Association Between Glycemic Control and Morning Blood Pressure Surge With Vascular Endothelial Dysfunction in Type 2 Diabetic Patients

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OBJECTIVE

Morning blood pressure surge (MBPS) is an independent predictor of cardiovascular events. However, little is known about the association between glycemic control and MBPS, and its effect on vascular injury in patients with type 2 diabetes mellitus (T2DM). The current study examined the association between glycemic control and MBPS, and the involvement of MBPS in the development of vascular dysfunction in T2DM patients.

RESEARCH DESIGN AND METHODS

We examined MBPS in T2DM patients (25 male patients/25 female patients; mean age, 60.1 ± 13.2 years; *n* = 50) using 24-h ambulatory blood pressure monitoring, and assessed vascular function by brachial artery flow-mediated dilation (FMD) and nitroglycerin-mediated dilation (NMD).

RESULTS

HbA_{1c} (ρ = 0.373, *P* = 0.009) and triglyceride (TG) (ρ = 0.375, *P* = 0.009) levels correlated significantly and positively with MBPS. In multiple regression analysis, including TG and HbA_{1c} levels in addition to age and 24-h systolic blood pressure (SBP) as independent variables, HbA_{1c} (β = 0.328, *P* = 0.016) and TG (β = 0.358, *P* = 0.014) were associated significantly in a positive manner with MBPS. In a non-insulin user, when homeostasis model assessment ratio (HOMA-R) was included in place of TG, HOMA-R emerged as a significant factor. MBPS (ρ = −0.289, *P* = 0.043) and HbA_{1c} (ρ = −0.301, *P* = 0.035) correlated significantly and negatively with FMD, whereas 24-h SBP correlated with both FMD (ρ = −0.359, *P* = 0.012) and NMD (ρ = −0.478, *P* = 0.004). In multiple regression analysis, including age, gender, 24-h SBP, MBPS, LDL cholesterol, and HbA_{1c}, MBPS (β = −0.284, *P* = 0.044) alone associated significantly in a negative manner with FMD, but not with NMD.

CONCLUSIONS

The current study demonstrated that poor glycemic control and insulin resistance are independently associated with the occurrence of MBPS in T2DM patients, which might be significantly associated with endothelial dysfunction.

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Patients with diabetes mellitus (DM) tend to exhibit accelerated arteriosclerosis and are consequently at higher risk of cardiovascular disease (CVD), including stroke and coronary heart disease (1). DM is often complicated with other comorbidities that contribute to increased risk of CVD (i.e., hypertension, chronic kidney disease, and hyperlipidemia).

It has been increasingly recognized that the early morning blood pressure surge (MBPS) (i.e., the increase in blood pressure [BP] that occurs during the period from night to early morning), which can be detected by ambulatory BP monitoring (ABPM), provides a clinically relevant measure to predict CVD risk, independent of age and 24-h systolic BP (SBP) (2). This concept is supported by data indicating that cerebral and cardiac events occur most often in the morning (3). It is possible that inadequate glycemic control (4) or the occurrence of insulin resistance (5) activate sympathetic activity, which leads to MBPS in DM patients. Furthermore, hypertensive patients with exaggerated MBPS exhibit elevated levels of macrophages, T cells, and tumor necrosis factor-α in atherosclerotic plaques obtained from the carotid artery compared with those without exaggerated MBPS, suggesting an association between MBPS and vascular injury in hypertensive patients (6). Together, these results suggest that poor glycemic control could accelerate vascular injury in DM patients by causing MBPS.

In this study, we evaluated *1*) the association of insulin resistance and glycemic control with MBPS; and *2*) the association between MBPS and vascular endothelial dysfunction, as assessed by endothelium-dependent flow-mediated dilation (FMD) and nitroglycerin-mediated dilation (NMD), in type 2 DM (T2DM) patients.

