Clinical Study

Obesity and Cytokines in Childhood-Onset Systemic Lupus Erythematosus

Nailú Angélica Sinicato, 1 Mariana Postal, 2 Fernando Augusto Peres, 2
Karina de Oliveira Pelçari, 2 Roberto Marini, 3 Allan de Oliveira dos Santos, 4
Celso Dario Ramos, 4 and Simone Appenzeller 1, 2

1 Faculty of Medical Science, State University of Campinas, Cidade Universitaria, 13083-970 Campinas, SP, Brazil
2 Rheumatology Unit, Department of Medicine, Faculty of Medical Science, State University of Campinas, Cidade Universitária, 13083-970 Campinas, SP, Brazil
3 Department of Pediatrics, Faculty of Medical Science, State University of Campinas, Cidade Universitaria, 13083-970 Campinas, SP, Brazil
4 Department of Radiology, Nuclear Medicine Division, State University of Campinas, Cidade Universitaria, 13083-970 Campinas, SP, Brazil

Correspondence should be addressed to Simone Appenzeller; appenzellersimone@gmail.com

Received 28 July 2013; Revised 18 October 2013; Accepted 1 November 2013; Published 3 March 2014

1. Introduction

Systemic lupus erythematosus (SLE) is a chronic systemic inflammatory disease affecting mainly women during childbearing age [1]. Although life expectancy has improved significantly, no changes in morbidity and mortality related to cardiovascular disease (CVD) have been observed in SLE patients in the past decades [2, 3]. In addition to traditional risk factors, many lupus-specific factors are linked to the increased risk of CVD observed in SLE [4–6].

Obesity-associated systemic inflammation is characterized by increased circulating proinflammatory cytokines and activation of several kinases that regulate inflammation [7–9]. Recent evidence supports that obesity-induced inflammation is mediated primarily by immune cells such as the macrophages and T lymphocytes present in metabolic tissues [9]. Adipose tissue derived cells can produce inflammatory cytokines, such as tumor necrosis factor alpha (TNF-α), interleukin (IL) 6, and IL-10 [10, 11].

TNF-α and IL-6 are proinflammatory cytokines associated with an increased insulin resistance, inhibition of insulin receptor autophosphorylation, and signal transduction. These mechanisms lead to insulin resistance,
hyperglycemia, and dyslipidemia [12–18]. IL-10 is also known as an antiatherogenic cytokine. Upregulation of IL-10 locally or systemically reduces atherosclerosis development in mouse models [13–15].

The aim of this study was to evaluate the association between obesity, measures of body fat content, and serum TNF-α, IL-6, and IL-10 in cSLE.

2. Patients and Methods

2.1. Subjects. Fifty-two consecutive cSLE patients, recruited from the Pediatric Rheumatology Outpatient Clinic of the State University of Campinas were included in this study. Patients were included in the present study if they (i) fulfilled at least four criteria of the American College of Rheumatology (ACR) [19]; (ii) were below 18 years of age at disease onset; and (iii) had a follow-up duration of at least 6 months (time necessary to evaluate damage index).

Fifty-two healthy volunteers (caregivers or students) matched by age, gender, and sociodemographic characteristics were included as a control group. None of the controls had any history of chronic disease, including autoimmune diseases.

This study was approved by the ethics committee at our institution, and the informed written consent was obtained from each participant and/or legal guardian.

2.2. Clinical Features. All patients had their medical histories and clinical, and serological characteristics entered at the time of cSLE diagnosis into special computer database programs. Features included in this protocol were age at the onset of disease (defined as the age at which the first symptoms clearly attributable to SLE occurred), age at diagnosis (defined as the age when patients fulfilled four or more of the 1987 revised criteria for the classification of SLE [19]), and follow-up time (defined as the time from disease onset until December 2012).

