Altered Levels of Adipocytokines in Association with Insulin Resistance in Patients with Systemic Lupus Erythematosus

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ABSTRACT. ***Objective.*** The metabolic syndrome, closely associated with cardiovascular disease, is characterized by increased insulin resistance (IR). Although accelerated atherosclerosis is frequently observed in systemic lupus erythematosus (SLE), the prevalence and significance of IR remain to be elucidated. We evaluated IR in association with plasma concentrations of adipocytokines in patients with SLE.

Methods. Outpatients with SLE (n = 37) and healthy controls (n = 80) were studied. A value of the homeostasis model assessment index (HOMA-IR) > 2.0 was considered to be IR. Plasma concentrations of adiponectin and tumor necrosis factor-α (TNF-α) were measured by ELISA and leptin by radioimmunoassay.

Results. HOMA-IR indices of the SLE patients were significantly higher than those of controls (2.3 ± 2.3 vs 1.3 ± 1.0, respectively; $p < 0.01$), although both groups exhibited a similar body mass index. The prevalence of hypertension and diabetes mellitus was significantly higher in patients with SLE compared with controls (48.6% vs 8.8% and 10.8% vs 0%). Twelve SLE patients (32%) with IR exhibited significantly higher incidence of hypertension and current proteinuria than SLE patients without IR. Plasma leptin, TNF-α, and, unexpectedly, adiponectin levels were higher in SLE patients than controls (adiponectin, 13.7 ± 5.0 vs 9.5 ± 3.9 μg/ml). Among the SLE patients, patients with IR showed significantly lower adiponectin levels than patients without IR (10.9 ± 4.6 vs 15.4 ± 4.4 μg/ml). Serum levels of adiponectin were significantly correlated inversely with HOMA-IR in SLE patients.

Conclusion. Elevated levels of adiponectin in SLE, despite inverse correlation with IR, suggest the possible involvement of adiponectin in IR and alterations in its effect on insulin sensitivity. (J Rheumatol 2006;33:1545–52)

Key Indexing Terms:
SYSTEMIC LUPUS ERYTHEMATOSUS ADIPONECTIN INSULIN RESISTANCE

Although the overall prognosis for patients with systemic lupus erythematosus (SLE) improved after the advent of immunosuppressive treatment[1,2], arterial vascular disorders including cardiovascular diseases (CVD), stroke, and peripheral vascular disease have become increasingly important causes of morbidity and mortality[3]. SLE has features of accelerated atherosclerosis in that vascular complications appear early in the course of the disease. The pathogenesis of these vascular complications in SLE has not been fully elucidated[4].

The metabolic syndrome, a concurrence of disturbed glucose and insulin metabolism, overweight and abdominal fat distribution, mild dyslipidemia, and hypertension, is closely associated with subsequent development of type 2 diabetes mellitus and cardiovascular disease[5,6]. It is characterized by increased insulin resistance and is also known as the insulin resistance (IR) syndrome. IR, present in over 80% of patients with type 2 diabetes[7], has recently been confirmed as an independent risk factor for CVD[8]. A US metaanalysis supported these findings, which estimated that IR roughly doubles the annual risk of a coronary heart disease event, irrespective of the presence of type 2 diabetes[9].

Recently, it has been shown that adipocytes secrete several factors including tumor necrosis factor-α (TNF-α), leptin, and adiponectin. Since these so-called "adipocytokines" influence insulin sensitivity and glucose metabolism profoundly, they might provide a molecular link between obesity and impaired insulin sensitivity. Indeed, leptin is considered to be a fundamental signal of satiety to the brain and has a variety of actions, ranging from interference with sympathetic activity to hematopoiesis and reproductive function[10]. Overproduction of TNF-α by adipose tissue is involved in IR in developing obesity[11]. Adiponectin is a recently described protein with important actions on both insulin sensitivity and

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inflammatory pathways[12,13]. Although it is mainly produced by adipose tissue, serum concentrations of adiponectin are inversely correlated with obesity[14,15]. Serum concentrations of adiponectin are also decreased in the presence of IR and are associated with the development of type 2 diabetes.

