Türk Biyokimya Dergisi [Turkish Journal of Biochemistry–Turk J Biochem] 2011; 36 (1) ; 35–42.

Research Article [Araştırma Makalesi]

Yayın tarihi 15 Mart, 2011 © TurkJBiochem.com

[Published online 15 March, 2011]

Serum Adiponectin and Vaspin Levels in Systemic Sclerosis

[Sistemik sklerozda serum adiponektin ve vaspin düzeyleri]

Metin Ozgen[1],
Suleyman Serdar Koca[1],
Bahar Isik[2],
Baris Gundogdu[1],
Bilal Ustundag[3],
Ahmet Isik[1]

[1]Firat University, Faculty of Medicine, Department of Rheumatology, Elazig, TURKEY
[2]Diskapi Yildirim Beyazit Education and Research Hospital, Department of Emergency Medicine, Ankara, TURKEY
[3]Firat University, Faculty of Medicine, Department of Biochemistry, Elazig, TURKEY

Yazışma Adresi
[Correspondence Address]

Süleyman Serdar Koca

Firat Universitesi, Tip Fakultesi, Ic Hastaliklari AD./Romatoloji BD., 23119-Elazig, TURKEY.
Tel: +90 424 2333555,
Fax: +90 424 2388096
e-mail: kocassk@yahoo.com

Registered: 16 September 2010; Accepted: 18 January 2011]
[Kayıt Tarihi : 16 Eylül 2010 ; Kabul Tarihi : 18 Ocak 2011]

ABSTRACT

Objective: Chronic inflammatory disorders such as rheumatoid arthritis and systemic lupus erythematosus (SLE), which are associated with insulin resistance and accelerated atherosclerosis, also lead to increased adipokines levels. However, it is not fully known whether systemic sclerosis (SSc), another chronic inflammatory disease, leads to insulin resistance and atherosclerosis and affects adipokine levels. Thus, the aim of the present study was to determine the serum adiponectin and vaspin levels and their possible effects on the *homeostasis model assessment for insulin resistance* (HOMA-IR) index and intima-media thickness (IMT) of the common carotid artery in a cohort of patients with SSc

Method: Twenty-three patients with SSc, 22 patients with SLE (serving as a patient control group), and 29 healthy controls (HCs) were included in this study. Serum adiponectin and vaspin levels and the HOMA-IR index and IMT were determined.

Results: Adiponectin level was significantly lower in the SSc group than in the SLE or HC groups and the decrease of vaspin level was significant after adjusting for age in the SSc group compared to the SLE group. HOMA-IR indexes were similar in the SSc and HC groups, but higher in the SLE group. IMTs were higher in both patient groups than in the HC group. Adiponectin and vaspin serum levels were not correlated with either HOMA-IR index or IMT in SSc.

Conclusion: SSc is associated with decreased adipokines levels, but does not induce insulin resistance, in contrast to SLE. Similar to SLE, SSc accelerates atherogenesis. Further studies are needed to elucidate the role of adipokines in SSc.

Key words: Systemic sclerosis, systemic lupus erythematosus, adiponectin, vaspin, insulin resistance.

ÖZET

Amaç: Romatoid artrit ve sistemik lupus eritematoz (SLE) gibi kronik inflamatuar hastalıklar insülin direnci ve hızlanmış ateroskleroza neden olmakta ve bu hastalıklarda adipokin düzeyleri de artmaktadır. Ancak, kronik inflamatuar bir hastalık olan sistemik skleroz (SSc)'un insülin direnci ve ateroskleroz gelişimini ve adipokin düzeylerini etkileyip-etkilemediği tam olarak bilinmemektedir. Bu çalışmanın amacı, SSc hastalarında serum adiponektin ve vaspin düzeylerinin belirlenmesi ve bu adipokinlerin *homeostasis model assessment for insulin resistance* (HOMA-IR) indeksi ve karotis intima-media kalınlığı (IMT) üzerine olasılı etkilerinin değerlendirilmesidir.

Yöntem: Çalışmaya 23 SSc, 22 SLE hastası (hasta kontrol grubu) ve 23 sağlıklı kontrol (HC) alındı. Serum adiponektin ve vaspin düzeyleri, HOMA-IR indeksi ve IMT belirlendi.

Bulgular: SSc grubunda, adiponektin düzeyi SLE ve HC gruplarından düşüktü, vaspin düzeyi ise yaş için düzeltme yapıldığında SLE grubundan düşüktü. HOMA-IR indeksi ise SSc ve HC gruplarında benzerdi, ancak SLE grubunda artmıştı. IMT'ler her iki hasta grubunda da HC grubundan yüksekti. Serum adiponektin ve vaspin düzeyleri, SSc'de HOMA-IR indeksi ve IMT ile ilişkisizdi.

Sonuç: SSc'de adipositokin düzeyleri düşüktür ve SLE'nin aksine, insülin direnci gelişmemektedir. SLE'de olduğu gibi, SSc'de de aterogenez hızlanmaktadır. SSc'de adipokinlerin rolüne ilişkin başka çalışmaların yapılması gereklidir.

Anahtar kelimeler: Sistemik skleroz, sistemik lupus eritematoz, adiponektin, vaspin, insülin direnci.

Introduction

Adipose tissue is not simply a storage tissue for lipids, but is also an active contributor to whole-body homeostasis. In particular, adipocytes are known to secrete several bioactive peptides termed adipo(cyto)kines [1]. These peptides include tumor necrosis factor alpha (TNF-α), leptin, resistin, adiponectin, and vaspin, and they participate in a wide variety of physiological or pathological processes, such as atherosclerosis, insulin resistance, inflammation, and immunity [1-4].

