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Hypoadiponectinemia in type 2 diabetes mellitus in men is associated with sympathetic overactivity as evaluated by cardiac ^{123}I-metaiodobenzylguanidine scintigraphy

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Abstract

Hypoadiponectinemia is associated with insulin resistance. However, there is very limited information about the relationship between plasma adiponectin and cardiac autonomic nervous function. We tested the hypothesis that hypoadiponectinemia is associated with cardiac sympathetic overactivity in patients with type 2 diabetes mellitus. Thirty-three male type 2 diabetic patients not on insulin treatment were classified into a hypoadiponectinemia group (plasma adiponectin concentration, <4.0 μg/mL; age, 58.6 ± 8.6 years [mean ± SD]; n = 14) and an age-matched normoadiponectinemia group (serum adiponectin concentration, ≥4.0 μg/mL; age, 58.2 ± 8.1 years; n = 19). In each patient, baroreflex sensitivity, heart rate variability, plasma norepinephrine concentration, and cardiac ^{123}I-metaiodobenzylguanidine (MIBG) scintigraphic findings were assessed. Compared with the normoadiponectinemia group, the hypoadiponectinemia group had a higher body mass index ($P < .01$), higher plasma concentrations of glucose and insulin ($P < .05$ and $P < .01$, respectively), higher homeostasis model assessment of insulin resistance (HOMA-IR) values ($P < .005$), higher plasma triglyceride levels ($P < .05$), and lower plasma high-density lipoprotein cholesterol levels ($P < .05$). In the hypoadiponectinemia group, the autonomic function measurements included a lower baroreflex sensitivity ($P < .05$) and a lower delayed myocardial uptake of ^{123}I-MIBG ($P < .01$) with a higher washout rate ($P < .05$). Multiple regression analysis revealed that the plasma adiponectin level was independently associated with HOMA-IR (F = 9.916) and the percent washout rate of ^{123}I-MIBG (F = 5.985). Our results suggest that in middle-aged men with type 2 diabetes mellitus, hypoadiponectinemia is associated with cardiac sympathetic overactivity as determined by ^{123}I-MIBG scintigraphy.

1. Introduction

Adiponectin is a hormone that is produced by adipocytes [1]. In patients with type 2 diabetes mellitus, low plasma adiponectin levels are associated with insulin resistance [2,3]. Low plasma adiponectin levels have also been shown to be an independent predictor of type 2 diabetes mellitus [4]. Most importantly, plasma adiponectin and insulin resistance are strongly associated with the development of coronary artery disease [5,6]. Cardiac autonomic nerve dysfunction is strongly related to cardiovascular mortality in type 2 diabetic patients [7]. Although insulin resistance depresses cardiac autonomic nervous function in these patients [8-10], there is limited information on the relationship between plasma adiponectin and cardiac autonomic nervous function [11]. In subjects with insulin resistance, sympathetic overactivity may play a central role in pathogenesis [12,13]. In this regard, cardiac ^{123}I-metaiodobenzylguanidine (MIBG) scintigraphy is a sensitive diagnostic tool that allows the direct assessment of sympathetic nervous function [14]. Plasma adiponectin levels have been found to be lower in men than in women, probably because of the effects of androgen [15]. In the present study, we investigated the association between plasma adiponectin levels and cardiac autonomic function in relation to insulin resistance in middle-aged male patients with type 2 diabetes mellitus.

