systemic lupus erythematosus patients with "classic" or "hidden" overweight phenotypes and with "normal weight"

| Parameter | Overweight phenotypes | | Normal weight ($n = 12$) | $p$ |
|---|---|---|---|---|
| | classical ($n = 20$) | hidden ($n = 14$) | | |
| Age (years), M[25th; 75th percentile] | 45 [39; 52] | 36 [29, 40] | 37 [28; 51] | $p_{\text{k-w}} = 0.04$ <br> $p_{1-2} = 0.01$ <br> $p_{1-3} = 0.14$ <br> $p_{2-3} = 0.70$ |
| BMI (kg/m$^2$), Me [25th; 75th percentile] | 27.6 [26.7; 30.4] | 22.2 [20.4; 23.4] | 20.9 [19.3; 23.4] | $p_{\text{k-w}} < 0.0001$ <br> $p_{1-2} < 0.0001$ <br> $p_{1-3} < 0.0001$ <br> $p_{2-3} = 0.43$ |
| WC (cm), Me [25th; 75th percentile] | 95 [92; 99] | 80 [70; 83] | 77 [73; 83] | $p_{\text{k-w}} < 0.0001$ <br> $p_{1-2} < 0.0001$ <br> $p_{1-3} < 0.0001$ <br> $p_{2-3} = 0.74$ |
| WC/HC, Me [25th; 75th percentile] | 0.93 [0.90; 0.99] | 0.86 [0.84; 0.91] | 0.87 [0.82; 0.91] | $p_{\text{k-w}} = 0.013$ <br> $p_{1-2} = 0.008$ <br> $p_{1-3} = 0.024$ <br> $p_{2-3} = 0.94$ |
| Menopause, $n$ (%) | 8 (40) | 2 (14) | 3 (25) | $p_{1-2} = 0.22$ <br> $p_{1-3} = 0.63$ <br> $p_{2-3} = 0.85$ |
| SLE duration (years), Me[25th; 75th percentile] | 4.0 [0.8; 10.0] | 4.0 [3.0; 8.0] | 0.7 [0; 5.0] | $p_{\text{k-w}} = 0.06$ <br> $p_{1-2} = 0.40$ <br> $p_{1-3} = 0.12$ <br> $p_{2-3} = 0.015$ |
| SLEDAI-2K (score), Me[25th; 75th percentile] | 4 [1, 7] | 5 [2, 8] | 8 [5, 8] | $p_{\text{k-w}} = 0.052$ <br> $p_{1-2} = 0.46$ <br> $p_{1-3} = 0.017$ <br> $p_{2-3} = 0.13$ |
| Damage index SLICC (score), Me[25th; 75th percentile] | 10; 2] | 10; 3] | 0 [0; 2] | $p_{\text{k-w}} = 0.21$ <br> $p_{1-2} = 0.74$ <br> $p_{1-3} = 0.16$ <br> $p_{2-3} = 0.14$ |
| GC, $n$ (%) | 17 (85) | 13 (93) | 8(67) | $p_{1-2} = 0.87$ <br> $p_{1-3} = 0.44$ <br> $p_{2-3} = 0.23$ |
| GC duration (years), Me [25th; 75th percentile] | 4.0 [0.9; 11.0] | 3.0 [2.0; 8.0] | 1.8 [0.7; 8.0] | $p_{\text{k-w}} = 0.62$ <br> $p_{1-2} = 0.77$ <br> $p_{1-3} = 0.44$ <br> $p_{2-3} = 0.37$ |
| GC dose (recalculated for prednisone), mg/day, Me [25th; 75th percentile] | 10 [7.5; 10] | 10 [10; 13.8] | 8.75 [5, 10] | $p_{\text{k-w}} = 0.29$ <br> $p_{1-2} = 0.28$ <br> $p_{1-3} = 0.55$ <br> $p_{2-3} = 0.21$ |

