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White matter lesions are associated with the results of ^{123}I-metaiodobenzylguanidine myocardial scintigraphy in type 2 diabetes mellitus patients

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Abstract

White matter lesions (WMLs) and cardiovascular autonomic dysfunction are associated with high mortality in type 2 diabetes mellitus patients. This preliminary study was therefore designed to test the hypothesis that WML is associated with insulin resistance and cardiovascular autonomic dysfunction in type 2 diabetes mellitus patients without insulin treatment. Based on brain magnetic resonance imaging findings, 55 type 2 diabetes mellitus patients were divided into 2 groups: a WML-positive group (59 ± 5 years [mean ± SD], n = 21) and a WML-negative group (58 ± 6 years, n = 34). Cardiovascular autonomic function was assessed by baroreflex sensitivity, heart rate variability, plasma norepinephrine concentrations, and cardiac ^{123}I-metaiodobenzylguanidine (MIBG) scintigraphy. Baroreflex sensitivity was lower in the WML-positive group than in the WML-negative group ($P < .01$). Early and delayed ^{123}I-MIBG myocardial uptake values were lower ($P < .005$ and $P < .001$, respectively) and the percentage washout rate (WR) of ^{123}I-MIBG was higher ($P < .0001$) in the WML-positive group than in the WML-negative group. The fasting plasma glucose ($P < .005$) and insulin concentrations ($P < .0001$) and the homeostasis model assessment (HOMA) index values ($P < .0001$) were higher in the WML-positive group than in the WML-negative group. Multiple logistic regression analysis revealed that HOMA index and percentage WR of ^{123}I-MIBG were associated with WML patients. Our results suggested that WML was associated with depressed cardiovascular autonomic function and insulin resistance and that HOMA index and the percentage WR of ^{123}I-MIBG were independent associations for WML in Japanese patients with type 2 diabetes mellitus.
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1. Introduction

Since the introduction in the 1980s of brain magnetic resonance imaging (MRI) with its high sensitivity and resolution capacity, the presence of cerebral hyperintensities in the deep and subcortical white matter has been a common finding in elderly people [1]. These cerebral white matter lesions (WMLs) are an important prognostic factor for the development of stroke [2,3]. Many studies have shown that age, hypertension, diabetes mellitus (DM), and history of either stroke or heart disease are the most important risk factors related to WML [1].

Impaired autonomic nervous activity has been recognized as crucial in cardiac dysfunction and is strongly associated with harmful events and overall mortality in diabetic patients [4,5]. Recently, we have reported that depressed cardiovascular autonomic function is related to insulin resistance in type 2 DM patients [6-8]. Furthermore, the presence of WML is associated with diabetes [9,10]. Although these results strongly suggest that WML, insulin resistance, and autonomic dysfunction are related, the significance of WML for diabetic cardiovascular autonomic function has not been adequately investigated.

Technical advances, including measurements of baroreflex sensitivity (BRS), heart rate variability (HRV), and the

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concentration of norepinephrine, allow cardiac autonomic function to be assessed. The reliability coefficients of these parameters, however, were shown to be around 50% [11]. A reduction in myocardial uptake of ^{123}I-metaiodobenzylguanidine (MIBG) reflects a reduction in the concentration of norepinephrine at presynaptic sites or a reduction in the neural density, whereas an enhanced washout rate (WR) of ^{123}I-MIBG reflects enhanced release of norepinephrine from presynaptic sites [12]. Cardiac ^{123}I-MIBG scintigraphy is a sensitive method for detecting sympathetic dysfunction in many clinical disorders, including DM [13,14].

We hypothesized that increased levels of WML are associated with cardiovascular autonomic dysfunction and insulin resistance in type 2 DM patients. To test our hypothesis, we compared BRS, HRV, plasma norepinephrine concentrations, and cardiac ^{123}I-MIBG scintigraphy in addition to the metabolic profiles of Japanese type 2 DM patients with and without WML; and independent predictors of WML in these populations were evaluated.

2. Materials and methods

2.1. Study population

We screened 115 subjects seen in the Department of First Internal Medicine of Oita University Hospital between April 2005 and March 2006 for the treatment of type 2 DM detected during medical examination. Of these, 55 patients (30 men and 25 women), with ages ranging from 49 to 66 years and with a mean ± SD age of 58 ± 6 years, fulfilled the inclusion criteria and were enrolled in the present study. The inclusion criteria were as follows:

1. No evidence of coronary artery disease on the basis of a normal result of rest and exercise electrocardiography (ECG) and normal result of stress ^{201}TI cardiac scintigraphy.
2. Absence of causes of secondary hypertension (ie, primary aldosteronism, renal vascular hypertension, hyperthyroidism, pheochromocytoma).
3. No history of chronic disease, such as renal failure (creatinine >1.5 mg/dL), pulmonary disease, liver dysfunction (aspartate aminotransferase >50 IU/L), arteriosclerotic obliterans, sleep apnea syndrome, and symptomatic cerebrovascular disease.
4. Patient not currently using insulin.
5. Patient not currently receiving treatment with antiarrhythmia drugs and β-blockers (the reason is because antiarrhythmia drugs and β-blockers were effects of cardiovascular autonomic function).

