Insufficient control of morning home blood pressure in Japanese patients with hypertension associated with diabetes mellitus

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ABSTRACT

Aims/Introduction: The combination of hypertension with diabetes mellitus (DM) has been recognized as a critical risk factor for cardiovascular disease (CVD). We investigated the blood pressure levels in hypertensive patients with DM (HDM patients) compared with those without DM (HnDM patients). Furthermore, we examined the effect of risk factors, including chronic kidney disease (CKD) and stroke, on the management of both office blood pressure (OBP) and morning home blood pressure (MHBP).

Materials and Methods: OBP and MHBP were evaluated in 1230 essential hypertensive patients in 30 institutions. Among them, 366 (30%) were complicated with DM.

Results: The ratio of masked hypertensives whose systolic OBP was <140 mmHg and systolic MHBP was more than 135 mmHg in HDM patients was significantly higher than that in HDM patients (P < 0.02). HDM patients had significantly lower systolic and diastolic OBP and diastolic MHBP than HnDM patients (P < 0.05, respectively). However, systolic MHBP in HDM patients tended to be higher compared with HnDM patients (P = 0.0623). A stratified analysis showed that HDM patients with CKD or stroke had significantly higher systolic MHBP than others (P < 0.05, respectively). The adjusted odds ratio for morning hypertension defined by a systolic MHBP more than 135 mmHg was significantly higher in the HDM patients with CKD (1.98) compared with HnDM patients without CKD (reference).

Conclusions: Diabetes, CKD and stroke are risk factors for MHBP. More intensive treatment is needed to achieve the therapeutic goal for systolic MHBP in HDM patients, especially those who are complicated with CKD or stroke. (J Diabetes Invest, doi: 10.1111/j.2040-1124.2010.00056.x, 2010).

KEY WORDS: Chronic kidney disease, Diabetes mellitus, Morning home blood pressure

INTRODUCTION

Hypertension is a classical risk factor for cardiovascular disease events. Accumulative evidence has shown that the morning home blood pressure (MHBP) level is a predictor for the occurrence of cardiovascular disease (CVD) events1,2. Use of MHBP has allowed us to classify hypertension into four subgroups: (i) sustained hypertension; (ii) white-coat hypertension; (iii) masked hypertension, which is characterized by normal office blood pressure (OBP) and elevated MHBP; and (iv) normotension. Recent clinical studies have shown that masked hypertensive patients are at high risk of CVD mortality and morbidity, similar to sustained hypertensives3–5.

Diabetes mellitus (DM) is also one of the major risk factors for CVD. The combination of hypertension with DM has been shown to be higher risk factor for CVD6. Furthermore, the coexistence of hyperglycemia and hypertension markedly increases the risk of diabetic nephropathy in patients with type 2 diabetes7. Many large-scale clinical studies have shown the clinical benefit of blood pressure (BP) reduction in hypertensive patients with DM in preventing CVD events8–11. Based on these trials, recent guidelines have recommend that BP in patients with DM should preferably be under 130/80 mmHg9,11. However, these trials only monitored OBP. Thus, it is clinically important to investigate the management of both OBP and MHBP levels in patients with DM. Several smaller studies have suggested the association between MHBP and diabetic complications in patients with type 2 DM15–17; however, there are just two studies, to our knowledge, that directly compare the management of both OBP and MHBP levels in hypertensive patients with DM to those without DM18,19, thereby, little is known about the effects of risk factors on BP in HDM patients.
In the present study, we investigated BP levels in hypertensive patients with DM compared with those without DM, and evaluated the effect of other risk factors on both OBP and MHBP.

