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High-sensitivity C-reactive protein is associated with insulin resistance and cardiovascular autonomic dysfunction in type 2 diabetic patients

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Abstract

We tested the hypothesis that elevated levels of plasma high-sensitivity C-reactive protein (HSCRP) are associated with insulin resistance/hyperinsulinemia and cardiovascular autonomic dysfunction in type 2 diabetic patients without insulin treatment. The study group consisted of 17 type 2 diabetic patients with high HSCRP (0.3-1.0 mg/dL; age, 59 ± 8 years, mean ± SD; high HSCRP group). The control group consisted of 18 age-matched type 2 diabetic patients with low HSCRP (<0.3 mg/dL; 59 ± 7 years; low HSCRP group). Cardiovascular autonomic function was assessed by baroreflex sensitivity, heart rate variability, plasma norepinephrine concentration, and cardiac metaiodobenzylguanidine (MIBG) labeled with iodine 123 scintigraphic findings. Baroreflex sensitivity was lower in the high HSCRP group than in the low HSCRP group ($P < .05$). Early and delayed ^{123}I-MIBG myocardial uptake values were lower ($P < .05$ and $P < .005$, respectively) and the percent washout rate of ^{123}I-MIBG was higher ($P < .01$) in the high HSCRP group than in the low HSCRP group. Fasting plasma insulin concentration ($P < .01$) and the homeostasis model assessment index ($P < .01$) were higher in the high HSCRP group than in the low HSCRP group. Multiple regression analysis revealed that the level of HSCRP was independently predicted by fasting plasma insulin concentration and myocardial uptake of ^{123}I-MIBG at a delayed phase. Our results suggest that high levels of HSCRP are associated with depressed cardiovascular autonomic function and hyperinsulinemia and that fasting plasma insulin concentration and myocardial uptake of ^{123}I-MIBG at a delayed phase are independent predictors of HSCRP level in our Japanese patients with type 2 diabetes mellitus.

1. Introduction

It has been reported that measurement of inflammatory markers such as high-sensitivity C-reactive protein (HSCRP) is an important method of identifying individuals at risk for cardiovascular events [1-3]. In diabetic patients, cardiovascular autonomic dysfunction is strongly related to cardiovascular mortality [4]. We have reported that depressed cardiovascular function is associated with insulin resistance in type 2 diabetic patients [5,6]. Although plasma C-reactive protein (CRP) is reported to be associated with insulin resistance in type 2 diabetic patients [7,8], the significance of increased HSCRP in diabetic cardiovascular autonomic function has not been adequately investigated.

We hypothesized that increased levels of HSCRP are associated with cardiovascular autonomic dysfunction and insulin resistance in type 2 diabetic patients. To test our hypothesis, we compared in the present study the baroreflex sensitivity (BRS), heart rate variability (HRV), plasma norepinephrine concentrations, and cardiac metaiodobenzylguanidine (MIBG) labeled with iodine 123 scintigraphic findings in addition to metabolic profiles of Japanese type 2 diabetic patients with low HSCRP with those of patients with high HSCRP, followed by evaluating the independent predictors of HSCRP in these populations.

2. Subjects and methods

The study was approved by the ethics review board of our institution and prior informed consent was obtained from all patients. Seventy-five consecutive Japanese patients with type 2 diabetes mellitus who were admitted to our