Of the 115 screened patients, 60 were excluded from further evaluation because of extenuating circumstances. Of those excluded, 24 patients were being treated with insulin, 6 patients had angina pectoris, 5 patients had renal failure, 5 patients were being treated with antiarrhythmia drugs, 4 patients were not included in the BRS analysis (systolic blood pressure [SBP] and RR intervals of correlation coefficient less than 0.8 were not accepted for this analysis), 4 patients had symptomatic cerebrovascular disease, 3 patients were being treated with β-blockers, 3 patients had arteriosclerotic obliterans, 3 patients had secondary hypertension (2 patients had primary aldosteronism and, 1 patient had renal vascular hypertension), 3 patients had liver dysfunction (1 patient had hepatitis B, 2 patients had hepatitis C), 2 patients had lung cancer, and 2 patients had sleep apnea syndrome. Therefore, only 55 patients were selected for the study.

All subjects gave their written informed consent to participate in the study, and the study protocol was approved by the ethics committee of the Oita University Hospital.

2.2. Patients and methods

Hypertension was defined by performing BP measurement, registered as the average of 3 measurements obtained with a mercury-column sphygmomanometer after 10 minutes of physical resting by the patients. *Essential hypertension* was defined as diastolic blood pressure (DBP) of at least 90 mm Hg, SBP of at least 140 mm Hg, or self-reported use of antihypertensive medication [15].

Blood was taken at 7:00 AM from the antecubital vein with the patient in the recumbent position after an overnight fast. All patients underwent routine laboratory tests including assays for serum electrolytes, serum total cholesterol, serum

Table 1
Clinical characteristics of studied patients

	WML negative	WML positive	*P* value
Age (y)	58 ± 6	59 ± 5	NS
Sex (men/women)	19/15	11/10	NS
Duration of diabetes (y)	7.3 ± 3.9	8.2 ± 2.7	NS
Hypertension (%)	62	67	NS
Dyslipidemia (%)	38	43	NS
Drug use (%)			
Sulfonylurea	41	38	NS
α-Glucosidase inhibitors	32	33	NS
Statin	35	33	NS
Calcium channel antagonists	41	43	NS
Diuretics	12	14	
ACE inhibitors	21	24	NS
Angiotensin receptor blocker	38	33	NS
BMI (kg/m^2)	25.0 ± 2.7	26.6 ± 1.8	.0233
SBP (mm Hg)	129 ± 17	132 ± 12	NS
DBP (mm Hg)	76 ± 8	77 ± 7	NS
Heart rate (beats/min)	67 ± 6	68 ± 8	NS
Total cholesterol (mg/dL)	199 ± 26	209 ± 37	NS
Triglyceride (mg/dL)	125 ± 38	156 ± 53	.0140
HDL-C (mg/dL)	48 ± 11	41 ± 8	.0146
FPG (mg/dL)	139 ± 16	156 ± 24	.0032
F-IRI (μU/mL)	6.0 ± 1.2	8.9 ± 2.1	<.0001
HOMA index	2.0 ± 0.5	3.4 ± 0.9	<.0001
HbA_{1c} (%)	7.7 ± 1.1	7.8 ± 1.3	NS
Uric acid (mg/dL)	5.6 ± 1.3	6.5 ± 1.0	.0119
Creatinine (mg/dL)	0.7 ± 0.2	0.8 ± 0.2	NS

Data are mean ± SD. ACE indicates angiotensin-converting enzyme.

triglycerides, serum high-density lipoprotein cholesterol (HDL-C), fasting plasma glucose (FPG), and fasting immunoreactive insulin (F-IRI). Insulin resistance was evaluated by the homeostasis model assessment (HOMA) index, as follows: (fasting plasma insulin [in microunits per milliliter] × FPG [in millimoles per liter])/22.5 [16].

The clinical characteristics of the patients in the 2 WML groups are summarized in Table 1. Fourteen of the 21 patients in the WML-positive group and 21 of the 34 patients in the WML-negative group met the criteria for essential hypertension. All of these patients were being treated with calcium channel antagonists, diuretics, angiotensin-converting enzyme inhibitors, and/or angiotensin II receptor blockers. *Dyslipidemia* was defined as fasting triglycerides levels of at least 200 mg/dL or HDL-C concentration of less than 45 mg/dL for women and less than 35 mg/dL for men [17]. There were 14 of the 34 patients in the WML-positive group and 21 of the 56 patients in the WML-negative group who met the criteria for dyslipidemia.

2.3. Evaluation of WMLs

All participating patients underwent brain MRI using a superconducting magnet at a field of 1.5 T on proton density–, T_1-, and T_2-weighted images in axial planes at 5-mm–thick slices. Details of the image interpretation protocols used were the same as those of the Rotterdam Study [18]. Patients were classified by consensus as having the following: (1) normal-result scans (WMLs absent), if there were either absent or only slight periventricular hyperintensity (small caps or pencil-thin lining), fewer than 5 focal lesions, and no confluent lesions; or (2) WMLs present, if there were moderate or severe periventricular hyperintensity, 5 or more focal lesions, or confluent lesions. All MRI scans were examined by 2 raters who were blinded to all clinical information. In case of a disagreement of more than 1 point, a consensus reading was held; in all other cases, the readings of both readers were averaged. The interrater and intrarater studies showed a good to excellent agreement.