MATERIALS AND METHODS

Subjects

This was a cross-sectional study based on the investigation of both OBP and MHBP management in hypertensive outpatients in the recruitment for a Multicenter PROBE study; a comparison of the effects of angiotensin II type 1 receptor blockers on self-monitored home blood pressure in patients with morning hypertension (MUSCAT study), the details of which have previously been published elsewhere. Briefly, this investigation for the MUSCAT study was carried out from 1 July 2004 to 30 June 2005 by 52 physicians and 30 institutions in Japan. To examine the management of blood pressure levels in hypertensive outpatients with DM (HDM patients) or without DM (HnDM patients), we analyzed subjects who were HDM patients (n = 366) and HnDM patients (n = 864). In accordance with physician’s charts, cardiovascular risk factors of each patient were evaluated: body mass index (BMI), smoking, hyperlipidemia, DM, ischemic heart disease (IHD), stroke, chronic kidney disease (CKD), habitual alcohol drinking and the number of antihypertensive drugs being taken. Patients with a current smoking habit were defined as smokers. Hyperlipidemia was defined as a total cholesterol level above 220 mg/dL or a triglyceride level above 150 mg/dL. DM was defined as either a fasting blood glucose level above 126 mg/dL or a casual glucose level above 200 mg/dL in patients not receiving any treatment for diabetes. Those who had already been diagnosed with DM or had taken any antidiabetic agents were also considered to have DM. IHD was defined as a diagnosed history of angina or previous myocardial infarction. Silent myocardial infarction was not included. Stroke was defined as a diagnosed history of cerebral infarction, subarachnoid hemorrhage and cerebral bleeding. Transient ischemic attack was not included. CKD was defined in accordance with NHANES III: (i) structural or functional abnormalities – abnormal findings on histological examination, urinalysis, biochemical examination, or imaging studies for a duration of 3 months or longer regardless of glomerular filtration rate (GFR); and (ii) GFR < 60 mL/min/1.73 m², regardless of the primary disease, using the Cockcroft–Gault equation. Patients who drank alcohol everyday were regarded as habitual alcohol drinker. The ethics committee of Okayama University Institutional Review Board (accredited ISO9001/2000), Okayama, Japan, approved the protocol. Written informed consent was obtained from every participant.

Blood Pressure Measurement

OBP was measured at a doctor’s office after 5 min of resting in a sitting position. MHBP was determined by an electronically automated manometer, HEM 747 IC (Omron Colin, Tokyo, Japan). The average value taken at least three consecutive days before visiting a physician’s office was considered to be the patient’s MHBP. The details have been described previously.

All patients were assigned into four categories: (i) sustained hypertensive, those who had uncontrolled systolic OBP (OSBP ≥ 140 mmHg) and uncontrolled systolic MHBP (MHSBP ≥ 135 mmHg); (ii) masked hypertensive, those who had controlled OSBP (<140 mmHg) and uncontrolled MHSBP; (iii) white coated hypertensive, those who had uncontrolled OSBP and controlled MHSBP (<135 mmHg); and (iv) normotensive, those who had both controlled OSBP and MHSBP.

Statistical Analysis

Data were expressed as means ± standard deviation without any explanation. Differences between HDM patients and HnDM patients were examined by unpaired t-test, Mann–Whitney U-test or χ²-test where appropriate. One-way ANOVA followed by the Tukey–Kramer post-hoc test were used to analyze differences among the four groups. Multiple logistic regression analysis was carried out to examine the independent associations between factors. A difference of P < 0.05 was considered as statistically significant.

RESULTS

Characteristics of All Subjects

The characteristics of participants are shown in Table 1. Among all hypertensive subjects, 30% suffered from DM. The prevalence of HDM patients in the male population, smoking, IHD and

Table 1 | Characteristics of subjects

| Characteristic | HnDM (n = 864) | HDM (n = 366) | P-value |
|----------------|---------------|---------------|---------|
| Age (years)   | 66 ± 11       | 67 ± 9        | 0.0858  |
| Sex (male/female) | 361/503    | 187/179       | 0.0033  |
| BMI (kg/m²)   | 24.1 ± 0.14   | 24.7 ± 0.23   | 0.0108  |
| Smoking (%)    | 15/25         | <0.0001       |         |
| Hyperlipidemia (%) | 42/43       | 43/43         | 0.7262  |
| IHD (%)        | 8/13          | 0.013         |         |
| Stroke (%)     | 8/10          | 0.2974        |         |
| CKD (%)        | 14/29         | <0.0001       |         |
| Habitual drinking (%) | 24/31      | 0.0213        |         |
| Number of medications | 1.49 ± 0.03 | 1.64 ± 0.05 | 0.0142  |
| ARB (%)        | 48/58         | 0.0009        |         |
| ACE inhibitor (%) | 12/17       | 0.0141        |         |
| CCB (%)        | 65/62         | 0.4296        |         |
| β Blocker (%)  | 8/8           | 0.7578        |         |
| α Blocker (%)  | 9/7           | 0.3502        |         |
| Diuretics (%)  | 5/6           | 0.7298        |         |
| Other (%)      | 3/5           | 0.1693        |         |

