Original Paper

Masked Hypertension in Diabetes Mellitus: A Potential Risk

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The prevalence and clinical significance of masked hypertension (MHT) in diabetics have infrequently been described. The authors assessed the association of MHT (defined using a clinic blood pressure [BP] <140/90 mm Hg and daytime ambulatory BP ≥135/85 mm Hg) with microvascular and macrovascular end organ damage in 81 clinically normotensive Japanese diabetic persons. The prevalence of silent cerebral infarcts (SCIs), increased left ventricular mass, and albuminuria were evaluated. Of 81 patients, 38 (46.9%) were classified as having MHT and showed significantly more SCIs (mean ± SE: 2.5±0.5 vs 1.1±0.2; P=.017), and more albuminuria (39% vs 16%; P=.025), but no increase in left ventricular mass index, than the normotensive persons in office and on ambulatory BP monitoring group. The prevalence of MHT in this diabetic population was high (47%). Diabetic patients with MHT showed evidence of brain and kidney damage. Hence, out-of-office monitoring of BP may be indicated in diabetics whose BP is normal in the clinic. (J Clin Hypertens. 2007;9:601–607)

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Hypertension in diabetes mellitus is known to be closely associated with microvascular and macrovascular target organ damage and cardiovascular disease. Based on previous clinical trials, the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) and other international guidelines have stated that blood pressure (BP) in diabetics should be lowered to <130/80 mm Hg.[1] In diabetic persons, unrecognized hypertension is a serious problem, and hypertensive target organ damage progresses faster than in patients without diabetes.

Masked hypertension (MHT) is defined as a combination of normal clinic BP plus elevated BP out of the clinic[2] and has been reported to be associated with hypertensive target organ damage[3,4] and a poor cardiovascular prognosis.[5,6] Although a small number of diabetic patients have been included in these reports, there has only been one report thus far regarding the clinical significance of MHT in diabetes mellitus.[7] We performed the current study to examine the prevalence and severity of target organ damage in diabetic MHT.

METHODS

This was a prospective study to look at the role of ambulatory BP (ABP) in predicting target organ damage in patients attending general internal medicine clinics.

Study Patients

We studied 81 Japanese patients with type 2 diabetes (mean age, 63.5±9.0 years; 46 men and 35 women) whose BP in the clinic was <140/90 mm Hg (for both systolic and diastolic BP)[8] at the time of the study. The patients with diabetes were enrolled consecutively at 3 hospitals from

1999 to 2004 and agreed to undergo ABP monitoring (ABPM). The diagnosis of diabetes was made according to the guidelines of the American Diabetes Association[9] or based on current antidiabetic medication use with a previous diagnosis of diabetes mellitus.

We excluded patients with type 1 diabetes, renal dysfunction (serum creatinine level >1.2 mg/dL), hepatic damage, secondary diabetes, ischemic heart disease or other cardiac diseases, congestive heart failure, arrhythmia (including atrial fibrillation and other arrhythmia), stroke (including transient ischemic attack), or other severe concomitant diseases. The duration of diabetes was based mainly on information from medical records and by self-report of a diagnosis made by a physician with or without treatment.

Clinic BP was measured on at least 2 different occasions after resting for at least 5 minutes in the sitting position. Clinic BP in treated patients was measured at the time of ABPM while off of antihypertensive medication. BP was evaluated on 2 separate occasions during a 2-week period in untreated patients. In treated patients, BP was measured at the time of the clinic visits when the ABPM was hooked up and when it was detached 1 or 2 days later. The patients took no antihypertensive medications for a minimum of 7 days before ABPM, and most took no medication during the 14 days preceding the ABPM study.

Ambulatory BP Monitoring

Noninvasive ABPM was performed on a weekday with an automatic system using electric-powered cuff inflation (TM2421, TM2425, or TM2431, A&D, Tokyo, Japan), which recorded both BP (via the oscillometric method) and pulse rates every 30 minutes for 24 hours. The accuracy of these devices was previously confirmed.

MHT was defined as an awake BP on ABPM of ≥135/85 mm Hg and clinic BP of <140/90 mm Hg as the cutoffs, as described in previous reports.[8] Since there are no recommendations for the upper limit of normal ABPM in diabetes, we chose to use the same cutoffs that were also used in 3 earlier studies describing white coat hypertension in type 1[10] and type 2 diabetes[11] and MHT in diabetes.[7] One other report of ABPM that included diabetic patients used daytime BP of <130/85 mm Hg as the upper limit of normal.[12] We considered using lower cutoffs of clinic BP (130/80 mm Hg) and 24-hour BP (130/80 and 135/85 mm Hg) in our study, but the number of diabetes mellitus/MHT patients would have been only 12 and 6, respectively.