Adiponectin, the most abundant adipokine secreted from adipose tissue, is known to have anti-atherogenic effects [2,3] as well as an insulin-sensitizing effect [3]. Thus, decreased adiponectin levels have been correlated with obesity and diabetes mellitus [4], both of which are associated with insulin resistance. Increased adiponectin levels have been reported in inflammatory diseases including rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and inflammatory bowel diseases (IBDs) [5-7]. These inflammatory diseases related with increased adiponectin level lead to insulin resistance and accelerated atherosclerosis [8-10]. However, the increases in adiponectin levels in these diseases are questioned, since pro-inflammatory cytokines suppress the production of adiponectin [11]. A further controversy is that adiponectin levels are lower in metabolic diseases characterized by insulin resistance, atherosclerosis, and low-grade inflammation [4].

Vaspin (visceral adipose tissue-derived serine protease inhibitor) has recently been identified as an adipokine that is expressed predominantly in visceral adipose tissue [12]. Vaspin mRNA expression has been positively correlated with body mass index (BMI) [12], and administration of vaspin to obese mice has improved glucose tolerance and insulin sensitivity [13]. An inverse association between serum vaspin level and carotid stenosis has also been documented [14]. However, Senolt et al. [15] have demonstrated elevated levels of vaspin in synovial fluid of patients with RA.

Systemic sclerosis (SSc), an autoimmune inflammatory disorder of unknown etiology, is characterized by severe and progressive fibrosis of the skin and of the visceral organs. Although the pathogenesis of SSc is not fully understood, it appears to involve interactions between blood vessels, fibroblastic activity, and immunological processes [16]. Whether SSc affects the production of adipokines, leads to insulin resistance and atherosclerosis, has not yet been established, although several inflammatory disorders including RA, SLE and IBD associated with insulin resistance and accelerated atherosclerosis [8-10] do alter adipokine levels [5-7]. The aim of the present study was to determine the serum adiponectin and vaspin levels in a cohort of patients with SSc and to establish their possible effects on the *homeostasis model assessment for insulin resistance* (HOMA-IR) index and intima-media thickness (IMT) of the common carotid artery in these patients.

Materials and Methods

Participants: Twenty-three patients with SSc, 22 patients with SLE (serving as a patient control group), and 29 healthy controls (HCs) were included in this study. Patients were recruited from those treated and followed up in the Rheumatology Department of Firat University Hospital, Elazig, Turkey. HCs were selected from staff members employed in our institute. SSc was diagnosed according to the American College of Rheumatology (ACR) preliminary criteria classification of SSc [17], which include findings of either the sole major criterion, i.e., thickening of skin proximal to the metacarpophalangeal joints, or two or more of the minor criteria, i.e., 1) sclerodactyly, 2) digital pitting scars of fingertips or loss of substance of the distal finger pad, and 3) bilateral basilar pulmonary fibrosis. SLE was diagnosed according to the ACR revised classification criteria for SLE [18], which has 11 items, objective clinical, and laboratory variables. Diagnosis of SLE requires the presence of at least four criteria. This study protocol was approved by the institutional Ethics Committee, and all the participants gave informed consent before enrolling in the study.

Detailed histories of all of the participants were obtained and systemic and rheumatologic examinations were performed. Corticosteroid usage was also recorded. For all the participants, body weight (BW) and body height (BH) were measured to determine the BMI, expressed as: BMI=BW (kg)/BH $(m)^2$.

Patients with hypertension, diabetes mellitus, liver or kidney diseases, endocrine disorders, receiving statins, smokers, and history of atherosclerosis and/or familial dyslipidemia were excluded from this study.

In the SSc group, the disease activity was determined by the Valentini disease activity index that includes modified Rodnan skin score, scleredema, changes in skin symptoms, vascular symptoms and cardiopulmonary symptoms within the last month, as well as digital necrosis, arthritis, lung diffusion capacity, erythrocyte sedimentation rate (ESR), hypocomplementemia, and total disease activity score of 10 (if it was ≥3, SSc was defined as active) [19]. The disease damage and severity in the SSc group was determined by Medsger disease severity scale [20]. This scale assesses disease involvement in 9 organ systems; namely, general health, peripheral vascular, skin, joint/tendon, muscle, gastrointestinal tract, lungs, heart, and kidneys. Each organ system was scored separately from 0 to 4, depending on whether there is no, mild, moderate, severe, or end-stage involvement [20].

The SLE activity status was assessed using the SLE Disease Activity Index (SLEDAI) [21]. SLEDAI is a global index including 24 weighted objective clinical and laboratory variables. Disease activity can range from 0 to 105, and active SLE was defined as a SLEDAI score of ≥6 [21]. The disease damage and severity was determined by Systemic Lupus International Collaborating Cli-

Table 1. Demographics and clinical characteristics of the SSc, SLE, and HC groups

	SSc (n=23)	SLE (n=22)	HC (n=29)	*P*
Age (years)	43.8±13.5[a]	34.4±11.3	38.0±10.3	0.029*
Female/Male	22/1	20/2	23/6	0.175**
BMI (kg/m^2)	25.2±4.3	23.5±4.5	26.0±4.7	0.158*
SBP (mmHg)	109±12	106±12	102±16	0.217*
DBP (mmHg)	70±9[b]	65±8	62±10	0.016*
Disease duration (years)	4.51±6.91	4.10±4.22	-	0.328
Corticosteroid usage (%)	39	91	-	<0.001**
Corticosteroid dose (mg/d)[#]	3.7±6.8	7.1±9.1	-	0.246*

SSc: systemic sclerosis, SLE: systemic lupus erythematosus, HC: healthy controls, BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure.
Data were presented as mean ± SD.
P values of *ANOVA, and **Chi-square tests.
vs. the SLE group: [a]p<0.05.
vs. the HC group: [b]p<0.05.
[#]equivalent prednisolone dosage of corticosteroids.