RESEARCH DESIGN AND METHODS

Subjects and Design

The study protocol was approved by the Ethics Committee of Osaka City University Graduate School of Medicine (registration no. 1857). This study was performed between October 2011 and November 2012. Written informed consent was obtained from each patient. Patients with T2DM (n = 50), who participated in DM educational and/or complication-check programs in our university, were consecutively enrolled in this study. The diagnosis of T2DM was made on the basis of a history of DM or according to the Japan Diabetes Society criteria (7). The subjects were excluded if they exhibited renal dysfunction (estimated glomerular filtration rate [eGFR] $\leq$60 mL/min/1.73 m^2), type 1 or secondary DM, prevalent liver disease, or CVD. Nine of these patients were treated with dietary therapy alone; 18 were treated with insulin; 5 were treated with sulfonylureas; 1 was treated with α-glucosidase inhibitors; 11 were treated with biguanides; and 6 were treated with a combination of oral hypoglycemic agents. Twenty-two patients received therapy with statins. Among the antihypertensive drugs, 14 patients received calcium channel blockers (CCBs), and 16 patients received an angiotensin-converting enzyme inhibitor (ACEI) and/or an angiotensin receptor blocker (ARB). None of patients received α-blockers or β-blockers. BMI was calculated as body weight (in kilograms)/height (in square meters).

BP Measurements and Analysis of ABPM Data

Noninvasive ABPM was performed in a hospital setting with an automated system (TM2431; A&D, Tokyo, Japan) that records BP using the oscillometric method and pulse rate every 30 min for 24 h, as described previously (8). Awake and sleep time were defined on the basis of written diaries recorded by the patients during the ABPM. The morning BP was defined as the average of the four BP values obtained during the first 2 h after waking up. The lowest BP was defined as the average of the three BP readings centered around the lowest nighttime reading (i.e., the lowest nighttime reading plus the readings immediately before and after). The MBPS was calculated as the morning SBP minus the lowest SBP, as reported previously (9).

Measurement of FMD and NMD Using a Novel Ultrasound System

Endothelium-dependent FMD and endothelium-independent NMD were assessed according to international guidelines (10). The subjects did not smoke, eat, or drink anything containing caffeine for 12 h before the FMD measurement. FMD was measured between 9:00 and 10:00 A.M., before the patient received any medications.

FMD was assessed in the right arm using a high-resolution ultrasound device (UNEXEF; UNEX Corporation, Nagoya, Japan), as described previously (11). A 5-cm transverse section of the brachial artery was recorded for intervals of 30 s at baseline and during peak reactive hyperemia (after deflation of the BP cuff, which had previously been inflated to 50 mmHg above the SBP around the forearm for 5 min). NMD was determined by measuring the maximum dilation of the brachial artery at the same point in response to sublingual administration of glyceryl trinitrate (75 μg) after a resting period of at least 15 min. In eight subjects, NMD was not measured because of allergy to glyceryl trinitrate, hypotension, or glaucoma. FMD and NMD were calculated as follows: FMD or NMD (%) = (maximum diameter-diameter at rest) $\times$ 100/diameter at rest. Impaired FMD was defined as $<$10.0%, which was reported as an independent predictor of coronary artery disease (12).

Biochemical and Physiological Parameters

Blood and urine samples were obtained after overnight fasting. Plasma glucose levels were measured with the glucose oxidase method. Glycated hemoglobin A1c (HbA_{1c}) was determined by routine high-performance liquid chromatography and a latex agglutination immunoassay, and was expressed as the National Glycohemoglobin Standardization Program equivalent value (13). Homeostasis model assessment ratio (HOMA-R), which was calculated as fasting insulin (in microunits per milliliter) $\times$ fasting plasma glucose (FPG) (in milligrams per deciliter)/405, was used to assess insulin sensitivity in the subjects without insulin (n = 32). Serum creatinine, triglyceride (TG), LDL cholesterol (LDL-C), and HDL cholesterol (HDL-C) levels were measured using an autoanalyzer (7450; Hitachi Co., Tokyo, Japan). Serum insulin and urinary

albumin were determined by electrochemical luminescence immunoassay (Roche Co., Tokyo, Japan) and turbidimetric immunoassay (Wako Co., Tokyo, Japan), respectively. eGFR, as a measure of renal function, was based on the following equation proposed by the Japanese Society of Nephrology (14): eGFR (milliliters per minute per 1.73 m^2) = 175 × serum creatinine − 1.154 × age − 0.203 × 0.742 (if female).

Statistical Analysis

Continuous variables were expressed as the mean ± SD. Median (limits of observed values) was used for the DM duration, HOMA-R, and urine albumin-to-creatinine ratio (UACR), because of their skewed distribution. Unpaired samples were analyzed nonparametrically using Mann-Whitney *U* test. Correlation coefficients were calculated by simple and multiple regression analyses. Simple regression analysis was performed using nonparametric Spearman rank correlation test. *P* values <0.05 were considered statistically significant. All data were analyzed using Stat View version 5.0 J (Abacus Concepts, Inc., Berkeley, CA).