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department in 2002 were screened. Among them, 48 patients who did not have an organic heart disease as determined by physical examination, chest x-ray, 12-lead electrocardiography (ECG), echocardiography, treadmill exercise ECG, and thallium 201 cardiac scintigraphy were enrolled. All patients underwent clinical examination to exclude the presence of secondary hypertension. Essential hypertension was defined as diastolic blood pressure equal to 90 mm Hg or higher, systolic blood pressure equal to 140 mm Hg or higher, or self-reported use of antihypertensive medication [9]. Patients with abnormal plasma creatinine concentrations ($\geq$1.2 mg/dL) or those with macroalbuminuria ($\geq$300 mg/d) were excluded from the study. For physical examinations, all patients were evaluated on the next morning of admission after an overnight fast and were instructed to avoid drinking fluids. We measured height, weight, and waist and hip circumferences. Body mass index and waist-to-hip circumference ratio (waist-hip ratio) were calculated. For measurements of HSCRP, blood was sampled in each patient after a 12-hour overnight fast from the antecubital vein. Serum from blood samples was separated and stored in a deep freezer at -20°C until assayed. High-sensitivity assays for CRP were performed according to previously described methods (Dade Behring, Tokyo, Japan) [10]. By this assay, 17 patients were assigned to have high HSCRP (0.3-1.0 mg/dL; high HSCRP group) [11]. We also recruited 18 age-matched patients with low HSCRP (<0.3 mg/dL; low HSCRP group) who were selected from the original 48 enrolled patients. Patients who showed higher levels of CRP (ie, >1.0 mg/dL) were excluded from the study [12]. The clinical characteristics of patients from the low and high HSCRP groups are summarized in Table 1. Eleven of 17 patients from the high HSCRP group and 11 of 18 patients from the low HSCRP group met the criterion of essential hypertension and all these patients were being treated with calcium channel antagonists, angiotensin-converting enzyme (ACE) inhibitors, and/or angiotensin II receptor blockers. None of the patients were being treated with aspirin, diuretics, β- or α-blockers, or insulin. Dyslipidemia was defined as fasting triglycerides equal to 200 mg/dL or higher or HDL cholesterol below 45 mg/dL for women and below 35 mg/dL for men [9]. Eight of 17 patients from the high HSCRP group and 6 of 18 patients from the low HSCRP group met the criterion of dyslipidemia.

Table 1
Clinical characteristics of studied patients

	Low HSCRP group	High HSCRP group	*P*
Age (y)	59 ± 7	59 ± 8	ns
Sex distribution (men/women)	8:10	9:8	ns
HSCRP (mg/dL)	0.052 ± 0.028	0.591 ± 0.179	<.0001
Duration of diabetes (y)	7.8 ± 3.3	9.3 ± 5.1	ns
Hypertension (%)	61	65	ns
Dyslipidemia (%)	33	47	ns
Drug use (%)			
Sulfonylurea	50	53	ns
α-Glucosidase inhibitors	44	35	ns
Pioglitazone	6	6	ns
Statin	33	29	ns
Calcium channel antagonists	39	41	ns
ACE inhibitors	28	24	ns
Angiotensin receptor blocker	56	53	ns
Body mass index (kg/m^2)	24.5 ± 4.2	28.0 ± 4.3	<.01
Waist circumference (cm)	79.3 ± 7.7	85.9 ± 9.5	<.05
Hip circumference (cm)	95.6 ± 7.0	96.6 ± 5.5	ns
Waist-hip ratio	0.83 ± 0.07	0.89 ± 0.07	<.05
Systolic blood pressure (mm Hg)	127 ± 19	133 ± 16	ns
Diastolic blood pressure (mm Hg)	76 ± 10	77 ± 8	ns
Heart rate (bpm)	68 ± 8	70 ± 7	ns
Fasting plasma glucose (mg/dL)	144 ± 32	169 ± 55	ns
Fasting immunoreactive insulin (μU/mL)	5.6 ± 1.9	8.0 ± 2.4	<.01
Homeostasis model assessment index	1.9 ± 0.8	3.3 ± 1.4	<.01
Hemoglobin A1c (%)	7.8 ± 1.3	8.0 ± 1.5	ns
Total cholesterol (mg/dL)	198 ± 32	209 ± 24	ns
Triglyceride (mg/dL)	140 ± 69	148 ± 40	ns
HDL cholesterol (mg/dL)	47 ± 9	40 ± 8	<.05
Uric acid (mg/dL)	5.3 ± 1.6	6.2 ± 1.3	ns
Creatinine (mg/dL)	0.7 ± 0.2	0.8 ± 0.2	ns
Creatinine clearance (mL/min)	106 ± 29	92 ± 23	ns
Urine albumin excretion (mg/d)	48 ± 77	171 ± 141	<.01

Data are mean ± SD. ns indicates not significant.

2.1. Echocardiography

M-mode 2-dimensional echocardiography and cardiac Doppler recordings were obtained using a phase-array echo-Doppler system. Echocardiograms were obtained in a standard manner using standard parasternal, short axis, and apical views. The left ventricular mass was calculated according to Devereux et al [13]: left ventricular mass = $\{1.04\ ([\text{LVIDd} + \text{IVSTd} + \text{PWTd}]^3 - \text{LVIDd}^3) - 14\ \text{g}\}$, where LVIDd indicates left ventricular internal dimension at end diastole; IVSTd, intraventricular septal thickness at end diastole; and PWTd, posterior wall thickness at end diastole. The left ventricular mass was divided by body surface area to calculate the left ventricular mass index. Pulsed Doppler recordings were made from standard apical 4-chamber view. Mitral inflow velocity was recorded with the sample volume at the mitral annulus level taking the average of 3 or more cardiac cycles. The peak velocity of early (E) and late ventricular filling (A) was determined, and the ratio (E/A) and deceleration time were recorded.

