Elevated Soluble Intercellular Adhesion Molecule-1 Levels in Patients with Systemic Lupus Erythematosus: Relation to Insulin Resistance

TIM K. TSO and WEN-NAN HUANG

ABSTRACT. ***Objective.*** Intracellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) are members of the immunoglobulin supergene family and play a central role in cell-to-cell and in cell-to-extracellular matrix-mediated immune responses. Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterized by a wide variety of immunological abnormalities. The relationship between soluble adhesion molecules and insulin resistance has been observed in different populations. However, the association of circulating levels of soluble cell adhesion molecules with insulin resistance and/or hyperinsulinemia in patients with SLE has not been extensively established.

Methods. We evaluated the relationship of soluble ICAM-1 (sICAM-1) and VCAM-1 (sVCAM-1) to insulin resistance in 68 patients with SLE and 34 age-matched healthy controls.

Results. Patients with SLE had significantly higher fasting insulin levels, homeostasis model assessment insulin resistance (HOMA-IR), HOMA ß-cell, and plasma levels of sICAM-1 and sVCAM-1 than controls. SLE patients with HOMA-IR in the top quartile had the highest plasma levels of sICAM-1. However, there was no statistical difference in plasma levels of sVCAM-1 between patients in the respective quartiles of insulin sensitivity-related variables. Plasma levels of sICAM-1, but not sVCAM-1, were significantly correlated with fasting insulin ($r = 0.327$, $p = 0.006$), HOMA-IR ($r = 0.278$, $p = 0.022$), and HOMA ß-cell ($r = 0.359$, $p = 0.003$). In addition, fasting insulin was responsible for sICAM-1 variability in patients with SLE.

Conclusion. The elevation of plasma levels of sICAM-1 was associated with a status of insulin resistance in patients with SLE. (First Release Feb 15 2007; J Rheumatol 2007;34:726–30)

Key Indexing Terms:
INSULIN RESISTANCE SOLUBLE INTRACELLULAR ADHESION MOLECULE-1
SOLUBLE VASCULAR CELL ADHESION MOLECULE-1
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Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterized by activation of T and polyclonal B cells, and a wide variety of immunological abnormalities[1]. Adhesion molecules are a large group of cell-surface molecules that play a crucial role in the recruitment of neutrophils and other inflammatory cells to the site of acute or chronic inflammation. Intracellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) are members of the immunoglobulin supergene family and play a central role in cell-to-cell and in cell-to-extracellular matrix-mediated immune responses[2-4]. Soluble cell adhesion molecules are released from cells and can be found in the circulation[5]. For instance, soluble ICAM-1 (sICAM-1) and soluble VCAM-1 (sVCAM-1) have been detected in plasma/serum and also serve as a useful index of endothelial cell activation in different diseases including SLE[5-8].

Insulin resistance, a common metabolic state defined as a subnormal biologic response to given physiological levels of insulin, might itself promote inflammation by impairing the antiinflammatory action of insulin[9]. A number of tests are available for evaluating insulin sensitivity or resistance but each of these methods has limitations. Homeostasis model assessment (HOMA)[10], however, is the most commonly used method in clinical practice and in population-based studies[11] for assessing insulin resistance and secretion using the fasting glucose and insulin concentrations. We previously reported that patients with SLE had a higher risk of insulin resistance and abnormal insulin secretion than age-matched healthy controls according to fasting insulin concentration, HOMA insulin resistance (HOMA-IR), and HOMA ß-cell[12]. Recent studies also found hyperinsulinemia and insulin resistance in SLE[13-16].

The relationship between soluble adhesion molecules and insulin resistance has been observed in obese subjects[17,18] and

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in diabetic subjects[19], but also in healthy individuals[20]. However, the association of circulating soluble cell adhesion molecules with insulin resistance and/or hyperinsulinemia in SLE has not been established. We evaluated the relationship between plasma concentrations of sICAM-1 and sVCAM-1 and insulin resistance based on HOMA in patients with SLE.

