ORIGINAL INVESTIGATIONS

Clinical significance of leptin in systemic lupus erythematosus

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Objective: *to study the frequency of hyperleptinemia in patients with systemic lupus erythematosus (SLE), its relationship with clinical and laboratory manifestations of the disease, drug therapy, and other metabolic disorders.*

Patients and methods. *The cross-sectional study included 46 women with a definite diagnosis of SLE (median age 40 [31; 48] years) and disease duration 3.0 [0.9; 9.0] years. Glucocorticoids (GC) were received by 38 (83%) patients, hydroxychloroquine – by 35 (76%), immunosuppressants – by 10 (22%), biologic disease-modifying antirheumatic drugs – by 5 (11%). In all patients, fasting levels of glucose, leptin, apolipoprotein B (ApoB) and immunoreactive insulin were determined, and homeostatic model assessment for insulin resistance (HOMA-IR) was calculated. Concentration of leptin ⩾11.1 ng/ml, ApoB – >1.6 mg/ml were considered an elevated level. HOMA-IR index ⩾2.77 corresponded to the presence of insulin resistance (IR).*

Results and discussion. *Hyperleptinemia was found in 34 (74%) patients with SLE, an increased level of ApoB – in 19 (41%), IR – in 10 (22%). In patients with hyperleptinemia, serositis, positivity for anti-double-stranded DNA (aDNA) and hypocomplementemia were less common, overweight and obesity were more frequent, the SLEDAI-2K index was lower, the aDNA level was lower, and the concentration of the C3 component of complement, insulin, HOMA-IR index, body mass index (BMI) and disease duration were higher ($p<0.05$ for all cases). BMI <25 kg / m² had 26 (57%) women, 14 (54%) of whom had hyperleptinemia. In patients with BMI <25 kg / m², we found a relationship between leptin concentration and disease duration ($r=0.4$, $p=0.04$), SLE activity according to SLEDAI-2K ($r=-0.6$, $p=0.003$), levels of aDNA ($r=-0.6$, $p<0.001$), C3 component of complement ($r=0.5$, $p=0.01$), maximum ($r=0.7$, $p<0.001$) and supporting ($r=0,5$, $p=0.023$) GC doses. In patients with BMI ⩾25 kg/m² (n=20), no such relationship was observed.*

Conclusion. *Hyperleptinemia was found in the majority of women with SLE; elevated levels of ApoB and IR were much less common. Patients with hyperleptinemia are characterized by a longer duration and less activity of the disease, as well as the presence of overweight and obesity and an increase in the HOMA-IR index. In SLE patients with normal body weight, the concentration of leptin increased along with GC dose elevation.*

Key words: *leptin; systemic lupus erythematosus; insulin resistance; obesity; apolipoprotein B.*
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In clinical medicine, there is a constant search for new biochemical markers, predictors of the course and prognosis of various diseases. Due to the high prevalence of obesity, in recent years special attention is paid to adipocytokines (adipokines) synthesized in adipose tissue, including leptin, which is responsible for the regulation of appetite and energy balance. In the general population, leptin is considered a protein associated with obesity and cardiovascular risk. Overweight patients with hyperleptinemia are more likely to develop insulin resistance (IR), type 2 diabetes mellitus (DM), and cardiovascular complications [1]. Since the discovery of leptin, data have been obtained indicating the importance of this protein both for the regulation of metabolism and for the formation of the immune response. Leptin stimulates activation of macrophages and secretion of proinflammatory cytokines, production of autoantibodies by B-cells, proliferation of naive CD4+ T-cells, inhibits the function of regulatory T-lymphocytes, enhances Th17- helper response, maintains the expression of proteins that prevent apoptosis, which indicates possibility of its participation in the pathogenesis of immune-inflammatory rheumatic diseases (RD) [2].

Systemic lupus erythematosus (SLE) is a classic immune-inflammatory RD characterized by disorders of both congenital and acquired B- and T-lymphocytic immune response. Most studies have shown that the level of leptin in patients with SLE is higher than in those without RD [3, 4], although several studies have obtained opposite results [5, 6]. The rare occurrence of SLE in men and an increase in the concentration of leptin in women with this disease suggest an association of adipokines with sex [7]. However, in general, the data on the role of leptin in SLE are contradictory.