RESULTS

Clinical and Biochemical Profiles of the Patients

The clinical and biochemical profiles of the T2DM patients (*n* = 50) enrolled in the current study are shown in Table 1. The mean age was 60.1 ± 13.2 years, and 50% were male. The median duration of DM was 9.0 years (range 0.1 to 46.0 years). Among the patients, 14 patients (28%) were smokers. The mean 24-h SBP and MBPS were 123 ± 11 and 17 ± 14 mmHg, respectively. Sixteen patients (32%) were undergoing treatment with ARB/ACEI, and 14 patients (28%) were undergoing treatment with CCB. No significant differences existed in MBPS between patients receiving treatment and not receiving treatment with ARBs/ACEIs or CCBs (18.4 ± 16.8 vs. 16.2 ± 13.0 mmHg, *P* = 0.581; 14.8 ± 15.4 vs. 17.8 ± 14.0 mmHg, *P* = 0.422). The mean FPG level was 112.3 ± 26.0 mg/dL. The fasting morning immunoreactive insulin level was 9.1 ± 5.2 μU/mL, and the median HOMA-R was 2.2 (range 0.4 to 7.4). The mean HbA_{1c} level was 8.7 ± 1.4% (72 ± 12 mmol/mol). The mean TG, LDL-C, and HDL-C values were 112.6 ± 36.3, 99.2 ± 29.1, and 41.0 ± 10.3 mg/dL, respectively. Twenty-two patients (44%) received statins. MBPS did not differ significantly between those receiving and not receiving treatment with statins (18.3 ± 12.7 vs. 15.8 ± 15.7 mmHg, respectively; *P* = 0.999). TG levels did not differ significantly between those receiving and not receiving treatment with statins (102.1 ± 25.9 vs. 120.9 ± 41.4 mg/dL, respectively; *P* = 0.085), and treatment with ARBs/ACEIs (110.8 ± 22.1 vs. 113.5 ± 41.7 mg/dL, respectively; *P* = 0.778). The mean cortisol level at 8:00 A.M. was 16.8 ± 4.9 μg/dL. Noninsulin users with insulin resistance (HOMA-R ≥2.5) exhibited a serum cortisol level significantly higher than those without (HOMA-R <2.5; 17.7 ± 3.8 [*n* = 11] vs. 14.4 ± 3.0 μg/dL [*n* = 21]; *P* = 0.025). The median UACR was 10.9 mg/g (range 2.4–189.6 mg/g). Forty-four patients (88%) were classified as having normoalbuminuria (UACR <30.0 mg/g). The mean FMD and NMD were 7.7 ± 4.2% and 18.9 ± 7.0%, respectively. Although 11 patients (22%) exhibited normal FMD, 39 patients (78%) exhibited FMD values below the normal lower limit. MBPS was significantly lower in patients with normal FMD than in those with impaired FMD (8.5 ± 18.3 vs. 19.2 ± 12.3 mmHg; *P* = 0.040). While FMD was significantly lower in the patients receiving treatment with ARBs/ACEIs than in those not receiving it (5.9 ± 4.0% vs. 8.6 ± 3.9%, *P* = 0.025), it did not differ between patients receiving treatment with CCBs or statins and those not receiving such treatment (CCBs 6.6 ± 3.9% vs. 8.2 ± 4.1%, *P* = 0.248; statins: 6.4 ± 3.5% vs. 8.8 ± 4.3%, *P* = 0.062).

Table 1—Clinical and biochemical profiles of the enrolled patients

Measure	*n* = 50
Sex (*n*)	
Male	25
Female	25
Age (years)	60.1 ± 13.2
DM duration (years)	9.0 (0.1–46.0)
BMI (kg/m^2)	26.6 ± 5.8
24-h SBP (mmHg)	123 ± 11
MBPS (mmHg)	17 ± 14
Smoker (%)	14 (28)
ARB/ACEI (%)	16 (32)
Statin (%)	22 (44)
Insulin (%)	18 (36)
FPG (mg/dL)	112.3 ± 26.0
HbA_{1c}	
%	8.7 ± 1.4
mmol/mol	72 ± 12
TG (mg/dL)	112.6 ± 36.3
LDL-C (mg/dL)	99.2 ± 29.1
HDL-C (mg/dL)	41.0 ± 10.3
eGFR (mL/min/1.73m^2)	77.2 ± 16.0
UACR (mg/g)	10.9 (2.4–189.6)
FMD (%)	7.7 ± 4.2
IRI (μU/mL) (*n* = 32)	9.1 ± 5.2
HOMA-R (*n* = 32)	2.2 (0.4–7.4)
NMD (%) (*n* = 42)	18.9 ± 7.0

Continuous variables are summarized as the mean ± SD, whereas variables with skewed distribution are summarized as the median (limits of observed values). IRI, immunoreactive insulin.