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2. Methods and design

2.1. Subjects

Sixty-five consecutive Japanese male patients with type 2 diabetes mellitus who were admitted to our department in 2003 were screened. Type 2 diabetes mellitus was defined as a fasting plasma glucose concentration of 126 mg/dL or greater or a 2-hour plasma glucose concentration of 200 mg/dL or greater after a 75-g oral glucose load, or the self-reported use of antidiabetic medication [16]. Of the 65 patients, the 33 patients who did not have organic heart disease were enrolled. Patients with macroalbuminuria (>300 mg/d) or abnormal plasma creatinine concentrations (≥1.2 mg/dL) were excluded. Patients treated with insulin were also excluded. Plasma adiponectin concentrations were measured in venous blood obtained between 6:00 and 7:00 AM after an overnight fast by using a commercially available enzyme-linked immunosorbent assay kit (Otsuka Pharmaceuticals, Tokyo, Japan) [6]. Hypoadiponectinemia was defined as a plasma adiponectin concentration of less than 4.0 μg/mL [6]. Based on these results, 33 patients were classified as belonging to either the hypoadiponectinemia group (age, 58.6 ± 8.6 years [mean ± SD]; n = 14) or the normoadiponectinemia group (age, 58.2 ± 8.1 years; n = 19). The clinical characteristics of the studied patients are summarized in Table 1. After secondary hypertension was excluded, essential hypertension was defined as a diastolic blood pressure of 90 mm Hg or higher, a systolic blood pressure of 140 mm Hg or higher, or self-reported use of antihypertensive medication [17]. Dyslipidemia was defined as fasting triglyceride level of 200 mg/dL or higher or high-density lipoprotein (HDL) cholesterol level less than 35 mg/dL [17]. Insulin resistance was evaluated by using the homeostasis model assessment of insulin resistance (HOMA-IR) according to the following formula: HOMA-IR = {(fasting plasma insulin [μU/mL] × fasting plasma glucose [mmol/L])/22.5} [18]. Prior written informed consent was obtained from all patients, and the study protocol was approved by the institutional review board of Oita University.

2.2. Echocardiography

M-mode 2-dimensional echocardiography and cardiac Doppler recordings were obtained by using a phase-array echo-Doppler system. The left ventricular mass was calculated according to Devereux et al [19]: left ventricular mass = {1.04([LVIDd + IVSTd + PWTd]^3 − LVIDd^3) − 14 g}, where LVIDd is the left ventricular internal dimension at end diastole; IVSTd the interventricular septal thickness at end diastole, and PWTd the posterior wall thickness at end diastole. To calculate the left ventricular mass index (LVMI), the left ventricular mass was divided by the body surface area. Based on pulsed Doppler recordings, the peak velocity of early (E) and late ventricular filling (A) was determined, and the ratio (E/A) and deceleration time were measured to assess cardiac diastolic function.

2.3. Plasma norepinephrine concentration, heart rate variability, and baroreflex sensitivity

All subjects were studied while in the supine position in a quiet room between 9:00 and 11:00 AM [6-8]. A catheter was inserted into the right cubital vein, and the arterial blood pressure was recorded noninvasively by tonometry (Jentow-7700; Nihon Colin, Komaki, Japan) [20]. Arterial blood pressure and a 12-lead electrocardiogram (ECG) were monitored simultaneously; data were stored in a PCM data recorder (RD-200T; TEAC, Tokyo, Japan). Holter ECG recordings (model 459, Del Mar Avionics, Irvine, CA) were also obtained. After an interval of 30 minutes to allow the patient to stabilize, the patient was asked to breathe at a rate of 15 breaths per minute measured with a metronome. Subsequently, blood samples were obtained from the venous catheter to measure plasma norepinephrine concentration. The baroreflex sensitivity (BRS) was assessed with the phenylephrine method [8-10]. Phenylephrine (2-3 μg/kg) was injected over 15 seconds to increase the systolic blood pressure by 15 to 40 mm Hg. The BRS was calculated as the slope of the linear regression line relating the systolic blood pressure changes to the 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 mean of the 2 slope values was taken as the BRS value.