The aim of the study was to assess the frequency of hyperleptinemia in patients with SLE, its relationship with clinical and laboratory manifestations of the disease, drug therapy, and other metabolic disorders.

Patients and methods. A cross-sectional study included 46 women with SLE who were hospitalized at V.A. Nasonova Research Institute of Rheumatology in 2019–2020 and signed informed consent.

Inclusion criteria: age over 18; reliable diagnosis of SLE (according to the criteria of the American College of Rheumatology, ACR) 1997 [8, 9] and / or the criteria of SLICC (Systemic Lupus International Collaborating Clinics) / ACR 2012 [10].

Exclusion criteria: concomitant type 1 or 2 DM, fasting hyperglycemia (venous blood glucose ⩾6.1 mmol/L), taking antihyperglycemic drugs, pregnancy, lactation.

The median age of the patients was 40 [31; 48] years, disease duration – 3.0 [0.9; 9.0] years. Clinical characteristics of patients with SLE are presented in Table 1.

SLE activity was determined using the SLEDAI-2K index (Systemic Lupus Erythematosus Disease Activity Index, 2K modification) [11]. At the time of the study, in 5 (11%) women with achieved remission or low disease activity the test for antinuclear antibodies (ANA) was negative, although previously they had been repeatedly detected in the diagnostic titer. To assess irreversible changes, the damage index (DI) SLICC (Systemic Lupus International Collaborating Clinics) was used [12].

We measured the patients' height, body weight, and fasting levels of glucose, leptin (enzyme-linked immunosorbent assay using DBS-Diagnostics Biochem Canada Inc.), apolipoprotein B (Apo B; enzyme-linked immunosorbent assay, Assaypro LLC kits) and immunoreactive insulin (Elecsys kits for electrochemiluminescence analyzer Cobas e411, Roche Diagnostics). The levels of leptin ⩾11.1 ng/mL, ApoB – >1.6 mg/mL were considered elevated. The Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) was determined by the formula: HOMA-IR = glucose (mmol/L) × insulin (μU/mL) / 22,5 [13]. HOMA-IR index value ⩾2.77 corresponded to the presence of IR.

Statistical processing of the obtained data was carried out on a personal computer using the methods of parametric and nonparametric statistics of the Statistica 8.0 programs (StatSoft Inc., USA). For qualitative characteristics we used absolute and relative values (n, %), for quantitative ones – the median and interquartile range (Me [25th; 75th percentile]). When comparing two independent groups for quantitative characteristics, the Mann–Whitney test was used, for qualitative ones – χ^2 test (for low frequencies – with Yates's correction). The relationship of the characteristics was assessed using the Spearman rank correlation test (r). Differences were considered statistically significant at $p < 0.05$.

Results. The median leptin concentration was 29.6 [10,3; 75.5] ng/mL. An increased level of leptin was found in 34 (74%) patients with SLE, ApoB – in 19 (41%), IR – in 10 (22%).

In contrast to women with normal adipokine concentrations, patients with

Table 1. Characteristics of SLE patients (n = 46)

Characreristics	Values
Age, years, Me [25th; 75th percentile]	40 [31; 48]
SLE duration, years, Me [25th; 75th percentile]	3.0 [0.9; 9.0]
SLE features, n (%):	
skin lesions	15 (33)
alopecia	5 (11)
mucosal ulcers	2 (4)
arthritis	13 (28)
serositis	3 (7)
nephritis	4 (9)
neuropsychiatric disorders	0
hematological disorders	16 (35)
isolated positive Coombs' test	3 (7)
Immunological disorders, n (%):	
positive ANA	41 (89)
positive aDNA	28 (61)
positive aSm	1 (2)
positive aPL	10 (22)
hypocomplementemia	27 (59)
SLE activity, n (%):	
remission (SLEDAI-2K=0)	8 (17)
low (SLEDAI-2K=1–5)	17 (37)
moderate (SLEDAI-2K=6–10)	19 (41)
high (SLEDAI-2K ≥11)	2 (4)
SLEDAI-2K, scores, Me [25th; 75th percentile]	5 [2; 8]
DI SLICC, scores, Me [25th; 75th percentile]	1 [0; 2]
Treatment:	
GCs, n (%)	38 (83)
Maintenance daily GCs dose (prednisone equivalent, mg/day), Me [25th; 75th percentile]	10 [7.5; 10]
duration of GCs intake, years, Me [25th; 75th percentile]	3 [1; 9]
HCQ, n (%)	35 (76)
Immunosuppressive drugs, n (%)	10 (22)
Biological agents (rituximab, belimumab), n (%)	5 (11)
APS, n (%)	8 (17)
SS, n (%)	13 (28)