2.4. Echocardiography

M-mode and 2-dimensional echocardiography and cardiac Doppler recordings were obtained using a phased-array echo-Doppler system. Echocardiograms were obtained using standard parasternal, short-axis, and apical views. The left ventricular (LV) mass was calculated as $1.04 \times ([\text{LVIDd} + \text{IVSTd} + \text{PWTd}]^3 - \text{LVIDd}^3) - 14$ g, where LVIDd is the left ventricular internal diameter at the end diastole, IVSTd is the intraventricular septal thickness at the end diastole, and PWTd is the posterior wall thickness at the end diastole. The LV mass was divided by the body surface area to calculate the left ventricular mass index (LVMI). Pulsed Doppler recordings were made from a standard apical 4-chamber view. The LV diastolic filling pattern was obtained with the sample volume at the tips of the mitral valve in the apical 4-chamber view and recorded at the end-expiratory phase during quiet breathing [19]. The peak velocity of early rapid filling (*E* velocity) and the peak velocity of atrial filling (*A* velocity) were recorded, and the ratio of *E* to *A* (*E*/*A*) was calculated. The deceleration time (DcT) of the *E* velocity was measured as the time interval from the *E*-wave peak to the decline of the velocity to baseline values.

2.5. Cardiovascular autonomic function tests

Autonomic function was assessed according to methods described in previous studies [6-8]. During the tests, which were performed between 9:00 AM and 11:00 AM, all subjects were in a supine position in a quiet room with dimmed lights. Autonomic function tests were performed in the morning after an overnight (≥12 hours) fast. For measurement of the plasma norepinephrine concentration, a blood sample was obtained from a catheter inserted in the right cubital vein 30 minutes earlier. We measured plasma norepinephrine concentration according to methods described in previous studies [6-8]. Arterial BP was recorded noninvasively through a tonometric sensor attached over the left radial artery (Jentow-7700; Nihon Colin, Komaki, Japan). The tonometric sensor was attached over the left radial artery. The accuracy of continuous BP monitoring has been demonstrated previously [20]. Arterial BP and a standard 12-lead ECG were monitored simultaneously; data were stored in a PCM data recorder (RD-200T; TEAC, Tokyo, Japan). Three-lead precordial Holter ECG recordings (model-459; Del Mar Avionics, Irvine, CA) were also obtained throughout the procedure for analysis of HRV.

After an interval of 30 minutes to permit stabilization of the cardiovascular baroreflex mechanism, the patient was asked to breathe at a rate of 15 breaths per minute using a metronome to stabilize the relationship between respiration and cardiovascular function. Baroreflex sensitivity was assessed by the phenylephrine method [6-8]. Briefly, phenylephrine (2-3 μg/kg) was injected for 15 seconds to obtain a 15– to 40–mm Hg rise in SBP.

Baroreflex sensitivity was calculated as the slope of the linear regression line relating SBP changes to RR interval. The beat-by-beat time series of SBP and RR intervals were searched for 3 consecutive beats in which (1) the SBP and RR intervals of the following beat changed in the same direction (either increasing or decreasing) and (2) regression lines with more than 20 data points and a correlation coefficient (r) greater than 0.8 were accepted for analysis. Baroreflex sensitivity was calculated from these data sets as the slope of the regression line between SBP and RR interval.

Heart rate analysis (HRV) was analyzed using a 300-second interval on Holter ECG recordings (Marquette Electronics, Milwaukee, WI) immediately before phenylephrine injection [21]. The power spectrum of the RR interval was computed by a fast Fourier transformation and expressed as the area under the power spectrum. We calculated the power of 2 spectral bands: the normal-

Table 2
Echocardiographic findings

	WML negative	WML positive	*P* value
EF (%)	69 ± 5	67 ± 4	NS
LVIDd (mm)	48 ± 4	49 ± 4	NS
LVIDs (mm)	31 ± 3	32 ± 3	NS
IVSTd (mm)	8.8 ± 1.1	9.3 ± 1.3	NS
PWTd (mm)	9.3 ± 1.2	9.8 ± 1.0	NS
LVMI (g/m^2)	113 ± 19	118 ± 25	NS
E/*A* ratio	0.95 ± 0.16	0.86 ± 0.14	.0468
DcT (ms)	236 ± 33	252 ± 25	.0484

Data are mean ± SD. LVIDs indicates left ventricular internal dimension at end systole.

frequency (LF) component at 0.04 to 0.15 Hz and the high-frequency (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) also was computed.

^{123}I-Metaiodobenzylguanidine (111 MBq) (Dai-ichi Radioisotope Laboratories, Tokyo, Japan) was injected intravenously into the patients under resting and fasting conditions. Fifteen minutes and 4 hours after the injection, static planner images were acquired in the anterior view using a rotating gamma camera (ZLC 7500; Siemens, Munich, Germany). The anterior planar images from early and delayed ^{123}I-MIBG studies were analyzed visually. For semiquantitative analysis, regions of interest were identified within the whole heart; and a 10 × 10–pixel 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 percentage WR of the tracer from the myocardium was determined over a 4-hour period.