Table 2. Laboratory data for the SSc, SLE and HC groups

	SSc (n=23)	SLE (n=22)	HC (n=29)	*P**
TC (mg/dL)	174±35	171±68[a]	206±36	0.021
LDL-C (mg/dL)	112±24	122±44	134±28	0.069
HDL-C (mg/dL)	40±12[b]	44±12	52±12	0.004
Triglyceride (mg/dL)	134±54	146±80	128±47	0.577
FBG (mg/dL)	94±41	84±8	89±13	0.054
Insulin (IU/mL)[†]	7.8±4.2	9.9±6.8	6.7±3.3	0.033
C-peptide (ng/mL)	2.9±1.2[b]	3.1±1.4[c]	2.0±0.5	<0.001
HOMA-IR	1.9±1.8	2.0±1.4	1.4±0.7	0.092
ESR (mm/h)	29.6±19.5[d]	42.6±23.3[c]	18.4±9.8	<0.001
CRP (mg/L)	11.1±15.6	7.6±8.3	6.5±7.9	0.367
TNF-α (pg/mL)[†]	13.6±5.2[d]	21.4±17.8[c]	11.4±9.5	<0.001
IL-6 (pg/mL)[†]	11.8±17.7[b]	8.8±11.1[a]	3.6±4.9	0.006
Adiponectin (μg/mL)	6.6±3.2[b,e]	10.6±1.8	9.1±3.8	<0.001
Vaspin (pg/mL)[†]	341±284	552±325	434±343	0.177
IMT (mm)	0.677±0.081 [c]	0.644±0.074 [c]	0.547±0.035	<0.001

SSc: systemic sclerosis, SLE: systemic lupus erythematosus, HC: healthy controls, TC: total cholesterol, LDL-C: low-density lipoprotein cholesterol, HDL-C: high-density lipoprotein cholesterol, FBG: fasting blood glucose, HOMA-IR: *homeostasis model assessment for insulin resistance*, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, TNF: tumor necrosis factor, IL: interleukin, IMT: intima-media thickness.
Data were presented as mean ± SD.
[†]Logarithmic transformations were applied to data with skewed distribution before statistical analysis.
P values of *ANOVA.
vs. the HC group: [a]p<0.05, [b]p<0.01, [c]p<0.001.
vs. the SLE group: [d]p<0.05, [e]p<0.001.

nics/American College of Rheumatology (SLICC/ACR) damage index in the SLE group [22]. The index has 41 items covering 12 systems. It includes specific comorbidities associated with SLE, and total score is 47 [22].

Laboratory analysis: Blood samples were drawn from all the participants, who had fasted overnight. Serum samples were stored at –20°C until further analysis. Complete blood cell counts were assessed with a CELL-DYN 3700 hematology analyzer (Abbott Laboratories, Illinois, USA) using commercial kits (Abbott Laboratories, Illinois, USA). Fasting blood glucose (FBG), lipid profile, and hepatic and renal function tests were measu-

red with an Olympus AU600 analyzer (Olympus Optical Co. Ltd, Tokyo, Japan) using commercial kits (Olympus Corporation, Tokyo, Japan). ESR was determined by Westergren method (Vacuplus ESR-120, Len-med, Ankara, Turkey), and C-reactive protein (CRP) levels were determined with a Dade Behring BN II nephelometer (Siemens, Marburg GmbH, Germany) using commercial kit (CardioPhase, Siemens, Marburg GmbH, Germany).

Serum insulin and C-peptide levels were determined*e*-with chemiluminescence *assays* (DPC-Immulyte-2000 Washington, USA) using appropriate commercial kits (Diagnostic Products Corporation, Los Angeles, CA, USA). Insulin resistance was calculated by the HOMA-IR index using the following equation: HOMA-IR=(fasting blood insulin (μU/mL) x FBG (mmol/L)/22.5). HOMA-IR values > 2.7 were considered to indicate insulin resistance.

Serum TNF-α and interleukin (IL)-6 (BioSource International, Inc. Camarillo, California USA), adiponectin (Phoenix Pharmaceuticals, Inc. Karlsruhe, Germany), and vaspin (Alpco Diagnostics, Salem, New Hampshire, USA) levels were determined using by enzyme-linked immunosorbent assay (ELISA) (ELx 800 Plate Reader, BioTek Instruments, Vermont, USA) methods following the manufacturer's instructions.

Carotid intima-media thickness: The subjects were studied in the early afternoon under standardized conditions, in a quiet room at a comfortable temperature. All participants had fasted before testing and were asked to refrain from strenuous exercise or drinking alcohol or caffeine-containing beverages for 24 h before the study. Upon arrival at the investigation unit, the subjects were equipped with measurement devices and then rested supine for about 15–20 min, until heart rate and mean blood pressure (BP) trends demonstrated that satisfactory baseline conditions had been achieved. Arterial BP and carotid artery values were measured during the last 5 min of the resting period. All study cases underwent carotid ultrasonography; all studies were performed by an experienced research sonographer using an identical protocol and were interpreted by a single cardiologist, who was blinded to the subjects' clinical and laboratory findings. The common carotid arteries were evaluated with high-resolution B-mode ultrasonography using an echotomographic system (Acuson Sequaoi 512 machine; Acuson, Minnesota, USA) with a 7.5 MHz linear transducer. Patients were examined in the supine position, with the neck rotated 45^0 in the direction opposite the site that was being examined. IMT was measured on the far wall at 5, 10, and 15 mm proximal to the carotid bifurcation, over both right and left common carotid arteries. The IMT was defined as the distance from the leading edge of the first echogenic line to the leading edge of the second echogenic line. Reproducibility of the IMT measurement was deemed acceptable, as demonstrated by a coefficient of variation (CV) of 3% for the IMT. The mean IMT, defined as the mean of the six measurements (three for each side), was used for statistical analysis.

