Adipokines and Systemic Lupus Erythematosus: Relationship with Metabolic Syndrome and Cardiovascular Disease Risk Factors

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ABSTRACT. ***Objective.*** To study concentrations of adipokines in patients with systemic lupus erythematosus (SLE) and the relationship among adipokines, the metabolic syndrome (MeS), and cardiovascular disease (CVD) risk factors.

Methods. We enrolled 50 SLE patients and 26 controls, all women. Leptin, resistin, visfatin, and adiponectin were measured by commercial ELISA kits.

Results. MeS prevalence was increased among subjects with SLE. Leptin levels were higher in patients with SLE than controls. Among SLE patients, independent determinants of leptin were insulin levels ($p < 0.0001$), triglycerides ($p = 0.03$), body mass index ($p = 0.02$), corticosteroid dosage ($p = 0.02$), and SLE Disease Activity Index ($p = 0.005$). Other adipokines did not differ between SLE patients and controls.

Conclusion. Leptin was increased in SLE patients and could play a role in SLE-related cardiovascular diseases. (First Release Dec 15 2008; J Rheumatol 2009;36:295–7; doi:10.3899/jrheum.080503)

Key Indexing Terms:
ADIPOKINES
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The role of cardiovascular diseases (CVD) has become increasingly important in the morbidity and mortality of patients with systemic lupus erythematosus (SLE), in particular among young fertile women[1]. Metabolic syndrome (MeS), a new independent CVD risk factor, characterized by insulin-resistance (IR), obesity, dyslipidemia, and hypertension, has been shown to be highly prevalent among SLE patients, increasing the interest in the role of adipose tissue in rheumatic diseases[2,3]. White adipose tissue (WAT) secretes a variety of bioactive peptides, called adipokines, including leptin, resistin, visfatin, and adiponectin. These molecules are involved in a wide spectrum of biological activity, playing a role in atherogenesis and modulating insulin sensitivity[4,5]. Further, a deregulation in adipokine concentrations has been demonstrated in numerous inflammatory and autoimmune diseases[6-8]. To date, it has not yet been clarified whether adipokine levels in SLE are related to metabolic alterations and/or to the inflammatory milieu. The aim of our study was to determine the adipokine levels in patients with SLE versus healthy subjects and to identify different cardiovascular and metabolic variables associated with adipokines in this population.

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MATERIALS AND METHODS

Study population. Fifty eligible patients, who met the Hochberg modified American College of Rheumatology classification criteria for SLE[9], and 26 control subjects were enrolled in this study. Patients and controls, all women, were stratified according to fertile or menopausal status. The study was approved by the Ethical Committee of "Campus Bio-Medico" University of Rome. All participants gave written informed consent.

For patients with SLE, disease activity was assessed at time of enrollment in the study using the SLE Disease Activity Index (SLEDAI) and the European Consensus Lupus Activity Measurement (ECLAM) index[10].

Metabolic syndrome and CVD risk factors. All subjects were evaluated for CVD risk factors. To estimate 10-year CVD risk, we used an individual risk calculator according to the Italian Global Cardiovascular Risk Score (IGCRS/CUORE)[11]. The diagnosis of MeS was made according to the criteria of the World Health Organization (WHO)[12] and the European Group for the study of Insulin-Resistance (EGIR)[13].

Adipokines. Serum levels of leptin were determined by a commercial sandwich ELISA kit (DRG Instruments GmbH, Marburg, Germany). Serum resistin, visfatin, and adiponectin were measured by commercial ELISA kits (AdipoGen Inc., Seoul, Korea).

Statistical analysis. Data were analyzed with Prism 5.0 software (Prism Inc., San Diego, CA, USA). Comparisons of continuous variables among groups were performed by Mann-Whitney U test. The categorical variables

were analyzed by Fisher F test. Correlations were calculated by Spearman tests. Multivariate analysis for leptin level independent determinants was performed by multiple regression, using a stepwise model. Two-sided p values < 0.05 were considered statistically significant.

RESULTS

Clinical characteristics, metabolic syndrome, and CVD risk factors. Forty (80%) and 10 (20%) patients with SLE versus 16 (61.5%) and 10 (38.5%) controls were fertile and menopausal, respectively (p = 0.10).

The overall prevalence of MeS by WHO definition was 28% in SLE and 7.7% in controls (p = 0.043). Moreover, 30% of SLE patients and 3.8% of controls met EGIR criteria (p = 0.007).

Compared to controls, SLE patients showed higher levels of fasting insulin (p = 0.004), HOMA-IR (homeostasis model assessment for insulin resistance; p = 0.03), body mass index (BMI; p = 0.04), waist circumference (p = 0.04), systolic blood pressure (p = 0.03), homocysteine (p < 0.0001), and C-reactive protein (p = 0.01). Other results are reported in Table 1.

