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PAPER

Adipokines, tumor necrosis factor and its receptors in female patients with systemic lupus erythematosus

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Objectives: To analyze the association of adipokines and tumor necrosis factor α (TNFα) and its receptors with characteristics of systemic lupus erythematosus (SLE) and to investigate the correlation between adipokines and the TNF system. **Methods:** One hundred and thirty-six SLE women, aged ≥18 years old, were assessed. TNFα, soluble TNFα receptors 1 (sTNFR1) and 2 (sTNFR2) and adipokines were analyzed by ELISA kits. **Results:** The median (IQR) of age was 41.5 (33.0–49.7) years old and of disease duration 11.3 (7.8–15.8) years. The median (IQR) of disease activity was 0 (0–4) and of damage index was 2 (1–3). Higher levels of sTNFR1 and sTNFR2 were associated with nephritis ($p < 0.001$ for both), and sTNFR1 ($p = 0.025$) and TNFα ($p = 0.014$) were positively associated with arthritis. Higher sTNFR1 levels were found in participants that were not using antimalarial drugs ($p = 0.04$). Independent correlation was found between sTNFR1 ($\beta = 0.253$; $p = 0.003$) and sTNFR2 ($\beta = 0.297$; $p < 0.001$) levels and disease activity and damage index (sTNFR1: $\beta = 0.367$; $p < 0.001$; sTNFR2: $\beta = 0.335$; $p < 0.001$). Higher adiponectin levels were independently associated with nephritis ($p = 0.009$) and antimalarial drugs use ($p = 0.015$). There was a positive correlation between leptin and sTNFR2 levels ($p = 0.002$) and between resistin levels and sTNFR1 ($p < 0.001$) and sTNFR2 ($p < 0.001$). **Conclusion:** The correlation between adipokines and TNF system allows a better understanding of the role of adipokines in the inflammatory response in SLE patients. *Lupus* (2017) **26,** 10–16.

Key words: Adipokines; tumor necrosis factor; tumor necrosis factor receptors; systemic lupus erythematosus

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease, pathogenesis is complex and still not completely understood. In SLE, stimulation of the immune system results in autoantibody production, immune complex deposition and inflammatory cytokine release. Cytokines are soluble factors that can participate in the differentiation, maturation and activation of the immune system.[1]

Tumor necrosis factor α (TNFα) is a pleiotropic cytokine that elicits different reactions under various physiological and pathological conditions. TNFα participates in the activation and development of B and T lymphocytes and can induce apoptosis.[2] It also contributes to the pathogenesis of SLE through inflammatory actions and through the regulation of immune function.[3] TNFα can stimulate the production of membrane receptors,[4] which become soluble and bind to serum TNFα, avoiding its inactivation by other inhibitory cytokines.[5] Some studies have shown that TNFα and its receptors might be elevated in the serum of patients with SLE.[6,7] TNFα and its receptors are associated with higher disease activity and kidney involvement.[4,8]

Adipokines also participate in the regulation of the immune system and systemic inflammation.[9] Leptin and resistin usually have pro-inflammatory effects, and adiponectin has an anti-inflammatory action in individuals without autoimmune disorders.[10] In chronic inflammatory diseases such as SLE, adipokines, leptin and adiponectin in

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particular, are usually elevated, compared with healthy individuals.[11–13] In these, adipokines, particularly leptin, might stimulate the production of TNFα by macrophages, thus modifying the cytokine profile.[13]

Few studies have addressed the associations between adipokines (leptin, adiponectin and resistin) and inflammatory cytokines or between the former and clinical, laboratory and treatment-related manifestations in individuals with SLE.[14,15] It is also not yet known whether the TNF system, composed of TNFα and its soluble receptors 1 (sTNFR1) and 2 (sTNFR2), mediate the inflammatory action of adipokines in SLE.[16,17] In this context, the aim of the present study was to assess how adipokines and the TNF system are associated with each other, as well as the clinical, laboratory and treatment-related characteristics of SLE.