MATERIALS AND METHODS

Patients. Sixty-eight Chinese women with SLE randomly selected from outpatient clinics at Taichung Veterans General Hospital (Taichung, Taiwan) and 34 age-matched healthy women from the local community were studied. All qualified patients fulfilled the 1982 revised American College of Rheumatology criteria[21]. Patients' disease activity was evaluated according to the SLE Disease Activity Index (SLEDAI)[22]. Patients were excluded if they had cardiovascular diseases, renal disease, or common metabolic disorders, such as Type 2 diabetes mellitus. To investigate the association of circulating s-CAM with insulin resistance and/or hyperinsulinemia, all patients were classified into subgroups based on the quartiles of fasting insulin, fasting glucose, HOMA-IR, and HOMA ß-cell. Written informed consent was obtained from all participants and the hospital's ethical committee approved this study.

Experimental assays. Blood specimens were obtained after an overnight fast for measurements of studied variables. Anti-double-stranded DNA (anti-dsDNA) was measured according to ELISA using a Quanta Lite™ dsDNA Kit (Inova Diagnostics, San Diego, CA, USA). Quantitative determinations of complement factor 3 and complement factor 4 in patients' sera were conducted using N antisera to human complement factor reagents with Behring nephelometers (Dade Behring, Newark, DE, USA). Anticardiolipin antibodies (aCL) were measured using a Quanta Lite™ ACA IgM/G (HRP) kit (Inova Diagnostics). Plasma cortisol concentrations were determined by solid-phase technique chemiluminescence immunoassays (Immulite 2000; DPC, Los Angeles, CA, USA).

Quantitative measurement of patients' fasting insulin concentrations was conducted using an Abbott IMx Insulin Kit based on a microparticle enzyme immunoassay (MEIA; Abbott Laboratories, Dainabot, Tokyo, Japan). The fasting glucose concentration was determined using an enzymatic colorimetric method (Sigma, St. Louis, MO, USA). HOMA-IR and HOMA ß-cell were calculated based on the equations in the HOMA model[10]: HOMA-IR = [fasting insulin (μU/ml) × fasting glucose (mmol/l)]/22.5; HOMA ß-cell = [20 × fasting insulin (μU/ml)]/[fasting glucose (mmol/l) – 3.5].

Plasma levels of sICAM-1 and sVCAM-1 were assessed by ELISA using a human soluble ICAM-1 immunoassay kit and a human soluble VCAM-1 immunoassay kit, respectively (R&D Systems,, Minneapolis, MN, USA) in accordance with the manufacturer's instructions and analyzed with a Dynex MRX II microplate reader (Dynex Technologies, Chantilly, VA, USA) at a wavelength of 450 nm.

Statistical analysis. Tested variables in this study for comparison of means were expressed as mean ± standard error of mean (SEM). The distribution of tested variables was examined graphically for normality. The significance for the mean difference between patients with SLE and age-matched healthy controls was determined by an independent sample t test. One-way analysis of variance was applied to analyze the differences in plasma levels of sICAM-1 and sVCAM-1 between patients in the respective quartiles of insulin sensitivity-related variables, followed by the Bonferroni test for post hoc analysis. Pearson's correlation analysis was used to examine the association of s-CAM with insulin sensitivity-related variables. Then a stepwise regression analysis was performed to determine the independent variables for sICAM-1 and sVCAM-1. P values < 0.05 were considered significant for all statistical analyses. All analyses in this study were performed using SPSS 10.0 for Windows (SPSS, Chicago, IL, USA).

