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Adipokine interactions promote the pathogenesis of systemic lupus erythematosus

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ABSTRACT

Background: Adipokines are chemical mediators released from adipose tissue involved in regulation of appetite, insulin sensitivity, immune system and inflammatory responses. Adipokines contributes to low grade inflammatory response in autoimmune disease like Systemic Lupus Erythematosus (SLE) but the pathophysiology is yet not clear. The aim of this study is to understand role of adipokine interactions in SLE disease pathogenesis. *Methods:* Sixty newly diagnosed treatment naïve SLE patients fulfilling the ACR criteria and forty age-sex matched healthy subjects were enrolled in thiscase-control study. Disease activity in SLE patients was evaluated using SELENA-SLEDAI.

Array of adipokines, C1q circulating immune complexes (C1q-CIC), anti-C1q, anti-ribososmal P0 (anti-RibP0) and anti-mitochondrial antibodies (AMA) levels were detected by ELISA. Antinuclear antibodies (ANA) and anti-dsDNA autoantibodieswere detected by Indirect Immunofluorescence (IIF), while antigen specificities were detected by Immunoassay blot. Serum levels of C3 and C4 complement factors were assessed by nephlometer. *Results:* Statistically significant elevation in progranulin, adipsin and resistin levels was seen among SLE patients when compared to healthy controls **($p < 0.0001$)**. Leptin and omentin levels were significantly reduced in SLE patients **($p < 0.0001$)**. There was no statistically significant difference in serum adiponectin, chemerin and visfatin levels when these two groups were compared **($p > 0.05$)**. Adiponectin, adipsin and resistin levels were

Abbreviations: ACR/SLICC, American College of Rheumatology/Systemic Lupus International Collaborating Clinics; AMA, Anti-mitochondrial Antibodies; Anti-dsDNA, anti-double stranded deoxynucleic acid; Anti-RibP0, anti-ribosomal P0; ANA, Antinuclear Antibody; BUN, Blood Urea Nitrogen; C1q-CIC, C1q Circulating Immune Complexes; CKD, Chronic Kidney Disease; DC, Dendritic cells; ENA, Extractable Nuclear Antigen; ESRD, End Stage Renal Disease; ESRF, End Stage Renal Failure; GFR, Glomerular Filteration Rate; HEp-2, Human Epithelial type 2; IIF, Indirect Immunofluorescence; LN, Lupus Nephritis; MRL/lpr, MRL lymphoproliferation strain; pDCs, plasmacytoid Dendritics cells; SLE, Systemic Lupus Erythematosus; Sm, Smith; sVCAM-1, soluble Vascular Cell Adhesion Molecule-1

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elevated in SLE patients with renal manifestations **(p < 0.05)**. Reduced leptin levels were significantly associated with presence of renal manifestations **(p < 0.05)**. Adiponectin levels positively correlated with disease activity **(r = 0.294, p = 0.027)** whereas negatively correlated with C3 levels **(r = −0.439, p = 0.0007)**. A positive correlation was observed between hypocomplementemia and leptin levels **(p < 0.05)**. Leptin levels were negatively correlated with disease activity, anti-dsDNA, C1q-CIC and anti-C1q levels **(p < 0.05)**. A significant positive correlation was observed between progranulin levels and anti-ribosomal P0 antibodies **(r = 0.499, p < 0.0001)**.

Conclusion: Adipokines levels and associated clinical manifestations suggest involvement of adipokines in disease pathogenesis of SLE. SLE disease activity and complement components may suggest regulatory effect of adipokines (adiponectin and leptin) on disease pathogenesis. Further studies on adipokines in SLE patients with renal manifestations may propose them as prognostic markers in renal damage.

Trial Registration: NA

1. Introduction

Systemic Lupus Erythematosus (SLE) is a chronic autoimmune disease affecting multiple organs by autoantibody production against self leading to formation of immune complexes. Inflammatory responses in SLE result in imbalance of pro-and anti-inflammatory cytokines. Environmental triggers, genetic predisposition, microbiological invasion, cardiovascular disorders, hormonal imbalances and metabolic disturbances are some of the stated predisposing factors for disease onset [1]. Fat storing adipose tissue has been recently linked to insulin resistance, atherosclerosis, metabolic syndrome and inflammatory immune responses [2,3]. Adipocytokines, or simply referred as adipokines are the endocrine mediators secreted from adipose tissue. Extensive studies on these adipokines have exhibited active participation of these mediators in rheumatic and other inflammatory diseases [4].