Patients and methods

Patients

This cross-sectional study was approved by The Research Ethics Committee of UFMG and the Teaching, Research and Extension Board, HC/UFMG (ETIC no. 272/08) and was conducted at the Rheumatology Unit of the *Hospital das Clínicas*, *Universidade Federal de Minas Gerais – UFMG*.

Participants were female individuals diagnosed with SLE (ACR 82/97),[18,19] who were older than 18 years of age and who signed an informed consent form. None of the patients had acute or chronic infection, cancer, and severe renal or hepatic impairment. Female and male individuals cannot be studied as a single group due to the differences in body composition. As in our cohort the number of male patients was very small the authors decided to study only the females in order to achieve reliable results.

Methods

Data on sociodemographic characteristics, clinical and laboratory manifestations according to the ACR 82/97 lupus criteria[18,19] and use of medication were collected via forms and interviews. Disease activity was measured using the modified Systemic Lupus Erythematosus Disease Activity Index 2000, without the serologic variables anti-dsDNA and complement (SLEDAI-2 K*m*).[20,21] Irreversible cumulative damage was measured by means of the Systemic Lupus International Collaborating Clinics/ACR Damage Index (SLICC/SDI).[22]

The patients were divided into two groups according to disease activity: SLEDAI-2 K$m < 4$ (low disease activity) and SLEDAI-2 K$m \geq 4$ (moderate to severe disease activity) at study inclusion.[23]

According to body mass index (BMI), patients were classified as normal weight (BMI = 18.6–24.9 kg/m^2), overweight (BMI = 25–29.9 kg/m^2) and obese (BMI $\geq$ 30 kg/m^2) based on the criteria of the World Health Organization.[24]

At the time of clinical assessment serum samples were collected in sterile tubes, centrifuged for 20 min, frozen and stored at −70°C. The serum was diluted 10-fold prior to measuring cytokine levels, except for TNFα. Adiponectin, leptin, resistin, TNFα, sTNFR1 and sTNFR2 were analyzed using enzyme-linked immunosorbent assay (ELISA) kits (Duoset, R&D Systems, Minneapolis, MN, USA) according to the manufacturer's instructions.

The test sensitivity was 2.5 pg/ml for TNFα and 5.0 pg/ml for the remainder of the assessed molecules.

Statistical analysis

A database was created using the software EpiData® version 3.1 (EpiData Association, Odense, Denmark). The software Statistical Package for Social Sciences (SPSS®) version 19.0 (SPSS Inc., Chicago, IL, USA) was used for the statistical analysis.

In order to assess potential associations between clinical characteristics and the TNF system or adipokines, the non-parametric *U*-Mann–Whitney, Chi-square or Fisher's exact tests were used when appropriate. Associations between the TNF system and adipokines were investigated by means of Spearman's correlation test.

Multiple linear regression was used for multivariate analysis after logarithmic transformation of the dependent variables included in the models. The independent variables to be included in the model were selected based on their statistical significance in the univariate analysis and their likely biological association. To fit the model, four patients with outliers of sTNFR1 levels were excluded.

The significance level was set to 5% ($p < 0.05$) in all analyses.

Results

Patients' characteristics

The median and interquartile range (IQR) of age and disease duration of the 136 assessed women

were 41.5 (33.0–49.7) years old and 11.3 (7.8–15.8) years; 105 (77.2%) participants were classified as nonWhite, and 67 (49.3%) were postmenopausal. According to ACR classification, patients characteristics at study inclusion indicated mucocutaneous manifestations in 19.1%, hematological disorders in 35.3% (leukopenia in 15.4%, lymphopenia in 32.4% and thrombocytopenia in 2.9%), arthritis in 6.6%, nephritis in 16.2%, nephrotic syndrome in 1.5%, serositis (pleurisy) in 0,7%, vasculitis in 2.9%. No patient had neuropsychiatric disorders. Regarding treatment, 69.1% of patients were using corticosteroids, 64.7% antimalarial drugs and 49.3% immunosuppressors (azathioprine in 28.0%, methotrexate in 16.2% and cyclophosphamide in 5.1%).