Table 1
Clinical characteristics of the studied patients

	Hypo-AD (n = 14)	Normo-AD (n = 19)	P
Age (y)	58.6 ± 8.6	58.2 ± 8.1	NS
Duration of diabetes (y)	7.9 ± 5.4	7.2 ± 5.8	NS
Essential hypertension (%)	65	74	NS
Dyslipidemia (%)	48	53	NS
Drug use (%)			
Sulfonylurea	48	53	NS
α Glucosidase inhibitors	42	41	NS
Statin	39	41	NS
Calcium-channel antagonists	47	41	NS
Angiotensin-converting enzyme inhibitors	29	24	NS
Angiotensin receptor blockers	52	59	NS
Body mass index (kg/m^2)	27.0 ± 1.4	24.3 ± 3.4	< .01
Systolic blood pressure (mm Hg)	132 ± 18	130 ± 14	NS
Diastolic blood pressure (mm Hg)	77 ± 11	75 ± 9	NS
Heart rate (beats/min)	68 ± 6	67 ± 9	NS
Fasting plasma glucose (mg/dL)	156 ± 28	140 ± 25	< .05
Fasting immunoreactive insulin (μU/mL)	8.3 ± 2.6	6.1 ± 1.7	< .01
HOMA-IR	3.2 ± 1.0	2.1 ± 0.7	< .005
Hemoglobin A_{1c} (%)	7.7 ± 1.2	7.5 ± 1.0	NS
Total cholesterol (mg/dL)	211 ± 23	196 ± 27	NS
Triglyceride (mg/dL)	165 ± 55	132 ± 32	< .05
HDL cholesterol (mg/dL)	37 ± 8	45 ± 13	< .05
Uric acid (mg/dL)	6.4 ± 1.6	5.9 ± 1.3	NS
Creatinine (mg/dL)	0.8 ± 0.2	0.7 ± 0.2	NS
Creatinine clearance (mL/min)	83 ± 36	104 ± 32	NS

Data are mean ± SD unless otherwise indicated. Hypo-AD indicates hypoadiponectinemia group; Normo-AD, normoadiponectinemia group.

Heart rate variability (HRV) was analyzed by using a 300-second interval on the Holter ECG recordings obtained 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 [8-10]. We calculated the power of 2 spectral bands, the low-frequency component (LF) at 0.04 to 0.15 Hz and the high-frequency component (HF) 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. Whereas HF represents cardiac vagal activity, LF is a mixture of vagal and sympathetic activities [21]. The LF/HF was used to estimate cardiac sympathetic activity [21].

2.4. Cardiac ^{123}I-MIBG scintigraphy

Metaiodobenzylguanidine is a guanethidine analogue that is accumulated in the norepinephrine storage granules in postganglionary sympathetic neurons. Radioactive labeling of MIBG allows visualization of the sympathetic neuronal tissue in richly innervated organs such as the heart [14]. Planar and single-photon emission computed tomography studies were performed at 15 minutes and 4 hours after the injection of 111 MBq of ^{123}I-MIBG with a rotating gamma camera (ZLC 7500, Siemens, Munich, Germany). The data were analyzed using analysis software (SCINTIPAC, Shimadzu, Kyoto, Japan). The anterior planar images from the early and delayed ^{123}I-MIBG studies were analyzed visually. To do the 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-mediastinum (H/M) ratio. After correcting for the physical decay of iodine 128, the percent washout rate (WR) of the tracer from the myocardium was determined over a 4-hour period.

2.5. 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 Fisher exact probability test as appropriate. A value of $P < .05$ was considered statistically significant. Simple (Spearman rank) correlation coefficients between the plasma adiponectin concentration and the various variables were calculated, and a stepwise multiple regression analysis was then used to evaluate the independent association of these variables with plasma adiponectin concentration. On the multivariate analysis, F values of 4 or greater were considered statistically significant.

3. Results

As shown in Table 1, the 2 groups had a similar mean age and there were no significant differences with respect to duration of diabetes, number of patients with essential hypertension or dyslipidemia, and medications administered. The hypoadiponectinemia group had significantly higher body mass index ($P < .01$), fasting plasma glucose concentrations ($P < .05$), and insulin concentrations ($P < .01$), resulting in a higher HOMA-IR ($P < .005$). There was no significant difference in hemoglobin A_{1c} between the 2 groups. The plasma triglyceride was higher ($P < .05$) and the HDL cholesterol was lower ($P < .05$) in the hypoadiponectinemia group. The plasma creatinine and creatinine clearance were not significantly different. The hemodynamic data listed in Table 1 were obtained immediately before BRS assessment. The resting heart rate, as well as the systolic and diastolic blood pressures, was not significantly different. With respect to the echocardiographic findings, there were no significant differences in LVIDd and LVIDs at end systole (48 ± 4 vs 50 ± 4 mm and 31 ± 4 vs 33 ± 3 mm, respectively), IVSTD (9.0 ± 1.3 vs 9.5 ± 1.5 mm), PWTd (9.5 ± 1.2 vs 10.1 ± 1.2 mm), ejection