Statistical analysis; Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS 11.0, Chicago, IL, USA). Results were presented as mean ± standard deviation (S.D.). The normal distribution of the variables was evaluated with the Kolmogorov-Smirnov test, and logarithmic transformations were performed to normalize data with skewed distribution (insulin, TNF-α, IL-6, and vaspin). Statistical differences among the groups were identified with one-way analysis of variance (ANOVA) followed by the Tukey's post hoc test. Chi-square test was used to compare the categorical variables. Correlation analysis was performed using the Pearson correlation coefficient. Analysis of covariance (ANCOVA) was also used to adjust variables for age, gender and BMI. *P* values less than 0.05 were considered to be significant.

Results

The demographics and laboratory data in the SSc, SLE, and HC groups are summarized in Tables 1 and 2. The mean age was higher in the SSc group than in the SLE group ($p<0.05$), while the mean ages in the SLE and SSc groups were simila to those of the HC group ($p>0.05$ for both). The female/male ratios and the BMIs were similar among all groups. The Valentini and Medsger scores were 3.7±1.2 and 6.2±2.4, respectively, and the disease duration was 4.5±6.9 years, in the SSc group. The SLEDAI and SLICC/ACR scores were 7.9±6.2 and 0.77±1.19, respectively, and the disease duration was 4.1±4.2 years, in the SLE group. The disease activity indexes and severity scores were not associated with the adiponectin or vaspin levels in the SSc and SLE groups ($p>0.05$).

When compared with the HC group, the high-density lipoprotein cholesterol (HDL-C) level was lower in the SSc group ($p<0.01$), while the total cholesterol (TC) level was lower in the SLE group ($p<0.05$).

The FBG levels were similar among all groups. Although insulin and C-peptide levels in all groups were different by ANOVA ($p=0.033$ and $p<0.001$, respectively), post-hoc tests did not demonstrate any differences in terms of insulin level, in paired comparisons. However, the C-peptide levels were higher in the SSc and SLE groups ($p<0.01$ and $p<0.001$, respectively) than in the HC group. After adjustment for age, HOMA-IR indexes were similar in the SSc and HC groups, and higher in the SLE group than in the HC groups (ANCOVA $p<0.05$ for both). Moreover, while 3.4% of the control group and 13% of the SSc group (odds ratio [OR]: 1.8, 95% confidence interval [CI]: 0.9-3.5, $p=0.197$) showed insulin resistance, it was more frequent in the SLE group (22.7% of SLE patients had insulin resistance, and OR: 2.2, 95% CI: 1.3-3.7, $p=0.034$).

The ESR and TNF-α levels were higher in the SLE group than in the SSc ($p<0.05$ for both) and the HC ($p<0.001$ for both) groups. The CRP levels were similar among all three groups. The levels of IL-6 were higher in the SSc

and SLE groups ($p<0.01$ and $p<0.05$, respectively) than in the HC group.

The adiponectin levels were similar in the SLE and HC groups, while adiponectin level was lower in the SSc group compared to the SLE and HC groups ($p<0.001$ and $p<0.01$, respectively). The significant decrease in the adiponectin level was found consistently in the SSc group even after adjustment for age. Adiponectin level was positively correlated with the CRP ($r=0.513$, $p=0.012$) and IL-6 ($r=0.472$, $p=0.041$) levels in the SSc group, while it was correlated with the levels of low-density lipoprotein cholesterol ($r=0.491$, $p=0.024$), insulin ($r=0.501$ $p=0.021$), C-peptide ($r=0.581$, $p=0.006$), and HOMA-IR index ($r=0.536$, $p=0.012$) in the SLE group (Table 3). In the SLE group, adiponectin level was higher in the insulin resistant patients compared to the patients who did not show insulin resistance (12.3±1.7 vs. 10.1±1.5 µg/mL, $p=0.017$).

Neither one-way ANOVA nor post-hoc tests demonstrated any differences in the vaspin levels among all groups. However, the vaspin level was lower in the SSc group than in the SLE group (ANCOVA $p<0.05$), after adjustment for age.

The IMTs were higher in both patient groups than in the HC group ($p<0.001$ for both). After adjustment for age the increase in IMTs remained significant (ANCOVA $p<0.001$ for both). The IMT was correlated with the age ($r=0.421$, $p=0.046$), systolic BP ($r=0.531$, $p=0.009$), diastolic BP ($r=0.433$, $p=0.039$), triglyceride ($r=0.459$, $p=0.032$), and C-peptide ($r=0.494$, $p=0.016$) levels in the SSc group. In the SLE group, the IMT was correlated with the age ($r=0.441$, $p=0.040$) and TC ($r=0.444$, $p=0.038$), while it was correlated with C-peptide ($r=0.373$, $p=0.032$) and TNF-α ($r=0.390$, $p=0.037$) levels in the HC group (Table 3).

Nine patients in the SSc group (mean equivalent dose of 3.7±6.8 mg/day prednisolone), and 20 patients in the SLE group (mean equivalent dose of 7.1±9.1 mg/day prednisolone) were receiving corticosteroids ($p<0.001$). However, no effect of corticosteroid usages was noted with respect to the levels of adiponectin and vaspin, or with the HOMA-IR index in the SSc and SLE groups (data not shown).

Discussion

In our study, serum adiponectin and vaspin levels were lower in the SSc group in contrast to the SLE group. Although SSc does not induce the development of insulin resistance, it does accelerate atherosclerosis. However, both increased insulin resistance and accelerated atherosclerosis are prominent issues in SLE. To our knowledge, this is the first study demonstrating that serum adiponectin and vaspin levels are lower in SSc patients. Interestingly, although the levels of these two insulin sensitizer adipokines were lower, no increase in insulin resistance was observed in patients with SSc.