2.6. Statistical analysis

All data are classified into 2 groups, that is, the normal and the WML, and are summarized as the means ± SD (Table 1). For each variable in Table 1, the 2-sided test with level of significance of .05 was performed to test the difference between the 2 groups. The Student *t* test was used for continuous variables; and for categorical variables, the χ^2 test was carried out. Logistic regression analysis was used to assess the influence of exploratory variables on WML, where the exploratory variables were age, sex, body mass index (BMI), duration of diabetes, hypertension, dyslipidemia, BP, heart rate, total cholesterol, triglyceride, HDL-C, FPG, F-IRI, HOMA index, hemoglobin A_{1c} (HbA_{1c}), uric acid, creatinine, ejection fraction (EF), LVMI, *E*/*A* ratio, DcT, plasma norepinephrine, HF power, LF/HF, BRS, the percentage WR of ^{123}I-MIBG, and the *H*/*M* ratio at the early and delayed phase after ^{123}I-MIBG administration and where sex, hypertension, and dyslipidemia were dichotomized as 1 (presence) and 0 (absence) by cutoff values defined in the previous section.

For WML, the positive was represented as 1; and the negative, as 0. To determine factors among all exploratory variables used, a backward elimination procedure was used. To conduct regression using backward elimination, all

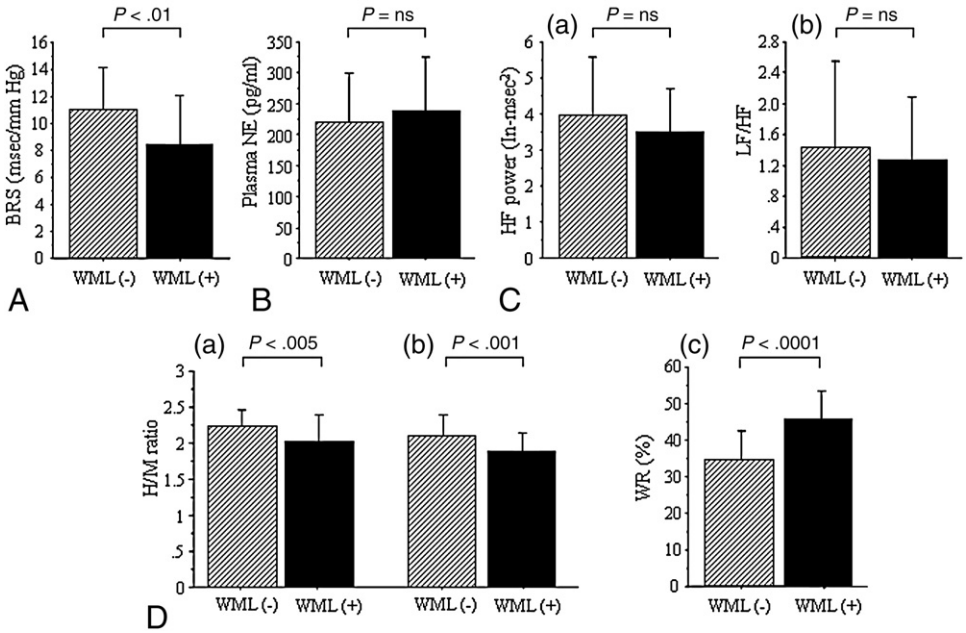

Fig. 1. Comparison of autonomic function tests between type 2 DM patients who were WMLs positive (WML[+]) and WMLs negative (WML[−]). A, Baroreflex sensitivity. B, Plasma norepinephrine (NE) concentration. C, Heart rate variability. Power of HF component (0.15-0.40 Hz, a) and the ratio of the LF power (0.04-0.15 Hz) to HF power (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. Percentage WR of ^{123}I-MIBG (c). Data are mean ± SD.

potential predictors of the outcome variable are initially entered into the model. Afterward, predictors are deleted from the model, one at a time, based on which predictor would result in the smallest amount of change in variance explained when deleted. Predictors continued to be deleted from the model, one at a time, until deletion of any of the remaining predictors results in a meaningful reduction in variance mode [22].

For the procedure, the BMI, triglyceride, HDL-C, FPG, F-IRI, HOMA index, uric acid, BRS, the percentage WR of ^{123}I-MIBG, and the *H*/*M* ratio at the early and delayed phase after ^{123}I-MIBG administration were determined as significant factors influencing WML.

All the analyses were performed using a standard statistical package (JMP 6.0; SAS Institute, Cary, NC).