Note. aDNA – antibodies to double-stranded DNA; aSm – antibodies to Sm antigen; aPL – antiphospholipid antibodies; GCs – glucocorticoids; HCQ – hydroxychloroquine; APS – antiphospholipid syndrome; SS – Sjogren's syndrome.

Table 2. Characteristics of SLE patients with and without hyperleptinemia

Characteristics	SLE with hyperleptinemia (n=34)	SLE without hyperleptinemia (n=12)
Age, years, Me [25th; 75th percentile]	40 [35; 48]	37 [28; 51]
SLE duration, years, Me [25th; 75th percentile]	4.0 [2; 9]*	0.7 [0; 5,0]
SLEDAI-2K, scores, Me [25th; 75th percentile]	4 [2; 8]*	8 [5; 8]
DI SLICC, scores, Me [25th; 75th percentile]	1 [0; 2]	0 [0; 2]
aDNA, IU/mL, Me [25th; 75th percentile]	23.8 [10.6; 51.9]*	122.1 [41.5; 200.0]
C3, g/L, Me [25th; 75th percentile]	0.95 [0.74; 1.10]*	0.74 [0.57; 0.87]
C4, g/L, Me [25th; 75th percentile]	0.15 [0.10; 0.20]	0.14 [0.06; 0.17]
GCs, n (%)	30 (88)	8 (67)
Duration of GCs intake, years,	3.5 [1.0; 11.0]	1.8 [0.7; 8.0]
Me [25th; 75th percentile]		
Maintenance daily GCs dose (prednisone equivalent, mg/day), Me [25th; 75th percentile]	10 [7.5; 10]	8.8 [5; 10]
Maximum GCs dose (prednisone equivalent, mg/day), Me [25th; 75th percentile]	40 [25; 60]	27.5 [10; 40]
Treatment: HCQ, n (%)	27 (79)	8 (67)
Immunosuppressive drugs, n (%)	8 (24)	2 (17)
Biological agents (rituximab, belimumab), n (%)	3 (9)	2 (17)

Note. * - p <0.05 compared with patients without metabolic disorders.

hyperleptinemia were less likely to be diagnosed with serositis, aDNA positivity and hypocomplementemia: 25, 92, 92% and 0, 50, 47%, respectively (p<0.05). Characteristics of patients with and without hyperleptinemia are presented in Table 2.

Patients with hyperleptinemia compared with women with normal leptin levels had a higher body mass index – BMI (26.1 [22.3; 28.1] kg/m^2 versus 20.9 [19.3; 23.4] kg/m^2; p<0.001), insulin level (8.99 [6.64; 13.46] ng/mL versus 5.30 [3.77; 6.13] ng/mL; p<0.001) and HOMA-IR (2.05 [1.47; 2.81] versus 1.18 [0.85; 1.45]; p=0.006); they were also more likely to be overweight and obese (59% versus 0%; p=0.001). There were no significant differences in serum glucose concentrations (4.9 [4.6; 5.2] mmol/L versus 5.0 [4.7; 5.3] mmol/L; p=0.4) and ApoB (1.6 [1.5; 1.7] mg/mL versus 1.5 [1.4; 1.7] mg/mL; p=0.6), the frequency of IR (29% versus 0%; p=0.09) and increased ApoB (44% versus 33%; p=0.8).