One report describes a high prevalence of IR among patients with SLE[16]. We hypothesized that adipocytokines might be related to the development of IR in SLE, and we assessed whether treatment, metabolic factors, and inflammatory mediators are independently related to IR in patients with SLE.

MATERIALS AND METHODS

Study population. A total of 37 patients with SLE attending an outpatient clinic at Okayama University Hospital were studied. Patients were recruited from August 2003 to April 2004. All patients fulfilled the diagnostic criteria of the American College of Rheumatology for SLE. Inclusion criteria were (1) duration of disease over one year, (2) no hospitalization for at least 6 months prior to recruitment, and (3) dosage of prednisolone < 20 mg/day. Exclusion criteria were (1) overlap syndrome, (2) persistent serum creatinine concentrations > 2.0 mg/dl, (3) pregnancy, (4) cancer, (5) liver cirrhosis, or (6) receiving insulin. Eighty age and sex matched healthy volunteers served as controls. Written informed consent was obtained from all patients and controls, and Okayama University Hospital's ethical committee approved the study.

Clinical and laboratory assessment. Information was obtained through a structured interview, physical examination, laboratory tests, and review of medical records.

Blood specimens were collected after an overnight fast for the measurement of a complete blood count and levels of insulin, glucose, creatinine, total cholesterol, adiponectin, TNF-α, and leptin. Creatinine clearance was calculated as an indicator of renal function with the Cockcroft-Gault formula, and current proteinuria was assessed by dipstick measurement. In patients with SLE, C-reactive protein levels, antiphospholipid antibody (considered positive if either the level of IgG anti-$ß_2$ glycoprotein I exceeded 3.5 units/ml or lupus anticoagulant was positive), tests for antibodies against double-stranded DNA, and the total hemolytic complement were also determined.

The homeostasis model assessment index (HOMA-IR) was used for evaluation of insulin resistance. HOMA-IR was calculated according to the formulas in the HOMA model[17]. HOMA-IR exceeding 2.0 was considered to indicate insulin resistance, as described[18].

Subjects were considered to have (1) hypertension if they were taking antihypertensive agents or if they had systolic blood pressure ≥ 140 mm Hg or diastolic pressure ≥ 90 mm Hg; (2) hyperlipidemia if taking antihyperlipid drugs or if their total cholesterol was ≥ 220 mg/dl; and (3) diabetes if taking antidiabetes drugs or if fasting glucose level was > 126 mg/dl.

The diagnosis of lupus nephritis was made after histological evaluation of kidney specimens obtained from renal biopsy.

Adipocytokines. Serum levels of leptin were measured by radioimmunoassay using a commercial kit (Linco Research, St. Charles, MO, USA). The limit of sensitivity for leptin was 0.5 ng/ml. The interassay and intraassay coefficients of variation were < 10% across the range of measured results. TNF-α was measured using a commercial ELISA kit (Jimro, Gunma, Japan). The detection range for adiponectin was 15–1000 pg/ml, with a sensitivity of 0.4 pg/ml. The interassay and intraassay coefficients of variation were < 10% across the range of measured results. Serum adiponectin was measured with an enzyme immunoassay (Otsuka Pharmaceutical Co., Tokushima, Japan). The detection range for adiponectin was 0.375–12.0 μg/ml with a sensitivity of 23.4 pg/ml. Coefficients of variation were < 10%. In every assay, we observed a proper standard curve by using serial dilutions of recombinant human leptin, TNF-α, or adiponectin as described in the manufacturer's instructions.

Statistical analysis. Comparisons among multiple groups were made by means of 2-sample t tests or Mann-Whitney U tests (in the case of nonparametric distribution) for continuous variables, and by chi-square analysis for categorical variables. Two-sided p values < 0.05 were considered statistically significant.

RESULTS

Comparison of clinical variables of SLE patients and controls. Characteristics for the 37 patients with SLE and 80 controls are shown in Table 1. Hypertension and diabetes were more common in patients with SLE than controls. Blood pressure levels in patients with SLE were significantly higher than controls. Creatinine clearance was similar in the 2 groups. HOMA-IR for patients with SLE was higher than that of controls, although the body mass index (BMI) was comparable in the 2 groups.