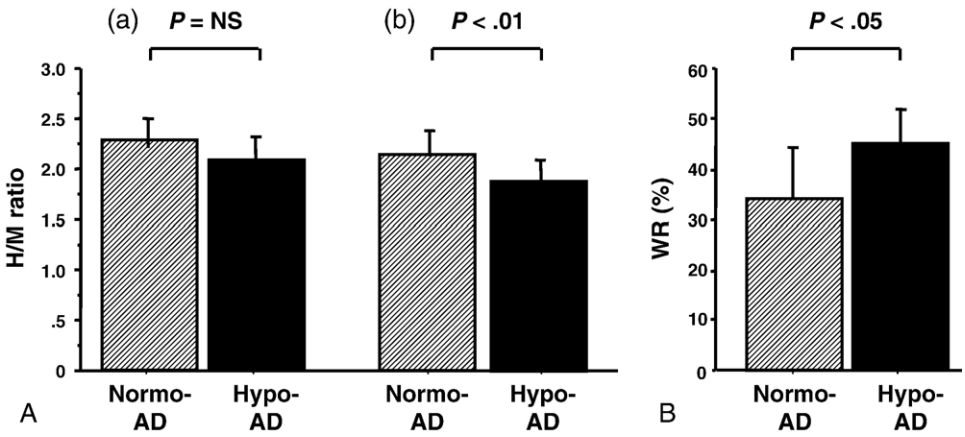

Fig. 1. Comparison of cardiac ^{123}I-MIBG scintigraphic findings in the type 2 diabetic patients with normoadiponectinemia (Normo-AD) and hypoadiponectinemia (Hypo-AD). A, Myocardial uptake of ^{123}I-MIBG in the early (a) and delayed (b) phases. Myocardial uptake of ^{123}I-MIBG is expressed as the mean H/M ratio. B, Percent WR of ^{123}I-MIBG. Data are mean ± SD.

fraction (70% ± 5% vs 69% ± 4%), and LVMI (113 ± 29 vs 121 ± 19 g/m^2). However, the E/A ratio was greater (0.95 ± 0.27 vs 0.77 ± 0.18, $P < .05$) and the deceleration time was longer (253 ± 27 vs 230 ± 31 msec, $P < .05$) in the hypoadiponectinemia group.

With respect to the results of the cardiovascular autonomic function tests, the BRS was lower in the hypoadiponectinemia group (6.0 ± 3.3 vs 9.4 ± 4.8 ms/mm Hg, $P < .05$), whereas plasma norepinephrine concentrations were similar (239 ± 99 vs 217 ± 112 pg/mL, P = not significant [NS]). The HRV analysis showed that the HF power and the LF/HF ratio were not significantly different (4.1 ± 1.7 vs 3.8 ± 1.4 ln ms^2, P = NS; 1.6 ± 0.9 vs 1.3 ± 0.9, P = NS, respectively). On cardiac ^{123}I-MIBG scintigraphy, although the H/M ratio in the early phase was not significantly different (2.12 ± 0.22 vs 2.27 ± 0.25, P = NS; Fig 1A[a]), in the delayed phase, the H/M ratio was lower in the hypoadiponectinemia group (1.94 ± 0.35) than in the normoadiponectinemia group (2.33 ± 0.31, $P < .01$; Fig. 1A[b]). The percent WR of ^{123}I-MIBG was higher in the hypoadiponectinemia group (42.5% ± 9.0% vs 34.5% ± 11.8%, $P < .05$; Fig. 1B). Table 2 shows the correlations between plasma adiponectin concentration and clinical variables for all of the patients in both groups. Plasma adiponectin concentration correlated negatively with body mass index, fasting plasma insulin, HOMA-IR, triglyceride, and percent WR of ^{123}I-MIBG, and positively with plasma HDL cholesterol, BRS, and H/M ratios in the early and delayed phases. Stepwise multiple regression analysis was done using these 9 variables. Plasma adiponectin concentration was found to be independently associated with HOMA-IR (F = 9.196) and the percent WR of ^{123}I-MIBG (F = 5.985) (Table 3).