2.2. Cardiovascular autonomic function tests

All subjects were studied while in the supine position in a quiet room with dimmed lights between 9:00 and 11:00 AM [5,14]. A catheter was inserted in the right cubital vein, and arterial blood pressure was recorded noninvasively by tonometry (Jentow-7700, Nihon Colin, Komaki, Japan).

Table 2
Echocardiographic findings

	Low HSCRP group	High HSCRP group	*P*
EF (%)	71 ± 3	70 ± 4	ns
LVIDd (mm)	47 ± 3	49 ± 3	ns
LVIDs (mm)	30 ± 2	32 ± 3	ns
IVSTd (mm)	8.7 ± 0.7	8.9 ± 1.3	ns
PWTd (mm)	8.8 ± 0.9	9.2 ± 1.1	ns
LVMI (g/m^2)	106 ± 16	112 ± 25	ns
E-peak velocity (cm/s)	65 ± 10	62 ± 9	ns
A-peak velocity (cm/s)	69 ± 11	79 ± 10	<.01
E/A ratio	0.97 ± 0.18	0.79 ± 0.13	<.01
Deceleration time (ms)	232 ± 23	250 ± 26	<.05

Data are mean ± SD. EF indicates ejection fraction; LVIDd, left ventricular internal dimension at end diastole; LVIDs, left ventricular internal dimension at end systole; IVSTd, interventricular septal thickness at end diastole; PWTd, posterior wall thickness at end diastole; LVMI, left ventricular mass index.

The tonometric sensor was attached over the left radial artery. The accuracy of continuous blood pressure monitoring has been demonstrated previously [15]. Arterial blood pressure and a standard 12-lead ECG were monitored simultaneously; data were stored in a PCM data recorder (RD-200T, TEAC, Tokyo). Three-lead precordial Holter ECG recordings (model 459, Del Mar Avionics, Irvine, Calif) were also obtained throughout the procedure for analysis of HRV.

After an interval of 30 minutes to permit stabilization of the cardiovascular baroreflex mechanism, each patient was asked to breathe at a rate of 15 breaths per minute using a metronome to maximize regularity between respiration and cardiovascular function. Blood samples were obtained from the venous catheter to measure plasma norepinephrine by *radioenzymatic assay* [16]. Baroreflex sensitivity was assessed by the phenylephrine method as described previously [5,14]. Briefly, phenylephrine (2-3 μg/kg) was injected over a 15-second period to obtain a 15 to 40 mm Hg rise in systolic blood pressure. Baroreflex sensitivity was calculated as the slope of the linear regression line relating systolic blood pressure changes to RR interval changes. Regression lines with more than 20 data points and a correlation coefficient (r) greater than 0.8 were accepted for analysis. The average of the 2 slope values was taken as the BRS value [14].

Heart rate variability was analyzed using a 300-second interval on Holter ECG recordings immediately before phenylephrine injection. The power spectrum of the RR interval was computed by a fast Fourier transform and expressed as the area under the power spectrum [17]. We calculated the power of 2 spectral bands, the low-frequency (LF) component at 0.04 to 0.15 Hz and the high-frequency