RESULTS

Characteristics of patients. The mean age of patients was 38 years. Average disease duration of SLE when patients were participating in this study was 9 years and the median value for SLEDAI was 4. The mean levels (mean ± SEM) for anti-dsDNA, C3, and C4 were 368.35 ± 49.84 IU/ml, 81.94 ± 2.88 g/l, and 15.41 ± 0.92 g/l, respectively. About 28% of patients carried aCL and mean comparisons by an independent sample t test for their sICAM-1 levels (mean ± SEM: 291.31 ± 45.89 ng/ml, n = 19, vs 263.28 ± 22.53 ng/ml, n = 49; p = 0.545) and sVCAM-1 (mean ± SEM: 861.66 ± 121.89 ng/ml, n = 19, vs 913.24 ± 97.66 ng/ml, n = 49; p = 0.768) were not significantly different from those in patients not carrying aCL. About 90% of patients with SLE took prednisone and the mean dosage was 7.75 mg/day. There were no correlations between dosage of prednisone and insulin sensitivity-related variables and s-CAM (data not shown). There was no statistical difference in plasma cortisol concentrations among quartiles of HOMA-IR in patients with SLE (mean ± SEM: 5.65 ± 0.97, 4.65 ± 0.76, 5.00 ± 1.14, 6.87 ± 1.50 μg/dl; p = 0.518).

sICAM-1, sVCAM-1, and insulin sensitivity-related variables. The comparisons of test variables for the 68 patients with SLE and 34 controls are shown in Table 1. Patients had significantly higher fasting insulin levels, HOMA-IR, HOMA ß-cell, and plasma levels of sICAM-1 and sVCAM-1 than controls. Mean levels of plasma sICAM-1 and sVCAM-1 in the respective quartiles of insulin sensitivity-related variables in patients are shown in Table 2. SLE patients with HOMA-IR in the top quartile had the highest plasma levels of sICAM-1 (p = 0.038). Differences in plasma levels of sICAM-1 between patients in the respective fasting insulin quartiles were close to a statistical significance (p = 0.059). However, there was no statistical difference in plasma levels of sVCAM-1 between patients in the respective quartiles of insulin sensitivity-related variables.

In addition, the association of plasma levels of sICAM-1 and sVCAM-1 with insulin sensitivity-related variables in patients with SLE and controls is shown in Table 3. Plasma levels of sICAM-1, but not sVCAM-1, were significantly correlated with fasting insulin (r = 0.327, p = 0.006), HOMA-IR (r = 0.278, p = 0.022), and HOMA ß-cell (r = 0.359, p = 0.003) in patients with SLE. Moreover, in a stepwise regression analysis (Table 4), both fasting insulin and C3 were responsible for sICAM-1 variability (adjusted r^2 = 0.446, f-value = 14.302, p < 0.001) in patients with SLE.

DISCUSSION

We found that patients with SLE had significantly higher plasma levels of sICAM-1 compared with age-matched healthy controls, and also that the elevation of plasma sICAM-1 was associated with insulin resistance.

Recently, elevation of circulating levels of adhesion molecules in patients with SLE has been described[23-25] and this elevation is correlated with disease activity[23,25,26] or clinical manifestations[5,26]. Circulating levels of sICAM-1 were significantly higher in patients with SLE than in controls[23,25] and

Table 1. Insulin sensitivity-related variables and soluble adhesion molecules of patients with SLE and healthy controls. Values are mean ± standard error of mean.

	SLE Patients, n = 68	Healthy Controls, n = 34	p*
Insulin, μU/ml	8.83 ± 0.63	4.93 ± 0.39	0.000
Glucose, mmol/l	4.64 ± 0.05	4.84 ± 0.08	0.043
HOMA-IR	1.84 ± 0.14	1.08 ± 0.10	0.000
HOMA ß-cell	178.52 ± 15.37	66.51 ± 10.08	0.000
sICAM-1, ng/ml	271.12 ± 20.56	204.70 ± 5.71	0.026
sVCAM-1, ng/ml	898.83 ± 77.76	532.09 ± 18.44	0.001

HOMA-IR: homeostasis model assessment insulin resistance; sICAM-1: soluble intercellular adhesion molecule-1; sVCAM-1: soluble vascular cell adhesion molecule-1. * Statistical significance ($p < 0.05$) was determined by an independent sample t test.