Table 2
Correlations of plasma adiponectin with other variables

Parameters	Univariate	
	r	P
Age	−0.212	NS
Duration of diabetes mellitus	−0.190	NS
Body mass index	−0.372	.0332
Systolic blood pressure	−0.242	NS
Diastolic blood pressure	−0.120	NS
Heart rate	−0.335	NS
Total cholesterol	−0.089	NS
Triglyceride	−0.369	.0346
HDL cholesterol	−0.422	.0114
Uric acid	−0.228	NS
Fasting plasma glucose	−0.334	NS
Fasting immunoreactive insulin	−0.427	.0132
HOMA-IR index	−0.496	.0033
Hemoglobin A_{1c}	−0.206	NS
Creatinine	−0.202	NS
Creatinine clearance	0.333	NS
EF	0.155	NS
LVIDd	−0.317	NS
LVIDs	−0.236	NS
IVSTd	−0.153	NS
PWTd	−0.316	NS
LVMI	−0.297	NS
E/A ratio	0.151	NS
Deceleration time	−0,189	NS
Baroreflex sensitivity	0.407	NS
Plasma norepinephrine	−0.111	NS
HF power	0.091	NS
LF/HF	−0.252	NS
H/M ratio at early phase	0.401	.0206
H/M ratio at delayed phase	0.482	.0046
Percent WR of ^{123}I-MIBG	−0.423	.0142

Table 3
Stepwise regression analyses between plasma adiponectin and various parameters

Independent variable	Regression coefficient	SE	Standard regression coefficient	F
To adiponectin intercept	19.312			
HOMA-IR	−2.523	0.832	−0.444	9.196
Percent WR of ^{123}I-MIBG	−0.174	0.071	−0.358	5.985

F values equal to or greater than 4 were considered statistically significant.

4. Discussion

In the present study, middle-aged male type 2 diabetic patients with hypoadiponectinemia had a higher body mass index, higher fasting plasma concentrations of glucose and insulin, higher HOMA-IR, higher plasma triglyceride levels, and a lower plasma HDL cholesterol level than patients who had normoadiponectinemia. The body mass index, fasting plasma insulin concentration, HOMA-IR, plasma triglyceride concentration, and plasma HDL cholesterol concentration had a significant correlation with the plasma adiponectin concentration, which suggests a strong association between hypoadiponectinemia and insulin resistance [2,3]. Because there is a substantial association between these variables, it is possible that hypoadiponectinemia is associated with the overall abnormalities seen in glucose and lipid metabolism. Thus, although the present study was designed to assess the impact of hypoadiponectinemia, the obtained results might have been predominantly influenced by insulin resistance rather than hypoadiponectinemia.

In the present study, ^{123}I-MIBG scintigraphy showed that the H/M ratio in the delayed phase was decreased and the percent WR of ^{123}I-MIBG was increased in the hypoadiponectinemia group, and the percent WR of ^{123}I-MIBG was independently associated with plasma adiponectin concentration, which suggests that there is substantial sympathetic overactivity in patients with low plasma adiponectin concentration. These findings are novel. There is a growing body of evidence that sympathetic overactivity may play a central role in the pathogenesis of insulin resistance [22,23]. Recent experimental studies have also suggested that sympathetic overactivity has a role in the regulation of adiponectin expression [24,25]. Fasshauer et al [24] reported that adiponectin messenger RNA expression was inhibited by β-adrenergic stimulation via protein kinase A in 3T3-L1