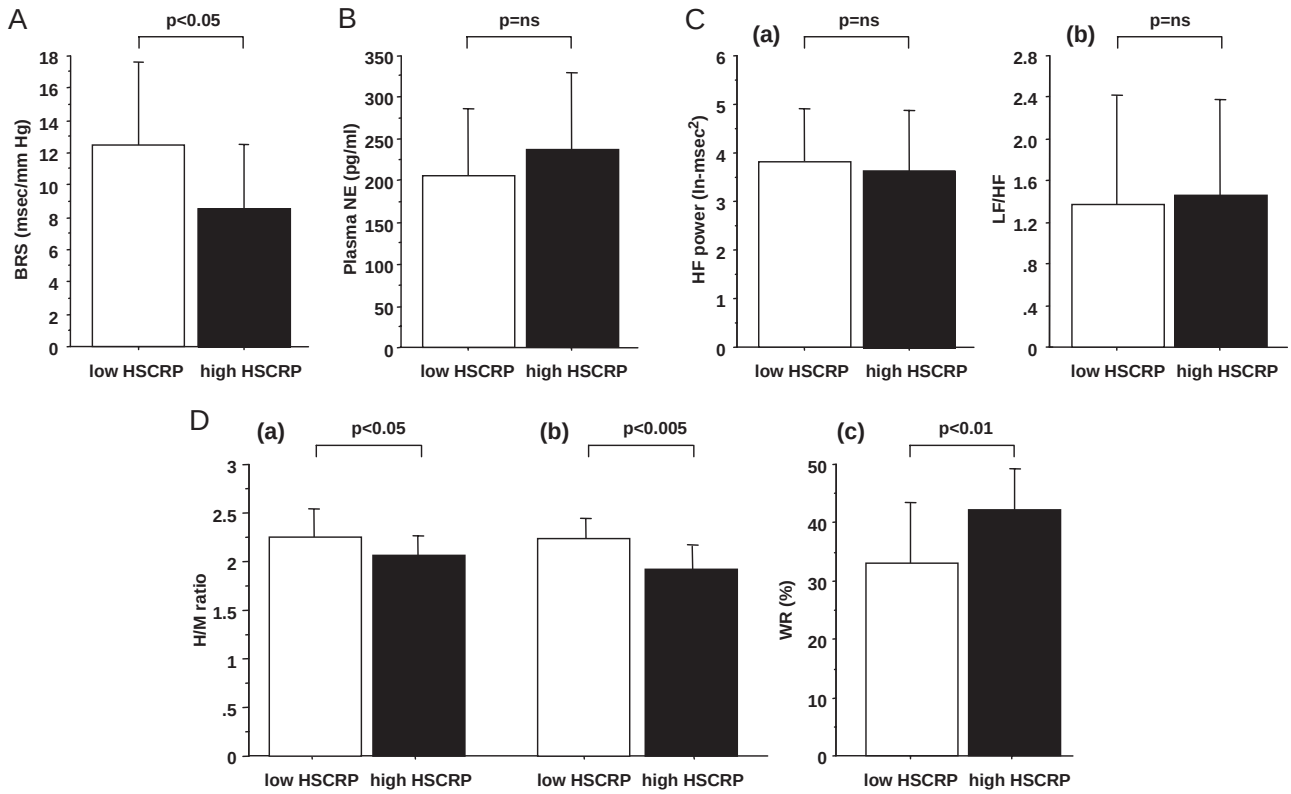

Fig. 1. Comparison of autonomic function tests between type 2 diabetic patients with low HSCRP and those with high HSCRP. A, BRS. B, Plasma norepinephrine (NE) concentration. C, HRV. Power of HF component (0.15-0.40 Hz, a) and the ratio of the LF power (0.04-0.15 Hz) to HF power (LF/HF, b). The distribution of HRV values was skewed and the values were thus transformed to natural logarithmic values. D, Cardiac ^{123}I-MIBG scintigraphic findings. Myocardial uptake of ^{123}I-MIBG at early (a) and delayed (b) phases. Myocardial uptake of ^{123}I-MIBG is expressed as the mean H/M ratio. c, Percent WR of ^{123}I-MIBG. Data are mean ± SD. ns indicates not significant.

(HF) component at 0.15 to 0.40 Hz. Based on their skewed distribution, the measured values of HRV were transformed to natural logarithmic values. The ratio of LF to HF (LF/HF) was also computed.

Planar and single-photon emission-computed tomography studies were performed both at 15 minutes (early) and 4 hours (delayed) after the injection of 111 MBq of ^{123}I-MIBG using a rotating gamma camera (ZLC 7500, Siemens, Munich, Germany). Data were analyzed with an analysis software (SCINTIPAC, Shimadzu, Kyoto, Japan). The anterior planar images from early and delayed ^{123}I-MIBG studies were analyzed visually. For semiquantitative analysis, regions of interest were drawn over the whole heart and a 10 × 10 mm area over the upper mediastinum on the early and delayed planar images was used to calculate the mean heart-to-mediastinum (H/M) ratio. After correcting for the physical decay of ^{123}I, the percent washout rate (WR) of the tracer from the myocardium was determined over a 4-hour period. Insulin resistance was evaluated by the homeostasis model assessment (HOMA) index = {(fasting plasma insulin [μU/mL] × fasting plasma glucose [mmol/L])/22.5} [18].