Total doses and length of use of the corticosteroids since the onset of disease were calculated by careful review of the medical charts. Doses of oral and parenteral corticosteroids were converted to the equivalent doses of prednisone. The cumulative dose of corticosteroids used was calculated by the sum of the daily dosages versus the time (days) of treatment. We also calculated the cumulative corticosteroid dose adjusted by weight by summing up the daily corticosteroid dose per weight at each routine visit.

2.3. Disease Activity and Cumulative Damage. Disease activity was measured by the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) [20]. SLEDAI scores range between 0 and 105, and the scores of ≥3 were considered as active disease [21]. Adjusted SLEDAI scores over time were calculated by careful review of the medical charts and preview exams [22]. Cumulative SLE-related damage in all patients was determined by using the Systemic Lupus International Collaborating Clinics (SLICC)/ACR Damage Index (SDI) [23].

2.4. Body Mass Index. Body mass index (BMI) was calculated as weight (kg) divided by height (m) squared (kg/m²).

Criteria used to define nutritional status were based on the World Health Organization (WHO) criteria [24]. BMI cutoff points for Brazilian children and adolescents were used for individuals between 2 and 18 years [25]. Obesity was considered when BMI was above 30 Kg/m².

2.5. Dual X-Ray Absorptiometry (DXA). Percentual body fat (PBF), fat mass, and lean mass were obtained by DXA scan (Hologic Discovery Wii), through Whole Body Auto Fan Beam. This scan determines total fat mass and total lean mass in kilograms in addition to total fat mass and total lean mass as a percentage of total body mass.

2.6. Blood Sampling. Blood samples were collected from peripheral veins of all individuals in dry tubes and left to clot at room temperature for 30 minutes. Blood samples were then centrifuged for 15 minutes at 3000 rpm, and the serum was then stored in aliquots at −80°C for future use. We did not collect blood samples from individuals during an episode of acute or chronic infection.

2.7. Cytokine Assay. Commercially available kits from R&D Systems (London, UK) were used for the measurement of serum TNF-α, IL-6, and IL-10 levels by enzyme-linked immunosorbent assay (ELISA), carried out in accordance with the manufacturer’s instructions. The minimum detectable dose (MDD) was 0.106 pg/mL for TNF-α, 0.039 pg/mL for IL-6, and 3.9 pg/mL for IL-10.

2.8. Statistical Analysis. All the data were tested for their normal distribution (Kolmogorov-Smirnov test). Categorical variables were compared by χ² test. Nonnormal variables were compared by Fisher exact tests. Mann-Whitney U test was used to compare anthropometric measure and laboratory studies between patients and controls. Spearman’s correlation was used to correlate continuous variables (e.g., TNF-α levels, SLEDAI, and SDI scores). For all analyses, P value ≤ 0.05 was considered to be statistically significant. Statistical analysis was carried out using IBM SPSS Statistics 16.0 software (SPSS/IBM, Chicago, IL, USA).

3. Results

3.1. Demographics. We included 52 consecutive cSLE patients. Forty-seven (90.3%) were women with mean age of 17.6 years (standard deviation (SD) ± 3.7 years). Mean disease duration was 5.14 years (SD ± 4.05). The control group consisted of 52 controls (47 women) with mean age of 18.2 years (SD ± 6.4). Patients and healthy controls were statistically comparable in terms of age and sex (Table 1).

3.2. BMI Analyses. BMI was similar between patients (median 21.74 kg/m²; range: 16.1–31.12 kg/m²) and controls (median 21.43 kg/m²; range: 14.36–28.54 kg/m²) (P = 0.101). Sixteen (31%) cSLE patients were overweight compared to 6 (11.5%) controls (P = 0.018).
We did not observe an association between BMI and SLEDAI, SDI, and cumulative corticosteroid dose.