The accumulated characteristics of the disease during its course is reported in Table A (supplementary material online). The median (IQR) SLEDAI-2 K*m* was 0 (0–4) and the median (IQR) SLICC/SDI was 2 (1–3). The number (%) of patients with SLEDAI-2 K$m \geq 4$ was 35 (25.7%) and <4 was 101 (74.3%).

Serum cytokine concentrations

Table 1 presents the serum adipokines levels and the TNFα system components in the 136 participants as well as the serum levels of these factors according to disease activity as assessed by the SLEDAI-2 K*m*.

TNFα system and clinical manifestations analysis

Positive correlation between sTNFR1 and sTNFR2 levels (*r*s: 0.745; $p < 0.001$) was observed. However, no correlation was identified between TNFα and sTNFR1 (*r*s: 0.960; $p = 0.680$) or sTNFR2 (*r*s: 0.106; $p = 0.221$).

Higher sTNFR1 levels were associated with nephritis [no nephritis: 1.38 (1.08–1.80) ng/ml nephritis: 1.89 (1.38–3.07) ng/ml; $p < 0.001$] and arthritis [no arthritis: 1.38 (1.10–1.84) ng/ml *vs*. arthritis: 1.91 (1.70–2.31) ng/ml; $p = 0.025$]. Higher levels of sTNFR1 were correlated with age ($rs = 0.178$; $p = 0.039$) and the presence of menopause [no menopause: 1.34 (0.49–1.63) ng/ml *vs*. menopause: 1.65 (1.28–2.03) ng/ml; $p < 0.001$) and inversely correlated with creatinine clearance ($rs = -0.299$; $p < 0.001$]. Higher sTNFR1 levels were found among those participants who were not using antimalarial drugs [not using: 1.62 (1.11–1.93) ng/ml *vs*. using: 1.38 (1.04–1.78) ng/ml; $p = 0.04$].

Higher sTNFR2 levels were associated with the presence of nephritis [no nephritis: 4.35 (3.50–5.26) ng/ml *vs*. nephritis: 6.43 (4.94–9.63) ng/ml; $p < 0.001$] and higher serum TNFα levels were associated with arthritis [no arthritis: 0.03 (0.00–0.20) ng/ml *vs*. arthritis: 0.242 (0.05–1.48) ng/ml; $p = 0.014$].

Positive correlations were found between disease activity and serum sTNFR1 ($rs = 0.219$; $p = 0.011$) and sTNFR2 ($rs = 0.292$; $p = 0.003$) concentrations (Figure 1). Serum sTNFR1 ($p = 0.001$) and sTNFR2 ($p = 0.001$) levels were higher among the participants with moderate to severe lupus activity versus those with inactive/low disease activity (Table 1). Similarly, positive correlations were found between the damage index and sTNFR1 ($rs = 0.427$; $p < 0.001$) and sTNFR2 ($rs = 0.245$; $p = 0.005$) levels (Figure 1). However, no correlation was found between TNFα levels and disease activity or SLICC-ACR/DI score.

In the multivariate analysis, independent associations were found between sTNFR1 and sTNFR2 and disease activity and damage indexes (Table 2).

Adipokines and clinical manifestations

The BMI of the 136 participants was 26.4 (23.6–30.6) kg/m^2; 38% were of normal weight, 30.6%

Table 1 Comparison of adipokines and TNFα, sTNFR1 and sTNFR2 in 136 patients, according to activity index