| Parameter | Overweight phenotypes | | Normal weight ($n = 12$) | $p$ |
|---|---|---|---|---|
| | classical ($n = 20$) | hidden ($n = 14$) | | |
| Maximum GC dose during disease (recalculated for prednisone), mg/day, Me [25th; 75th percentile] | 30 [22.5; 40] | 50 [40; 60] | 27.5 [10, 40] | $p_{k\text{-}w} = 0.028$ $p_{1-2} = 0.06$ $p_{1-3} = 0.44$ $p_{2-3} = 0.008$ |
| Hydroxychloroquine, $n$ (%) | 17 (85) | 10 (71) | 8 (67) | $p_{1-2} = 0.59$ $p_{1-3} = 0.44$ $p_{2-3} = 0.87$ |
| Immunosuppressants, $n$ (%) | 3 (15) | 5 (36) | 2 (17) | $p_{1-2} = 0.32$ $p_{1-3} = 0.71$ $p_{2-3} = 0.52$ |
| Biological agents (rituximab, belimumab), $n$ (%) | 2 (10) | 1 (7) | 2 (17) | $p_{1-2} = 0.75$ $p_{1-3} = 1.0$ $p_{2-3} = 0.89$ |

$p_{k\text{-}w}$—$p$ value using the Kruskal–Wallis method for comparing three groups; $p_{1-2}$—$p$ value for comparing "classic" and "hidden" phenotypes; $p_{1-3}$—$p$ value for comparing the "classic" phenotype and "normal weight" groups; $p_{2-3}$—$p$ value for comparing the "hidden" phenotype and "normal weight" groups; BMI—body mass index; WC—waist circumference; HC—hip circumference; SLE—systemic lupus erythematosus; SLEDAI-2K—Systemic Lupus Erythematosus Disease Activity Index 2000; SLICC—Systemic Lupus International Collaborating Clinics; GC—glucocorticoids.

**Table 5.** Metabolic parameters in rheumatoid arthritis and systemic lupus erythematosus patients with "classic" or "hidden" overweight phenotypes and with "normal weight", Me [25th; 75th percentile]

| Parameter | Overweight phenotypes | | Normal weight ($n = 35$) | $p$ |
|---|---|---|---|---|
| | classical ($n = 35$) | hidden ($n = 22$) | | |
| Leptin, ng/mL | 39.7 [25.3; 80.8] | 24.0 [15.9; 28.8] | 5.6 [3.7; 7.4] | $p_{k\text{-}w} = 0.0005$ $p_{1-2} = 0.0003$ $p_{1-3} < 0.0001$ $p_{2-3} < 0.0001$ |
| Glucose, mmol/L | 5.1 [4.7; 5.4] | 4.9 [4.6; 5.2] | 4.9 [4.7; 5.3] | $p_{k\text{-}w} = 0.18$ $p_{1-2} = 0.07$ $p_{1-3} = 0.46$ $p_{2-3} = 0.23$ |
| Insulin, mcU/mL | 8.8 [6.6; 15.1] | 7.4 [5.2; 11.3] | 4.5 [3.4; 6.0] | $p_{k\text{-}w} < 0.0001$ $p_{1-2} = 0.15$ $p_{1-3} < 0.0001$ $p_{2-3} = 0.0005$ |
| HOMA-IR | 2.03 [1.44; 3.61] | 1.76 [1.16; 2.33] | 1.11 [0.69; 1.37] | $p_{k\text{-}w} < 0.0001$ $p_{1-2} = 0.10$ $p_{1-3} < 0.0001$ $p_{2-3} = 0.003$ |
| Total cholesterol, mmol/L | 5.1 [4.4; 5.9] | 5.5 [4.8; 5.9] | 4.3 [3.8; 5.4] | $p_{k\text{-}w} = 0.0014$ $p_{1-2} = 0.67$ $p_{1-3} = 0.003$ $p_{2-3} = 0.0009$ |

$p_{k\text{-}w}$—$p$ value using the Kruskal–Wallis method for comparing three groups; $p_{1-2}$—$p$ value for comparing "classic" and "hidden" phenotypes; $p_{1-3}$—$p$ value for comparing the "classic" phenotype and "normal weight" groups; $p_{2-3}$—$p$ value for comparing the "hidden" phenotype and "normal weight" groups; HOMA-IR—Homeostasis Model Assessment of Insulin Resistance.

comparable [35, 36]. The identified differences may be related to the demographic characteristics of patients and the method for determining IR. Characteristic features of our cohort were a relatively young age and the absence of obvious disorders of carbohydrate metabolism (DM and fasting hyperglycemia).

It is known that serum leptin concentration depends on the content of adipose tissue in the body, including in RA, and can potentially be used to assess its amount [37]. The combination of hyperleptinemia with low BMI may indirectly indicate sarcopenia and sarcopenic obesity.