### 3.3. Body Composition Analysis

On whole body analysis, we observed a median fat mass of 22.38 kg (range: 7.67 kg–36.62 kg), a median lean mass of 35.49 kg (range: 25.31 kg–52.14 kg), and a median PBF of 34.1% (range: 12.1%–54.4%) in cSLE. In the trunk region we observed a median fat mass of 8.62 kg (range 2.98 kg–17.59 kg), median lean mass of 16.80 kg (range: 11.24 kg–26.19 kg) and a PBF of 42.3% (range: 12.1%–54.4%).

### 3.4. Cytokine Assay

Serum TNF-α (P = 0.004), IL-6 (P = 0.002), and IL-10 (P < 0.001) levels were significantly increased in cSLE patients when compared to healthy controls (Table 2). We observed higher serum TNF-α levels in obese cSLE patients when compared to nonobese cSLE patients (P = 0.036), obese controls (P = 0.039) and nonobese controls (P < 0.0001) (Table 3). No difference in serum TNF-α levels was observed between obese and non-obese healthy controls (P > 0.05). We observed an association between TNF-α and PBF (P = 0.046) and total fat mass on trunk region (P = 0.035) analyzed by DXA scans.

No association between serum IL-6 and IL-10 levels and SLEDAI or SDI scores was observed. In addition, no difference in these cytokine levels in cSLE patients and controls with and without obesity was observed.

### 4. Discussion

Adipose tissue is known to be capable of secreting cytokines such as TNF-α, IL-6, and IL-10. Therefore, the purpose of this study was to assess whether the levels of these cytokines were increased in obese cSLE when compared to nonobese cSLE and healthy controls.

The observation that obese cSLE patients had higher serum TNF-α levels when compared to nonobese cSLE and healthy controls is the major finding of our study. In addition, we observed that serum TNF-α levels correlated with PBF and total fat mass in trunk region in cSLE.

Recent studies have demonstrated that increased adipose tissue mass contributes towards an increase in chronic inflammation [26, 27]. Chronic inflammation is further enhanced by inflammatory markers produced in the liver and other organs [28]. Recently, it has been demonstrated that obesity is associated with a low-grade inflammatory process, characterized by increased circulating levels of proinflammatory cytokines such as TNF-α, IL-6, and acute-phase proteins (CRP) [29–32]. The mechanism underlying increased inflammation in the setting of obesity remains unclear, but it is known that mononuclear cells are activated and proinflammatory cytokines are upregulated in obese individuals [33, 34].

We observed an association between serum TNF-α levels and PBF and total fat mass in trunk region. Studies analyzing the association between serum TNF-α and DXA scans have not been reported in cSLE so far, but studies on healthy women and type-2 diabetes patients showed an association between plasma levels of TNF-α and visceral adipose tissue volume measured by CT-scan [35–38]. Previous studies have shown that visceral fat accumulation is associated with increased risk of CV risk [37]. In addition, with an increase in TNF-α, a reduction in lipoprotein lipase activity in adipose tissue is observed [39]. There is also evidence that TNF-α has a local effect, regulating adipocyte size in the face of increasing energy consumption [40, 41].

Cytokines, such as TNF-α and IL-6, are primarily involved in the early stages of the inflammatory response culminating in atherosclerosis [39, 42]. Increased TNF-α levels in the endothelium promote initial atheroma plaque [39, 42]. However, so far, studies were not able to conclude whether TNF-α is a causative factor of atherosclerosis.

Both IL-6 and TNF-α are expressed and secreted by human adipose tissue [43]. In obesity, increased secretion of IL-6 may contribute to metabolic dysfunction [44, 45]. In addition, one previous study has shown that IL-6 correlated positively with BMI and with measures of insulin resistance in abdominal obese male subjects [45]. As previously described in adults SLE patients, we observed higher IL-6 and IL-10 levels in cSLE patients when compared to healthy controls [46–49]. However, no association with BMI was observed in our cSLE cohort.