Twenty-six (57%) patients had normal body weight (BMI <25 kg/m^2), 14 (54%) of them had hyperleptinemia. In women with normal body weight, a relationship was found between leptin concentration and duration of the disease (r=0.4, p=0.04), SLE activity according to SLEDAI-2K (r=-0.6, p=0.003), aDNA level (r=-0.6, p<0.001), C3 component of complement (r=0.5, p=0.01), maximum (r= 0.7, p<0.001) and maintenance (r=0.5, p=0.023) GC doses. There was no statistically significant relationship with the duration of GC therapy (r=0.5, p=0.053). In patients with BMI ⩾25 kg/m^2 (n=20) no such relationship was found.

Discussion. According to the study, 74% of SLE patients had hyperleptinemia, which turned out to be the most common metabolic disorder. An increase in the level of proatherogenic ApoB and IR was much less common. Patients with elevated leptin levels were characterized by a longer SLE duration and less disease activity, as well as the presence of overweight and obesity. At the same time, a significant part of women (41%) with hyperleptinemia had a normal weight (BMI<25 kg/m^2), which may indicate the presence of latent obesity in them, since leptin is almost completely synthesized in adipose tissue. In the group of patients with normal body weight, the adipokine concentration increased with the increase in the GC dose.

According to the data of cohort studies, leptin content in the blood of SLE patients varied greatly. The reasons for this heterogeneity remain unclear, since no relationship with ethnicity, sample size, and the method used for adipokine detection was found. One of possible explanations may be the difference in BMI and the proportion of patients with overweight and obesity, because their association with hyperleptinemia was noted in most foreign studies [4] as well as in our study.

It was shown that the administration of leptin to NZB × NZW mice with spontaneously developing lupus resulted in an increase in the production of autoantibodies and worsened the course of nephritis [14]. However, in SLE patients, no convincing evidence of a relationship between leptin levels and the activity or clinical

manifestations of the disease has been obtained so far [3, 4], and the available data are contradictory. Thus, in one of the studies, an association was found between a higher concentration of leptin and kidney damage [15], while in another study dependence of proteinuria on adipokines was not found [16]. D. Chougule et al. [6] showed that the level of leptin in the serum was lower in nephritis and hypocomplementemia, but higher in photosensitivity and hematological manifestations of SLE. According to D. Afroze et al. [17], arthritis was more common in SLE patients with hyperleptinemia, while M. Wislowska et al. [18], on the contrary, revealed a lower level of leptin in cases of joint and central nervous system involvement. The absence of a relationship between concentrations of leptin and SLE activity was demonstrated in several studies [5, 15, 19–21]; at the same time, M. Vadacca et al. [22] reported direct, while D. Chougule et al. [6] – reverse association of adipokines with disease activity indices. Our own results coincide with the conclusions formulated in one of the presented studies [6] and indicate that in women without hyperleptinemia, the disease activity is higher and immunological disorders (increased aDNA level, hypocomplementemia) and serositis are more common.

In healthy individuals, short-term (up to 1 week) use of dexamethasone or large doses of prednisolone increased the production and release of leptin from adipocytes [23, 24], while data on the effect of exogenous GCs on leptin levels in immune-inflammatory RD are insufficient. An increase in the level of leptin was noted against the background of GC therapy in dermatomyositis and antineutrophil cytoplasmic antibody-associated vasculitis [25]. Similar, but statistically insignificant data were obtained in idiopathic juvenile arthritis after 3 months of therapy [26]. At the same time, there are studies in which the very fact of using GCs in SLE and their dose did not have a significant effect on the concentration of leptin [5, 19].

Two mechanisms are known to explain the effect of GCs on leptin production: on the one hand, they cause accumulation of adipose tissue by increasing the differentiation of preadipocytes into adipocytes, and on the other, they stimulate their own receptors, directly increasing the synthesis of adipokines in mature fat cells [27–29]. In our study, only in patients with normal body weight there was a relationship between the maximum and maintenance doses of GCs and hyperleptinemia. It can be assumed that in this case the stimulation of GC-receptors had a definite effect on the increase in leptin concentration.