Adipokines. Leptin was higher among SLE patients compared to controls in the group as a whole and in fertile subjects (p = 0.04 and p = 0.005, respectively; Figure 1). Among SLE patients, leptin correlated with insulin levels (r = 0.8, p < 0.0001), HOMA-IR (r = 0.8, p < 0.0001), MeS (r = 0.7, p < 0.0001), triglycerides (r = 0.4, p = 0.002), BMI (r = 0.8, p < 0.0001), weight to height (W/H) ratio (r = 0.6, p < 0.0001), systolic and diastolic blood pressure (r = 0.5, p < 0.0001; r = 0.4, p = 0.001, respectively), IGCRS/CUORE score (r = 0.4, p = 0.003), SLEDAI (r = 0.5, p < 0.0001), and ECLAM (r = 0.6, p < 0.0001). In stepwise multiple regression analysis of leptin levels among SLE patients, model R^2 was 0.88 and adjusted R^2 was 0.87 (p < 0.0001). Variables entered stepwise were insulin levels (p < 0.0001), triglycerides (p = 0.03), BMI (p = 0.02), corticosteroid dosage (p = 0.02), and SLEDAI (p = 0.005).

Median resistin, visfatin, and adiponectin did not differ between SLE patients and controls. Regarding SLE patients, adiponectin levels were inversely correlated to plasma insulin (r = –0.3, p = 0.003), HOMA-IR (r = –0.3, p = 0.003), W/H ratio (r = –0.4, p = 0.006), triglycerides (r = –0.3, p = 0.02), and MeS diagnosis (r = –0.4, p = 0.007).

DISCUSSION

Adipokines have recently been implicated in insulin resistance, atherogenesis, and autoimmune diseases[4,5,14]. The aim of our study was to determine the adipokine levels in patients with SLE and to identify factors associated with

Table 1. Clinical characteristics, metabolic syndrome variables, and risk factors for cardiovascular disease. All patients and controls were female. Data are median (range).

	Total			Fertile Age Group			Menopausal Age Group		
	SLE, N = 50	Controls, N = 26	p	SLE, N = 40	Controls, N = 16	p	SLE, N = 10	Controls, N = 10	p
Metabolic syndrome									
Fasting glucose, mg/dl	83.5 (66–123)	88.5 (75–104)	0.13	81 (66–123)	86 (75–102)	0.27	89 (79–114)	96.5 (78–104)	0.38
Glucose 120′, mg/dl	83 (40–246)	87 (36–114)	0.85	83 (40–160)	89.5 (75–111)	0.093	101 (73–246)	80 (36–114)	0.11
Fasting insulin, mU/ml	8.2 (3.2–32.0)	6.1 (2.7–12.0)	0.004	7.9 (3.2–32.0)	5.1 (3.7–12.0)	0.005	10.5 (4.1–12.5)	7.6 (2.8–11.0)	0.082
HOMA-IR	1.6 (0.6–8.2)	1.3 (0.6–2.9)	0.03	1.5 (0.6–8.2)	1.0 (0.7–2.9)	0.008	2.1 (0.9–3.8)	1.8 (0.6–2.7)	0.21
Triglycerides, mg/dl	94 (42–209)	87 (39–155)	0.31	89 (42–200)	73 (39–130)	0.074	132 (71–209)	118 (71–155)	0.62
HDL cholesterol, mg/dl	65 (25–125)	60 (30–85)	0.11	65 (25–125)	65.5 (30–85)	0.73	79 (48–112)	54.5 (41–64)	0.01
BMI, kg/m^2	24.2 (19.8–35.0)	22.8 (19.0–37.3)	0.04	24 (19.8–35.0)	21 (19.0–26.4)	0.007	25.1 (20.0–34.7)	23.3 (22.0–37.3)	0.79
Waist/hip ratio	0.84 (0.68–1.18)	0.81 (0.72–0.94)	0.11	0.83 (0.68–1.18)	0.80 (0.72–0.88)	0.16	0.86 (0.74–1.12)	0.83 (0.73–0.94)	0.27
Waist circumference, cm	79 (64–118)	73 (64–111)	0.04	78 (64–118)	70 (64–88)	0.006	85 (65–110)	79 (67–111)	0.66
Systolic blood pressure, mm Hg	120 (90–160)	110 (100–140)	0.03	120 (90–160)	110 (100–140)	0.15	140 (120–160)	120 (100–140)	0.002
MeS prevalence (WHO criteria)	14 (28)	2 (7.7)	0.043	9 (22.5)	1 (6.25)	0.25	5 (50)	1 (10)	0.15
MeS prevalence (EGIR criteria)	15 (30)	1 (3.8)	0.007	10 (25)	0 (0)	0.047	5 (50)	1 (10)	0.14
Other CVD risk factors									
Family history of CHD, n (%)	6 (12)	6 (23)	0.31	2 (5)	3 (18.75)	0.13	4 (40)	3 (30)	1.0
CHD, n (%)	5 (10)	0	0.15	1 (2.5)	0	1.0	4 (40)	0	0.086
Total cholesterol, mg/dl	201 (153–286)	185 (115–326)	0.056	201 (153–275)	178 (115–245)	0.01	209 (180–286)	187 (178–326)	0.79
LDL cholesterol, mg/dl	112 (74–179)	97 (59–199)	0.057	113 (74–179)	87 (59–132)	0.0008	97 (89–158)	117 (90–199)	0.11
Current smoking, n (%)	2 (4)	2 (7.7)	0.60	2 (5)	2 (12.5)	0.59	0	0	—
Homocysteine, µU/l	12.0 (4.0–21.0)	7.0 (4.0–18.0)	< 0.0001	10.5 (4.0–19.0)	6.0 (4.0–9.0)	< 0.0001	14.0 (9.0–21.0)	10.5 (9.0–18.0)	0.58
C-reactive protein, mg/dl	2.0 (1.0–26.0)	1.0 (0.0–5.0)	0.01	2.0 (1.0–26.0)	1.5 (0.0–5.0)	0.19	3.0 (1.0–6.0)	1.0 (1.0–2.0)	0.007