Univariate Correlations of the Clinical Variable With MBPS in T2DM Patients

The correlations between MBPS and various clinical variables were examined by single-regression analysis in all subjects. Among various clinical variables, MBPS exhibited significant and positive correlations with levels of FPG (ρ = 0.300, *P* = 0.035), HbA_{1c} (ρ = 0.373, *P* = 0.009), and TG (ρ = 0.375, *P* = 0.009) (Fig. 1*A*). On the other hand, no significant correlations of age (ρ = 0.039, *P* = 0.782), gender (ρ = 0.015, *P* = 0.914), DM duration (ρ = −0.082, *P* = 0.564), BMI (ρ = 0.114, *P* = 0.425), 24-h SBP (ρ = 0.174, *P* = 0.224), status as current smoker (ρ = −0.094, *P* = 0.510), LDL-C (ρ = 0.123, *P* = 0.389), HDL-C (ρ = 0.046, *P* = 0.748), eGFR (ρ = −0.159, *P* = 0.266), or UACR (ρ = 0.209, *P* = 0.148) with MBPS were found.

Univariate Correlations of HOMA-R With MBPS in T2DM Patients

Hypertriglyceridemia is related in some part to the occurrence of insulin resistance (15). To further confirm the association of insulin resistance with MBPS in T2DM patients, we examined the correlation between HOMA-R, an established marker of insulin resistance, and MBPS in DM patients who were not undergoing insulin treatment. HOMA-R showed a significant and positive association with MBPS in T2DM patients (ρ = 0.436, *P* = 0.015) (Fig. 1*B*), strongly suggesting the