3. Results

As shown in Table 1, the mean ages of the WML-positive and WML-negative groups were similar; and there were no significant differences between the groups with respect to sex, duration of diabetes, and administered medications. The BMI values were larger in the WML-positive group than in the WML-negative group (P = .0233). Regarding glucose metabolism, the FPG and insulin concentrations and the HOMA index values were higher in the WML-positive group than in the WML-negative group (P = .0032, P < .0001, and P < .0001, respectively). There however was no significant difference in the levels of HbA_{1c}. With regard to lipid metabolism, the concentration of serum triglyceride was higher and the concentration of serum HDL-C was lower in the WML-positive group than in the WML-negative group (P = .0140 and P = .0146, respectively), whereas serum total cholesterol levels were not significantly different between the groups. The concentration of uric acid was higher in the WML-positive group than in the WML-negative group (P = .0119). Renal function tests showed no significant difference in serum concentration between the 2 groups.

Table 3
Univariate logistic regression analysis with WML as the dependent variables in type 2 DM

	WML		
	OR	95% CI	*P* value
Age	1.02	0.93-1.13	NS
Sex (men)	0.77	0.26-2.30	NS
BMI	1.35	1.03-1.76	.0305
Duration of diabetes	1.08	0.92-1.27	NS
Hypertension	0.85	0.45-2.23	NS
Dyslipidemia	1.15	0.63-2.78	NS
SBP	1.02	0.98-1.07	NS
DBP	1.04	0.95-1.14	NS
Heart rate	1.01	0.93-1.09	NS
Total cholesterol	1.01	0.99-1.03	NS
Triglyceride	1.02	1.00-1.03	.0219
HDL-C	0.93	0.87-0.99	.0194
FPG	1.05	1.01-1.08	.0067
F-IRI	2.98	1.70-5.22	.0005
HOMA index	8.77	3.58-18.7	.0001
HbA_{1c}	1.10	0.69-1.75	NS
Uric acid	1.85	1.12-3.08	.0179
Creatinine	2.68	0.59-7.86	NS
EF	0.96	0.86-1.08	NS
LVMI	1.01	0.99-1.04	NS
E/*A* ratio	0.67	0.60-1.03	NS
DcT	1.02	0.99-1.05	NS
Plasma norepinephrine	1.00	0.99-1.01	NS
HF power	0.78	0.53-1.14	NS
LF/HF	0.84	0.49-1.45	NS
BRS	0.80	0.68-0.95	.0108
H/*M* ratio at early phase	0.68	0.47-0.91	.0049
H/*M* ratio at delay phase	0.52	0.37-0.86	.0024
Washout	1.31	1.14-1.49	<.0001

Significant predictors of WMLs were explored among 3 parameters: sex (female = 0, men = 1), hypertension (absent = 0, present = 1), and dyslipidemia (absent = 0, present = 1).

The hemodynamic data listed in Table 1 were obtained immediately before BRS assessment. The resting heart rate and the SBP and DBP were not significantly different between the 2 groups.

Table 2 presents a summary of echocardiographic findings. The LV dimensions at end diastole and end systole, intraventricular septal and posterior wall thickness at end diastole, EF, and LVMI were essentially similar in the 2 groups. With regard to the LV diastolic function, the ratio of peak velocities of early to late ventricular filling (*E*/*A*) was lower in the WML-positive group than in the WML-negative group (P = .0468). The DcT was longer in the WML-positive group than in the WML-negative group (P = .0484).

Fig. 1 summarizes the results of the cardiovascular autonomic function tests. Baroreflex sensitivity was lower in the WML-positive group than in the WML-negative group (WML-positive group, 8.0 ± 4.2 vs WML-negative group, 10.9 ± 3.2 ms/mm Hg; P = .0065; Fig. 1A). Plasma norepinephrine concentration was similar in both groups (WML-positive group, 242 ± 86 vs WML-negative group, 210 ± 79 pg/mL; P = not significant [NS]; Fig. 1B). Furthermore, analysis of HRV in the WML-positive group and WML-negative group revealed that the HF power (3.3 ± 1.4 and 3.9 ± 1.6 ln-ms^2, respectively; P = NS) and the LF/HF ratios (1.3 ± 1.0 and 1.4 ± 1.1, respectively; P = NS; Fig. 1C) were not significantly different between the 2 groups. Cardiac ^{123}I-MIBG scintigraphy disclosed that the *H*/*M* ratios at early and delayed phases in the WML-positive group were significantly smaller than those in the WML-negative group (early phase, 2.01 ± 0.26 vs 2.24 ± 0.22, respectively; P = .0023; delayed phase, 1.86 ± 0.28 vs 2.12 ± 0.26, respectively; P = .0009; Fig. 1D).

The percentage WR of ^{123}I-MIBG was higher in the WML-positive group than in the WML-negative group (46.6% ± 6.1% vs 34.1% ± 7.7%, P < .0001, Fig. 1D).