IL-10 downregulates inflammatory activation of monocytes and macrophages by transcriptional and posttranscriptional inhibition of the entire range of proinflammatory cytokines [50]. IL-10 has been shown to reduce atherosclerosis and it can be found in atheromatous plaque due to local macrophages production [50]. However, IL-10 is involved in SLE pathogenesis and it is increased in SLE patients with CVD compared to SLE patients without CVD [51, 52]. In our study, we did not observe an association between sera IL-10 levels and obesity.
We also did not observe an association between sera IL-6 levels and obesity. In the literature, it has been described that plasma IL-6 levels are associated with increased CV risk and observed in SLE patients with metabolic syndrome [53] and in patients with type 2 diabetes [44, 54]. In a large healthy family population study where children were included, IL-6 levels were closely associated with traditional and nontraditional risk factors for atherosclerosis [55].

Although cSLE is rare, it is important to consider that one limitation of our study is the small number of patients and controls included.

Corticosteroids are associated with weight gain due to increased appetite and fluid retention. Corticosteroids also cause a redistribution of fat deposition, occurring predominantly in the trunk and face [56–59]. However, we did not observe an association between serum TNF-α, IL-6, and IL-10 levels and corticosteroid dose.

To the best of our knowledge, this is the first study to evaluate the association of BMI, body composition and serum TNF-α, IL-6, and IL-10 levels in cSLE patients. Although these cytokines have been shown to be associated with CVD in other populations, we only observed an association between serum TNF-α levels and obesity, and PBF and total fat mass in trunk region. Our findings suggest that total fat mass may contribute to increased levels of serum TNF-α levels in cSLE.

**Conflict of Interests**

The authors declare that there is no conflict of interests regarding the publication of this paper.

**Acknowledgments**

The authors thank Fundação de Amparo à Pesquisa do Estado São Paulo-Brasil (FAPESP 2008/02917-0 and 2010/13637-9 and 2011/03788-2), Conselho Nacional Pesquisa Desenvolvimento-Brasil CNPq (300447/2009-4 e 471343/2011-0 e 302205/2012-8).

**References**

[1] N. Danchenko, J. A. Satia, and M. S. Anthony, “Epidemiology of systemic lupus erythematosus: a comparison of worldwide disease burden,” *Lupus*, vol. 15, no. 5, pp. 308–318, 2006.

[2] M. Merrell and L. E. Shulman, “Determination of prognosis in chronic disease, illustrated by systemic lupus erythematous,” *Journal of Chronic Diseases*, vol. 1, no. 1, pp. 12–32, 1955.

[3] E. Svenungsson, K. Jensen-Urstad, M. Heimbürger et al., “Risk factors for cardiovascular disease in systemic lupus erythematous,” *Circulation*, vol. 104, no. 16, pp. 1887–1893, 2001.

[4] P. Poirier, T. D. Giles, G. A. Bray et al., “Obesity and cardiovascular disease: pathophysiology, evaluation, and effect of weight loss: an update of the 1997 american heart association scientific statement on obesity and heart disease from the obesity committee of the council on nutrition, physical activity, and metabolism,” *Circulation*, vol. 113, no. 6, pp. 898–918, 2006.

[5] Z. Wang and T. Nakayama, “Inflammation, a link between obesity and cardiovascular disease,” *Mediators of Inflammation*, vol. 2010, Article ID 535918, 17 pages, 2010.

[6] G. Fantuzzi and T. Mazzone, “Adipose tissue and atherosclerosis: exploring the connection,” *Arteriosclerosis, Thrombosis, and Vascular Biology*, vol. 27, no. 5, pp. 996–1003, 2007.

[7] A. Melmer, C. Lamina, A. Tschoner et al., “Body adiposity index and other indexes of body composition in the SAPPHIR study: association with cardiovascular risk factors,” *Obesity*, vol. 21, no. 4, pp. 775–781, 2013.

[8] B. Parker and I. N. Bruce, “The metabolic syndrome in systemic lupus erythematous,” *Rheumatic Diseases Clinics of North America*, vol. 36, no. 1, pp. 81–97, 2010.