Values are represented as means ± standard deviation. P-value was determined by unpaired t-test for age and body mass index, Mann–Whitney U-test for number of medications and χ²-test for others. ACE, angiotensin converting enzyme; ARB, angiotensin II receptor blocker; BMI, body mass index; CCB, calcium channel blocker; CKD, chronic kidney disease; HDM, hypertensive patients with diabetes mellitus; HnDM, hypertensive patients without diabetes mellitus; IHD, ischemic heart disease.
CKD were almost twice as high than those among HnDM patients. Also, habitual drinking was 30% higher in HDM patients than in HnDM patients, but the prevalence of stroke was comparable with HnDM patients. BMI in HDM patients was higher than in HnDM patients. HDM patients took Ras inhibitors, such as ACE-I or ARB, more frequently than HnDM patients with statistical significance (P < 0.001). HDM patients took more antihypertensive drugs compared with HnDM patients (P < 0.02).

Blood Pressure Management in HDM or HnDM Patients

The control of OSBP and diastolic OBP (ODBP) in HDM patients was significantly lower than in HnDM patients (P < 0.01, respectively; Table 2). With regard to MHBP, the management of diastolic MHBP (MHDBP) in HDM patients was also significantly lower than in HnDM patients (P < 0.01). In contrast, MHSBP in HDM patients was higher compared with HnDM patients (P = 0.0623). In categorization, 30% of HDM patients had masked hypertension and its prevalence was higher than in HnDM patients (P < 0.02, Figure 1).

HDM Patients with CKD or Stroke Had Significantly Higher MHSBP than Those without CKD Nor Stroke

To examine why HDM patients tended to have higher MHSBP despite better-controlled OSBP, ODBP and MHDBP compared with HnDM patients, we evaluated the effect of other complications on MHSBP. Subjects were categorized into four groups, those with or without DM and with or without one of the risk factors. Smoking, hyperlipidemia, IHD and habitual alcohol drinking had no effect on MHSBP level irrespective of HDM or HnDM (Table 3). With regard to CKD, the management of OSBP in HDM patients was lower than in patients with HnDM, irrespective of CKD (P < 0.05, Table 3). However, only HDM patients with CKD had MHSBP significantly higher than others (P < 0.01). A multiple logistic regression analysis showed that the complications of both DM and CKD, not just DM or CKD, was significantly associated with morning hypertension (MHSBP more than 135 mmHg) in hypertensive patients (Figure 2).

Regarding stroke, the management of OSBP in HDM patients was even or lower than HnDM patients (Table 3). Again, MHSBP in HDM patients with stroke was significantly higher than those without stroke (p < 0.05). A stratified analysis showed that, in HDM patients, at least one complication of CKD or stroke significantly increased MHSBP, irrespective of OSBP control (Table 4).

DISCUSSION

In the present study, we evaluated the effect of risk factors on both OSBP and MHBP level in HDM patients compared with those in HnDM patients. Although OSBP, ODBP and MHDBP in HDM patients were controlled at lower levels than those in HnDM patients, MHSBP in HDM patients showed insufficient control. Furthermore, they tended to be higher compared with that in HnDM patients. This observation indicates that more intensive treatment is needed to control MHSBP in HDM patients, regardless of OSBP level. Furthermore, HDM patients with CKD or stroke had significantly higher MHSBP, although

| Table 2 | Blood pressure of all subjects |
|-----------------|-----------------|-----------------|
|                  | HDM (n = 864)   | HnDM (n = 366)  |
| OSBP (mmHg)     | 143.3 ± 16.6    | 140.3 ± 16.8    | 0.0046 |
| ODBP (mmHg)     | 81.1 ± 10.6     | 76.0 ± 9.9      | <0.0001 |
| MHSBP (mmHg)    | 141.9 ± 16.6    | 143.9 ± 18.0    | 0.0623 |
| MHDBP (mmHg)    | 82.5 ± 10.1     | 79.0 ± 10.3     | <0.0001 |

Values are represented as means ± standard deviation. P-value was determined by unpaired T-test for each blood pressure value.

HDM, hypertensive patients with diabetes mellitus; HnDM, hypertensive patients without diabetes mellitus; MHDBP, morning home diastolic blood pressure; MHSBP, morning home systolic blood pressure; ODBP, office diastolic blood pressure; OSBP, office systolic blood pressure.
they had a similar level of OSBP as those without CKD or stroke. This result suggests that the management of MBHP in HDM patients with such risk factors was still inadequate compared with that in HnDM patients.