In univariate logistic regression analysis, the risk of WML was associated with BMI (odds ratio [OR] = 1.35, 95% confidence interval [CI] =1.03-1.76, P = .0305), triglyceride (OR = 1.02, 95% CI = 1.00-1.03, P = .0219), HDL-C (OR =

0.93, 95% CI = 0.87-0.99, $P = .0194$), FPG (OR = 1.05, 95% CI = 1.01-1.08, $P = .0067$), F-IRI (OR = 2.98, 95% CI = 1.70-5.22, $P = .0005$), HOMA index (OR = 8.77, 95% CI = 3.58-18.7, $P = .0001$), uric acid (OR = 1.85, 95% CI = 1.12-3.08, $P = .0179$), BRS (OR = 0.80, 95% CI = 0.68-0.95, $P = .0108$), *H*/*M* ratio at early phase (OR = 0.68, 95% CI = 0.47-0.91, $P = .0049$), *H*/*M* ratio at delayed phase (OR = 0.52, 95% CI = 0.37-0.86, $P = .0024$), and percentage WR of ^{123}I-MIBG (OR =- 1.31, 95% CI = 1.14-1.49, $P < .0001$) as the dependent lipid and glucose metabolic and cardiovascular autonomic function parameters in type 2 DM patients (Table 3).

Multivariate logistic analysis identified HOMA index (OR = 5.73, 95% CI = 1.51-13.8, $P = .0168$) and the percentage WR of ^{123}I-MIBG (OR = 1.23, 95% CI = 1.07-1.40, $P = .0026$) in type 2 DM patients as independent associations for WML.

4. Discussion

In our present study, type 2 DM patients in the WML-positive group had lower BRS, lower myocardial uptake, and enhanced clearance of ^{123}I-MIBG relative to the values in type 2 DM patients in the WML-negative group. Among the metabolic profiles, the FPG, insulin concentration, and HOMA index were higher in patients in the WML-positive group than in those in the WML-negative group. Multiple logistic analysis revealed that the HOMA index and the percentage WR of ^{123}I-MIBG were associated with the presence of WML in type 2 DM patients.

Several studies have examined the prevalence of WML in both normotensive and hypertensive subjects. Shimada et al [23] studied 28 normotensive and 20 hypertensive patients aged 59 to 83 years and found the prevalence of advanced WML at 25% and 40%, respectively. Sierra et al [24] reported the prevalence of WML among asymptomatic never-treated hypertensive patients with mean age of 54 years at 40.9%. The prevalence of WML was similar to the proportion (21/55 [38.2%]) of type 2 DM patients observed in the present study.

Several studies have suggested that the presence of WML is associated with diabetes [9,10]. The large community-based study, the Cardiovascular Determinants of Dementia study [9], reported that the prevalence of WML volume was higher in the diabetic group than in the nondiabetic group. Jongen et al [10] have recently reported that the combination of increased atrophy and increased WML volume indicates the likely association of mixed pathology in the brain with type 2 DM patients. In our study, the presence of WML is associated with insulin resistance by HOMA index in type 2 DM patients.

Although the specific mechanism that links the presence of WML and insulin resistance remains to be elucidated, several mechanisms could be explained based on our observation. First, glucose toxicity, abnormalities in cerebral insulin homeostasis, and microvascular abnormalities have been implicated [3]. Steinberg et al [25] reported that insulin-resistant states, such as diabetes and obesity, were associated with decreased endothelium-dependent vasodilation [25]; and arterial compliance may be a partially nitric oxide–dependent process [26]. Second, insulin has been shown to induce vascular smooth muscle proliferation and migration in cell cultures [27]. It is possible that interactions between the presence of WML and insulin resistance reinforce each other through mechanisms associated with endothelial dysfunction.

The relationship between cerebrovascular disease and cardiovascular autonomic function has been examined in previous studies with conflicting results using HRV analysis or BRS [28-30]. Tokgozoglu et al [28] reported that, of 62 patients with acute ischemic stroke, with a mean age of 62 years, 7 patients who experienced sudden death had a significantly reduced domain measure of HRV and a trend toward reduced low-frequency spectral power compared with survival. Robinson et al [29] reported that reduced BRS in the acute stroke phase was an independent predictor for all-cause mortality during a median 4-year follow-up. On the other hand, Rufa et al [30] reported that cardiac autonomic nervous systems by HRV were not associated with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy. However, these parameters had reliability coefficient of around 50% [11]. In the present study, HRV and plasma norepinephrine concentrations were not different between the 2 groups. However, a significant difference was seen in ^{123}I-MIBG parameters.

These results may suggest association of WML in diabetic patients with impairment of uptake-1 (norepinephrine transporter) as well as the acceleration of norepinephrine turnover in sympathetic nerve terminal. Impairment in uptake-1 in diabetic rats has been reported [31]. However, ^{123}I-MIBG uses the same uptake system and storage site as norepinephrine [32]. Our and others' previous studies [6-8,33] demonstrated that ^{123}I-MIBG scintigraphy is a fairly sensitive method for detecting cardiac sympathetic dysfunction in diabetic patients. The present results support the potential of ^{123}I-MIBG scintigraphy for diagnosis of cardiovascular autonomic dysfunction.

To our knowledge, this is the first report demonstrating the association between the presence of WML and cardiac ^{123}I-MIBG scintigraphic findings in diabetic patients.

What is the main cause of WML observed in the present study? We have recently reported that the presence of WML is associated with hyperhomocysteinemia, microalbuminuria, and insulin resistance in type 2 DM patients [34,35].