Adipokines like adiponectin and leptin originate exclusively from adipose tissue, whereas origin of resistin and visfatin is highly debated [5]. Pro-inflammatory mediators like TNF-α, IL-6, chemokines and complement components are not only secreted from different cells like endothelial cells, lymphocytes but also have origin from adipose tissue [6,7]. Adipokines are the pro- or anti-inflammatory mediators that play an important role in regulation of appetite, glucose metabolism, fat metabolism, vascular haemostasis, immune responses and inflammatory processes [8,9]. Imbalances in the expression of these adipokines have been linked to obesity and metabolic syndrome that may act as an initial predisposing factor for onset of autoimmune disease [10]. Several adipokines have been studied for their pathogenesis and associations with disease severity in autoimmune diseases like rheumatoid arthritis and SLE but the results have been confounding [11–13].

Though various adipokines have been studied for their different aspects in inflammatory autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis, psoriasis and inflammatory bowel diseases; their association with disease activity and pathophysiological role is still not fully understood [5,14]. In this study, we investigate adiponectin, leptin, progranulin, adipsin, omentin, chemerin, resistin and visfatin and their association with disease severity and immunological parameters to understand disease pathogenesis among Indian SLE patients.

2. Materials and methods

2.1. Study participants

Newly diagnosedSLE patients (n = 60) fulfilling the 2015 ACR-SLICC Revised Criteria for diagnosis of SLE [15] were enrolled from the Department of Rheumatology, King Edward Memorial Hospital, Parel, Mumbai, India over the period of two years (2015–2017). All these patients were treatment naïve at the time of evaluation. Patients with diabetes, malignancies, contemporaneous infections, cardiovascular complications and pregnancy were excluded from this study. Age and sex matched forty normal healthy individuals were also enrolled. Ethical approval was obtained from Ethics Committee of National Institute of Immunohaematology (ICMR-NIIH), Mumbai, India. Written consent form was obtained from these patients at the time of blood withdrawal. Disease activity of SLE patients was assessed using SELENA-SLEDAI [15].

2.2. Sample collection and laboratory testing

Five millilitres of overnight fasting venous blood sample was collected in clot activating vacutainer. Sera were separated by centrifugation and stored at −70 °C until further analysis. Serum adiponectin levels (Biovendor, Brno, Czech Republic) and leptin levels (DRG, NJ, USA) were assessed by ELISA. Serum progranulin, adipsin, omentin, chemerin, resistin and visfatin levels were measured by ELISA (Raybiotech, GA, USA). Anti-nuclear antibodies (ANA) and dsDNA antibodies were detected by indirect immunofluorescence (IFA) technique using HEp-2 cells (Biorad, USA) and Crithidia lucillae (AESKU, Germany) respectively. ANA profile was detected by LINE Blot assay whereas anti-dsDNA and anti-RibP0 antibodies were detected by ELISA

Table 1
Demographic details and clinical characteristics of SLE patients.

Demographic details	**(n = 60)**
Sex ratio (Female:Male)	10:1
Age at onset (years)	26.98 ± 8.44
Age at evaluation (years)	28.53 ± 8.70
SELENA-SLEDAI score	15 ± 6
Clinical manifestations	**n (%)**
Malar/Discoid rash	27 (45)
Photosensitivity	21 (36)
Alopecia	26 (43)
Oral ulcers	35 (58)
Arthritis	46 (76)
Serositis	12 (20)
Neurological disorders	04 (6)
Renal involvement	33 (55)
Haematological disorders	38 (63)
Immunological parameters	**n (%)**
ANA positivity	60 (1 0 0)
dsDNA positivity	46 (76)
Sm positivity	17 (28)
ENA positivity	42 (70)
Low C3 levels	42 (70)
Low C4 levels	38 (63)

ACR/SLICC - American College of Rheumatology/Systemic Lupus International Collaborating Clinics; Serositis includes pleuritis& pericarditis; Renal involvement includes proteinuria ≥ 3 + or ≥ 500 mg/day; Haematological involvement includes < 4000/mm^3 WBC count or thrombocytopenia < 100,000/mm^3 or haemolytic anemia. Low C3 and C4 levels were considered as < 90 mg/dl and < 15 mg/dl respectively. Qualitative variables are expressed as frequencies (%).