Adiponectin Concentrations in Sera From Patients With Type 2 Diabetes Are Negatively Associated With Sympathovagal Balance as Evaluated by Power Spectral Analysis of Heart Rate Variation

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OBJECTIVE — To investigate whether cardiac autonomic activity, particularly sympathovagal balance as estimated by power spectral analysis (PSA) of heart rate variation (HRV), is associated with serum adiponectin concentrations in patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS — We studied 105 patients with type 2 diabetes (51 women and 54 men). Serum adiponectin concentrations were measured by sandwich enzyme-linked immunosorbent assay. HRV was determined automatically every 5 min over 24 h using Holter electrocardiographic recording. PSA of R-R intervals was performed using fast Fourier transformation. Low-frequency (both sympathetic and parasympathetic activities), high-frequency (pure parasympathetic activity), and the ratio of low-frequency–to–high-frequency power (LF-to-HF ratio), an index of sympathovagal balance, were used as indexes of cardiac autonomic activity.

RESULTS — We found no significant correlation between serum adiponectin and low-frequency or high-frequency power in patients with diabetes. Serum adiponectin concentration correlated negatively with the 24-h LF-to-HF ratio ($r = -0.343$, $P = 0.0009$) and creatinine clearance ($r = -0.411$, $P < 0.0001$). Serum adiponectin concentrations were significantly higher in patients with overt albuminuria than in those with normoalbuminuria or microalbuminuria. In multivariate analysis controlling for sex, BMI, glycemic control, lipid profile, and renal function, serum adiponectin concentration showed an independent negative association with 24-h LF-to-HF ratio ($\beta = -0.332$, $P = 0.020$). Furthermore, sex, HDL cholesterol, and renal function retained significant influence on the serum adiponectin concentration in patients with diabetes.

CONCLUSIONS — Sympathovagal balance favoring relative sympathetic activation was associated with low serum concentrations of adiponectin in patients with type 2 diabetes.

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Abbreviations: CAD, coronary artery disease; Ccr, creatinine clearance; CVD, cardiovascular disease; HOMA-IR, homeostasis model assessment of insulin resistance; HRV, heart rate variation; LF-to-HF ratio, ratio of low-frequency to high-frequency power; PSA, power spectral analysis; UAE, urinary albumin excretion.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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Individuals with the metabolic syndrome, which includes diabetes, dyslipidemia, and hypertension, are at increased risk for cardiovascular disease (CVD) (1,2). Several studies have reported that serum concentrations of adiponectin, a protein produced in adipose tissue, are associated negatively with components of this metabolic syndrome, including obesity (3), insulin resistance, and dyslipidemia (4,5). Therefore, low serum adiponectin concentrations are associated with the metabolic syndrome (6). Furthermore, previous reports demonstrated a relationship between hypoadiponectinemia and development of type 2 diabetes or coronary artery disease (CAD) (7,8). Considered together, low serum adiponectin is a risk factor not only for the metabolic syndrome but also for CVD.

Low heart rate variation (HRV) and cardiac sympathetic overactivity are predictors of CVD (9,10). In particular, sympathetic overactivity may contribute to development of CVD as well as the metabolic syndrome through hypertension, insulin resistance, and increased hematocrit (10). Power spectral analysis (PSA) of HRV simultaneously quantifies both cardiac sympathetic and parasympathetic activities, allowing evaluation of the moment-to-moment preponderance between these activities, i.e., sympathovagal balance (11–13). In a previous study of children of patients with type 2 diabetes, sympathetic activation estimated as a ratio of low-frequency to high-frequency power (LF-to-HF ratio) by spectral analysis was associated with arterial hypertension and insulin resistance (14). Therefore, sympathetic activation has been considered to be a link between insulin resistance and hypertension. However, no reports have examined the

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relationship between serum adiponectin and cardiac autonomic nerve function.

Hypothesizing that low serum adiponectin concentration is associated with sympathetic activation in type 2 diabetes, we investigated whether cardiac autonomic activities or sympathovagal balance as estimated by PSA of HRV is associated with serum concentrations of adiponectin in patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS

We studied 105 patients with type 2 diabetes (51 women and 54 men). The patients were referred to the diabetes outpatient clinic at the Dokkyo University Hospital (Saitama, Japan) Type 2 diabetes was defined based on the criteria of the American Diabetes Association. All patients were treated with oral hypoglycemic agents (glibenclimide 5.0–7.5 mg/day) or insulin and were in poor glycemic control. All patients were hospitalized for a 2-week period to optimize glycemic control. The HbA_{1c} concentrations averaged 9.84 ± 1.88% (mean ± SD) on admission. All patients received an optimal diet therapy (25 kcal/kg of ideal body weight; 50% carbohydrate, 20% protein, and 30% fat). In the study group, diabetes was controlled with diet alone (n = 13), diet and oral hypoglycemic agents (n = 79), or diet and insulin (n = 14).