Brain Magnetic Resonance Imaging

Brain magnetic resonance (MR) imaging was performed in all 81 patients using a superconducting magnet with a main strength of 0.5 T (Toshiba MRT50GP, Tokyo, Japan) or 1.5 T (SIGNAMR/I HiSpeed 1.5T, GE Yokogawa Medical Systems, Tokyo, Japan) within 3 months of their ABPM. The brain was imaged in the axial plane at a 7-mm-slice thickness. The matrix size was 256×256 pixels. A silent cerebral infarct (SCI) was defined exclusively as a low–signal intensity area (≥3 mm, but all were <15 mm), depicted on T_1-weighted images, that was also visible as a hyperintense lesion on T_2-weighted images, as described previously.[13] The MR images of the patients were randomly stored and interpreted by reviewers blinded to the patients' names and characteristics. The significance of SCI as a marker of hypertensive target organ damage has been previously established,[14–16] and SCI has been included in the European Society Hypertension guidelines.[17] The severity of the damage is usually quantified as the number of SCIs.[18–21]

Other Measures

Body mass index (BMI) was calculated as weight (kg)/height $(m)^2$. Left ventricular mass index (LVMI), detected by echocardiography, was calculated by the method described previously.[22] Left ventricular hypertrophy was defined as ≥116 g/m^2 in men and ≥104 g/m^2 in women, as described previously.[23] Echocardiography was performed within 1 month of ABPM. Urinary albumin excretion (UAE) was measured by latex agglutination assay. In the present study, although all patients were enrolled from outpatient clinics, 24-hour collections of urine were commonly performed within 1 month of examination. If the patients could not collect urine for 24 hours, a spot urine was used. We defined microalbuminuria as UAE of 30 to 299 μg/mg·creatinine or 30 to 299 mg/24 hours and macroalbuminuria as ≥300 μg/mg·creatinine or ≥300 mg/24 hours.[24] Urinary albumin was checked on only one occasion. Hemoglobin A_{1c} (HbA_{1c})was calculated as the average of recent 5-year data. If data were available for less than 5 years, all of the data were averaged for the analysis. Smoking status was defined as a current smoker. This study was approved by the Institutional Ethics Committee, Jichi Medical School, Japan, and all participants provided informed consent for the study.

Statistical Analysis

All statistical analyses were performed with SPSS/Windows, version 13.0 (SPSS Inc, Chicago, IL).

Table I. Baseline Characteristics of the Study Population

Characteristic	MHT	Normotension
No. (male/female)	38 (21/17)	43 (25/18)
Age, y	63.3±8.5	63.7±9.5
Body mass index, kg/m^2	23.9±3.8	22.6±3.0
Current smoker, %	37	37
Hypertension, %	39	23
Duration of hypertension, y	2.7±5.5	1.4±4.0
Duration of diabetes, y	11.0±8.2	9.2±6.8
Hemoglobin A_{1c}, %	7.7±1.1	7.3±1.0
Total cholesterol, mmol/L	5.2±0.9	5.0±1.0
Triglycerides, mmol/L	1.8±1.1[a]	1.3±0.9
Creatinine, μmol/L	58.7±10.7	64.2±14.7
Blood Pressure	**MHT**	**Normotension**
Clinic SBP, mm Hg	130±9.3[a]	124±12
Clinic DBP, mm Hg	73±7.5	71±9.4
24-hour SBP, mm Hg	136±11[c]	118±8.3
24-hour DBP, mm Hg	79±6.8[c]	71±5.6
24-hour pulse rates, bpm	72±8.8[b]	66±6.6
Awake SBP, mm Hg	143±11[c]	122±8.2
Awake DBP, mm Hg	83±7.2[c]	73±5.9
Awake pulse rates, bpm	76±9.0[b]	70±7.1
Sleep SBP, mm Hg	123±14[b]	112±14
Sleep DBP, mm Hg	72±8.8[a]	68±7.2
Sleep pulse rates, bpm	64±9.9[a]	60±7.3

[a]P<.05, [b]P<.01, [c]P<.001 vs normotensive group. Abbreviations: bpm, beats per minute; DBP, diastolic blood pressure; MHT, masked hypertension; SBP, systolic blood pressure.