2.3. Statistical analysis

Data are presented as mean ± SD. Differences between the 2 groups were analyzed by the unpaired Student t test, χ^2 test, or by the Fisher exact probability test. A P value of less than .05 was considered statistically significant. Simple (Spearman rank) correlation coefficients between HSCRP and various parameters were calculated, and a stepwise multiple regression analysis was then used to evaluate the independent association of these variables with HSCRP. In our multivariate analysis, F values equal to 4 or higher were considered significant.

3. Results

As shown in Table 1, mean age was similar between the high and low HSCRP groups and there were no significant differences with respect to sex, duration of diabetes, and administered medications. Body mass index was higher in the high HSCRP group than in the low HSCRP group (P < .01). Waist circumference and waist-hip ratio but not hip circumference were greater in the high HSCRP group than in the low HSCRP group (P < .05 for each). Regarding glucose metabolism, fasting plasma insulin concentrations and HOMA index were higher (P < .01 for each) in the high HSCRP group than in the low HSCRP group. However, there was no significant difference in fasting plasma glucose concentration and hemoglobin A1c. With regard to lipid metabolism, serum HDL cholesterol was lower in the high HSCRP group than in the low HSCRP group (P < .05), whereas serum total cholesterol and triglyceride showed no significant difference between the groups. Regarding renal function, there was no significant difference in the serum creatinine concentration or creatinine clearance. However, urine albumin excretion was greater in the high HSCRP group than in the low HSCRP group (P < .01). The hemodynamic data listed in Table 1 were obtained immediately before BRS assessment. The resting heart rate and systolic and diastolic blood pressures were not significantly different between the 2 groups.

Table 2 presents a summary of echocardiographic findings. The left ventricular dimensions at end diastole and end systole, intraventricular septal and posterior wall thickness at end diastole, ejection fraction, and left ventricular mass index were essentially similar in the 2 groups. With regard to the left ventricular diastolic function, the peak velocity of late ventricular filling (A) was higher and the E/A ratio was lower in the high HSCRP group compared with the low HSCRP group (P < .01 for each). Deceleration time was longer in the high HSCRP group than in the low HSCRP group (P < .05).

Fig. 1 summarizes the results of the cardiovascular autonomic function tests. Baroreflex sensitivity was lower in the high HSCRP group than in the low HSCRP group (8.5 ± 4.0 vs 12.4 ± 5.1 ms/mm Hg; P < .05; Fig. 1A).

Table 3
Correlations of HSCRP to measures of variables

Parameters	Univariate	
	R	P
Age	0.080	.6490
Sex (Men)	0.129	.4616
Duration of diabetes mellitus	0.078	.6569
Body mass index	0.424	.0111
Waist circumference	0.432	.0096
Hip circumference	0.165	.3439
Waist hip ratio	0.365	.0311
Systolic blood pressure	0.293	.0878
Diastolic blood pressure	0.093	.5952
Heart rate	0.196	.2604
EF	0.145	.4058
LVIDd	0.305	.0752
LVIDs	0.316	.0648
IVSTd	0.229	.1864
PWTd	0.327	.0553
LVMI	0.198	.2621
E/A ratio	−0.415	.0132
Deceleration time	0.321	.0601
Total cholesterol	0.174	.3161
Triglyceride	0.241	.1627
HDL cholesterol	−0.405	.0158
Uric acid	0.286	.0959
Fasting plasma glucose	0.253	.1425
Fasting immunoreactive insulin	0.548	.0007
Homeostasis model assessment index	0.558	.0005
Hemoglobin A1c	0.125	.4729
Creatinine	0.182	.2946
Creatinine clearance	0.294	.0870
Urine albumin excretion	0.421	.0118
BRS	−0.376	.0258
Plasma norepinephrine	0.065	.7090
HF power	−0.123	.4826
LF/HF	0.023	.8972
H/M ratio at early phase	−0.370	.0286
H/M ratio at delayed phase	−0.601	.0001
WR	0.447	.0071

Certain abbreviations are explained in the footnote to Table 2.