Comparison of clinical variables of SLE patients with and without IR. There was no significant difference in age, age at diagnosis, and duration of disease between SLE patients with and those without IR (Table 2). Hypertension was more common in patients with IR compared to patients without IR (92.8% vs 26.0%, respectively). A history of lupus nephritis was more common in patients with IR (no statistical significance). Patients with IR had significantly higher levels of blood pressure (132 ± 18/81 ± 9 mm Hg vs 120 ± 12/74 ± 7 mm Hg) and higher incidence of current proteinuria (35.7% vs 4.3%) than those without IR. Although the disease activity, serum level of complement, and anti-double-stranded DNA antibodies were not different in the 2 groups, the frequency of antiphospholipid antibody tended to be higher in patients with IR (31.2% vs 9.2%). The average daily dosage of prednisolone was similar in the 2 groups.

Plasma levels of adipocytokines in SLE. Levels of adipocytokines associated with IR were compared in patients with SLE and controls (Figure 1). The serum levels of all the adipocytokines we investigated, adiponectin, leptin, and TNF-α, were significantly elevated in patients with SLE compared with controls. Since the HOMA-IR findings were quite different for SLE patients and controls, we performed further statistical analyses between these groups after adjustment of HOMA-IR. SLE patients exhibited higher serum levels of adiponectin, leptin, and TNF-α compared to the control group even after adjustment for HOMA-IR values — HOMA-IR, 1.67 ± 1.02 vs 1.63 ± 0.90; adiponectin, 14.3 ± 4.8 vs 8.5 ± 3.2 μg/ml; leptin, 22.5 ± 21.0 vs 10.1 ± 4.4 ng/ml; and TNF-α, 4.9 ± 5.3 vs 1.6 ± 2.6 pg/ml, for SLE vs controls, respectively (Figure 1). Furthermore, even after adjustment of the prevalence of hypertension, hyperlipidemia, and diabetes, SLE patients exhibited higher serum levels of adiponection, leptin, and TNF-α compared to controls — hypertension, 26.9% vs 26.9%; hyperlipidemia, 34.6% vs 34.6%; diabetes, 0% vs 0%; adiponectin, 15.4 ± 5.1 vs 10.3 ± 4.3 μg/ml; leptin, 23.5 ± 21.9 vs 10.0 ± 4.1 ng/ml; TNF-α, 5.8 ± 6.1 vs 1.8 ± 2.9 pg/ml, SLE vs controls, respectively (Figure 1). Serum levels of adiponectin were inversely correlated with HOMA-IR in patients with SLE (Figure 2A). Levels of adiponectin were

Table 1. Characteristics of patients with systemic lupus erythematosus and controls. Data are means ± SD.

	Patients	Controls	p
No. of subjects	37	80	
Age, yrs	44 ± 15	44 ± 6	NS
Hypertension, %	48.6	8.8	< 0.0001
Hyperlipidemia, %	34.2	36.2	NS
Diabetes, %	10.8	0	< 0.05
Body mass index, kg/m^2	22.1 ± 3.5	22.2 ± 3.2	NS
Blood pressure, mm Hg			
Systolic	124 ± 16	117 ± 16	< 0.05
Diastolic	77 ± 9	71 ± 10	< 0.005
Creatinine clearance, ml/min	85.5 ± 22.7	91.9 ± 18.6	NS
HOMA-IR	2.32 ± 2.34	1.32 ± 0.99	< 0.005

HOMA-IR: homeostasis model assessment index for insulin resistance. NS: not significant.

Table 2. Characteristics of SLE patients with and without insulin resistance (IR). Data are means ± SD.