Chronic inflammatory diseases such as RA and SLE increase insulin resistance and accelerate atherosclerosis [8-10,23,24]. However, whether same effect occurs with SSc has not yet been established. Adipokines are well known to play significant roles in the development of insulin resistance and in the pathogenesis of atherosclerosis [3,4,12,14]. Although serum adipokine levels have been associated with insulin resistance and atherosclero-

Table 3: Detected correlations in the study groups

Groups	Correlations	r	*P*
SSc	Adiponectin- CRP	0.513	0.012
	Adiponectin- IL-6	0.472	0.041
	IMT-Age	0.421	0.046
	IMT-SBP	0.531	0.009
	IMT-DBP	0.433	0.039
	IMT-TG	0.459	0.032
	IMT-C-peptide	0.494	0.016
SLE	Adiponectin-LDL	0.491	0.024
	Adiponectin-Insulin	0.501	0.021
	Adiponectin-C-peptide	0.581	0.006
	Adiponectin-HOMA-IR index	0.536	0.012
	IMT-Age	0.441	0.040
	IMT-TC	0.444	0.038
HC	IMT-C-peptide	0.373	0.032
	IMT-TNF-α	0.390	0.037

SSc: systemic sclerosis, SLE: systemic lupus erythematosus, HC: healthy controls, CRP: C-reactive protein, IL: interleukin, IMT: intima-media thickness, SBP: systolic blood pressure, DBP: diastolic blood pressure, TG: triglycerides, LDL: low-density lipoprotein cholesterol, HOMA-IR: *homeostasis model assessment for insulin resistance,* TC: total cholesterol, TNF: tumor necrosis factor.

sis in the general population [3,4,12,14], their contributions to insulin resistance and atherosclerosis in chronic inflammatory diseases are not yet known. In our study, although an accelerated atherogenesis was evident, no change in insulin resistance was determined in the patients with SSc. In contrast to other chronic inflammatory diseases [5-7,15], the decreased adiponectin and vaspin levels and the lack of any increase in insulin resistance in patients with SSc may be associated with the less-prominent intensity of inflammation associated with SSc. The accelerated atherosclerosis in patients with SSc may instead be explained by the extensive endothelial dysfunction in SSc. In addition, adiponectin and vaspin levels in SSc appear not to be associated with insulin resistance and atherosclerosis, in contrast to the general population.Adiponectin is most abundantly produced in white adipose tissue by both fat and non-fat cells [25] and exerts its insulin sensitizing actions through inhibition of gluconeogenesis in liver and activation of free-fatty acid oxidation in skeletal muscles [26]. Adiponectin is also reported to attenuate neointimal thickening in mechanically injured arteries [2]. Cross-sectional studies have also indicated a relationship between decreased adiponectin levels and atherosclerosis [4,27]. Adiponectin levels are lower in patients with insulin resistance and atherosclerosis, both of which are considered to represent low-grade inflammatory diseases [2-4]. On the other hand, increased pro-inflammatory cytokines such as TNF-α and IL-6 have been suggested to suppress production of adiponectin [11]. Thus, the high adiponectin levels that are seen in inflammatory diseases such as RA [5], SLE [6] and IBDs [7] are paradoxical. In our study, adiponectin levels were lower in the SSc group than in the SLE and HC groups.

While insulin resistance, glucose intolerance, and hypertriglyceridemia are consequences of hypoadiponectinemia [28], adiponectin also has anti-inflammatory [29] and anti-oxidant [30] effects. Oxidative stress is suggested to be involved in the pathogenesis of SSc [31]. Furthermore, SSc is characterized by excessive extracellular matrix (ECM) deposition in the skin and several visceral organs, while a decrease in matrix metalloproteinase (MMP) activities plays a significant role in the pathogenesis of this ECM deposition. Serum levels of tissue inhibitor of matrix metalloproteinase (TIMP)-1 are elevated in SSc patients, whereas serum MMP-1 levels are similar to those in normal controls [32]. These data suggest that a local or systemic MMP/TIMP imbalance may underlie the pathogenesis of fibrosis. Decreased MMP levels or decreased MMP activities due to increased TIMP-1 expression in SSc may lead to ECM accumulation due to impaired ECM degradation. Adiponectin has been reported to stimulate MMP activities [33]. Adiponectin level was lower in the SSc group than in the HCs in our study. Ehling et al. [34] demonstrated that adiponectin mRNA was not expressed by cultured fibroblasts harvested from scleroderma patients in contrast to fibroblasts from RA patients. The activities of MMPs may be reduced due to the decreased adiponectin levels in SSc. Thus, hypoadiponectinemia may contribute to the pathogenesis of SSc.

In SLE, diverse results concerning the level of serum adiponectin have been reported [6,35, 35]. Rovin et al. [6] noted that the adiponectin level was higher in SLE, and that it can be a predictor of renal SLE flare-up. Sada et al. [35] also described an increase in adiponectin level in conjunction with SLE. On the other hand, Vadaca et al. [36] observed no increase in the level of adiponectin in patients with SLE. We also observed no change adiponectin level in our study. These conflicting results may be associated with the heterogeneous nature of SLE and/or patient disease activity status. Indeed, different cytokines can be elevated during the different manifestations of SLE [37]. Other diverse results concerning levels of other adipocytokine have also been reported in SLE patients [35,38].