A total of 45 of the patients with diabetes had hypertension. Hypertension is defined as systolic blood pressure >140 mmHg, diastolic blood pressure >90 mmHg, and/or treatment with an antihypertensive agent. These medications included ACE inhibitors (5 patients), calcium channel blockers (32 patients), angiotensin receptor blockers (21 patients), and/or α-blockers (5 patients). None of the patients were taking β-blockers or antiarrhythmic drugs.

CVD was defined as CAD and/or stroke. CAD was defined as history of myocardial infarction, coronary artery bypass grafting, or abnormal result on coronary angiography. Stroke was defined as history of ischemic stroke confirmed by cerebral computed tomography or nuclear magnetic resonance imaging. Eight patients had CAD, and four patients had stroke.

To investigate whether diabetic nephropathy was associated with serum adiponectin concentration, patients with diabetes were divided into three groups according to urinary albumin excretion (UAE) in a 24-h collection: normoalbuminuria (group A), UAE <30 mg/24 h; microalbuminuria (group B), UAE 30–299 mg/24 h; and macroalbuminuria (group C), >300 mg/24 h. As an index of glomerular filtration rate, creatinine clearance (Ccr) was calculated using the same 24-h urine collection.

Venous blood was obtained between 6:00 and 6:30 A.M. after an overnight fast. Serum adiponectin concentrations were measured using a commercially available enzyme-linked immunosorbent assay (Otsuka Pharmaceuticals, Tokyo, Japan). Intra- and interassay coefficients of variation were 4.06% and 4.69%, respectively. HbA_{1c} levels were measured by high-performance liquid chromatography (Kyoto Daiichi-kagaku, Kyoto, Japan). Plasma insulin concentrations were determined by radioimmunoassay.

Insulin resistance was evaluated by homeostasis model assessment (HOMA-IR), calculated as fasting plasma insulin (μU/ml) × fasting plasma glucose (mmol/l)/22.5.

PSA of HRV

During a 2-week hospitalization, continuous 24-h electrocardiography was performed using a cassette-based two-channel Holter monitor (Nihon Kohden, Tokyo, Japan). Electrocardiographic signals were digitized and stored using a commercially available personal computer–based system. PSA of HRV was performed by fast Fourier transformation (Cardinyzer; Kissei Komtec, Matsumoto, Japan). The PSA was calculated automatically from a series of 256 consecutive intervals between normal *R* waves for each 5-min period over 24 h. The PSA software provided R-R variation data distributed in two bands: low-frequency power (0.04–0.15 Hz) and high-frequency power (0.15–0.40 Hz). Low-frequency power is believed to reflect both sympathetic and parasympathetic activities, whereas high-frequency power is determined solely by parasympathetic activity. A LF-to-HF ratio was calculated as a measure of sympathovagal balance that would reflect any shift toward sympathetic or parasympathetic activation. When a 5-min period included more than two series of 256 consecutive intervals between *R* waves, low frequency and high frequency were each averaged over a 5-min period.

PSA was evaluated over 24 h and at 6:00 A.M., 9:00 A.M., 1:00 P.M., 7:00 P.M., and 11:00 P.M.

Statistical analysis

Data are presented as means ± SD or medians and interquartile ranges. Differences between groups were analyzed by Student's unpaired *t* test or one-way ANOVA with the Newman-Keuls multiple comparison test and were also ana-

Table 1—*Linear regression analysis of relationships between the serum adiponectin and characteristics of patients with type 2 diabetes*