Furthermore, we previously reported that the presence of microalbuminuria, hyperhomocystinemia, and abdominal visceral fat accumulation is associated with insulin resistance and depressed cardiovascular autonomic function by cardiac ^{123}I-MIBG scintigraphy [6,7].

These findings are similar to the present observations. In those studies [6-8], it was discussed that the predominant

involvement of endothelial dysfunction was in the development of microalbuminuria, hyperhomocystinemia, abdominal visceral fat accumulation, and cardiovascular autonomic dysfunction. Endothelial dysfunction is associated with cardiac autonomic dysfunction and increased HRV [36,37].

Taken together, it is possible that WML, insulin resistance, and cardiac autonomic dysfunction reinforce each other through mechanisms associated with endothelial dysfunction.

There are several limitations to this study. Firstly, the exclusion of the subjects might influence the results of the present study. Secondly, subjects in the present study population had essential hypertension, which was treated with one or more antihypertensive drugs. These characteristics of the patients' backgrounds have been reported to affect insulin resistance [38,39] and sympathetic nerve function [40,41]. Our findings suggested that WML in diabetic patients is related to decreased LV function and insulin resistance. Finally, age is the key risk factor for WML; and therefore, patients with WML are generally older than those without WML [1,3]. In the present study, age is not significantly associated with the presence of WML in type 2 DM patients. Most studies have been performed on elderly people (>65 years old). In our study, ages ranged from 49 to 66 years, with a mean of 58 years. Further clinical investigations are needed to determine the relationship between age and the presence of WML in type 2 DM patients.

In conclusion, our findings suggest that the presence of WML in patients with type 2 DM is associated with both cardiovascular autonomic function assessed by the percentage WR of ^{123}I-MIBG and insulin resistance. In the future, large cohort studies including other populations may be beneficial.

References

[1] Pantoni L, Garcia JH. The significance of cerebral white matter abnormalities 100 years after Binswanger's report. Stroke 1995;26: 1293-301.

[2] Wong TY, Klein R, Sharrett AR. Cerebral white matter lesions, retinopathy, and incident clinical stroke. JAMA 2002;288:67-74.

[3] Vermeer SE, Hollander M, van Dijk EJ, et al. Silent brain infarcts and white matter lesions increase stroke risk in the general population: the Rotterdam Scan Study. Stroke 2003;34:1126-9.

[4] Tsuji H, Larson MG, Venditti Jr FJ, et al. Impact of reduced heart rate variability on risk for cardiac events. The Framingham Study. Circulation 1996;94:2850-5.

[5] La Rovere MT, Bigger Jr JT, Marcus FI. Baroreflex sensitivity and heart-rate variability in prediction of total cardiac mortality after myocardial infarction. ATRAMI (Autonomic Tone and Reflexes After Myocardial Infarction Investigators. Lancet 1998; 351:478-84.

[6] Takahashi N, Anan F, Nakagawa M, et al. Microalbuminuria, cardiovascular autonomic function, and insulin resistance in patients with type 2 diabetic patients. Metabolism 2004;53:1359-64.

[7] Anan F, Yonemochi H, Masaki T, et al. Homocysteine levels are associated with the results of ^{123}I-metaiodobenzylguanidine myocardial scintigraphy in type 2 diabetic patients. Eur J Nucl Med Mol Imaging 2007;34:28-35.

[8] Anan F, Masaki T, Yonemochi H, et al. Abdominal visceral fat accumulation is associated with the results of ^{123}I-metaiodobenzylguanidine scintigraphy in type 2 diabetic patients. Eur J Nucl Med Mol Imaging 2007;34:1189-97.

[9] Schmidt R, Launer LJ, Nilsson LG. CASCADE Consortium. Magnetic resonance imaging of the brain in diabetes: the Cardiovascular Determinants of Dementia (CASCADE) Study. Diabetes 2004;53: 687-92.

[10] Jongen C, van der Grond J, Kappelle LJ. Utrecht Diabetic Encephalopathy Study Group. Automated measurement of brain and white matter lesion volume in type 2 diabetes mellitus. Diabetologia 2007;50:1509-16.

[11] Gerritsen J, TenVoorde BJ, Dekker JM, et al. Measures of cardiovascular autonomic dysfunction nervous function: agreement, reproducibility, and reference values in middle age and elderly subjects. Diabetologia 2003;46:330-8.

[12] Sakata K, Shirotani M, Yoshida H. Cardiac sympathetic nervous system in early essential hypertension assessed by ^{123}I-MIBG. J Nucl Med 1999;40:6-11.

[13] Spallone V, Menzinger G. Diagnosis of cardiovascular autonomic neuropathy in diabetes. Diabetes 1997;46:S67-76.

[14] Watanabe K, Sekiya M, Tsuruoka T. Relationship between insulin resistance and cardiac sympathetic nervous function in essential hypertension. J Hypertens 1999;17:1161-8.

[15] Mancia G, De Backer G, Dominiczak A, et al. 2007 ESH-ESC practice guidelines for the management of arterial hypertension: ESH-ESC task force on the management of arterial hypertension. J Hypertens 2007; 25:1751-62.

[16] Matthews DR, Hosker JP, Rudenski AS, et al. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985; 28:412-9.