	With IR	Without IR	p
No. of subjects	14	23	
Age, yrs	44 ± 18	43 ± 13	NS
Age at diagnosis, yrs	34 ± 14	34 ± 15	NS
Duration of disease, yrs	9.4 ± 7.1	9.0 ± 6.3	NS
Hypertension, %	92.8	26.0	0.0001
Hyperlipidemia, %	35.7	34.8	NS
Diabetes, %	14.3	8.7	NS
History of nephritis, %	64.3	47.8	NS
Body mass index	23.6 ± 4.4	21.3 ± 2.7	0.0583
Blood pressure, mm Hg			
Systolic	132.8 ± 17.8	120.4 ± 12.7	0.0185
Diastolic	81.4 ± 9.3	74.3 ± 7.0	0.0117
Current proteinuria, %	35.7	4.3	0.0121
Creatinine clearance, ml/min	90.0 ± 26.9	82.9 ± 18.7	NS
CH50, mU/ml	36.3 ± 10.3	39.9 ± 7.0	NS
Anti-double-stranded DNA, IU/ml	30.8 ± 26.3	53.3 ± 111.5	NS
Antiphospholipid antibodies, %	31.2	9.1	NS
Maintenance dose of corticosteroid, mg/day	8.8 ± 3.8	8.2 ± 4.1	NS

NS: not significant.

also inversely correlated with BMI in patients with SLE and controls (Figure 2B). Levels of leptin were inversely correlated with the levels of adiponectin only in the controls (Figure 2C). No significant correlation was observed between adiponectin and TNF-α in the 2 groups (Figure 2D).

Next, patients with SLE were divided into subgroups with or without IR, and differences in the serum levels of adipocytokines were examined. Among these adipocytokines, serum levels of adiponectin were significantly elevated in SLE patients without IR compared with the controls. Among patients with SLE, lower levels of adiponectin were noted in patients with IR compared to patients without IR (Figure 3A). The levels of leptin and TNF-α were similar in patients irrespective of IR status (Figures 3B, 3C). Adiponectin levels in SLE patients with normal renal function were higher than those in the controls (Figure 4). Serum levels of adiponectin were not different comparing SLE patients with normal renal function and those with deteriorated renal function.

DISCUSSION

A report by Tim, *et al* demonstrated that patients with SLE had a higher risk of IR and abnormal insulin secretion compared with age matched healthy controls, regardless of the presence of anticardiolipin antibody and with varying disease activities[16]. In our case–control study, we assessed the prevalence of IR in SLE patients in association with serum levels of adipocytokines. The main findings are as follows: (1) the prevalence of IR is significantly higher among SLE patients; (2) increased IR may be associated with hypertension and current proteinuria; and (3) among the adipocytokines, the levels of adiponectin were found to be correlated inversely with IR in SLE patients, and those values were higher than in controls. These findings suggest that IR in SLE patients may potentially predispose to accelerated atherosclerosis.

Both SLE and control groups exhibited rather high incidence of hyperlipidemia. Although the prevalence of