	Relationship to adiponectin	
	r	*P*
Age (years)	0.0745	0.4503
BMI (kg/m^2)	−0.1007	0.3067
Duration of diabetes (years)	0.1938	0.0476
Systolic blood pressure (mmHg)	0.2153	0.0274
Diastolic blood pressure (mmHg)	0.0296	0.9764
Fasting plasma glucose (mmol/l)	0.0625	0.5267
HbA_{1c} (%)	−0.2282	0.0204
Total cholesterol (mmol/l)	0.3660	0.0001
Triglyceride (mmol/l)	−0.1209	0.2216
HDL cholesterol (mmol/l)	0.2178	0.0263
Fasting insulin (μU/ml)	−0.2682	0.0282
HOMA-IR	−0.3569	0.0004
Ccr (ml/min)	−0.4112	<0.0001
UAE ($\log_{10}$ · mg/24 h)	0.4874	<0.0001
24-h low-frequency power (ln · ms^2)	0.0209	0.8443
24-h high-frequency power (ln · ms^2)	0.0424	0.6912
24-h LF-to-HF ratio	−0.3433	0.0009

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lyzed using the Mann-Whitney *U* test or the Kruskal-Wallis with Dunn's multiple comparison tests. Correlation was determined by linear regression analysis or multivariate analysis. Significance of differences in prevalence between groups classified by UAE was analyzed using χ^2 test. Logarithmic transformation of low frequency, high frequency, and UAE was used to render the distribution normal for parametric tests. $P < 0.05$ was accepted as indicating statistical significance.

RESULTS — Among all patients with type 2 diabetes in this study, age was 58.7 ± 12.4 years, BMI was 24.5 ± 4.8 kg/m^2, and duration of diabetes was 10.2 ± 75 years. Fasting plasma glucose was 9.82 ± 3.20 mmol/l, and HbA_{1c} was 9.84 ± 1.88%. Serum concentrations of adiponectin were significantly higher in women than in men with diabetes (10.9 ± 7.58 vs. 8.04 ± 5.93 μg/ml, $P = 0.0320$).

By simple linear regression analysis, serum adiponectin concentrations in the 105 patients with type 2 diabetes correlated positively with duration of diabetes ($P < 0.05$), systolic blood pressure ($P < 0.05$), total cholesterol ($P = 0.0001$), HDL cholesterol ($P < 0.05$), and UAE ($P < 0.0001$). Serum adiponectin correlated negatively with HbA_{1c} ($P < 0.05$; Table 1), fasting serum insulin ($P < 0.05$; Table 1), HOMA-IR ($P < 0.001$; Table 1), Ccr ($P < 0.0001$; Fig. 1*B*), and the 24-h LF-to-HF ratio ($P < 0.001$; Fig. 1*A*). However, we found no significant correlation between serum adiponectin and BMI in patients with type 2 diabetes.

We then investigated correlations between serum adiponectin and LF-to-HF ratio at different periods during the day, including 6:00 A.M., 9:00 A.M., 1:00 P.M., 7:00 P.M., and 11:00 P.M., using linear regression analysis. Among various periods, we found the negative correlation between serum adiponectin and LF-to-HF ratio to be strongest at 6:00 A.M. ($r = -0.2735$, $P = 0.0008$). Serum adiponectin also showed a significant negative correlation with LF-to-HF ratio at 9:00 A.M. ($r = -0.2735$, $P = 0.0083$) and 3:00 A.M. ($r = -0.2058$, $P = 0.0491$). However, we found no significant correlation between serum adiponectin and LF-to-HF ratio at 1:00 P.M. ($r = -0.1922$, $P = 0.0679$) and 7:00 P.M. ($r = -0.1411$, $P = 0.1796$).

We next examined whether severity of diabetic nephropathy (classified by albuminuria as group A, B, or C) was related to glycemic control, Ccr, serum adiponectin concentration, and LF-to-HF ratio (Table 2). Systolic blood pressure was significantly higher in groups C ($P < 0.001$) and B ($P < 0.01$) than in group A and was also higher in group C than in group B ($P < 0.01$). Diastolic blood pressure was higher in group C than in group A ($P < 0.01$). HbA_{1c} was significantly lower in group C than in group A ($P < 0.01$) or group B ($P < 0.05$). Ccr was lower in groups B ($P < 0.05$) and C ($P < 0.001$) than in group A and was lower in group C than in group B ($P < 0.01$). Serum adiponectin concentrations were significantly higher in group C than in group A ($P < 0.001$) or B ($P < 0.001$). Hypertension was more prevalent in group C ($P < 0.05$). The 24-h LF-to-HF ratio was significantly lower in group C than in group A ($P < 0.01$).