[17] Liao D, Sloan RP, Cascio WE, et al. Multiple metabolic syndrome is associated with lower heart rate variability. The Atherosclerosis Risk in Communities Study. Diabetes Care 1998;21:2116-22.

[18] Breteler MM, van Swieten JC, Bots ML, et al. Cerebral white matter lesions, vascular risk factors, and cognitive function in a population-based study: the Rotterdam Study. Neurology 1994;44:1246-52.

[19] Rakowski H, Appleton C, Chan KL, et al. Canadian consensus recommendations for the measurement and reporting of diastolic dysfunction by echocardiography. J Am Soc Echocardiogr 1996;9: 736-60.

[20] Sato T, Nishinaga M, Kawamoto A, et al. Accuracy of a continuous blood pressure monitor based on arterial tonometry. Hypertension 1993;21:866-74.

[21] Anan F, Takahashi N, Nakagawa M, et al. High-sensitivity C-reactive protein is associated with insulin resistance and cardiovascular autonomic dysfunction in type 2 diabetic patients. Metabolism 2005; 54:552-8.

[22] Pedlhauzer EJ. Multiple regression in behavior research: explanation and prediction. 3rd ed. Fort Worth (Tex): Harcourt Brace; 1997.

[23] Shimada K, kawamoto A, Matsubayashi K. Silent cerebrovascular disease in the elderly. Correlation with ambulatory pressure. Hypertension 1990;16:692-9.

[24] Sierra C, de la Sierra A, Mercader J. Silent cerebral white matter lesions in middle-aged essential hypertensive patients. J Hypertens 2002;20:519-24.

[25] Steinberg HO, Chaker H, Leaming R. Obesity/insulin resistance is associated with endothelial dysfunction. Implications for the syndrome of insulin resistance. J Clin Invest 1996;97:2601-10.

[26] Hu CT, Chang KC, Wu CY, et al. Acute effects of nitric oxide blockade with L-NAME on arterial haemodynamics in the rat. Br J Pharm 1997; 122:1237-43.

[27] Indolfi C, Torella D, Cavuto L. Effects of balloon injury on neointimal hyperplasia in streptozotocin-induced diabetes and in hyperinsulinemic

nondiabetic pancreatic islet-transplanted rats. Circulation 2001;103: 2980-6.
[28] Tokgozoglu SL, Batur MK, Top uoglu MA, et al. Effects of stroke localization on cardiac autonomic balance and sudden death. Stroke 1999;30:1307-11.
[29] Robinson TG, Dawson SL, Eames PJ, et al. Cardiac baroreceptor sensitivity predicts long-term outcome after acute ischemic stroke. Stroke 2003;34:705-12.
[30] Rufa A, Guideri F, Acampa M, et al. Cardiac autonomic nervous system and risk of arrhythmias in cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL). Stroke 2007;38:276-80.
[31] Kinjyo Y, Kajiyama S, Fujiwara H, et al. Influence of the polyol pathway on transporter reduction in diabetic cardiac sympathetic nerve: implication for heterogeneous accumulation of MIBG. Eur J Nucl Med Imaging 2005;32:438-42.
[32] Glowniak JV, Kilty JE, Amara SG, et al. Evaluation of metaiodobenzylguanidine uptake by the norepinephrine, dopamine and serotonin transporters. J Nucl Med 1993;34:1140-6.
[33] Mantysaari M, Kuikka J, Mustonen J, et al. Noninvasive detection of cardiac sympathetic nervous dysfunction in diabetic patients using [^{123}I] metaiodobenzylguanidine. Diabetes 1992;41:1069-75.
[34] Shimomura T, Anan F, Umeno Y. Hyperhomocysteinaemia is a significant risk factor for white matter lesions in Japanese type 2 diabetic patients. Eur J Neurol 2008;15:289-94.
[35] Anan F, Masaki T, Iwao T. The role of microalbuminuria and insulin resistance as significant risk factor for white matter lesions in Japanese type 2 diabetic patients. Curr Med Res Opin 2008;24:1561-7.
[36] Ghiadoni L, Donald AE, Cropley M. Mental stress induces transient endothelial dysfunction in humans. Circulation 2000;102:2473-8.
[37] Hijmering ML, Stroes ES, Olijhoek J. Sympathetic activation markedly reduces endothelium-dependent, flow-mediated vasodilatation. J Am Coll Cardiol 2002;39:683-8.
[38] Gavras HP. Issues in hypertension: drug tolerability and special populations. Am J Hypertens 2001;14(Pt 2):231S-6S.
[39] Lender D, Arauz-Pacheco C, Breen L, et al. A double blind comparison of the effects of amlodipine and enalapril on insulin sensitivity in hypertensive patients. Am J Hypertens 1999;12:298-303.
[40] Kontopoulos AG, Athyros VG, Didangelos TP. Effect of chronic quinapril administration on heart rate variability in patients with diabetic autonomic neuropathy. Diabetes Care 1997;20:355-61.
[41] Rodgers JE, Patterson JH. Angiotensin II-receptor blockers: clinical relevance and therapeutic role. Am J Health Syst Pharm 2001;58: 671-83.