Vaspin is an adipokine newly identified by Hida et al. [13]. Its expression is reported to be related with glucose level, insulin sensitivity, and BMI or body fat mass [12, 39], and is higher in obesity, diabetes, and polycystic ovary syndrome, which are characterized by the presence of insulin resistance [12,39,40]. Elevated vaspin level seems to be a compensatory response to insulin resistance [12]. Administration of recombinant vaspin to obese Crl: CD-1 mice fed with high-fat high-sucrose chow results in improved insulin sensitivity and glucose tolerance [13]. Although no direct association was found between vaspin level and markers of insulin resistance in all groups, decreased vaspin levels were evident in the SSc group in our study.

Vaspin is likely to have anti-inflammatory action through its suppression of the production of TNF-α and pro-inflammatory adipokines [13]. In our study, although decreased vaspin levels were apparent in the SSc group and a relatively increased vaspin level was measured in the SLE group, no association was apparent between serum vaspin levels and disease activity indexes or severity scores in either the SSc or the SLE groups. Further studies are needed for more precise elucidation of the relationship of vaspin levels to SSc and SLE.

Subcutaneous adipose tissue atrophy is a characteristic feature of human scleroderma [41]. Peroxisome proliferator-activated receptor gamma (PPARγ) is a key mediator of adipogenesis and application of its agonist, rosiglitasone, protects against lipoatrophy and exerts an anti-fibrotic effect [42]. In addition, in human studies, treatments with PPARγ agonists increase serum adiponectin levels, possibly through regulation of adipogenesis [43]. Thus, the decreased adipocytokine levels detected in the SSc group in our study may be associated with subcutaneous adipose tissue atrophy. These decreased levels may also be a predictor of skin involvement in scleroderma. Rooney and Ryan [44] have reported dec-

reased adiponectin level in a patient with sclerodermatous chronic graft-versus-host disease, which imitates features of SSc skin and is characterized by the atrophy of subcutaneous fat tissue.

Adipokines have recently been implicated in insulin resistance, atherogenesis, and inflammatory diseases; thus, serum adiponectin and vaspin levels have been promoted as possible markers of atherosclerotic events [2,14]. In our study, the serum adiponectin level was positively related with markers of insulin resistance in SLE, which contrasts with previous reports that reported negative correlations between serum adiponectin level and the markers of atherosclerosis and insulin resistance [2-4]. Behre [45] has speculated that adiponectin is a protective defense protein in catabolism; therefore, high adiponectin levels are observed in catabolic states such as inflammatory diseases and starvation. Our results support the idea [45] that insulin resistance is developed in parallel with catabolic status issues that arise during inflammatory disease, in order to minimize the anabolic effects of insulin. Thus, correlation between adiponectin and insulin resistance, reflecting catabolism, may implicate adiponectin as a marker of catabolic statement [45].

The present study has some limitations. The numbers of participants may be too small to reach more significant associations. Our observations are based on cross-sectional analysis, and repeated measurements of adipokines over time could have provided additional information. Another limitation was differences in the mean ages among the study groups; SSc patients are often older than those with SLE. In addition, quantitation of fat mass and the presence of carotid artery plaque could have been evaluated. Although it is controversial whether anti-rheumatic therapies affect the levels of adipokines [46,47], insulin resistance [48], and atherosclerosis, we could also have recorded the usage of anti-rheumatic drugs.

In conclusion, SSc does not induce insulin resistance, although it is associated with decreased adipokine levels. On the other hand, SSc also accelerates the atherosclerotic process. Decreased adipokine levels may be caused by the atrophy of subcutaneous fat mass and may be involved in the pathogenesis of SSc. Further studies are needed to confirm whether the decrease in adiponectin and vaspin levels is an etiology or a consequence of SSc.

Conflict of Interest: The authors declare no conflict of interest.

References

[1] Lago F, Dieguez C, Gómez-Reino J, Gualillo O. (2007) Adipokines as emerging mediators of immune response and inflammation. Nat Clin Pract Rheumatol. 3: 716-724.

[2] Matsuda M, Shimomura I, Sata M, Arita Y, Nishida M, Maeda N, Kumada M, Okamoto Y, Nagaretani H, Nishizawa H, Kishida K, Komuro R, Ouchi N, Kihara S, Nagai R, Funahashi T, Matsuzawa Y. (2002) Role of adiponectin in preventing vascular stenosis. The missing link of adipo-vascular axis. J Biol Chem. 277: 37487-37491.

[3] Berg AH, Combs TP, Du X, Brownlee M, Scherer PE. (2001) The adipocyte-secreted protein Acrp30 enhances hepatic insulin action. Nat Med. 7: 947-953.

[4] Weyer C, Funahashi T, Tanaka S, Hotta K, Matsuzawa Y, Pratley RE, Tataranni PA. (2001) Hypoadiponectinemia in obesity and type 2 diabetes: close association with insulin resistance and hyperinsulinemia. J Clin Endocrinol Metab. 86: 1930-1935.

[5] Otero M, Lago R, Gomez R, Lago F, Dieguez C, Gómez-Reino JJ, Gualillo O. (2006) Changes in plasma levels of fat-derived hormones adiponectin, leptin, resistin and visfatin in patients with rheumatoid arthritis. Ann Rheum Dis. 65: 1198-1201.

[6] Rovin BH, Song H, Hebert LA, Nadasdy T, Nadasdy G, Birmingham DJ, Yung Yu C, Nagaraja HN. (2005) Plasma, urine, and renal expression of adiponectin in human systemic lupus erythematosus. Kidney Int. 68: 1825-1833.

[7] Karmiris K, Koutroubakis IE, Xidakis C, Polychronaki M, Voudouri T, Kouroumalis EA. (2006) Circulating levels of leptin, adiponectin, resistin, and ghrelin in inflammatory bowel disease. Inflamm Bowel Dis. 12: 100-105.

[8] Kaplan MJ. (2009) Premature vascular damage in systemic lupus erythematosus: an imbalance of damage and repair? Transl Res. 154: 61-69.