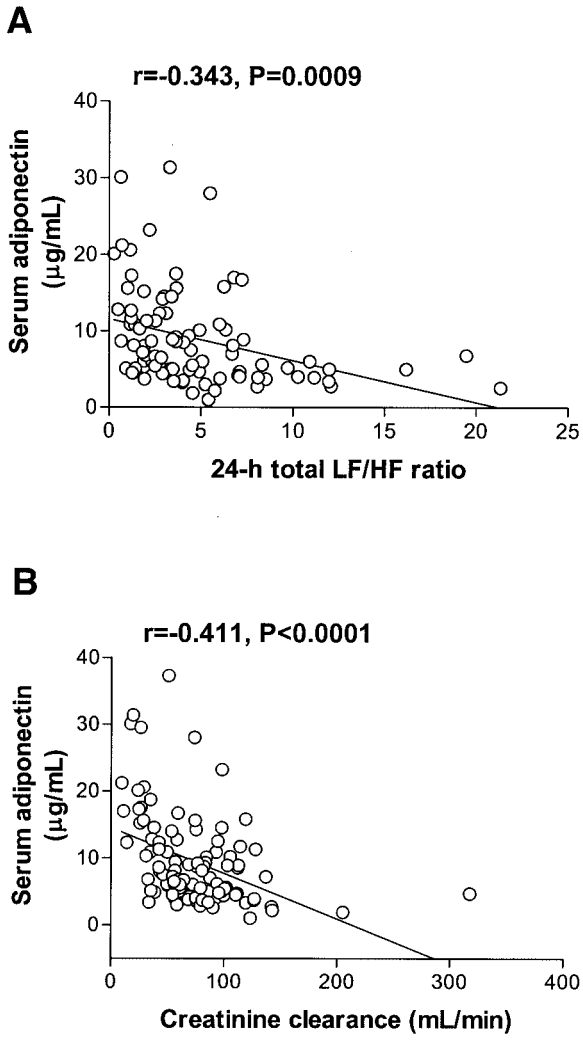

Figure 1—*Correlation between serum concentrations of adiponectin and LF-to-HF ratio* (A) *or Ccr* (B) *in patients with type 2 diabetes.*

We also investigated the effects of antihypertensive agents on LF-to-HF ratio in patients with diabetes. We found no significant differences in LF-to-HF ratio between diabetic patients treated with no antihypertensive agents (3.67 [2.00–6.71]) and those treated with calcium channel blockers (3.46 [1.92–5.07]) or α-blockers (3.31 [3.02–3.78]). However, LF-to-HF ratio tended to be lower in diabetic patients treated with α-blockers.

To determine independent factors for serum concentrations of adiponectin, we performed multivariate analysis controlling for sex, systolic blood pressure, total and HDL cholesterol, HbA_{1c}, and UAE. Considering the possibility of multicollinearity, fasting insulin and Ccr were ex-

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Table 2—*Patient characteristics and laboratory data in subgroups defined by UAE*

	Group A	Group B	Group C
n	45	32	28
Sex (women/men)	20 (44.4)/25 (55.6)	15 (46.9)/17 (53.1)	16 (57.1)/12 (42.9)
Age (years)	58.1 ± 13.2	57.9 ± 11.7	60.3 ± 12.2
BMI (kg/m^2)	23.8 ± 4.63	25.0 ± 5.12	25.0 ± 4.62
Duration of diabetes (years)	9.8 ± 7.9	10.1 ± 6.7	11.1 ± 7.6
Systolic blood pressure (mmHg)	115 ± 11.8	125 ± 12.3†	135 ± 14.9‡
Diastolic blood pressure (mmHg)	67.6 ± 9.0	70.0 ± 9.3	74.7 ± 10.3†
Fasting plasma glucose (mmol/l)	9.99 ± 3.01	10.6 ± 3.28	8.68 ± 3.23
HbA_{1c} (%)	10.4 ± 1.81	9.89 ± 1.49	8.86 ± 2.03†§
Ccr (ml/min)	93.9 ± 25.1	79.6 ± 26.1*	38.1 ± 19.8‡
Fasting insulin (μU/ml)	5.85 (3.75–9.50)	6.90 (3.80–9.40)	5.05 (2.85–9.90)
HOMA-IR	2.27 (1.29–4.23)	3.13 (1.52–4.96)	1.50 (1.18–3.58)
Serum adiponectin (μg/ml)	7.42 ± 4.89	7.70 ± 4.68	14.7 ± 8.98‡#
24-h low-frequency power (ln · ms^2)	10.9 ± 1.54	10.7 ± 1.28	10.1 ± 1.39
24-h high-frequency power (ln · ms^2)	10.7 ± 1.29	10.7 ± 1.22	10.3 ± 1.27
24-h LF-to-HF ratio	4.40 (2.59–7.69)	4.03 (2.27–6.14)	3.0 (1.23–3.53)†
Hypertension	15 (33.3%)	13 (40.6%)	17 (60.7%)*
Antihypertensive treatment	14 (31.1%)	12 (37.5%)	17 (60.7%)*
Treatment (D/OHA/Ins)	4 (8.9)/36 (80)/5 (11.1) 4	4 (125)/24 (75.0)/4 (12.5)	4 (14.3)/20 (71.4)/4 (14.3)