SLE: systemic lupus erythematosus; MeS: metabolic syndrome; HOMA-IR: homeostasis model assessment for insulin resistance; BMI: body mass index; CHD: coronary heart disease.

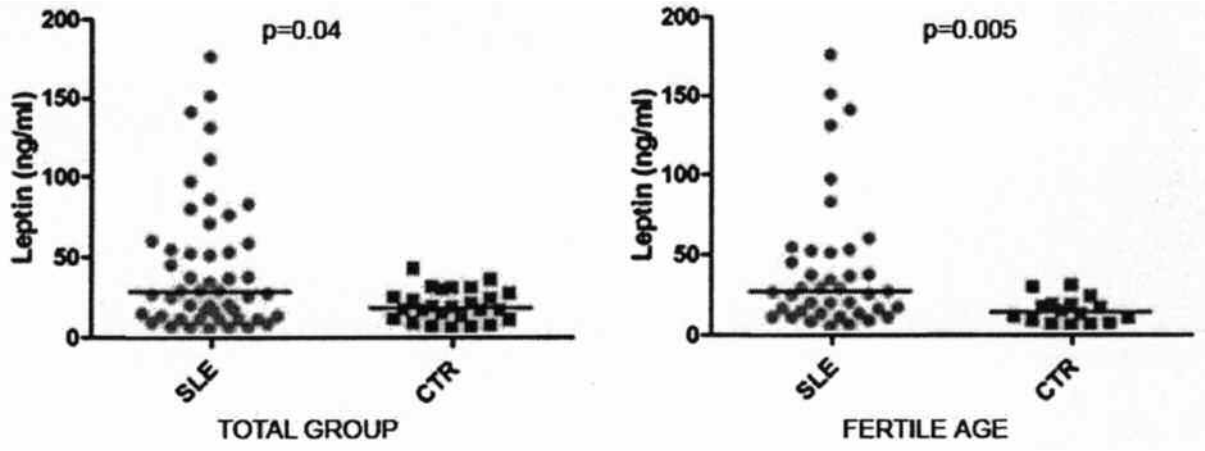

Figure 1. Leptin levels in patients with SLE and in controls (CTR) in the group as a whole and in fertile subjects.

adipokine levels in this population. Our results showed hyperexpression of leptin, notably, among fertile patients with SLE. In SLE, leptin correlated with insulin and HOMA-IR levels and with the MeS. Indeed, although the small sample size precluded adequate statistical power, our work represents the first evidence of an increased frequency of insulin resistance and MeS in an Italian SLE sample. Moreover, we found that leptin levels were related to CVD risk factors and to the IGCRS, a useful tool in evaluating the importance of CVD risk factors in an Italian population.

A few studies have been published regarding leptin levels and CVD in SLE; however, the West of Scotland Coronary Prevention Study[15] showed that leptin is an independent risk factor for coronary heart disease in the general population. Leptin levels have been described as directly correlated with inflammatory markers and disease activity in patients with rheumatoid arthritis[8]. In analogy with these data, we found a positive correlation between leptin and SLE-specific disease activity indexes.

Although we did not find higher levels of adiponectin in SLE, our data confirmed results of Sada, *et al* that demonstrated an inverse correlation between levels of adiponectin and HOMA-IR in SLE patients[7]. A possible involvement of adiponectin in insulin resistance in SLE requires further investigation.

Our results suggest that leptin may play a role regarding CVD risk factors and MeS in women with SLE, above all in the fertile years. Further, leptin seems to be implicated in disease activity. Further studies are required to clarify the role of adipokines in SLE immuno-imbalance and in SLE-related cardiovascular involvement.

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