[9] T. Ota, “Chemokine systems link obesity to insulin resistance,” *Journal of Diabetes & Metabolism*, vol. 37, no. 3, pp. 165–172, 2013.

[10] M. Postal and S. Appenzeller, “The role of Tumor Necrosis Factor-alpha (TNF-α) in complex cytokine effects in a complex autoimmune disease: tumor necrosis factor in systemic lupus erythematous,” *Arthritis Research & Therapy*, vol. 5, pp. 172–177, 2003.

[11] J. T. Cross and H. P. Benton, “The roles of interleukin-6 and interleukin-10 in B cell hyperactivity in systemic lupus erythematous,” *Inflammation Research*, vol. 48, no. 5, pp. 255–261, 1999.

[12] A. G. Pittas, N. A. Joseph, and A. S. Greenberg, “Adipocytokines and insulin resistance,” *Journal of Clinical Endocrinology and Metabolism*, vol. 89, no. 2, pp. 447–452, 2004.

[13] P. Welsh, H. M. Murray, I. Ford et al., “Circulating interleukin-10 and risk of cardiovascular disease events: a prospective study in the elderly at risk,” *Arteriosclerosis, Thrombosis, and Vascular Biology*, vol. 31, no. 10, pp. 2338–2344, 2011.

[14] L. J. Pinderski, M. P. Fischbein, G. Subbanagounder et al., “Overexpression of interleukin-10 by activated T lymphocytes

---

**Table 3: Cytokines levels and therapy information from subjects subdivided into obese and nonobese.**

| Cytokines levels     | Obese cSLE N = 16 | Nonobese cSLE N = 36 | Obese controls N = 7 | Nonobese controls N = 45 |
|----------------------|------------------|----------------------|----------------------|--------------------------|
| TNF-α (pg/mL)        | 3.1 (1–11.1)*    | 1.8 (0.8–11.1)       | 1.3 (0.5–2.1)        | 1.2 (0.2–3.9)            |
| IL-6 (pg/mL)         | 1.4 (0.3–6.9)    | 1.4 (0.3–9.7)        | 0.9 (0.4–5.9)        | 0.9 (0.3–3.6)            |
| IL-10 (pg/mL)        | 16.7 (7.6–26.3)  | 13.6 (3.9–39.7)      | 4.9 (3.9–6)          | 5.6 (3.5–9.5)            |

Therapy

| CE dose (mean ± SD)  | 17.3 ± 19.8      | 18.3 ± 19.8          | —                    | —                        |
| CE/Kg (mean ± SD)    | 535.1 ± 339.5    | 444.5 ± 245.9        | —                    | —                        |
| CE cumulative (mean ± SD) | 28036.7 ± 17611.5 | 23057 ± 16568.7       | —                    | —                        |

The cytokine data were given in median (range). *P < 0.05.
inhibits atherosclerosis in LDL receptor-deficient mice by altering lymphocyte and macrophage phenotypes,” *Circulation Research*, vol. 90, no. 10, pp. 1064–1071, 2002.

[15] J. H. V. D. Thüsen, J. Kuiper, M. L. Fekkes, P. De Vos, T. J. Van Berkel, and E. A. Biessen, “Attenuation of atherogenesis by systemic and local adenosinemediated gene transfer of interleukin-10 in LDLr−/− mice,” *The FASEB Journal*, vol. 15, no. 14, pp. 2730–2732, 2001.

[16] M. Coelho, T. Oliveira, and R. Fernandes, “Biochemistry of adipose tissue: an endocrine organ,” *Archives of Medical Science*, vol. 9, no. 2, pp. 191–200, 2013.

[17] C. Grunfeld, R. Gulli, A. H. Moser, L. A. Gavin, and K. R. Feingold, “Effect of tumor necrosis factor administration in vivo on lipoprotein lipase activity in various tissues of the rat,” *Journal of Lipid Research*, vol. 30, no. 4, pp. 579–585, 1989.