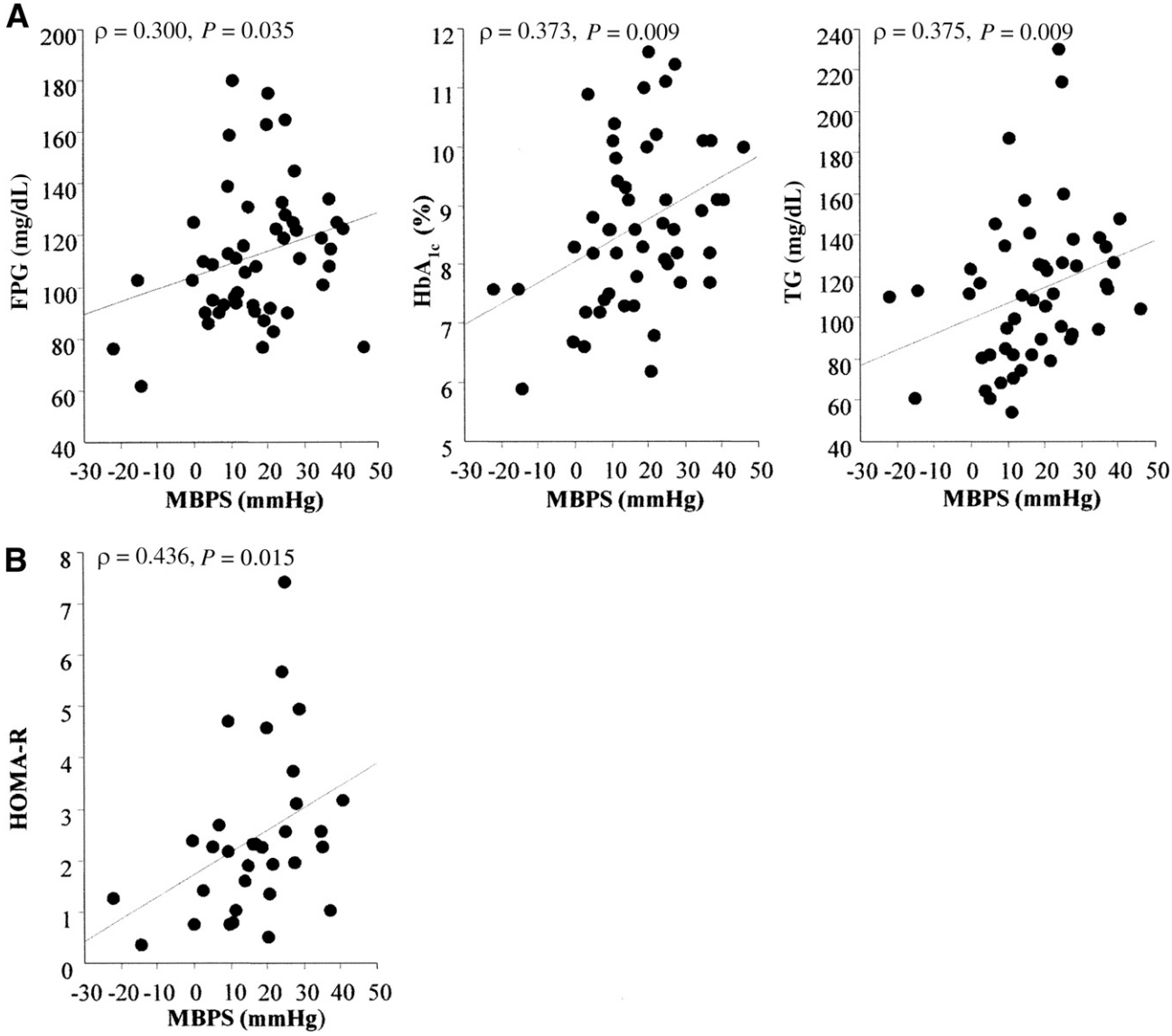

Figure 1—Correlations of FPG, HbA_{1c}, and TG levels, and HOMA-R with MBPS in T2DM patients. *A*: MBPS correlated significantly and positively with levels of FPG (ρ = 0.300, *P* = 0.035), HbA_{1c} (ρ = 0.373, *P* = 0.009), and TG (ρ = 0.375, *P* = 0.009) (*n* = 50). *B*: MBPS correlated significantly and positively with HOMA-R (ρ = 0.436, *P* = 0.015) (*n* = 32).

association between insulin resistance and MBPS.

Multivariate Association of the Clinical Variable With MBPS in T2DM Patients

Multivariate regression analysis showed that, among the various factors simply associated with MBPS, HbA_{1c} (β = 0.328, *P* = 0.016), and TG (β = 0.358, *P* = 0.014) levels emerged as significant factors that were associated independently with MBPS in the model, which included age and 24-h SBP as independent variables (Table 2). When HOMA-R was included in place of TG as a marker of insulin resistance after restriction of the patients to the non-insulin–treated patients, HOMA-R (β = 0.372, *P* = 0.023) was associated independently with MBPS, in addition to HbA_{1c} (β = 0.454, *P* = 0.009), suggesting the independent association of poor glycemic control and insulin resistance with MBPS in T2DM patients.

Univariate Correlation of MBPS With FMD, but Not NMD in T2DM Patients

We next examined the relationship between MBPS and vascular injury by measuring endothelium-dependent FMD and endothelium-independent NMD in T2DM patients. Among the various traditional risk factors for atherosclerosis, MBPS (ρ = −0.289, *P* = 0.043), smoking status (ρ = −0.293, *P* = 0.040), 24-h SBP (ρ = −0.359, *P* = 0.012), and HbA_{1c} level (ρ = −0.301, *P* = 0.035) emerged as significant factors that correlated in a negative manner with FMD. Furthermore, UACR (ρ = −0.278, *P* = 0.054) tended to correlate negatively with FMD. Although MBPS, HbA_{1c} level, and smoking status did not correlate with NMD, age (ρ = −0.406, *P* = 0.016) and 24-h SBP (ρ = −0.478, *P* = 0.004) correlated negatively with NMD.