Data are *n* (%), means ± SD, or median (interquartile range). Group A, UAE <30 mg/24 h; group B, UAE 30–299 mg/24 h; group C, UAE >300 mg/24 h. *P < 0.05, †P < 0.01, and ‡P < 0.001 vs. group A; §P < 0.05, ¶P < 0.01, and #P < 0.001 vs. group B. D, diet alone; OHA, oral hypoglycemic agents; Ins, insulin.

cluded from this multivariate analysis. The overall F value for this model was 6.882. In the model that explained 61.7% of variation of serum adiponectin, sex (β = 0.252, P = 0.020), HbA_{1c} (β = −0.226, P = 0.046), HDL cholesterol (β = 0.246, P = 0.020), UAE (β = 0.431, P = 0.000), and 24-h LF-to-HF ratio (β = −0.332, P = 0.027) were independent determinants of serum adiponectin in patients with type 2 diabetes (Table 3). To clarify a relative weighting of these independent factors to serum adiponectin, stepwise regression analysis was also performed. We found that UAE was the strongest independent factor for serum adiponectin in patients with diabetes (data not shown).

CONCLUSIONS — The present study demonstrated that the LF-to-HF ratio, a measure of sympathovagal balance, was an independent factor for serum concentrations of adiponectin in patients with type 2 diabetes. This finding suggested that a shift in sympathovagal balance toward sympathetic activation is associated with decreased serum adiponectin in type 2 diabetes. This is the first study to investigate the influence of sympathetic activity, as estimated by PSA of HRV, on serum adiponectin in type 2 diabetes. Adiponectin is an adipocyte-derived protein that sensitizes the liver and muscle to the action of insulin (15). Serum concentrations of this fat-derived protein are reduced in obesity (3), type 2 diabetes (7), and CAD (8), especially in the metabolic syndrome, which clusters these risk factors for CVD (6). Mechanisms underlying hypoadiponectinemia in obesity or type 2 diabetes have been unclear. Insulin resistance or chronic hyperinsulinemia might contribute to hypoadiponectinemia, because in previous human studies, plasma adiponectin correlated strongly with insulin sensitivity estimated by glucose clamp methods (4,16).

Sympathetic overactivity may be associated with the pathogenesis of insulin resistance/metabolic syndrome, because previous studies of healthy subjects demonstrated that insulin infusion augments muscle sympathetic activity (17) and increases the LF-to-HF ratio estimated by PSA of HRV (18). We hypothesized that a low serum adiponectin concentration might be a result of sympathetic activation in type 2 diabetes, demonstrating that sympathetic activation indeed contributes to hypoadiponectinemia in individuals with metabolic syndrome or type 2 diabetes. This conclusion is also supported by administration of β-adrenergic agonists in mice, which reduced adiponectin mRNA in adipose tissue and adiponectin concentrations in plasma, suggesting that sympathetic activation inhibited adiponectin production in adipose tissues (19). However, in patients with diabetes, we found no significant correlation between serum adiponectin and low-frequency power, considered a measure of sympathetic activity. One possible explanation is that low-frequency power may be less reliable than the LF-to-HF ratio in assessing sympathetic activity because low frequency reflects both sympathetic and parasympathetic activity (20).