[18] K. R. Feingold, M. Soued, I. Staprans et al., “Effect of Tumor Necrosis Factor (TNF) on lipid metabolism in the diabetic rat. Evidence that inhibition of adipose tissue lipoprotein lipase activity is not required for TNF-induced hyperlipidemia,” *Journal of Clinical Investigation*, vol. 83, no. 4, pp. 1116–1121, 1989.

[19] M. C. Hochberg, “Updating the american college of rheumatology revised criteria for the classification of systemic lupus erythematosus,” *Arthritis and Rheumatism*, vol. 40, no. 9, p. 1725, 1997.

[20] C. Bombardier, D. D. Gladman, M. B. Urowitz et al., “Derivation of the SLEDAI: a disease activity index for lupus patients,” *Arthritis and Rheumatism*, vol. 35, no. 6, pp. 630–640, 1992.

[21] C.-S. Yee, V. T. Farewell, D. A. Isenberg et al., “The use of systemic lupus erythematosus disease activity index-2000 to define active disease and minimal clinically meaningful change based on data from a large cohort of systemic lupus erythematosus patients,” *Rheumatology*, vol. 50, no. 5, pp. 982–988, 2011.

[22] D. Ibañez, M. B. Urowitz, and D. D. Gladman, “Summarizing disease features over time: I. Adjusted mean SLEDAI derivation and application to an index of disease activity in lupus,” *Journal of Rheumatology*, vol. 30, no. 9, pp. 1977–1982, 2003.

[23] D. Gladman, E. Ginzler, C. Goldsmith et al., “The development and initial validation of the systemic lupus international collaborating clinics/american college of rheumatology damage index for systemic lupus erythematosus,” *Arthritis and Rheumatism*, vol. 39, no. 3, pp. 363–369, 1996.

[24] World Health Organization, “Obesity: preventing and managing the global epidemic,” WHO Technical Report Series no. 894, 2000.

[25] W. L. Conde and C. A. Monteiro, “Body mass index cutoff points for evaluation of nutritional status in brazilian children and adolescents,” *Jornal de Pediatria*, vol. 82, no. 4, pp. 266–272, 2006.

[26] H. Rodríguez-Hernández, L. E. Simental-Mendia, G. Rodríguez-Ramírez, and M. A. Reyes-Romero, “Obesity and inflammation: epidemiology, risk factors and markers of inflammation,” *International Journal of Endocrinology*, vol. 2013, Article ID 678159, 11 pages, 2013.

[27] G. S. Hotamisligil, “Inflammation and metabolic disorders,” *Nature*, vol. 444, no. 7121, pp. 860–867, 2006.

[28] R. O. Escárcega, M. García-Carrasco, S. Fuentes-Alexandro et al., “Insulin resistance, chronic inflammatory state and the link with systemic lupus erythematosus-related coronary disease,” *Autoimmunity Reviews*, vol. 6, no. 1, pp. 48–53, 2006.

[29] F. X. Pi-Sunyer, “The obesity epidemic: pathophysiology and consequences of obesity,” *Obesity Research*, vol. 10, no. 2, pp. 975–1043, 2002.

[30] A. E. Caballero, “Endothelial dysfunction in obesity and insulin resistance: a road to diabetes and heart disease,” *Obesity Research*, vol. 11, no. 11, pp. 1278–1289, 2003.

[31] A. H. Berg and P. E. Scherer, “Adipose tissue, inflammation, and cardiovascular disease,” *Circulation Research*, vol. 96, no. 9, pp. 939–949, 2005.

[32] D. C. W. Lau, B. Dhillon, H. Yan, P. E. Szmitko, and S. Verma, “Adipokines: molecular links between obesity and atherosclerosis,” *American Journal of Physiology—Heart and Circulatory Physiology*, vol. 288, no. 5, pp. H2031–H2041, 2005.