[9] Aviña-Zubieta JA, Choi HK, Sadatsafavi M, Etminan M, Esdaile JM, Lacaille D. (2008) Risk of cardiovascular mortality in patients with rheumatoid arthritis: a meta-analysis of observational studies. Arthritis Rheum. 59: 1690-1697.

[10] Dagli N, Poyrazoglu OK, Dagli AF, Sahbaz F, Karaca I, Kobat MA, Bahcecioglu IH. (2010) Is inflammatory bowel disease a risk factor for early atherosclerosis? Angiology. 61: 198-204.

[11] Fantuzzi G. (2008) Adiponectin and inflammation: consensus and controversy. J Allergy Clin Immunol. 121: 326-330.

[12] Klöting N, Berndt J, Kralisch S, Kovacs P, Fasshauer M, Schön MR, Stumvoll M, Blüher M. (2006) Vaspin gene expression in human adipose tissue: association with obesity and type 2 diabetes. Biochem Biophys Res Commun. 339: 430-436.

[13] Hida K, Wada J, Eguchi J, Zhang H, Baba M, Seida A, Hashimoto I, Okada T, Yasuhara A, Nakatsuka A, Shikata K, Hourai S, Futami J, Watanabe E, Matsuki Y, Hiramatsu R, Akagi S, Makino H, Kanwar YS. (2005) Visceral adipose tissue-derived serine protease inhibitor: a unique insulin-sensitizing adipocytokine in obesity. Proc Natl Acad Sci U S A. 102: 10610-10615.

[14] Aust G, Richter O, Rohm S, Kerner C, Hauss J, Klöting N, Ruschke K, Kovacs P, Youn BS, Blüher M. (2009) Vaspin serum concentrations in patients with carotid stenosis. Atherosclerosis. 204: 262-266.

[15] Senolt L, Polanská M, Filková M, Cerezo LA, Pavelka K, Gay S, Haluzík M, Vencovsky J. (2010) Vaspin and omentin: new adipokines differentially regulated at the site of inflammation in rheumatoid arthritis. Ann Rheum Dis. 69: 1410-1411.

[16] Sakkas LI. (2005) New developments in the pathogenesis of systemic sclerosis. Autoimmunity. 38: 113-116.

[17] Subcommittee for Scleroderma Criteria of the American Rheumatism Association Diagnosis and Therapeutic Criteria Commitee. (1980) Preliminary Criteria for the classification of systemic sclerosis (scleroderma). Arthritis Rheum. 23: 581 -590.

[18] Hochberg MC. (1997) Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum. 40: 1725.

[19] Della Rossa A, Valentini G, Bombardieri S, Bencivelli W, Silman AJ, D'Angelo S, Cerinic MM, Belch JF, Black CM, Bec-

var R, Bruhlman P, Cozzi F, Czirják L, Drosos AA, Dziankowska B, Ferri C, Gabrielli A, Giacomelli R, Hayem G, Inanc M, McHugh NJ, Nielsen H, Scorza R, Tirri E, van den Hoogen FH, Vlachoyiannopoulos PG. (2001) European multicentre study to define disease activity criteria for systemic sclerosis. I. Clinical and epidemiological features of 290 patients from 19 centres. Ann Rheum Dis. 60: 585-591.

[20] Medsger TA Jr, Silman AJ, Steen VD, Black CM, Akesson A, Bacon PA, Harris CA, Jablonska S, Jayson MI, Jimenez SA, Krieg T, Leroy EC, Maddison PJ, Russell ML, Schachter RK, Wollheim FA, Zacharaie H. (1999) A disease severity scale for systemic sclerosis: development and testing. J Rheumatol. 26: 2159-2167.

[21] Bombardier C, Gladman DD, Urowitz MB, Caron D, Chang CH. (1992) Derivation of the SLEDAI. A disease activity index for lupus patients. The Committee on Prognosis Studies in SLE. Arthritis Rheum. 35: 630-64022. Gladman D, Ginzler E, Goldsmith C, Fortin P, Liang M, Urowitz M, Bacon P, Bombardieri S, Hanly J, Hay E, Isenberg D, Jones J, Kalunian K, Maddison P, Nived O, Petri M, Richter M, Sanchez-Guerrero J, Snaith M, Sturfelt G, Symmons D, Zoma A. (1996) The development and initial validation of the Systemic Lupus International Collaborating Clinics/American College of Rheumatology damage index for systemic lupus erythematosus. Arthritis Rheum. 39: 363-369.

[23] Ozgen M, Koca SS, Aksoy K, Dagli N, Ustundag B, Isik A. (2010) Visfatin levels and intima-media thicknesses in rheumatic diseases. Clin Rheumatol. doi:10.1007/s10067-010-1649-2.

[24] Ozgen M, Koca SS, Dagli N, Balin M, Ustundag B, Isik A. (2010) Serum adiponectin and vaspin levels in rheumatoid arthritis. Arch Med Res. 41: 457-463.

[25] Fain JN, Buehrer B, Bahouth SW, Tichansky DS, Madan AK. (2008) Comparison of messenger RNA distribution for 60 proteins in fat cells vs the nonfat cells of human omental adipose tissue. Metabolism. 57: 1005-1015.

[26] Stofkova A. (2009) Leptin and adiponectin: from energy and metabolic dysbalance to inflammation and autoimmunity. Endocr Regul. 43: 157-168.

[27] Beauloye V, Zech F, Tran HT, Clapuyt P, Maes M, Brichard SM. (2007) Determinants of early atherosclerosis in obese children and adolescents. J Clin Endocrinol Metab. 92: 3025-3032.

[28] Kubota N, Terauchi Y, Yamauchi T, Kubota T, Moroi M, Matsui J, Eto K, Yamashita T, Kamon J, Satoh H, Yano W, Froguel P, Nagai R, Kimura S, Kadowaki T, Noda T. (2002) Disruption of adiponectin causes insulin resistance and neointimal formation. J Biol Chem. 277: 25863-25866.