On the other hand, an increase in LF-to-HF ratio may reflect a relative sympathetic activation due to a predominant parasympathetic impairment, because parasympathetic neuropathy is believed to occur early in the natural course of diabetes. Recently, Kreier et al. (21) have demonstrated parasympathetic innervation of white adipose tissue in rats. They also found that the selective vagotomy of a unilateral retroperitoneal fat pad significantly decreased the mRNA expressions of resistin and leptin, suggesting that parasympathetic input may itself affect the synthesis of hormones in adipose tissue (21). Therefore, predominant parasympathetic hypoactivity rather than sympathetic overactivity may contribute

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Table 3—*Multivariate analysis of relationships between serum adiponectin concentrations and selected variables in patients with type 2 diabetes*

	t	β	*P*
Sex	5.856	0.252	0.020
BMI	0.609	−0.101	0.439
Systolic blood pressure (mmHg)	1.122	−0.128	0.295
HbA_{1c} (%)	4.200	−0.226	0.046
Total cholesterol (mmol/l)	0.171	0.040	0.681
HDL cholesterol (mmol/l)	5.826	0.246	0.020
HOMA-IR	1.052	−0.124	0.310
UAE ($\log_{10}$ · mg/24 h)	14.765	0.431	<0.0001
24-h low-frequency power (ln · ms^2)	3.968	0.306	0.055
24-h high-frequency power (ln · ms^2)	2.647	−0.304	0.111
24-h LF-to-HF ratio	5.856	−0.332	0.027

$R^2 = 0.617$ (adjusted multiple $R^2 = 0.525$).

to the negative correlation between serum adiponectin and the 24-h LF-to-HF ratio in patients with diabetes.

We found the stronger correlation between serum adiponectin and LF-to-HF ratio early in the morning. This suggests that a high LF-to-HF ratio during the first few hours after awaking may particularly contribute to clinically important decreases in serum adiponectin in patients with type 2 diabetes. Morning peaks in occurrence are now well documented for acute coronary syndrome and ischemic stroke (22). Although this morning increase in cardiovascular events may reflect a number of diurnal physiologic rhythms, the most important factors are increases in systemic blood pressure and heart rate, which are mediated partly by sympathetic activation (23). Adiponectin seems to have an antiatherogenetic role in experimental models of vascular injury, because it inhibits monocyte adhesion to endothelial cells, uptake of oxidized LDL into macrophages, and proliferation of smooth muscle cells after their migration (24). We suspect that early-morning sympathetic activation may contribute to a decrease in serum adiponectin, which in turn could link this to a morning excess in cardiovascular events.

We found a significant negative correlation between serum concentrations of adiponectin and Ccr, an index of glomerular function, in patients with type 2 diabetes. Serum adiponectin also correlated positively with UAE. Furthermore, serum adiponectin concentrations were significantly higher in the patients with overt albuminuria than in those with normoalbuminuria or microalbuminuria, in agreement with previous studies. Zoccali et al. (25) reported a marked elevation of serum adiponectin in patients with end-stage renal disease or nephrotic syndrome. These findings suggest that impaired renal clearance may contribute to an excess of circulating adiponectin in patients with diabetic overt nephropathy. In a very recent study, adiponectin was confirmed by Western analysis to be excreted into the urine and also to be significantly higher in serum and urine when diabetic patients had overt nephropathy (26). In our present study, multivariate analysis showed UAE to be a strong independent determinant of serum adiponectin in diabetic patients. Accordingly, we believe that renal function is an independent determinant of serum adiponectin, because the kidney is the main elimination site for circulating adiponectin.

Our multivariate analysis also demonstrated that female sex and high HDL cholesterol were independently associated with higher serum concentrations of adiponectin in patients with type 2 diabetes. Previous studies of normal subjects similarly reported that serum adiponectin was significantly higher in women than men (27,28). The mechanism responsible for this sex difference in serum adiponectin concentration remains unclear. One possible explanation is that androgens, specifically testosterone, reduce serum adiponectin via effects in adipocytes (29). Another explanation is that the difference in fat distribution between women and men may be related to the higher serum adiponectin concentrations. Because serum adiponectin is more closely related to intra-abdominal fat than subcutaneous fat (28), the higher serum adiponectin concentrations may be associated with higher subcutaneous and lower intra-abdominal fat. Several large cross-sectional studies have found that after adjustment for sex and adiposity, serum adiponectin showed a strong positive correlation with serum HDL cholesterol (7,30). Low HDL cholesterol is a component of the metabolic syndrome and represents a characteristic pattern of dyslipidemia in type 2 diabetes. Accordingly, serum adiponectin would be expected to be correlated with HDL cholesterol.

In conclusion, the present study confirmed that sex, HDL cholesterol, and renal function are independent factors for serum concentrations of adiponectin in patients with diabetes. Furthermore, we demonstrated that sympathovagal balance favoring relative sympathetic activation is associated low serum concentrations of adiponectin in these patients.

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