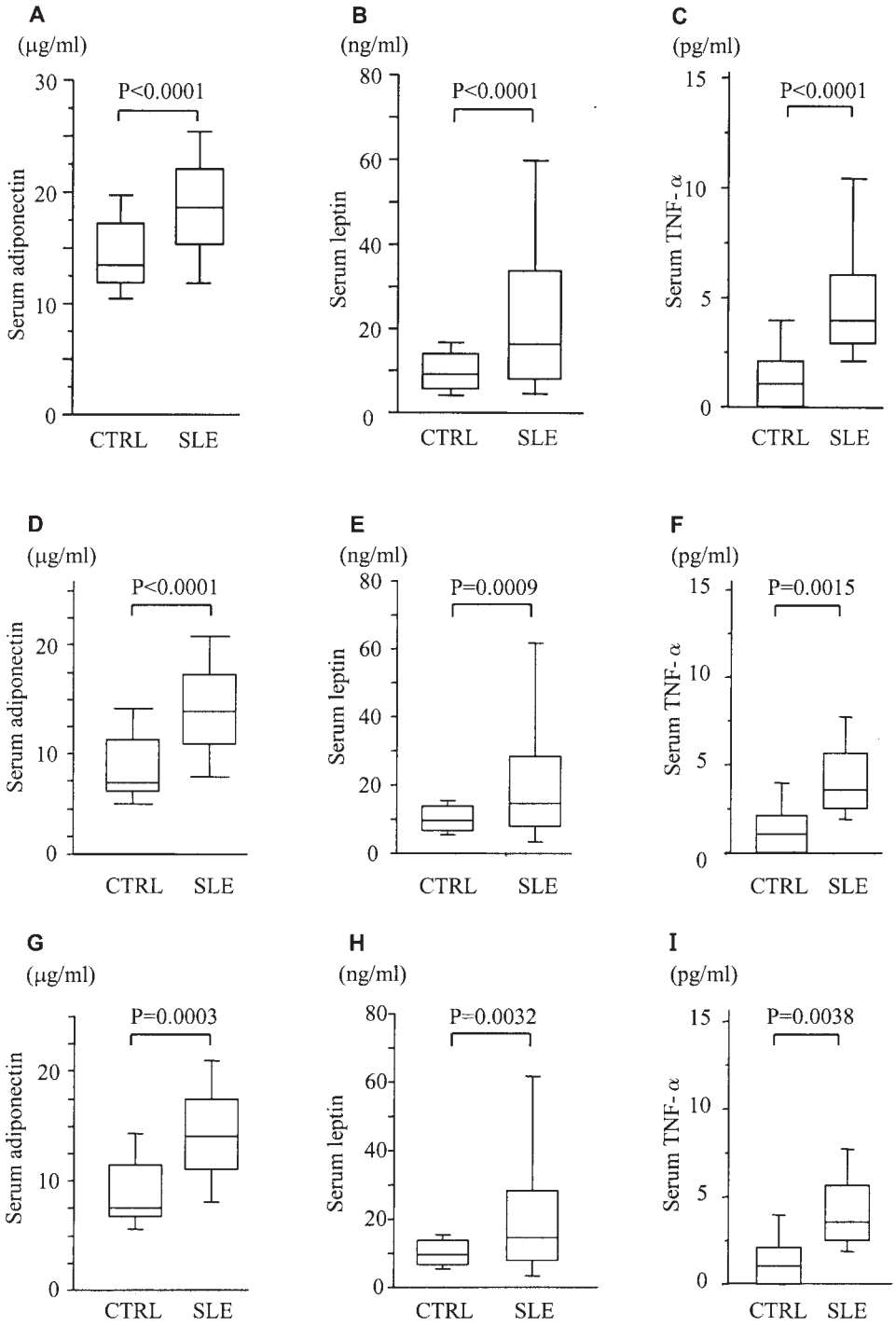

Figure 1. Serum levels of adiponectin, leptin, and TNF-α in controls and SLE patients. A-C: Unadjusted values. D-F: Comparison after adjustment for HOMA-IR value. G-I: Comparison after adjustment for prevalence of hypertension, hyperlipidemia, and diabetes. A, D, G: Serum levels of adiponectin. B, E, H: Serum levels of leptin. C, F, I: Serum levels of TNF-α. Boxes represent interquartile range (25th–75th centiles); horizontal lines represent medians; error bars represent 95% confidence intervals of the mean.

menopausal state was not available from our clinical records, this factor might have affected lipid metabolism, leading to the findings we observed. Additionally, menopausal status or hormone replacement therapy may affect secretion of adipocytokines via accumulation of visceral adipose tissue. However, the ratio of the hyperlipidemic population in our SLE group was similar to the control group. In addition, the mean HOMA-IR in the controls in this study was similar to