Table 2. Mean levels of plasma sICAM-1 and sVCAM-1 in the respective quartiles of insulin sensitivity-related variables in all SLE patients. Values are mean ± standard error of mean.

	sICAM-1, ng/ml	p*	sVCAM-1, ng/ml	p*
Insulin quartiles, μU/ml				
< 5.6	241.13 ± 35.80		832.17 ± 146.61	
5.6–7.7	255.90 ± 16.98		818.31 ± 96.53	
7.7–11.1	222.35 ± 25.13		983.23 ± 186.09	
> 11.1	365.06 ± 64.07		961.60 ± 185.65	
		0.059		0.830
Glucose quartiles, mmol/l				
< 4.3	303.46 ± 62.41		881.67 ± 140.60	
4.3–4.6	267.70 ± 42.14		828.76 ± 144.16	
4.6–4.8	240.31 ± 31.52		885.75 ± 143.61	
> 4.8	268.96 + 20.90		966.87 + 176.87	
		0.763		0.941
HOMA-IR quartiles				
< 1.1	241.13 ± 35.80		832.17 ± 146.61	
1.1–1.6	249.86 ± 16.71		854.92 ± 88.95	
1.6–2.3	221.97 ± 26.32		812.12 ± 131.35	
> 2.3	371.48 ± 62.92		1096.10 ± 226.55	
		0.038		0.545
HOMA ß-cell quartiles				
< 93	261.69 ± 24.33		920.49 ± 148.83	
93–139	241.78 ± 30.59		1172.25 ± 206.41	
139–221	250.03 ± 29.62		649.80 ± 85.63	
> 221	330.94 ± 66.04		852.78 ± 143.13	
		0.408		0.122

sICAM-1: soluble intercellular adhesion molecule-1; sVCAM-1: soluble vascular cell adhesion molecule-1; HOMA-IR: homeostasis model assessment insulin resistance. * Statistical significance ($p < 0.05$) was determined by ANOVA.

Table 3. Correlation of sICAM-1 and sVCAM-1 with insulin sensitivity-related variables in patients with SLE and healthy controls.

	SLE Patients, n = 68				Healthy Controls, n = 34			
	sICAM-1		sVCAM-1		sICAM-1		sVCAM-1	
	r	p	r	p	r	p	r	p
Fasting insulin	0.327	0.006	0.057	0.642	0.143	0.419	0.112	0.528
Fasting glucose	0.002	0.987	0.118	0.338	0.346	0.045	0.338	0.051
HOMA-IR	0.278	0.022	0.067	0.589	0.173	0.327	0.144	0.415
HOMA ß-cell	0.359	0.003	0.021	0.862	0.028	0.875	0.030	0.865

sICAM-1: soluble intercellular adhesion molecule-1; sVCAM-1: soluble vascular cell adhesion molecule-1; HOMA-IR: homeostasis model assessment insulin resistance.

Table 4. Stepwise multiple regression analysis for sICAM-1 in all SLE patients. $R^2 = 0.480$, adjusted $R^2 = 0.446$. Stepwise multiple regression analysis was performed with sICAM-1 as a dependent variable and independent variables included fasting insulin, fasting glucose HOMA-IR, HOMA ß-cell, anti-dsDNA, C3, C4, SLEDAI, and prednisone.