Table 4
Stepwise regression analyses between HSCRP and various parameters

Independent variable	Regression coefficient	SE	Standard regression coefficient	F
To HSCRP intercept	1.092			
H/M ratio at delayed phase	−0.529	0.149	−0.470	12.522
F-IRI	0.048	0.016	0.391	8.669

F-IRI indicates fasting immunoreactive insulin.

Plasma norepinephrine concentration was similar in both groups (high HSCRP, 239 ± 89 pg/mL; low HSCRP, 206 ± 81 pg/mL; P = ns; Fig. 1B). Analysis of HRV revealed that the HF power and the LF/HF ratio were not significantly different between the 2 groups (3.6 ± 1.3 vs 3.8 ± 1.1 [P = ns] and 1.5 ± 0.9 vs 1.4 ± 1.0 ln-ms^2 [P = ns], respectively; Fig. 1C). Cardiac ^{123}I-MIBG scintigraphy disclosed that the H/M ratios at early and delayed phases were lower in the high HSCRP group than in the low HSCRP group (2.06 ± 0.21 vs 2.24 ± 0.28 [$P < .05$] and 1.92 ± 0.24 vs 2.23 ± 0.20 [$P < .005$], respectively; Fig. 1D). The percent WR of ^{123}I-MIBG was higher in the high HSCRP group than in the low HSCRP group (42.1% ± 7.0% vs 33.1% ± 10.1%; $P < .01$; Fig. 1D).

Table 3 depicts the correlation between HSCRP and age, body mass index, and various other variables in all the patients from both the high and low HSCRP groups. High-sensitivity C-reactive protein correlated positively with body mass index, waist circumference, waist-hip ratio, fasting plasma insulin, HOMA index, urine albumin excretion, and percent WR of ^{123}I-MIBG, whereas it correlated negatively with E/A ratio, HDL cholesterol, BRS, and H/M ratios at early and delayed phases. Multiple regression analysis was performed using these 12 variables with the stepwise procedure. The level of HSCRP was independently predicted by fasting plasma insulin and H/M ratio at a delayed phase (Table 4).

4. Discussion

In our present study, type 2 diabetic patients with high HSCRP had lower BRS and myocardial uptake and enhanced clearance of ^{123}I-MIBG, relative to the values in type 2 diabetic patients with low HSCRP. The body mass index, waist circumference, and waist-hip ratio were significantly greater in the low HSCRP group than in the high HSCRP group. Among the metabolic profiles, the fasting plasma insulin concentration and the HOMA index were higher in patients with high HSCRP than in those with low HSCRP. Multiple regression analysis revealed that the level of HSCRP was independently predicted by fasting plasma insulin concentration and H/M ratio at a delayed phase in our Japanese patients with type 2 diabetes.

Recent studies have demonstrated a close relationship between elevated CRP and insulin resistance [19,20]. Yudkin et al [19] reported that low but relatively elevated CRP in healthy subjects is related to insulin resistance when assessed by body mass index, HOMA index, blood pressure, HDL cholesterol, and triglyceride and that increased proinflammatory cytokines, interleukin-6 and tumor necrosis factor-α, play an important role in the low level of chronic inflammatory state. Subsequently, by analyzing the nondiabetic population of the Insulin Resistance Atherosclerosis Study (IRAS) [21], Festa et al [20] also reported that the level of CRP correlated with body mass index, insulin sensitivity (assessed by intravenous glucose tolerance test), and fasting plasma levels of insulin and proinsulin. They suggested that CRP is not only a predictor of cardiovascular events but also an independent predictor of insulin sensitivity. In the present study, consistently, the level of HSCRP correlated with body mass index, HDL cholesterol, fasting plasma insulin concentration, and HOMA index. Being different from those 2 prior studies [19,20], our study enrolled type 2 diabetic patients who did not receive insulin treatment. We used a cutoff value of HSCRP of 0.3 mg/dL to divide our patients into low and high HSCRP groups (<0.3 and 0.3-1.0 mg/dL) based on the American Heart Association (AHA)/Centers for Disease Control (CDC) scientific statement [11]. As shown in Table 1, the parameters that correlated with CRP, including body mass index, HDL cholesterol, fasting plasma glucose concentration, and HOMA index, but not others, were higher in the high HSCRP group than in the low HSCRP group. Taken together, we postulate that this criterion is appropriately applicable to our selected Japanese type 2 diabetic patients.