The data were expressed as the mean (SD) or percentage. Differences between variables were compared with Student *t* test. The chi-square test was used to calculate proportions. Multiple linear regression analysis was performed to analyze the factors associated with the number of SCIs, LVMI, and the prevalence of albuminuria. Factors associated with SCI, LVMI, and albuminuria in the univariate analysis or confirmed associated factors were entered as independent variables in this model. The null hypothesis was rejected when 2-tailed P<.05.

RESULTS

Of the 81 patients studied, 38 (46.9%) were classified as having MHT. There were no differences in baseline characteristics between the 2 groups (Table I) with regard to age, BMI, duration of diabetes, HbA_{1c} level, and serum creatinine level. A previous diagnosis of hypertension had been made in 39% of the MHT group and 23% of the group with normal BP. Twenty-nine percent of the those with MHT and 26% of normotensive participants had been taking antihypertensive drugs before the study (Table II). To better assess the true prevalence of different categories of hypertension, we included participants with a previous diagnosis of hypertension, on the grounds that the diagnosis might have been based on a transient elevation of BP. Seven of the 43 patients in the normotensive group received monotherapy, while 5 of the 38 patients in the MHT group also received monotherapy; 4 of the 43 patients in the normotension group were given combination therapy, and 6 of the 38 patients in the MHT also received combination therapy.

Both clinic systolic BP and ABP were significantly higher in the MHT group than in the normotensive group (Table I). ABP was by definition significantly higher in the MHT than in the normotensive group. As shown in Table II, the use of antihypertensive and antidiabetic drugs was similar between the 2 groups except for use of insulin and an aldose reductase inhibitor (which is used for treatment of diabetic sensory neuropathy).

The number of SCIs per patient (mean ± SE, 2.5±0.5 vs 1.1±0.2; P=.017) and the percentage of patients with albuminuria (39% vs 16%; P=.025) were both significantly higher in the MHT group than in the normotensive group (more of these patients had previously been identified as hypertensive based on clinic BP) (Figure). There were no significant differences in the prevalence of SCI (66%

Table II. Use of Antihypertensive and Antidiabetic Drugs in the Study Population

Drugs	MHT	Normotension
Antihypertensive drug, %	29	26
Number of antihypertensive drugs per person	0.5±0.9	0.4±0.7
ACE inhibitors, %	11	7
Angiotensin receptor antagonists, %	5	9
Calcium channel blockers, %	24	12
Diuretics, %	5	5
β-Blockers, %	3	0
α-Blockers, %	3	0
Antidiabetic drug, %	74	65
Number of antidiabetic drugs per person	1.3±1.0	1.1±1.0
Sulfonylureas, %	37	51
α-Glucosidase inhibitors, %	42	33
Aldose reductase inhibitors, %	16[a]	2
Metformin, %	32	21
Pioglitazone, %	0	2.0
Insulin therapy, %	39[a]	14

[a]$P<.05$ vs normotensive group. Abbreviations: ACE, angiotensin-converting enzyme; MHT, masked hypertension.

Table III. Multivariate Regression Analyses Predicting Target Organ Damage

	No. of SCIs		LVMI		Albuminuria	
	β	*P* Value	β	*P* Value	β	*P* Value
Sex (male=1, female=0)	–0.125	.216	0.191	.131	0.041	.712
Age, y	0.150	.148	–0.031	.807	–0.152	.181
BMI, kg/m^2	–0.141	.162	0.116	.355	–0.053	.632
Hemoglobin A_{1c}, %	0.102	.322	0.154	.229	0.417	<.001
Antihypertensive medication (on=1, off=0)	0.319	.002	–0.001	.996	–0.051	.635
Insulin use (yes=1, no=0)	–0.032	.776	–0.069	.627	–0.025	.839
Clinic systolic BP, mm Hg	–0.095	.366	0.105	.421	0.000	.999
Daytime systolic BP, mm Hg	0.420	<.001	0.105	.441	0.282	.020

Abbreviations: BP, blood pressure; BMI, body mass index; LVMI, left ventricular mass index; SCI, silent cerebral infarct.

vs 47%; *P*=.117), LVMI (mean ± SE, 114±4.5 vs 107±3.7 g/m^2; *P*=.280), and the prevalence of left ventricular hypertrophy (44.7% vs 37.2%; *P*=.51) between the 2 groups. In multiple linear regression analyses, daytime BP, but not clinic BP, was associated with the number of SCIs and the presence of albuminuria independent of other variables. LVMI was not associated with any variables in the same model, however (Table III).