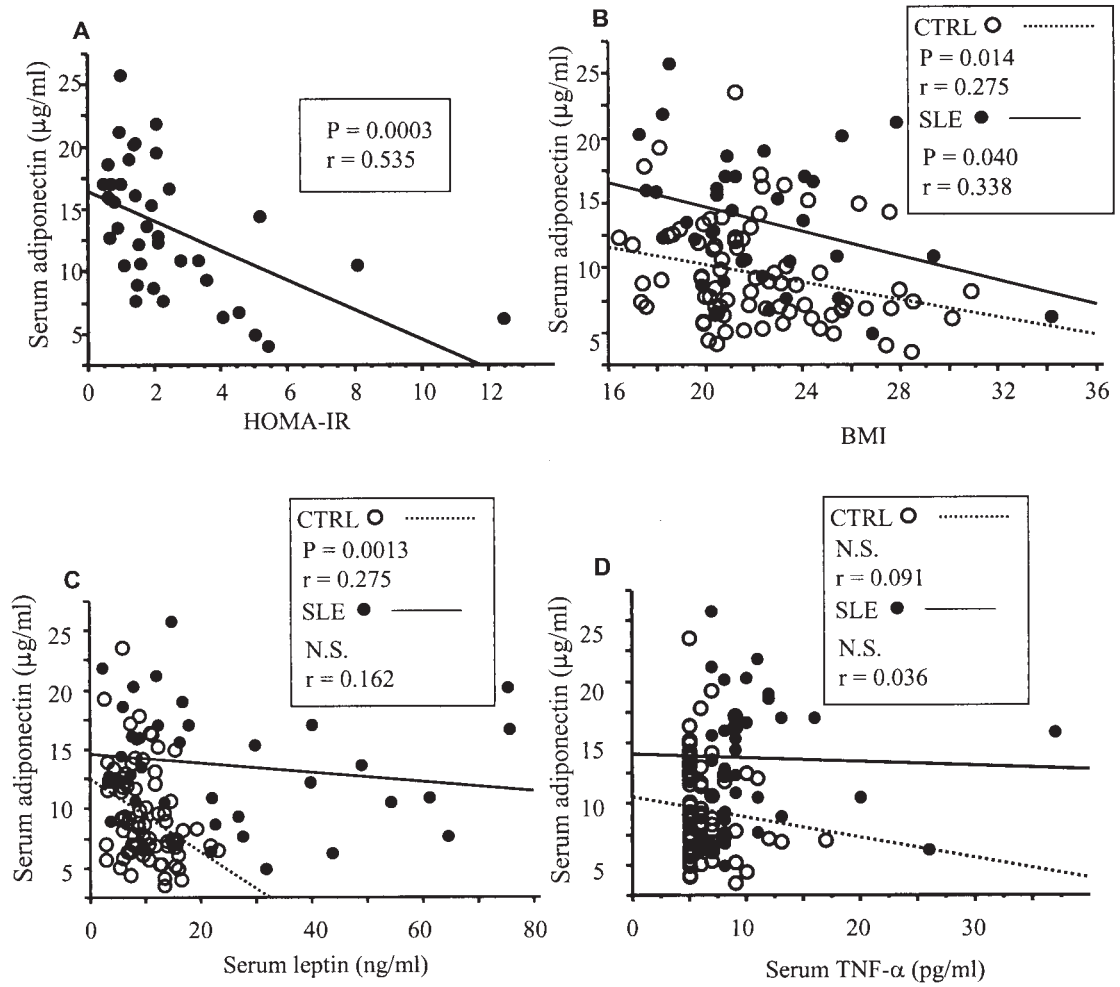

Figure 2. Relationship between serum adiponectin and HOMA-IR (A), BMI (B), serum leptin (C), and serum TNF-α (D) in SLE patients and controls. Data are shown as Pearson product moment correlation coefficients and p values. NS: not significant.