[29] Ouchi N, Walsh K. (2007) Adiponectin as an anti-inflammatory factor. Clin Chim Acta. 380: 24-30.

[30] Motoshima H, Wu X, Mahadev K, Goldstein BJ. (2004) Adiponectin suppresses proliferation and superoxide generation and enhances eNOS activity in endothelial cells treated with oxidized LDL. Biochem Biophys Res Commun. 315: 264-271.

[31] Gabrielli A, Svegliati S, Moroncini G, Pomponio G, Santillo M, Avvedimento EV. (2008) Oxidative stress and the pathogenesis of scleroderma: the Murrell's hypothesis revisited. Semin Immunopathol. 30: 329-337.

[32] Young-Min SA, Beeton C, Laughton R, Plumpton T, Bartram S, Murphy G, Black C, Cawston TE. (2001) Serum TIMP-1, TIMP-2, and MMP-1 in patients with systemic sclerosis, primary Raynaud's phenomenon, and in normal controls. Ann Rheum Dis. 60: 846-851.

[33] Choi HM, Lee YA, Lee SH, Hong SJ, Hahm DH, Choi SY, Yang HI, Yoo MC, Kim KS. (2009) Adiponectin may contribute to synovitis and joint destruction in rheumatoid arthritis by stimulating vascular endothelial growth factor, matrix metalloproteinase-1, and matrix metalloproteinase-13 expression in fibroblast-like synoviocytes more than proinflammatory mediator. Arthritis Res Ther. 11: R161.

[34] Ehling A, Schäffler A, Herfarth H, Tarner IH, Anders S, Distler O, Paul G, Distler J, Gay S, Schölmerich J, Neumann E, Müller-Ladner U. (2006) The potential of adiponectin in driving arthritis. J Immunol. 176: 4468-4478.

[35] Sada KE, Yamasaki Y, Maruyama M, Sugiyama H, Yamamura M, Maeshima Y, Makino H. (2006) Altered levels of adipocytokines in association with insulin resistance in patients with systemic lupus erythematosus. J Rheumatol. 33: 1545-1552.

[36] Vadacca M, Margiotta D, Rigon A, Cacciapaglia F, Coppolino G, Amoroso A, Afeltra A. (2009) Adipokines and systemic lupus erythematosus: relationship with metabolic syndrome and cardiovascular disease risk factors. J Rheumatol. 36: 295-297.

[37] al-Janadi M, al-Balla S, al-Dalaan A, Raziuddin S. (1993) Cytokine profile in systemic lupus erythematosus, rheumatoid arthritis, and other rheumatic diseases. J Clin Immunol. 13: 58-67.

[38] Wislowska M, Rok M, Stepień K, Kuklo-Kowalska A. (2008) Serum leptin in systemic lupus erythematosus. Rheumatol Int. 28: 467-473.

[39] Youn BS, Klöting N, Kratzsch J, Lee N, Park JW, Song ES, Ruschke K, Oberbach A, Fasshauer M, Stumvoll M, Blüher M. (2008) Serum vaspin concentrations in human obesity and type 2 diabetes. Diabetes. 57: 372-377.

[40] Tan BK, Heutling D, Chen J, Farhatullah S, Adya R, Keay SD, Kennedy CR, Lehnert H, Randeva HS. (2008) Metformin decreases the adipokine vaspin in overweight women with polycystic ovary syndrome concomitant with improvement in insulin sensitivity and a decrease in insulin resistance. Diabetes. 57: 1501-1507.

[41] Elder DE, Elenitsas R, Johnson BL Jr, Murphy GF, editors. (2005) Lever's Histopathology of the skin. Philadelphia: Lippincott Williams & Wilkins. p. 310-311.

[42] Wu M, Melichian DS, Chang E, Warner-Blankenship M, Ghosh AK, Varga J. (2009) Rosiglitazone abrogates bleomycin-induced scleroderma and blocks profibrotic responses through peroxisome proliferator-activated receptor-gamma Am J Pathol. 174: 519-533.

[43] Yang WS, Jeng CY, Wu TJ, Tanaka S, Funahashi T, Matsuzawa Y, Wang JP, Chen CL, Tai TY, Chuang LM. (2002) Synthetic peroxisome proliferator-activated receptor-gamma agonist, rosiglitazone, increases plasma levels of adiponectin in type 2 diabetic patients. Diabetes Care. 25: 376-380.

[44] Rooney DP, Ryan MF. (2006) Diabetes with partial lipodystrophy following sclerodermatous chronic graft vs. host disease. Diabet Med. 23: 436-440.

[45] Behre CJ. (2008) Adiponectin: a defense protein in catabolism. J Allergy Clin Immunol. 122: 1236.

[46] Laurberg TB, Frystyk J, Ellingsen T, Hansen IT, Jørgensen A, Tarp U, Hetland ML, Hørslev-Petersen K, Hornung N, Poulsen JH, Flyvbjerg A, Stengaard-Pedersen K. (2009) Plasma adiponectin in patients with active, early, and chronic rheumatoid arthritis who are steroid- and disease-modifying antirheumatic drug-naive compared with patients with osteoarthritis and controls. J Rheumatol. 36: 1885-1891.

[47] Cuchacovich R, Espinoza LR. (2009) Does TNF-alpha blockade play any role in cardiovascular risk among rheumatoid arthritis (RA) patients? Clin Rheumatol. 28: 1217-1220.

[48] Dessein PH, Joffe BI, Stanwix AE. (2005) Editorial: should we evaluate insulin sensitivity in rheumatoid arthritis? Semin Arthritis Rheum. 35: 5-7.