In SLE patients, as in the general population, leptin levels correlate with the development of atherosclerosis and its complications, thickness of the intima-media complex [30], stiffness of the vascular wall [22], and plaques in the carotid arteries [21]. Recently, a multi-parameter index PREDICTS (Predictors of Risk for Elevated Flares, Damage Progression, and Increased Cardiovascular Disease in Patients with SLE) was developed [31], in which leptin is included along with three other biomarkers (proinflammatory high-density lipoprotein, soluble TNF-like weak inducer of apoptosis – sTWEAK – and homocysteine), age and DM. Long-term follow-up of women with SLE showed that an initially high PREDICTS index was associated with an increased risk of cardiovascular complications.

At the same time, the relationship of leptin with IR and changes in the lipid profile in SLE patients has been little studied, although it is known that adipokine level is higher in the presence of metabolic syndrome [30]. Earlier, S.R. Shung et al. [32] demonstrated the association of leptin with IR, and M. McMahon et al. [21] – with such biomarkers of atherosclerosis as lipoprotein (a), pro-inflammatory high-density lipoproteins, and oxidized phospholipids on ApoB-containing particles. However, in the study of K.E. Sada et al. [33] leptin concentration did not depend on IR. In our study, hyperleptinemia was accompanied by an increase in insulin levels and, as a result, in the HOMA-IR index. Moreover, IR was registered only in this group of patients, although the differences in the frequency of the latter turned out to be insignificant, probably due to the small number of women with normal adipokine levels in the blood serum. At the same time, we did not find an association between hyperleptinemia and the level of ApoB, which is the structural basis of low and very low-density lipoproteins, chylomicrons, and is a reliable indicator of atherosclerosis risk.

Conclusion. Thus, the present study revealed a high incidence of hyperleptinemia in women with SLE, the development of which was associated with an increase in the duration and decrease in the activity of the disease, overweight and the use of high doses of GCs. Despite the close relationship with obesity, hyperleptinemia occurred in more than a half of SLE patients with a BMI <25 kg/m^2. An increased level of leptin in SLE should be as the first stage of metabolic disorders leading to IR, and later to prediabetes and type 2 DM, while proatherogenic disorders of lipid metabolism are associated with it to a lesser extent. A personalized approach to the diagnosis and prevention of carbohydrate metabolic disorders in SLE patients should include assessment of leptin levels, especially when deciding on the target maintenance dose of GCs in patients with normal body weight.

REFERENCES

1. Dessie G, Ayelign B, Akalu Y, et al. Effect of leptin on chronic inflammatory disorders: insights to therapeutic target to prevent further cardiovascular complication. *Diabetes Metab Syndr Obes.* 2021 Jul 17;14:3307-22. doi: 10.2147/DMSO.S321311. eCollection 2021.

2. Yuan Q, Chen H, Li X, Wei J. Leptin: an unappreciated key player in SLE. *Clin Rheumatol.* 2020 Feb;39(2):305-17. doi: 10.1007/s10067-019-04831-8. Epub 2019 Nov 9.

3. Kuo CY, Tsai TY, Huang YC. Insulin resistance and serum levels of adipokines in patients with systemic lupus erythematosus: a systematic review and meta-analysis. *Lupus.* 2020 Aug;29(9):1078-84. doi: 10.1177/0961203320935185. Epub 2020 Jun 30.

4. Yuan Q, Zhang L, Tian Y, et al. Circulating leptin level, soluble leptin receptor level and their gene polymorphism in patients with systemic lupus erythematosus: a systematic review and meta-analysis. *Clin Exp Rheumatol.* Nov-Dec 2020;38(6):1238-46. Epub 2020 Jun 30.

5. De Sanctis JB, Zabaleta M, Bianco NE, et al. Serum adipokine levels in patients with systemic lupus erythematosus. *Autoimmunity.* 2009 May;42(4):272-4. doi: 10.1080/08916930902828031.