[33] A. Oeser, C. P. Chung, Y. Asanuma, I. Avalos, and C. M. Stein, “Obesity is an independent contributor to functional capacity and inflammation in systemic lupus erythematosus,” *Arthritis and Rheumatism*, vol. 52, no. 11, pp. 3651–3659, 2005.

[34] H. Ghanim, A. Aljada, D. Hofmeyer, T. Syed, P. Mohanty, and P. Dandonia, “Circulating mononuclear cells in the obese are in a proinflammatory state,” *Circulation*, vol. 110, no. 12, pp. 1564–1571, 2004.

[35] M. Garaulet, F. Perez-Llamas, T. Fuente, S. Zamora, and F. J. Tebar, “Anthropometric, computed tomography and fat cell data in an obese population: relationship with insulin, leptin, tumor necrosis factor-alpha, sex hormone-binding globulin and sex hormones,” *European Journal of Endocrinology*, vol. 143, no. 5, pp. 657–666, 2000.

[36] A. Katsuki, Y. Sumida, S. Murashima et al., “Serum levels of tumor necrosis factor-α are increased in obese patients with noninsulin-dependent diabetes mellitus,” *Journal of Clinical Endocrinology and Metabolism*, vol. 83, no. 3, pp. 859–862, 1998.

[37] E. Bertin, P. Nguyen, M. Guenonou, V. Durlach, G. Potron, and M. Leutenegger, “Plasma levels of Tumor Necrosis Factor-alpha (TNF-α) are essentially dependent on visceral fat amount in type 2 diabetic patients,” *Diabetes and Metabolism*, vol. 26, no. 3, pp. 178–182, 2000.

[38] M. Pedersen, H. Bruunsgaard, N. Weis et al., “Circulating levels of TNF-alpha and IL-6–relation to truncal fat mass and muscle mass in healthy elderly individuals and in patients with type-2 diabetes,” *Mechanisms of Ageing and Development*, vol. 124, no. 4, pp. 495–502, 2003.

[39] L. P. Luz and D. Favaro, “Chronic cardiac disease,” *Arquivos Brasileiros de Cardiologia*, vol. 72, pp. 5–21, 1999.

[40] P. A. Kern, M. Saghizadeh, J. M. Ong, R. J. Bosch, R. Deem, and R. B. Simoso, “The expression of tumor necrosis factor in human adipose tissue. Regulation by obesity, weight loss, and relationship to lipoprotein lipase,” *Journal of Clinical Investigation*, vol. 95, no. 5, pp. 2111–2119, 1995.

[41] G. S. Hotamisligil, P. Arner, J. F. Caro, R. L. Atkinson, and B. M. Spiegelman, “Increased adipose tissue expression of tumor necrosis factor-α in human obese tissue. Regulation by obesity, weight loss, and relationship to lipoprotein lipase,” *Journal of Clinical Investigation*, vol. 95, no. 5, pp. 2409–2415, 1995.

[42] A. Wykretowicz, J. Furmaniuk, J. Smielecki et al., “The oxygen stress index and levels of circulating interleukin-10 and interleukin-6 in patients with chronic heart failure,” *International Journal of Cardiology*, vol. 94, no. 2–3, pp. 283–287, 2004.

[43] P. A. Kern, M. Saghizadeh, J. M. Ong, R. J. Bosch, R. Deem, and R. B. Simoso, “The expression of tumor necrosis factor in human adipose tissue. Regulation by obesity, weight loss, and relationship to lipoprotein lipase,” *Journal of Clinical Investigation*, vol. 95, no. 5, pp. 2111–2119, 1995.
6

Journal of Immunology Research

[44] V. Mohamed-Ali, S. Goodrick, A. Rawesh et al., “Subcutaneous adipose tissue releases interleukin-6, but not tumor necrosis factor-α, in vivo,” *Journal of Clinical Endocrinology and Metabolism*, vol. 82, no. 12, pp. 4196–4200, 1997.