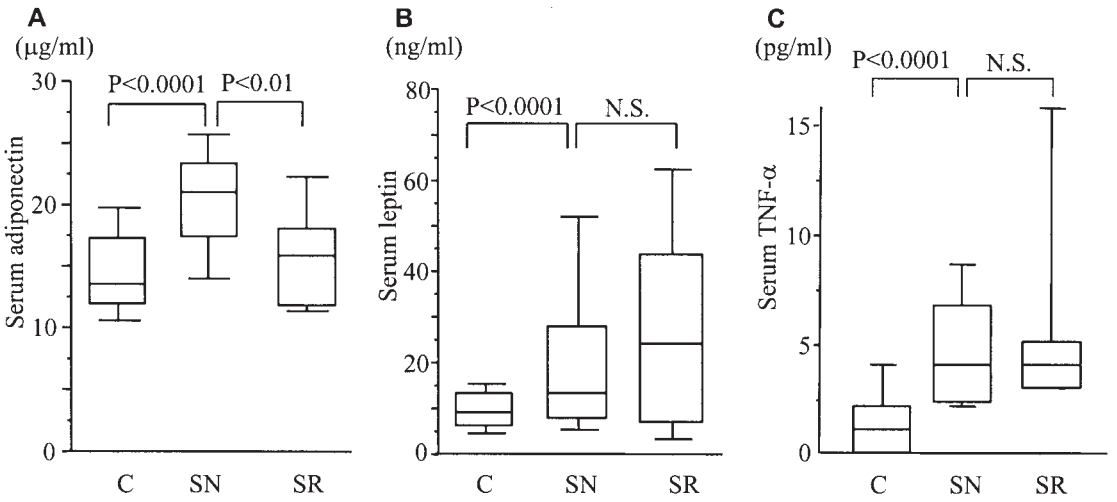

Figure 3. Serum levels of adiponectin (A), leptin (B), and TNF-α (C) in controls ("C") and SLE patients with ("SR") and without ("SN") insulin resistance. Boxes represent interquartile range (25th–75th centiles); horizontal lines represent medians; error bars represent 95% confidence intervals of the mean. NS: not significant.

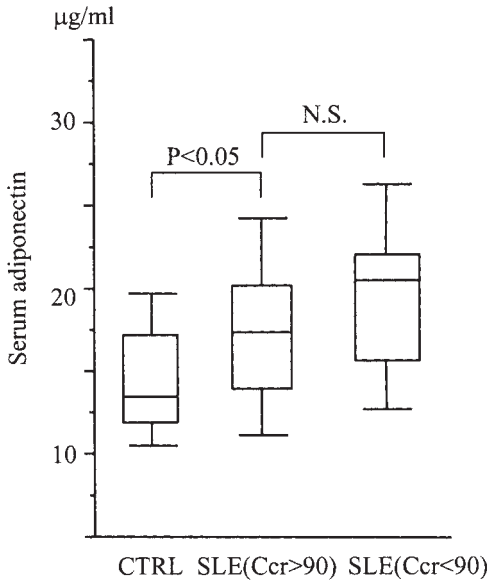

Figure 4. Serum levels of adiponectin in controls and SLE patients with normal (Ccr > 90) and deteriorated renal function (Ccr < 90). Boxes represent interquartile range (25th–75th centiles); horizontal lines represent medians; error bars represent 95% confidence intervals of the mean. Ccr: creatinine clearance, ml/min; NS: not significant.

previous reports[19]. Therefore, we consider our observations in patients with SLE to be valid and significant.

A previous report described elevated serum levels of leptin in SLE[20], which is consistent with our results showing significantly elevated serum levels of leptin in SLE compared to controls. To our knowledge, this is the first report examining serum levels of adiponectin in patients with SLE. Although the levels of leptin were inversely correlated with the levels of adiponectin in the controls, no significant correlation was observed in the SLE group. In SLE patients, levels of adiponectin correlated inversely with the HOMA-IR, suggesting that adiponectin plays an important role in developing IR in SLE.

Recently, adipocytes have been recognized to secrete adipocytokines such as TNF-α, leptin, and adiponectin, potentially leading to the development of metabolic syndrome[21]. Among them, adiponectin is an insulin-sensitizing hormone that is exclusively expressed in adipose tissues. Reduced production of adiponectin is considered to be associated with the pathophysiology of IR and atherosclerosis[22,23]. In our study, serum levels of adiponectin correlated inversely with BMI in SLE, which is consistent with a report of a strong negative correlation between plasma adiponectin levels and BMI in a general population study[24]; the BMI was comparable in patients with SLE and the controls. Although we were able to assess BMI from medical records, further information to determine the mass of visceral adipose tissue, such as abdominal computer tomographic scanning, or values for abdominal obesity by waist circumference, was not available. Since development of central obesity is one of the potential adverse effects accompanying corticosteroid therapy, it is possible that BMI values would not be an adequate indication of the mass of visceral adipose tissue in patients with SLE. This point needs further evaluation in future studies.