Cytokines *Median (IQR)*	*Total* N = *136*	*SLEDAI-2 K*m < *4* N = *101*	*SLEDAI-2 K*m ≥ *4* N = *35*	p[a]
Leptin, ng/ml	1.75 (1.52–1.98)	1.75 (1.55–1.99)	1.75 (1.49–1.92)	0.743
Resistin, ng/ml	2.07 (1.65–2.56)	2.05 (1.64–2.59)	2.09 (1.60–2.46)	0.917
Adiponectin[b], ng/ml	11.30 (7.07–18.03)	10.76 (7.07–16.56)	14.64 (6.37–19.20)	0.176
TNFα, pg/ml	0.04 (0.00–0.25)	0.03 (0.03–0.25)	0.04 (0.08–0.14)	0.502
sTNFR1, ng/ml	1.42 (1.12–1.87)	1.38 (1.07–1.74)	1.81 (1.34–2.32)	0.001
sTNFR2, ng/ml	4.58 (3.62–5.86)	4.32 (3.56–5.52)	5.74 (4.06–7.56)	0.001

[a]Mann–Whitney.
[b]$N = 135$.
IQR: interquartile range; SLEDAI-2 k*m*: Systemic Lupus Erythematosus Disease Activity Index 2000 modified (without anti-dsDNA and complement); TNFα: tumor necrosis factor α: sTNFR1: soluble TNF receptor 1; sTNFR2: soluble TNF receptor 2

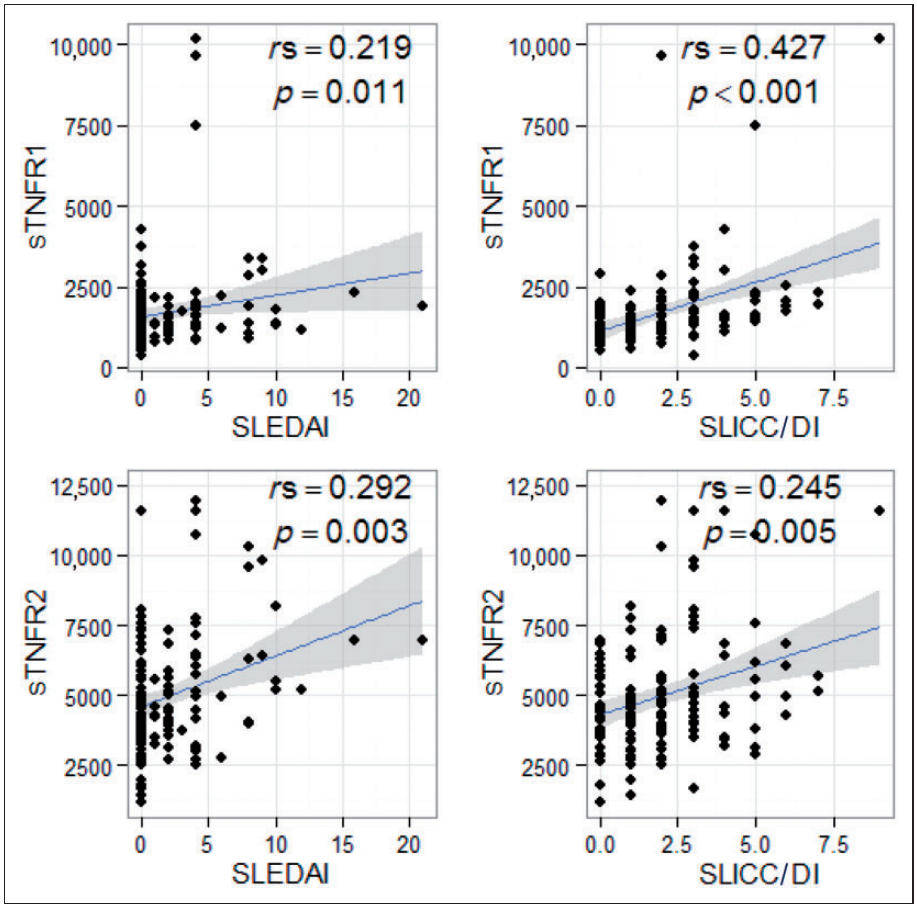

Figure 1 Positive Spearman correlation between sTNFR1 and sTNFR2 levels and disease activity and damage index.
SLEDAI: Systemic Lupus Disease Activity Index; SLICC/DI: Systemic Lupus International Collaborating Clinics Damage Index; sTNFR1: soluble TNF receptor 1; sTNFR2: soluble TNF receptor 2