	Beta	t	p
Fasting insulin	0.693	4.938	< 0.001
C3	–0.534	–3.801	0.001
f = 14.302 (p < 0.001)			

a positive correlation was observed between sICAM-1 levels and SLEDAI[23]. Ho, *et al* showed that plasma sVCAM-1 correlated significantly with SLEDAI, and SLE patients with renal disease had significantly higher plasma levels of sVCAM-1 compared with SLE patients without renal disease[26]. Kaplanski, *et al*[5] reported that serum levels of sVCAM-1 were significantly increased in patients with primary antiphospholipid syndrome (APS), SLE-associated APS, or pure SLE compared with control patients with thrombosis and healthy control subjects. Taken together, these reports suggest that sVCAM-1 measurement serves as an indicator for monitoring patients with lupus nephritis[26-28], and sICAM-1 measurement is considered as an additional serologic marker of disease activity in patients with SLE[23].

We did not observe any correlation between circulating levels of soluble cell adhesion molecules and disease activity. That may be because the median value for SLEDAI for all patients was 4, indicating that most patients had inactive or moderately active disease status[29-31]. In addition, about 28% of patients with SLE in our study carried aCL, and there was no significant effect of aCL on the plasma levels of sICAM-1 and sVCAM-1. However, our finding agreed with the previous observations that plasma levels of sICAM-1 and sVCAM-1 were elevated in patients with SLE compared with those in healthy individuals.

Circulating sICAM-1 is a marker related to atherosclerotic process and inflammatory disease[32]. The relationship between sICAM-1 and insulin sensitivity was observed not only in diabetic subjects[33] and in obese subjects[17,18], but also in healthy individuals[20,33]. Circulating sICAM-1 levels significantly correlated with fasting insulin and HOMA-IR[34]. The degree of insulin resistance was significantly correlated with sICAM-1 concentration in healthy normotensive and nondiabetic individuals[20]. Acute hyperglycemia in nondiabetic subjects induced an elevation of plasma levels of sICAM-1, and this effect was modulated by the ambient plasma insulin concentration[33]. A population-based study indicated that insulin was associated with sICAM-1 in nondiabetic elderly, whereas no association with sVCAM-1 was found[35]. An increase in plasma level of sICAM-1 was reported in normoglycemic obese subjects and the elevation of sICAM was related to tumor necrosis factor-α (TNF-α) system activation and insulin resistance. One recent study of the insulin effect on ICAM-1-mediated leukocyte adhesion and migration in diabetic rats indicated that insulin modulated TNF-α-induced ICAM-1 expression on microvascular endothelium control, leukocyte adhesion, and migration[36].

Posadas-Romero, *et al*[13] reported that hyperinsulinemia was more prevalent in SLE, and patients with SLE had significantly higher plasma insulin concentrations compared with healthy controls. El-Magadmi, *et al*[15] showed that patients with SLE significantly decreased in sensitivity to insulin according to HOMA equations. In our study, we confirmed our previous observations that patients with SLE had a higher risk of insulin resistance and abnormal insulin secretion than age-matched healthy controls[12], but also found that plasma levels of sICAM-1, but not sVCAM-1, were significantly correlated with fasting insulin, HOMA-IR, and HOMA ß-cell. However, such a significant relationship between plasma levels of sICAM-1 and insulin sensitivity-related variables was not observed in our healthy controls. This could be due to the low prevalence of insulin resistance based on a value of HOMA-IR greater than 2.0 in healthy controls (prevalence of insulin resistance in this study: 29% in patients with SLE vs 3% in controls)[16]. In addition, SLE patients with HOMA-IR in the top quartile had the highest plasma levels of sICAM-1, and fasting insulin was responsible for sICAM-1 variability. It seems that for patients with SLE, the insulin resistance-related phenomenon is associated more with circulating sICAM-1 than with sVCAM-1. However, the mechanism that triggers this phenomenon needs to be investigated further.

We showed that elevated plasma levels of sICAM-1 corresponded with increases in fasting insulin levels and the status of insulin resistance in patients with SLE. This finding suggests that in addition to the disease activity and clinical manifestations, abnormal insulin sensitivity in terms of hyperinsulinemia and/or insulin resistance also shows a significant relation to circulating sICAM-1 in patients with SLE.

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