6. Chougule D, Nadkar M, Venkataraman K, et al. Adipokine interactions promote the pathogenesis of systemic lupus erythematosus. *Cytokine.* 2018 Nov;111:20-27. doi: 10.1016/j.cyto.2018.08.002. Epub 2018 Aug 8.

7. Barranco C. Systemic lupus erythematosus: Leptin linked to SLE. *Nat Rev Rheumatol.* 2016 Nov;12(11):623. doi: 10.1038/nrrheum.2016.161. Epub 2016 Sep 22.
8. Tan EM, Cohen AS, Fries JF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum.* 1982 Nov;25(11):1271-7. doi: 10.1002/art.1780251101.
9. Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum.* 1997 Sep;40(9):1725. doi: 10.1002/art.1780400928.
10. Petri M, Orbai AM, Alarcon GS, et al. Derivation and Validation of the Systemic Lupus International Collaborating Clinics Classification Criteria for Systemic Lupus Erythematosus. *Arthritis Rheum.* 2012 Aug;64(8):2677-86. doi: 10.1002/art.34473.
11. Gladman DD, Ibanez D, Urowitz MB. Systemic lupus erythematosus disease activity index 2000. *J Rheumatol.* 2002 Feb;29(2):288-91.
12. Gladman D, Ginzler E, Goldsmith C, et al. The development and initial validation of the Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) Damage Index for Systemic Lupus Erythematosus. *Arthritis Rheum.* 1996 Mar;39(3):363-9. doi: 10.1002/art.1780390303.
13. Matthews DR, Hosker JP, Rudenski AS, et al. Homeostasis model assessment: insulin resistance and β-cell function from fasting plasma glucose and insulin concentration in man. *Diabetologia.* 1985 Jul;28(7):412-9. doi: 10.1007/BF00280883.
14. Lourenco EV, Liu A, Matarese G, La Cava A. Leptin promotes systemic lupus erythematosus by increasing autoantibody production and inhibiting immune regulation. *Proc Natl Acad Sci U S A.* 2016 Sep 20; 113(38):10637-42. doi: 10.1073/pnas.1607101113. Epub 2016 Sep 1.
15. De Suosa Barbosa V, Francescantonio PL, Silva NA. Leptin and adiponectin in patients with systemic lupus erythematosus: clinical and laboratory correlations. *Rev Bras Reumatol.* Mar-Apr 2015;55(2):140-5. doi: 10.1016/j.rbr.2014.08.014. Epub 2014 Oct 24.
16. Diaz-Rizo V, Bonilla-Lara D, Gonzalez-Lopez L, et al. Serum levels of adiponectin and leptin as biomarkers of proteinuria in lupus nephritis. *PLoS One.* 2017 Sep 12;12(9): e0184056. doi: 10.1371/journal.pone.0184056. eCollection 2017.
17. Afroze D, Yousuf A, Ali R, et al. Serum leptin levels, leptin receptor gene (LEPR) polymorphism, and the risk of systemic lupus erythematosus in Kashmiri population. *Immunol Invest.* 2015;44(2):113-25. doi: 10.3109/08820139.2014.909457. Epub 2014 Nov 10.
18. Wislowska M, Rok M, Stepien K, Kuklo-Kowalska A. Serum leptin in systemic lupus erythematosus. *Rheumatol Int.* 2008 Mar; 28(5):467-73. doi: 10.1007/s00296-008-0526-7. Epub 2008 Jan 15.
19. Garcia-Gonzalez A, Gonzalez-Lopez L, Valera-Gonzalez IC, et al. Serum leptin levels in women with systemic lupus erythematosus. *Rheumatol Int.* 2002 Aug;22(4):138-41. doi: 10.1007/s00296-002-0216-9. Epub 2002 Jun 27.
20. Afifi AEA, Shaat RM, Gharbia OM, et al. Role of serum leptin levels and leptin receptor gene polymorphisms in systemic lupus erythematosus. *Clin Rheumatol.* 2020 Nov; 39(11):3465-72. doi: 10.1007/s10067-020-05120-5. Epub 2020 May 6.