The novel and important finding of the present study is that patients with elevated HSCRP level had depressed cardiovascular autonomic function compared with those with low HSCRP when assessed by BRS and ^{123}I-MIBG scintigraphic findings. The lower BRS has been established as a marker of depressed reflex vagal function. The reduced myocardial uptake of ^{123}I-MIBG (H/M ratio) reflects reduced norepinephrine content at presynaptic sites or reduced neural density, whereas an enhanced WR of ^{123}I-MIBG reflects enhanced release of norepinephrine from presynaptic sites [22]. In our study, the myocardial uptake of ^{123}I-MIBG was lower and its clearance was higher in the high HSCRP group than in the low HSCRP group. In particular, the myocardial uptake of ^{123}I-MIBG at a delayed phase was identified as an independent predictor for the level of CRP. To our knowledge, this is the first report demonstrating an association between HSCRP and cardiac ^{123}I-MIBG scintigraphic findings, appearing to support a previous report demonstrating that disturbance of cardiac autonomic activity (sympathetic predominance) when assessed by HRV and inflammatory markers (including interleukin-6 and CRP) may be causes of metabolic syndrome [23].

What is the main cause of elevated HSCRP observed in the present study? We recently reported that the presence of microalbuminuria is characterized by depressed cardiovascular autonomic function and insulin resistance in type

2 diabetic patients who were not undergoing insulin treatment and that the fasting plasma insulin concentration, HOMA index, and the myocardial uptake of ^{123}I-MIBG at a delayed phase were independent predictors of urinary albumin excretion [6], very similar to the present observations. In that study, we discussed the predominant involvement of endothelial dysfunction in the development of microalbuminuria and depressed cardiovascular autonomic dysfunction. In fact, in a recent report demonstrating that CRP modifies the relation between blood pressure and microalbuminuria, the authors stressed the central role of endothelial dysfunction in this interaction [24]. Together with our present observation that urinary albumin excretion correlated with HSCRP, further studies are necessary to investigate the role of endothelial dysfunction in depressed cardiovascular autonomic dysfunction and insulin resistance in diabetic patients with high HSCRP.

Some methodological issues have to be addressed. First, 65% and 61% of our patients with high HSCRP and low HSCRP, respectively, had been diagnosed earlier with associated essential hypertension. All these patients were being treated with one or more antihypertensive drugs, including ACE inhibitors, angiotensin II receptor blockers, and calcium channel antagonists, before enrolment. In this regard, all these 3 drug classes have been reported to improve insulin resistance [25,26] and cardiovascular autonomic function [27-29]. In addition, 29% and 33% of our patients with high HSCRP and low HSCRP, respectively, had been diagnosed with dyslipidemia. All these patients were being treated with statin drugs, including simvastatin and pravastatin, before enrolment. In this regard, all these drug classes have been reported to decrease the level of CRP [30,31]. Therefore, these medications might have beneficially affected our results. As to antidiabetic medications, a considerable number of patients were being treated with sulfonylurea and/or α-glucosidase inhibitors, whereas only one patient in each group was treated with pioglitazone, an insulin-sensitizing drug reported to reduce HSCRP in type 2 diabetic patients [32]. Second, sex differences in various aspects of cardiovascular autonomic function and metabolism are well recognized. In the present study, there was no significant difference in these measures between the men and women (data not shown). Third, no patients enrolled in the present study underwent coronary angiography. Although ischemic heart disease could not be completely excluded, severe coronary artery disease was unlikely to be present in view of the normal treadmill exercise ECG testing and ^{201}Tl cardiac scintigraphy. Finally, we assessed metabolic profiles including fasting plasma glucose and insulin and cardiovascular autonomic function measurements only once during admission. It can be conceivable that reduction in plasma glucose and insulin by therapies including diet, exercise, and medication results in an improvement of cardiovascular autonomic function. Therefore, it remains to be studied as to what extent might the levels of plasma glucose and insulin at the time of the evaluations have affected the measurements of cardiovascular autonomic function.

In conclusion, our findings suggest that the level of HSCRP in our Japanese patients with type 2 diabetes is associated with depressed cardiovascular autonomic function and hyperinsulinemia and that the fasting plasma insulin concentration and the myocardial uptake of ^{123}I-MIBG at a delayed phase are independent predictors of the level of HSCRP.

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