DISCUSSION

In the diabetic patients who were normotensive in the clinic, daytime ABP was more closely associated with hypertensive target organ damage than was clinic BP. In this study, MHT in diabetes mellitus was thus shown to be associated with target organ damage in the brain and kidneys, but this could not be explained simply on the basis of participants' slightly higher clinic BP. Our finding of a higher clinic BP in patients with MHT (clinic systolic BP >130 mm Hg) than in the normotensive patients was in agreement with one previous report,[25] but this report did not associate clinic BP with target organ damage using multivariable models. To the best of our knowledge, this is the second report of MHT studied in diabetes mellitus. Although the number of patients in this study was small, we believe that the significance of the findings suggest that, as in nondiabetic patients, BP measured out of the office may give a better prediction of cardiovascular risk than traditional clinic readings. The prevalence of MHT in diabetes was somewhat different than in the other recent report (47% vs 30%[7]), but this could be related to a number of factors such as age, race, BMI, and the length of time off of antihypertensive medication (mostly 2 weeks vs 1 week[7]) for treated patients: in both studies it was common. This is important

because so far, there are no recommendations from organizations such as the American Diabetes Association that ABPM or home BP monitoring is clinically useful.

Silent Cerebral Infarcts

An SCI is a useful surrogate end point for future stroke,[26–28] and is associated with age, high BP, diabetes, and insulin resistance. In the present study, the number of SCIs in the MHT group was significantly higher than in the normotensive group. As shown in the multivariable analysis, taking antihypertensive treatment was significantly associated with the number of SCIs. Daytime ABP, but not clinic BP, was significantly associated with SCI independent of the presence of antihypertensive treatment. Glycemic control status and insulin use were not associated with the number of SCIs. This is consistent with our previous report which showed that ABP is a better marker of SCI than glycemic factors in diabetic hypertensive patients[21] and further emphasizes the importance of accurate BP measurement and good BP control in diabetic patients.

Left Ventricular Mass Index

The coexistence of hypertension with diabetes also acts synergistically on left ventricular mass and left ventricular remodeling.[29–31] In the present study, LVMI in the diabetic MHT group was not different from that in the normotensive group. In previous reports of (nondiabetic) MHT, LVMI was higher than in normotension.[3,4] Because regression of left ventricular hypertrophy in diabetic individuals has been reported to be less severe than in nondiabetic individuals after antihypertensive treatment,[32] it is possible that the lack of differences in LVMI between MHT and normal groups may not have been due to any regression of LVMI in the MHT group. Two explanations can be suggested for why LVMI was not different between the 2 groups in the present study: first, MHT was defined by daytime ABP. In diabetes, nighttime BP may be more closely associated with target organ damage[33,34] even in normotensive patients.[35] In the present study, nighttime systolic BP was marginally associated with LVMI (r=0.19; P=.09) but daytime systolic BP was not (r=0.13; P=.23). Second, LVMI is reported to be high in diabetic patients, which may be the result of factors other than BP,[29,30,36] but in the present study the duration of diabetes and control of HbA_{1c} did not differ between the 2 groups. In addition, insulin resistance may be associated with increased LVMI even in normotensive patients.[37] Since insulin resistance was not