adipocytes. More recently, Delporte et al [25] demonstrated that β-adrenergic stimulation down-regulated adiponectin messenger RNA in cultured mouse explants from the visceral and subcutaneous regions. Based on these experimental observations, it can be postulated that in patients with insulin resistance substantial sympathetic overactivity might reduce the adiponectin gene expression. However, it is still unclear whether low plasma adiponectin concentration, as observed in the clinical setting, is the cause or the result of sympathetic overactivity. With respect to vagal function, the BRS value was lower in patients with hypoadiponectinemia than in patients with normoadiponectinemia and was positively correlated with plasma adiponectin. Because there is a strong interaction between sympathetic and vagal activity [11], it is uncertain whether the low BRS value observed in the hypoadiponectinemia patients reflects relatively depressed vagal activity in response to sympathetic overactivity.

Until now, very limited information was available on the relationship between plasma adiponectin and cardiac autonomic nervous function. Wakabayashi and Aso [11] studied the relationship between plasma adiponectin concentration and the power spectral analysis of HRV in 105 patients with type 2 diabetes mellitus (51 women and 54 men); they reported that plasma adiponectin concentration showed an independent negative association with the 24-hour LF/HF ratio. Based on this observation, they concluded that a sympathovagal balance favoring relative sympathetic activation was associated with hypoadiponectinemia in patients with type 2 diabetes mellitus [11]. Although our HRV analysis did not show an association with plasma adiponectin concentration, our ^{123}I-MIBG scintigraphic findings appear to support their conclusion.

It is noteworthy that diastolic function, as determined by E/A ratio and deceleration time, is depressed in patients with hypoadiponectinemia. The exact mechanisms that explain the association between hypoadiponectinemia and diastolic dysfunction have not been elucidated. In a recent study demonstrating the association between insulin resistance and diastolic function in patients with type 2 diabetes mellitus and subjects with impaired glucose tolerance [26], the authors speculated that the insulin resistance may be involved in the onset of cardiac fibrosis, as shown in an experimental rat model of the prestage of type 2 diabetes mellitus [27].

Some methodological issues have to be addressed. First, 64% of hypoadiponectinemia patients and 74% of normoadiponectinemia patients had been diagnosed as having essential hypertension. In addition, 48% of hypoadiponectinemia patients and 53% of normoadiponectinemia patients had been diagnosed as having dyslipidemia. All these patients were being treated with one or more antihypertensive drugs and/or a statin, as shown in Table 1. These medications might have affected our results. Second, the present study included a relatively small number of patients because of our strict inclusion criteria. Third, there is currently no "gold standard" for the assessment of human sympathetic nervous activity to use as a comparison with other techniques. In fact, the reason why the patients with hypoadiponectinemia did not show an altered HRV or altered plasma norepinephrine levels, as expected, cannot be explained rationally. Regarding the HRV analysis, we analyzed ECG recording data using a 300-millisecond interval at rest obtained immediately before phenylephrine injection. The analysis using 24-hour data could have detected the sympathetic overactivity such as increased LF/HF. With respect to the levels of plasma norepinephrine, Grassi and Esler [28] mentioned that plasma norepinephrine measurements provide global indices of sympathetic nervous function but provide no information on regional sympathetic nervous system function. The authors, therefore, suggested that the sensitivity of the plasma norepinephrine approach in detecting increased sympathetic activity is not optimal [28]. Based on our observations, it is likely that ^{123}I-MIBG scintigraphy may be fairly sensitive in detecting cardiac sympathetic overactivity, at least in the population of patients that we studied. Finally, we divided the patients into 2 groups based on the criteria used for Japanese patients with coronary artery disease [6]. It remains to be determined whether this cutoff index (<4.0 μg/mL) is valid for use in type 2 diabetic patients.

In conclusion, the present study suggests that, in middle-aged male patients with type 2 diabetes mellitus, hypoadiponectinemia is associated with sympathetic overactivity as evaluated by cardiac ^{123}I-MIBG scintigraphy.

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