Table 2—Multivariate association of the clinical variable with MBPS in T2DM patients (n = 50)

	MBPS (mmHg)			
	n = 50		n = 32	
Covariates	β	P	β	P
Age (years)	0.205	0.165	0.102	0.518
24-h SBP (mmHg)	0.025	0.854	0.005	0.975
HbA_{1c} (%)	0.328	0.016*	0.454	0.009*
TG (mg/dL)	0.358	0.014*	—	—
HOMA-R	—	—	0.372	0.023*
R^2	0.252		0.368	
P	0.009		0.012	

*$P < 0.05$

No significant correlations of age (ρ = −0.191, P = 0.189), gender (ρ = 0.227, P = 0.112), DM duration (ρ = −0.265, P = 0.064), BMI (ρ = 0.075, P = 0.600), FPG (ρ = 0.024, P = 0.864), TG (ρ = 0.044, P = 0.760), LDL-C (ρ = 0.189, P = 0.186), HDL-C (ρ = −0.081, P = 0.569), eGFR (ρ = 0.185, P = 0.195), or UACR (ρ = −0.278, P = 0.054) with FMD were found. In noninsulin users, no significant correlations of HOMA-R (ρ = −0.196, P = 0.276) with FMD was found.

Multivariate Association of MBPS With FMD, but Not NMD in T2DM Patients

To examine whether an independent association existed between increased MBPS and impaired FMD, multiple regression analyses were performed using a model that included MBPS and HbA_{1c} level measured simultaneously, in addition to DM duration, gender, LDL-C level, and one of the clinical variables (i.e., 24-h SBP, UACR, smoking status, and treatment with ARBs/ACEIs because of their intertwining effect on each other) (Table 3). In model 1, which included MBPS and HbA_{1c} level measured simultaneously as independent variables, in addition to DM duration, gender, and LDL-C level, MBPS (β = −0.309, P = 0.028), but not HbA_{1c}, was associated significantly in a negative manner with FMD. Similarly, MBPS retained its significant and independent association with FMD in models 2–5.

Multiple regression analyses were performed to identify the factors that were associated independently with NMD in DM patients and showed that age (β = −0.334, P = 0.042) and 24-h SBP (β = −0.470, P = 0.005), but not MBPS, were associated significantly in a negative manner with NMD, when MBPS and 24-h SBP were included simultaneously as independent variables, in addition to age, gender, and LDL-C level.

CONCLUSIONS

In the current study, we demonstrated that higher HbA_{1c} levels, as well as TG levels or HOMA-R, were significantly and independently associated with higher MBPS in patients with T2DM, and that MBPS was significantly and independently associated in a negative fashion with FMD, but not NMD. These data suggested that poor glycemic control or insulin resistance is associated with the occurrence of MBPS in T2DM patients, which might be associated with the development of endothelial dysfunction in those patients.

Among the various factors studied, FPG and HbA_{1c} level, as well as TG level, correlated significantly in a positive manner with MBPS in 50 T2DM patients. Because it was suggested that TG level might provide an index for insulin resistance (15), we next examined the correlations of the established markers of insulin resistance, HOMA-R with MBPS, after the subjects were restricted to 32 DM patients not receiving insulin therapy. A significant correlation between HOMA-R and MBPS supported the notion that the occurrence of insulin resistance, as well as poorer glycemic control, might be involved in the development of MBPS in the T2DM patients. This concept was further validated by the multiple regression analysis to elucidate independent

Table 3—Multivariate association of the clinical variable with FMD in T2DM patients (n = 50)

	Model 1		Model 2		Model 3		Model 4		Model 5	
Covariates	β	P	β	P	β	P	β	P	β	P
DM duration (years)	−0.202	0.149	−0.148	0.289	−0.198	0.167	−0.206	0.139	−0.187	0.168
Sex (0, if male; 1, if female)	0.230	0.079	0.191	0.140	0.218	0.117	0.163	0.254	0.211	0.096
LDL-C	0.146	0.297	0.107	0.439	0.123	0.390	0.106	0.457	0.103	0.449
HbA_{1c} (%)	−0.195	0.161	−0.158	0.250	−0.209	0.140	−0.199	0.152	−0.224	0.100
MBPS (mmHg)	−0.309	0.028*	−0.281	0.042*	−0.306	0.032*	−0.304	0.030*	−0.273	0.047*
24-h SBP (mmHg)	—	—	−0.236	0.089	—	—	—	—	—	—
UACR (mg/g)	—	—	—	—	−0.075	0.581	—	—	—	—
Current smoker (0, if no; 1, if yes)	—	—	—	—	—	—	−0.161	0.262	—	—
ARB/ACEI treatment (0, if no; 1, if yes)	—	—	—	—	—	—	—	—	−0.271	0.049*
R^2	0.231		0.355		0.320		0.330		0.367	
P	0.004		0.003		0.009		0.006		0.002	

*$P < 0.05$

associations of HbA_{1c} and TG levels/HOMA-R with MBPS.