Interestingly, the levels of adiponectin were significantly higher in SLE patients compared with controls, despite the higher prevalence of IR. Only a few other conditions such as renal failure, nephrotic syndrome, and advanced diabetes are associated with increased plasma adiponectin concentrations[25-27]. In patients with endstage renal disease, changes in glomerular filtration rate (GFR) account for the elevated adiponectin concentrations. Our study showed no relation between renal function and adiponectin in SLE patients; and as well, higher levels of adiponectin were observed in SLE patients with normal renal function as compared to controls, indicating that the elevated adiponectin concentrations in SLE are not attributable to deteriorated glomerular clearance rate. One report has shown that GFR calculated by the Cockcroft-Gault formula may have underestimated renal function in patients with lupus nephritis[28]. We evaluated SLE patients receiving maintenance therapy, and these patients were not in the active stage of the disease. Although some studies found no clear correlation between true GFR and the Cockcroft-Gault formula in SLE patients without disease activity, we may have underestimated creatinine clearance by this method. However, the Cockcroft-Gault formula was applied in all patients and controls in our study, and we consider that use of the formula in estimating creatinine clearance did not significantly affect the results we observed.

A history of lupus nephritis and diabetes was more common in patients with IR, although this was not statistically significant. IR affects the development of diabetes in general populations and may also affect the development of diabetes in SLE. With a larger study population, a history of lupus nephritis may be found to be associated with IR and development of diabetes. Therefore, we cannot deny the potential association of these factors with IR in SLE. In our study, the disease activity of all SLE patients was controlled — no patient was in the active disease stage. Thus, we are unable to draw conclusions about the potential influence of disease activity on adipocytokine levels, and this needs further investigation. Based on our findings, we speculate that the effect of adiponectin on regulating insulin sensitivity might be attenuated in patients with SLE.

It has been suggested that corticosteroids have a role in modifying IR[29,30]. One study found that prednisolone and high doses of pulsed glucocorticoid were independently associated with decreased insulin sensitivity in patients with rheumatoid arthritis[31]. Another report described that glucocorticoids inhibit the synthesis of adiponectin in humans, as shown by both acute exogenous administration to healthy subjects and chronic endogenous hypercortisolism[32]. However, in our study, the daily dosage of corticosteroid as maintenance therapy was similar in the 2 groups, and there was no associ-

ation between adiponectin and the dosage of corticosteroid or duration of disease (data not shown), suggesting the absence of an influence of corticosteroid on IR. Alternatively, a higher incidence of proteinuria in SLE patients with IR may suggest an aggravated response to treatment in this population.

Our study showed that IR was significantly correlated with hypertension in patients with SLE. The Bogalusa Heart Study showed that adolescents with hypertension exhibited decreased insulin sensitivity as well as a family history of diabetes and hypertension[33]. Possible pathophysiological effects induced by IR that are linked to the hemodynamic variable of blood pressure are an increased sodium and volume retention, altered peripheral vascular resistance, and increased activation of the sympathetic nervous system[34-36]. Our findings suggest that IR in SLE patients is one of the important causes of hypertension. In addition, the frequency of positivity for antiphospholipid antibody tended to be higher in patients with SLE. It is well known that general populations positive for antiphospholipid antibody frequently develop vascular complications[37]. Therefore, antiphospholipid antibody positivity suggestive of the background of vasculitis and hypertension may serve as an important cause of accelerated atherosclerosis in addition to IR in patients with SLE.

Patients with SLE exhibited a relatively high prevalence of insulin resistance in association with hypertension and current proteinuria. Although levels of adiponectin were correlated inversely with IR in SLE patients, they were higher than in controls. Whereas the precise mechanism of adiponectin in developing IR in SLE is not clear, we speculate that the effect of adiponectin on insulin sensitivity might be attenuated in patients with SLE. Further analysis of levels of adiponectin receptors or signaling pathways may clarify the biological roles of adiponectin in IR in SLE.

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