Table 2 Multiple linear regression of activity and damage index with sTNFR1 and sTNFR2 of patients

	Log sTNFR1		*Log sTNFR2*	
Variable	*B (95% CI)*	p	*B (95% CI)*	p[a]
SLEDAI-2K*m*	0.02 (0.01–0.03)	0.003	0.01 (0.06–0.22)	<0.001
SLICC/DI	0.04 (0.02–0.05)	<0.001	0.03 (0.02–0.05)	<0.001

[a]Multiple linear regression. Adjusted for: age, menopause, creatinine clearance and antimalarial use.
Log: logarithmic; sTNFR1: soluble TNF receptor 1; sTNFR2: soluble TNF receptor 2; CI: confidence interval; SLEDAI-2 K*m*: Systemic Lupus Erythematosus Disease Activity Index 2000 modified (without anti-dsDNA and complement); SLICC/DI: Systemic Lupus International Collaborating Clinics Damage Index

were overweight and 31.4% were obese. A weak positive correlation was found between serum leptin levels and BMI ($rs = 0.168$; $p = 0.051$), and an inverse correlation was found between serum adiponectin levels and BMI ($rs = 0.287$; $p = 0.001$). No correlation was found between BMI and resistin levels ($rs = 0.058$; $p = 0.501$).

Regarding organ damage, there was no correlation between SLICC/SDI and serum leptin levels ($rs = -0.055$; $p = 0.528$), resistin ($rs = 0.101$; $p = 0.243$) or adiponectin ($rs = -0.062$; $p = 0.479$). Similarly, there was no association between the serum adipokines levels and disease activity (Table 2).

Higher serum adiponectin levels were correlated with thrombocytopenia [no trombocytopenia: 11.11(1.28–2.03) ng/ml vs. trombocytopenia: 19.72 (17.34–25.50) ng/ml; $p = 0.022$]; [no nephritis: 10.63 (6.79–16.52) ng/ml vs. nephritis: 16.01 (11.62–21.95) ng/ml; $p = < 0.013$]; not using antimalarial: 9.13 (5.42–14.27) ng/ml vs. using antimalarial: 12.35 (8,63–19.35) ng/ml; $p = 0.008$; [not using azathioprine: 1.71 (1.51–1.93) ng/ml vs. using azathioprine 1.93 (1.64–2.08) ng/ml; $p = 0.013$.

In the multivariate analysis, higher serum adiponectin levels were independently associated with the presence of thrombocytopenia and nephritis, and use of antimalarial drugs (Table 3).

Table 3 Multiple linear regression of adiponectin with clinical characteristics and medication of 136 patients

Variable	*B (95% CI)*	p[a]
Thrombocytopenia	0.146 (−0.016–0.530)	0.065
Nephritis	0.212 (0.044–0.297)	0.009
Antimalarial	0.196 (0.024–0.219)	0.015

[a]Multiple linear regression. Adjusted for: age, body mass index and creatinine clearance.
CI: confidence interval

TNFα, its receptors and adipokines

Leptin serum levels were correlated with sTNFR2 ($rs = 0.414$; $p = 0.002$) concentrations and resistin with sTNFR1 ($rs = 0.489$; $p < 0.001$) and sTNFR2 ($rs = 0.298$; $p < 0.001$) concentrations. The association between leptin and resistin and the TNFα receptors remained after adjustment for age, BMI, creatinine clearance, modified SLEDAI-2 K and menopause.

Discussion

In the current study, a positive association was observed between TNFα receptor levels and nephritis, arthritis, disease activity and damage index. Adiponectin levels were associated with nephritis and antimalarial drugs use, while resistin and leptin levels were associated with TNFα receptors.