MBPS is considered to result from increased activities of the sympathetic nervous system, the renin angiotensin system, and the hypothalmic-adrenal-pituitary (HPA) axis during the latter half of the sleep cycle (16). Because insulin resistance is known to stimulate sympathetic activity by affecting the metabolism of adipocytokines, such as leptin (5), the association of TG level and HOMA-R with MBPS might be explained through increased sympathetic activity by insulin resistance. Furthermore, it remains possible that insulin-stimulated reabsorption of sodium at the renal tubule (17) might contribute to the development of MBPS. The activity of the HPA axis shows a clear circadian rhythm exhibiting a rapid rise during the latter half of the sleep cycle, with the highest levels occurring in the early morning (18) in parallel with the time-course change of BP (19), suggesting the involvement of a diurnal change in HPA axis in the generation of MBPS. It was reported that T2DM patients exhibit higher baseline levels of serum cortisol (20). Although we did not monitor the diurnal change of serum cortisol in the current study, its serum level at 8:00 A.M. was significantly higher in those with insulin resistance than in those without. Therefore, it is possible that insulin resistance might make the association with MBPS significant by its stimulatory effect on HPA axis early in the morning.

Chronic hyperglycemia is reported to cause endothelial dysfunction by accumulating advanced glycosylation end products in the vascular wall (21), resulting in the development of vascular injury. In fact, hypertensive DM patients exhibit higher levels of plasma advanced glycosylation end products than their nonhypertensive counterparts (22).

Impaired FMD of the brachial artery, which is mainly caused by the loss of endothelium-derived nitric oxide (NO) (23), has been established as a relevant marker for endothelial dysfunction (12). MBPS appears to play the most important role in the development of endothelial dysfunction, as reflected by the strongest association of MBPS with CVD risk (2). Because MBPS might acutely increase mechanical stretch on endothelial cells, it augmented the production of endothelium-derived superoxide, resulting in the inactivation of NO (24). Indeed, it was reported that marked fluctuations in BP in sinoaortic-denervated rats significantly impaired endothelial function by reducing acetylcholine-induced NO release from aortic rings (25). In the current study, HbA_{1c} level correlated significantly in a negative manner with FMD in univariate regression analyses, but not in multiple regression analyses including MBPS as an independent variable, suggesting the intimate involvement of MBPS in the association of HbA_{1c} level and FMD. The previous study, demonstrating the association of a blunted dip in BP during sleep with endothelial dysfunction in T2DM patients (26), might support our data suggesting MBPS as an important factor to accelerate vascular damage in T2DM patients.

Our study showed that MBPS was associated with impaired FMD, a marker for endothelium injury, but not NMD, a marker of vascular smooth muscle function (27). Because it was reported that DM patients showed vascular injury more predominantly in the endothelium than on the arterial wall (28), the preferential association of MBPS with FMD, but not NMD, might validate the importance of MBPS in the development of vascular injury in T2DM patients. Alternatively, T2DM patients with preexisting CVD were negated from this study, and thus their atherosclerotic changes were in the early but not advanced stage. In the early stage of DM, endothelial dysfunction, as reflected by impaired FMD, might predominately occur over arterial smooth muscle dysfunction as represented by impaired NMD.

The limitations of our study are as follows. First, this is a cross-sectional study and is insufficient to disentangle potential relationships among poor glycemic control, insulin resistance, and MBPS because HbA_{1c} level, HOMA-R, and MBPS are measured at a single point. Second, ABPM is ideally conducted at home in a routine daily environment. In this study, ABPM was performed within several days after admission to the hospital to avoid the interindividual difference in the effect of the resting condition of hospital admission on diurnal BP variation. Third, because DM patients enrolled in the study were treated with various drugs, including antihypertensive drugs and statins, the effect of those treatments on MBPS could not be totally negated.

In conclusion, our results demonstrate that poor glycemic control and insulin resistance are significantly and positively associated with increased MBPS in patients with T2DM, and that MBPS is significantly and independently associated in a negative manner with FMD, but not NMD. Therefore, the current study raised the possibility that MBPS might be one of the major targets for preventing vascular damage in T2DM patients.

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