[45] J. M. Bruun, C. Verdich, S. Toubro, A. Astrup, and B. Richelsen, “Association between measures of insulin sensitivity and circulating levels of interleukin-8, interleukin-6 and tumor necrosis factor-α. Effect of weight loss in obese men,” *European Journal of Endocrinology*, vol. 148, no. 5, pp. 535–542, 2003.

[46] M. Linker-Israeli, R. J. Deans, D. J. Wallace, J. Prehn, T. Ozeri-Chen, and J. R. Klinenberg, “Elevated levels of endogenous IL-6 in systemic lupus erythematosus: a putative role in pathogenesis,” *Journal of Immunology*, vol. 147, no. 1, pp. 117–123, 1991.

[47] Y. B. Park, S. K. Lee, D. S. Kim, J. Lee, C. H. Lee, and C. H. Song, “Elevated interleukin-10 levels correlated with disease activity in systemic lupus erythematosus,” *Clinical and Experimental Rheumatology*, vol. 18, no. 5, pp. 565–570, 2000.

[48] C. Skamra and R. Ramsey-Goldman, “Management of cardiovascular complications in systemic lupus erythematosus,” *International Journal of Clinical Rheumatology*, vol. 5, no. 1, pp. 75–100, 2010.

[49] A. M. Beebe, D. J. Cua, and R. De Waal Malefyt, “The role of interleukin-10 in autoimmune disease: Systemic Lupus Erythematosus (SLE) and multiple sclerosis (MS),” *Cytokine and Growth Factor Reviews*, vol. 13, no. 4-5, pp. 403–412, 2002.

[50] N. Haddy, C. Sass, S. Droesch et al., “IL-6, TNF-α and atherosclerosis risk indicators in a healthy family population: the STANISLAS cohort,” *Atherosclerosis*, vol. 170, no. 2, pp. 277–283, 2003.

[51] Lupus Fundation of America, 2013, http://www.lupus.org/.

[52] The American College of Rheumatology Ad Hoc Committee on Systemic Lupus Erythematosus Guidelines, “Guidelines for referral and management of systemic lupus erythematosus in adults,” *Arthritis & Rheumatism*, vol. 42, no. 9, pp. 1785–1796, 1999.

[53] J. M. Sabio, J. Vargas-Hitos, M. Zamora-Pasadas et al., “Metabolic syndrome is associated with increased arterial stiffness and biomarkers of subclinical atherosclerosis in patients with systemic lupus erythematosus,” *Journal of Rheumatology*, vol. 36, no. 10, pp. 2204–2211, 2009.

[54] S. K. Fried, D. A. Bunkin, and A. S. Greenberg, “Omental and subcutaneous adipose tissues of obese subjects release interleukin-6: depot difference and regulation by glucocorticoid,” *Journal of Clinical Endocrinology and Metabolism*, vol. 83, no. 3, pp. 847–850, 1998.

[55] N. Haddy, C. Sass, S. Droesch et al., “IL-6, TNF-α and atherosclerosis risk indicators in a healthy family population: the STANISLAS cohort,” *Atherosclerosis*, vol. 170, no. 2, pp. 277–283, 2003.

[56] Lupus Fundation of America, 2013, http://www.lupus.org/.

[57] The American College of Rheumatology Ad Hoc Committee on Systemic Lupus Erythematosus Guidelines, “Guidelines for referral and management of systemic lupus erythematosus in adults,” *Arthritis & Rheumatism*, vol. 42, no. 9, pp. 1785–1796, 1999.

[58] G. K. Bertsiass, J. P. A. Ioannidis, J. Boletis et al., “EULAR recommendations for the management of systemic lupus erythematosus. Report of a task force of the EULAR standing committee for international clinical studies including therapeutics,” *Annals of the Rheumatic Diseases*, vol. 67, no. 2, pp. 195–205, 2008.

[59] W. Maidhof and O. Hilas, “Lupus: an overview of the disease and management options,” *Pharmacy and Therapeutics*, vol. 37, no. 4, pp. 240–246, 2012.