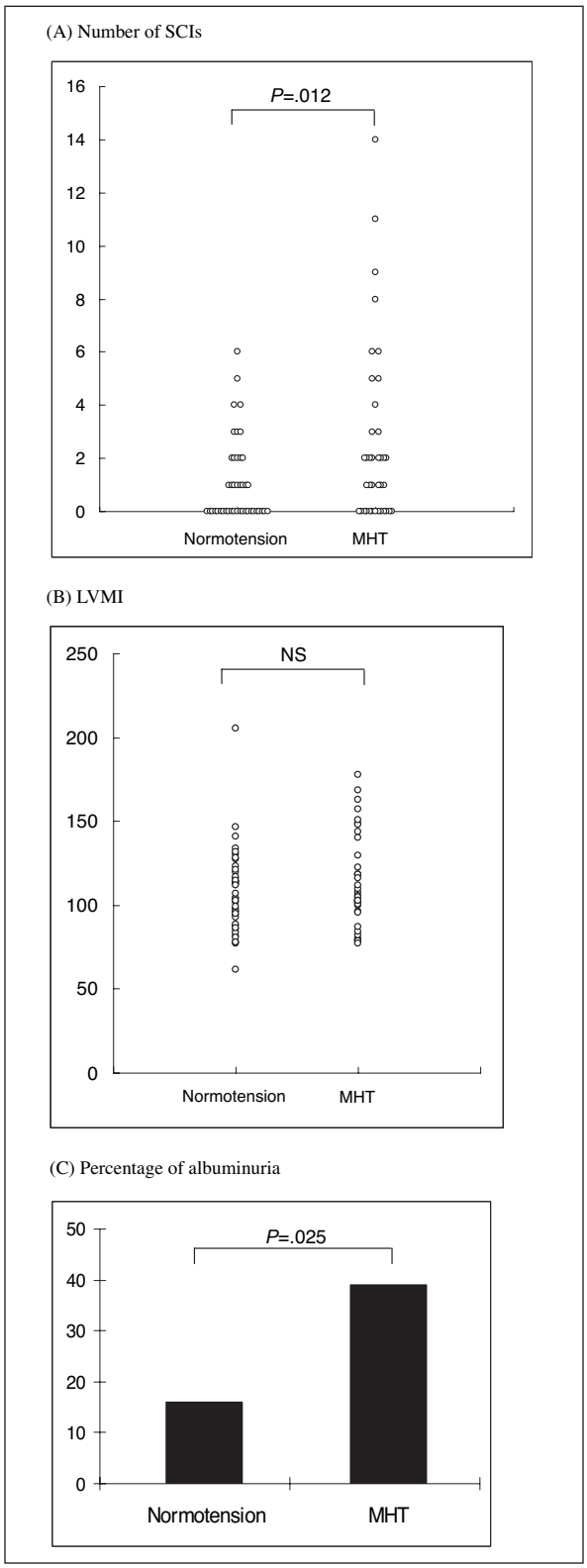

Figure. Comparison of the number of silent cerebral infarcts (SCIs) (A), left ventricular mass index (LVMI) (B), and prevalence of albuminuria (C) between masked hypertensive and normotensive groups. MHT indicates masked hypertension; NS, not significant.

measured in the present study, we cannot exclude differences between the 2 groups. The influence of blood glucose[38] could have obscured the difference of LVMI between groups.

Urinary Albumin

UAE is a sensitive marker of kidney damage in diabetes,[24,39] and is closely associated with BP levels,[40,41] cardiovascular autonomic neuropathy,[42] and other diabetic complications such as retinopathy and neuropathy.[43] In the present study, the prevalence of albuminuria in the MHT group was significantly higher than in the normotensive group. Again, a greater number of patients in the MHT group had been diagnosed as being hypertensive. Three mechanisms can be suggested for this result: first, BP levels between the 2 groups were different. In the MHT group, not only the ABP but also clinic systolic BP was higher than in the normotensive group. BP is a strong determinant of albuminuria.[44] Second, the patients with MHT might have had a higher incidence of diabetic neuropathy, which is a major associating factor of albuminuria in diabetes. This is supported by the data showing that the use of an aldose reductase inhibitor was increased in the MHT group. Third, diabetes itself was slightly more advanced in the MHT group, as shown by the higher percentage of insulin users. Poor glycemic control is an established risk factor for albuminuria in type 2 diabetes.[45] Daytime BP was associated with the presence of albuminuria independent of clinic BP and HbA_{1c}, however.

Study Limitations

There are some limitations of this study. Because the majority of our diabetic patients had hypertension, the number of normotensive patients was small. As a result, the comparison of left ventricular parameters might have been underpowered. The cutoff of 140/90 mm Hg for clinic and 135/85 for awake BP might be somewhat arbitrary, but our sample size was not large enough to try various cutoffs, and the cutoffs we used have been widely accepted in papers on white coat hypertension and MHT. The very recent paper on MHT in diabetes used the same cutoff.[7]

Our participants, including both treated and untreated patients, were somewhat heterogeneous. But we believe that this is a common feature of diabetic patients in general internal medicine clinics. In fact, treated and untreated patients have been combined in previous papers on MHT.[3,6,7,46] To minimize the heterogeneity of the patients in our study, treated patients stopped their medication, as done in previous papers.[3,7,46] Therefore, the condition of our study patients was probably similar to never-treated patients, although the effects of prior treatment on left ventricular hypertrophy could not be analyzed because of the cross-sectional design.

CONCLUSIONS

The prevalence of MHT was as high as 47% in a population of apparently normotensive Japanese diabetic patients. Diabetic patients with MHT showed evidence of target organ damage in the brain and kidneys, but no increase in LVMI. Based on these data, out-of-office BP monitoring should be recommended in diabetic patients whose clinic BP is normal.

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