Other authors have found similar association between TNFα receptors and disease activity,[4] renal[8,25] and cutaneous involvement.[26] Mahmoud et al. analyzed 44 patients and found that those with diffuse proliferative lupus nephritis exhibited the highest serum TNFα and sTNFR2 concentrations.[27] The evidence suggesting the role of TNFα in the pathogenesis of nephritis was published by Takemura et al., who demonstrated TNFα deposition in the glomeruli of patients with SLE and different types of nephritis,[28] and by Zhu et al., who detected greater TNFα gene expression in patients with class III and IV nephritis.[8]

In the present study we found an association, so far unpublished, between arthritis and the sTNFR1. This is very interesting data considering the observation of arthritis improvement during treatment of lupus patients with TNFα inhibitors.[29] We also described a reduction in sTNFR1 levels in the patients using antimalarial drugs. Sacre et al. demonstrated that the inhibition of the toll-like receptors (TLRs) TLR7 and TLR9, in dendritic cells in particular, by antimalarial drugs, could interfere with interferon γ production and consequently in TNFα release.[30]

Correlation of sTNFR1 and sTNFR2 with organ damage was shown in this study. The association of high TNFα serum levels and the accrued organ damage after five year follow-up has been previously described.[31] The highest levels of TNFα receptors might be considered a marker of worse prognosis and indicative of the persistence of inflammation in those patients with lupus who have permanent damage.

In the present study, we did not find an association between adipokines and disease activity, similar to other studies.[11,32–36] However, Almehed et al. studied 163 women with SLE and found an association between resistin and lower complement levels.[14] Regarding the damage index, contrasting with our results greater damage index has been reported in individuals with higher resistin and leptin levels.[15,33,36]

Higher levels of adiponectin were associated with the presence of nephritis and antimalarial drugs use. Others studies suggested that adiponectin might be considered a marker of renal disease activity.[37,38] Considering that this adipokine usually behaves as an anti-inflammatory cytokine, the results presented here indicate a possible counter-regulation of the immune system that would stimulate adiponectin production in response to inflammatory stimuli associated with nephritis. Furthermore, adiponectin can behave as pro-inflammatory adipokine in SLE, depending upon the isoform. The high-molecular weight isoforms, but not the low-molecular weight, induce the expression of the pro-inflammatory chemokines MCP-1 and IL-8.[37]

Positive association was established between leptin levels and azathioprine use. The role of leptin in the inflammatory response of SLE patients and its serum levels modification in response to medications is not yet established.[39]

In the present study, higher serum resistin levels were correlated with lower creatinine clearance, which was also reported by Baker et al.[33] This might be explained by the fact that resistin is mainly excreted in the urine.[40–42]

An original contribution of our study is the identification, in SLE patients, of a correlation between the adipokines' (leptin and resistin) levels and TNFα receptors. We found independent association between leptin and sTNFR2, and between resistin and both sTNFR1 and sTNFR2. The correlation of leptin and TNF system has been described in individuals without lupus.[16,17,43] Leptin can induce T cell activation and modification of T cell response to Th1 pattern, in addition

to inhibiting regulatory T cells.[10,44,45] TNFα can stimulate leptin release by adipose tissue, while leptin can increase the expression of inflammatory mediators such as TNFα.[13] It is known that resistin can induce the production of IL6, IL1β and TNFα[46] and is also elevated in inflammatory diseases like rheumatoid arthritis[47] and inflammatory bowel disease.[43]

As a limitation, we quote the cross-sectional design of the present study, which does not allow the assessment of changes in the levels of adipokines and TNF system with fluctuations of disease activity. Prospective studies are more suitable to address the relation between these two classes of molecules. We also hypothesized that the low modified SLEDAI-2 K of patients in the present study may have affected the identification of correlation between clinical manifestations and disease activity and serum levels of adipokines.

In conclusion, TNFα, its receptors and adipokines were associated with arthritis and nephritis. The sTNFR1 correlated with global activity and the organic injury of lupus, suggesting that this could be used as a marker of disease activity. Resistin and leptin were associated with higher concentrations of TNF receptors. This correlation between the two systems (adipokines and TNF system) allows a better understanding of the role of adipokines in the inflammatory response in SLE patients.

Declaration of Conflicting Interests

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