Recent guidelines recommend Ras inhibitors, ACE-I or ARB, as a first choice drug in the treatment of DM patients with hypertension because of not only their antihypertensive effect, but also pleiotropic effects beyond BP reduction, such as amelioration of insulin resistance or albuminuria. In the present study, more HDM patients took Ras inhibitors than HnDM patients, suggesting that the participants were treated following these guidelines. The increase of the total number of
antihypertensive agents in HDM patients compared with that in HnDM patients implied that HDM patients might be resistant to achieve a target OBP level of 130/80 mmHg in HDM patients, which is 10 mmHg lower than the level in HnDM patients.

There is a significant difference in BP status between the present study and the former two large-scale studies that showed the comparison of HDM patients with HnDM patients. With regard to OSBP, the present study showed HDM patients had lower OSBP than HnDM patients, meanwhile the former studies showed the opposite. This discrepancy suggests that the current study population were controlled by physicians who were following recent guidelines more strictly than the former populations. Nevertheless, the achieved OSBP level in HDM patients was still higher than that recommended in these guidelines. Unlike OSBP, MHSBP in HDM patients was not significantly reduced compared with MHSBP in HnDM patients. In addition, MHSBP in HDM patients did not accomplish the recommended BP level in the guidelines. Notably, the current study showed that the ratio of masked hypertension in HDM patients was significantly higher than that in HnDM patients. Thus, more aggressive BP treatment, especially for the reduction of MHSBP, would be needed in HDM patients. Indeed, the clinical significance of MHSBP in patients with type 2 DM has been reported. Regarding ODBP and MHDBP, the present study showed that BP levels in HDM patients were well-controlled, as they reached the targeted BP levels, as did one of the former studies. These lower levels in ODBP and MHDBP might imply the progression of arteriosclerosis in HDM patients.

CKD, involving an early stage of renal damage, has been identified as a risk factor of CVD, as well as other classical risk factors. It has been shown that CKD is closely related to MHBP in hypertensives. In addition, many studies have reported that patients with type 2 DM have higher MHBP, which is associated with both microvascular and macrovascular complications, including diabetic nephropathy. Thus, the clinical impact of CKD on BP in HDM patients needs to be elucidated. Among the risk factors, the current study showed that the co-existence of CKD exerted a significant effect on MHSBP level in HDM patients. Furthermore, a multiple logistic regression analysis confirmed the association of the co-existence of CKD and DM, not only CKD or DM, with higher MHSBP levels in hypertensive patients, after adjustment by risk factors. Taken together, our findings suggest that MHSBP measurement could be useful to detect CKD with DM in treated hypertensive patients.

The present study revealed the effect of stroke on MHSBP level in HDM patients to be equivalent to CKD. However, multiple logistic regression analysis failed to show a significant relationship between the co-existence of stroke with DM and morning hypertension (odds ratio: 1.91, 95% confidence interval [CI]: 0.61–5.96). In addition, especially in HDM patients, multiple logistic regression analysis again failed to show a significant relationship between the co-existence of CKD with stroke and morning hypertension (odds ratio: 7.15, 95% CI: 0.82–62.07). These might be partially because of the relatively small number of hypertensive patients who suffered stroke with DM, or partially because the other risk factors, such as age, had a strong association with stroke. A larger study is required in future.

The influence of habitual alcohol drinking on CVD events and MHSBP level is still argued. The present study showed no effect of habitual drinking on MHSBP, irrespective of HDM or HnDM patients. However, there is one report that has shown habitual drinking to be an independent determinant for masked hypertension in the treated hypertensives in Japan. This discrepancy might be observed as a result of a lack of information of the total alcohol intake. Total assumption of alcohol intake has been recently regarded as a determinant of CVD events.

The present study had some limitations. First, the only available data were OBP and self-measured MHBP, not 24-h ambulatory BP. This might reduce the opportunity to find a potential risk of morning surge, non-dipper or riser in nocturnal BP. However, morning surge is related to a raise of MHBP, in addition, Mancia et al. showed that elevation of each home, office or ambulatory BP level leads to an increase in the risk of mortality. Second, the Cockcroft–Gault formula was used to determine CKD in the present study. Very recently, an isotope dilution mass spectrometry-derived new modification of diet in renal disease study (MDRD) equation was formulated to predict estimated GFR in the Japanese population. However, in our protocol, we declared we used NHANES III criteria to define CKD.

In conclusion, HDM patients were still poorly controlled in the treatment of MHSBP. The current study also showed the significant effect of CKD and stroke on MHSBP level in HDM patients. Further interventional study is required to investigate whether lowering MHSBP protects HDM patients with CKD or stroke from CVD events.

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**APPENDIX**

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