21. McMahon M, Skaggs BJ, Sahakian L, et al. High plasma leptin levels confer increased risk of atherosclerosis in women with systemic lupus erythematosus, and are associated with inflammatory oxidised lipids. *Ann Rheum Dis.* 2011 Sep;70(9):1619-24. doi: 10.1136/ard.2010.142737. Epub 2011 Jun 13.
22. Vadacca M, Zardi EM, Margiotta D, et al. Leptin, adiponectin and vascular stiffness parameters in women with systemic lupus erythematosus. *Intern Emerg Med.* 2013 Dec;8(8):705-12. doi: 10.1007/s11739-011-0726-0. Epub 2011 Nov 30.
23. Rieth N, Jollin L, Le Panse B, et al. Effects of short-term corticoid ingestion on food intake and adipokines in healthy recreationally trained men. *Eur J Appl Physiol.* 2009 Jan;105(2):309-13. doi: 10.1007/s00421-008-0904-6. Epub 2008 Nov 5.
24. Jollin L, Rieth N, Thomasson R, et al. Changes in adipokines but not in body composition after one week of prednisone intake in physically fit women. *Endocrine.* 2013 Apr; 43(2):444-6. doi: 10.1007/s12020-012-9816-7. Epub 2012 Oct 13.
25. Conklin LS, Merkel PA, Pachman LM, et al. Serum biomarkers of glucocorticoid response and safety in anti-neutrophil cytoplasmic antibody-associated vasculitis and juvenile dermatomyositis. *Steroids.* 2018 Dec; 140:159-66. doi: 10.1016/j.steroids.2018.10.008. Epub 2018 Oct 21.
26. Markula-Patjas K, Valta H, Pekkinen M, et al. Body composition and adipokines in patients with juvenile idiopathic arthritis and systemic glucocorticoids. *Clin Exp Rheumatol.* Nov-Dec 2015;33(6):924-30. Epub 2015 Aug 27.
27. Tomabechi Y, Tsuruta T, Saito S, et al. Extra-adrenal glucocorticoids contribute to the postprandial increase of circulating leptin in mice. *J Cell Commun Signal.* 2018 Jun; 12(2):433-9. doi: 10.1007/s12079-017-0403-9. Epub 2017 Jul 25.
28. Malaise O, Relic B, Charlier E, et al. Glucocorticoid-induced leucine zipper (GILZ) is involved in glucocorticoid-induced and mineralocorticoid-induced leptin production by osteoarthritis synovial fibroblasts. *Arthritis Res Ther.* 2016 Oct 4;18(1):219. doi: 10.1186/s13075-016-1119-6.
29. Vicennati V, Garelli S, Rinaldi E, et al. Cross-talk between adipose tissue and the HPA axis in obesity and overt hypercortisolemic states. *Horm Mol Biol Clin Investig.* 2014 Feb;17(2):63-77. doi: 10.1515/hmbci-2013-0068.
30. Demir S, Erten G, Artim-Esen B, et al. Increased serum leptin levels are associated with metabolic syndrome and carotid intima media thickness in premenopausal systemic lupus erythematosus patients without clinical atherosclerotic vascular events. *Lupus.* 2018 Aug;27(9):1509-16. doi: 10.1177/0961203318782424. Epub 2018 Jun 28.
31. Skaggs BJ, Grossman J, Sahakian L, et al. A Panel of Biomarkers Associates with Increased Risk for Cardiovascular Events in Women With Systemic Lupus Erythematosus. *ACR Open Rheumatol.* 2021 Apr;3(4):209-20. doi: 10.1002/acr2.11223. Epub 2021 Feb 19.
32. Chung CP, Long AG, Solus JF, et al. Adipocytokines in systemic lupus erythematosus: relationship to inflammation, insulin resistance and coronary atherosclerosis. *Lupus.* 2009 Aug;18(9):799-806. doi: 10.1177/0961203309103582.
33. Sada KE, Yamasaki Y, Maruyama M, et al. Altered levels of adipocytokines in association with insulin resistance in patients with systemic lupus erythematosus. *J Rheumatol.* 2006 Aug;33(8):1545-52.

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Conflict of Interest Statement

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