On the other hand, an increase in leptin synthesis reflects morphofunctional changes in adipose tissue, as it is associated with hypertrophy and apoptosis of adipocytes, recruitment of immune cells (primarily M1 macrophages), and the production of proinflammatory cytokines that contribute to the development of IR and epithelial dysfunction [22, 38]. Within the framework of this concept, hyperleptinemia should be considered as the first stage in the formation of "metabolic ill-health," which subsequently leads to various adverse outcomes. This point of view is confirmed by the results of two studies in RA. In one of them, high leptin levels were associated with an increased risk of death due to cardiovascular causes, with stronger correlations observed in non-obese patients [39]. In another, high leptin level was associated with the risk of various concomitant diseases, including dyslipidemia, hypertension, diabetes, heart failure, as well as overall mortality and mortality due to malignant neoplasms [40].

In this work, we propose to use the determination of leptin in combination with BMI to identify individuals with different overweight phenotypes—"classic", "hidden", and "healthy", reflecting a certain level of metabolic disorders. Slightly less than half of the patients with RA and about a quarter of the patients with SLE had normal weight without hyperleptinemia. Among all the overweight phenotypes, "healthy" turned out to be quite rare, which was found only in some, mostly young, patients with RA. Metabolic parameters at the "healthy" phenotype did not differ from those in women with a BMI of up to 25 kg/m$^2$ without hyperleptinemia. In general, the "classic" phenotype was diagnosed most often both in RA and in SLE, although in the subgroup under 45 years of age it gave way to the "hidden" phenotype. These two phenotypes, compared with the patients who had "normal weight," were characterized by changes in biochemical parameters (increased concentrations of total cholesterol, insulin, and HOMA-IR index), although not always clinically significant, a higher frequency of hypertension. The "classic" phenotype was also characterized by an increase in IR.

Women with a "classic," but not "hidden," phenotype, as well as one patient with "normal weight," reported CVC events. In the last case, risk factors not associated with obesity (for example, antiphospholipid syndrome, the presence of which was confirmed in this SLE patient) could have played a role in the development of stroke. The fact that "hidden" overweight, unlike "classic" overweight, was not associated with any cardiovascular events confirms that it can be considered as a certain "window of opportunity" for primary prevention.

The detection of metabolically unfavorable phenotypes depended on age and GC use. Low disease activity was of additional importance in SLE. All this apparently led to excess accumulation of fat mass. RA patients with a "hidden" phenotype received biologics somewhat more frequently. It is known that the use of drugs from the group of tumor necrosis factor α inhibitors promotes weight gain due to the accumulation of adipose tissue [41, 42]. The possibility of indirect effects of biologics should also be taken into account. Their prescription for RA, as a rule, is a consequence of a severe course of the disease, which could cause the development of sarcopenia and a decrease in BMI in previously obese patients and, on the other hand, serve as a basis for the use of GCs. The effect of IIRDs therapy on the formation of various overweight phenotypes requires further research.

Thus, the proposed stratification of patients with IIRDs allows us to identify two subgroups of patients— with "classic" and "hidden" overweight phenotypes—who require regular monitoring of lipid profile, blood pressure, insulin levels, as well as prevention of carbohydrate metabolism disorders and cardiovascular events. In this case, basic measures should be aimed, first of all, at reducing the mass of adipose tissue, including a calorie-restriction diet, regular long-term aerobic exercises, and, if they are ineffective, drug therapy. At a "healthy" phenotype, weight maintenance and sarcopenia prevention are recommended. The introduction of appropriate recommendations into the complex of treatment of patients with IIRDs will help reduce the prevalence of obesity-associated diseases such as type 2 diabetes mellitus, coronary artery disease, and heart failure, as well as reduce material costs for their treatment and increase the life expectancy of patients.

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## ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by the Local Ethics Committee of the Nasonova Research Institute of Rheumatology (protocol no. 02 dated January 27, 2022). All participants signed voluntary informed consent to participate in the study.

## CONFLICT OF INTEREST

The authors of this work declare that they have no conflicts of interest. All authors took part in developing the concept of the article and writing the manuscript. The authors are solely responsible for submitting the final version of the manuscript for publication. The final version of the manuscript was approved by all authors. The authors did not receive any royalties for the article.

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