Original Article

Masked Hypertension Determined by Self-Measured Blood Pressure at Home and Chronic Kidney Disease in the Japanese General Population: The Ohasama Study

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Both chronic kidney disease (CKD) and masked hypertension (MHT) are known to be linked with an increased risk of cardiovascular disease (CVD), but their relationship has remained unclear. The present study aimed to evaluate the CKD incidence in individuals with MHT in the general Japanese population. We recorded self-measured blood pressure at home (HBP) and casual blood pressure (CBP) in 1,365 individuals (mean 63.0 years old; males, 32.5%; mean creatinine clearance [CCr], 60.9 mL/min; positive proteinuria, 6.7%) and classified the subjects into four groups: sustained normal blood pressure (SNBP, 60.3%), white-coat hypertension (WCHT, 14.9%), MHT (12.8%), and sustained hypertension (SHT, 12.0%). Kidney parameter results for the respective groups (SNBP, WCHT, MHT, and SHT) were as follows: 61.7 mL/min, 61.8 mL/min, 59.6 mL/min, and 57.3 mL/min for CCr, 4.2%, 8.9%, 10.3%, and 12.8% for the prevalence of positive proteinuria, and 2.3%, 3.0%, 6.3%, and 9.8% for the proportion with CCr<60 mL/min with proteinuria. Compared with the SNBP group, the MHT and SHT groups exhibited significant differences in these parameters ($p<0.05$, for each). The adjusted odds ratios for CCr<60 mL/min with proteinuria were significantly higher in the MHT (2.56) and SHT (3.60) groups compared with the SNBP group (reference). MHT, like SHT, is closely related to CKD, and HBP measurement could be a useful screening strategy to detect CKD in the general population. (*Hypertens Res* 2008; 31: 2129–2135)

***Key Words*: masked hypertension, white-coat hypertension, chronic kidney disease, general population, home blood pressure**

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Introduction

Accumulative evidence has revealed that a decreased glomerular filtration rate (GFR) and the presence of proteinuria are independent risk factors for death and/or cardiovascular disease (CVD) events among general populations (*1–3*). Thus, it is now recognized that chronic kidney disease (CKD) (*4*) is an emerging new target for investigation from the viewpoint of public health.

Hypertension, a classic risk factor for CVD events, can be clinically classified into subgroups: sustained hypertension (SHT), white-coat hypertension (WCHT), and masked hypertension (MHT) (*5*), which is characterized by normal casual blood pressure (CBP) and elevated home blood pressure (HBP) or ambulatory blood pressure (BP) levels. Among the subtypes, it has been revealed that patients with MHT are at a high risk for CVD morbidity and mortality similar to that of patients with SHT (*6*, *7*). Accordingly, it is clinically important to clarify the relationship between CKD and MHT in terms of screening high-risk populations and targeting therapeutic levels of BP in CKD patients; however, little is known regarding this issue.

The present cross-sectional study examined the CKD incidence in subjects with MHT in the Japanese general population.

Methods

Design

This study was a part of the Ohasama study, a longitudinal BP measurement project initiated in 1986. The socio-economic and demographic characteristics of this region and full details of the project have been described previously (*8*). The study was approved by the Institutional Review Board of Tohoku University School of Medicine and the Department of Health of the Ohasama Town Government.

Study Population

In Japan, annual health checkups are available for farmers, the self-employed, retirees, and dependents aged ≥35 years. Among the 7,496 residents of Ohasama, 3,076 were eligible for annual health checkups in 1992. A total of 2,192 residents participated in checkups from 1992 to 1997. Of the 2,192 participants, 215 were excluded due to missing serum creatinine levels, missing dipstick tests for spot-urine, and other confounding factors (age, gender, body mass index [BMI], current smoking, diabetes mellitus, hypercholesterolemia, antihypertensive treatment, and history of CVD). Participants who were hospitalized, mentally ill, or bedridden were also excluded (n=185). In addition, participants with less than 14 d of HBP measurements and participants with apparent hematuria were excluded from statistical evaluation (n=427). Thus, 1,365 subjects comprised the study population, representing 62% of the residents participating in checkups.

BP Measurements

HBP was measured with the HEM701C (Omron Healthcare Co. Ltd., Kyoto, Japan), a semi-automatic device based on the cuff-oscillometric method (*9*), which generates a digital display of both systolic and diastolic BP.

Physicians and public health nurses instructed individuals on how to measure their own BP at home. Subjects were asked to measure their BP every morning within 1 h of waking and again after having been in the sitting position for more than 2 min. The results were recorded over a 4-week period. Subjects receiving antihypertensive drugs measured their BP before taking their medication. We allowed the individuals to measure their own BP more than twice on each occasion, although only the first measurement value on each occasion was recorded on the worksheet, to exclude selection bias by the participants (*10*). The measurements taken each morning were averaged, and the averaged values were referred to as the HBP. These measurement procedures were in accordance with Japanese Society of Hypertension (JSH) Guidelines for Self-Monitoring of Blood Pressure at Home published by the Japanese Society of Hypertension (*10*).

At the time of annual health checkup, a technician or a public health nurse measured the CBP two consecutively times, after the subject had been sitting for a minimum of 2 min, using a semiautomatic device (USM-700F; UEDA Electronic Works, Tokyo, Japan). CBP was measured during the day from 10:00 to 13:00 h or 14:00 to 16:00 h. An average of the 2 CBP measurements was calculated, and the averaged values were referred to as the CBP.

The algorisms of both the HBP measuring device and the CBP measuring device have been validated previously (*11*) and meet the criteria of the Association for the Advancement of Medical Instrumentation (*12*).

Categorization of Participants According to BP

Subjects were classified into four groups as follows: sustained normal blood pressure (SNBP): HBP<135/85 mmHg, CBP<140/90 mmHg; WCHT: HBP<135/85 mmHg, CBP≥140/90 mmHg; MHT: HBP≥135/85 mmHg, CBP<140/90 mmHg; and SHT: HBP≥135/85 mmHg, CBP≥140/90 mmHg. The cut-off values were derived from several guidelines (*13–16*). In this study, the SNBP group was composed of all subjects with normal BP, including those with SNBP controlled by medication. The WCHT group included subjects with uncontrolled BP when measured in the medical setting and normal HBP. Conversely, the MHT group included subjects with normal CBP but uncontrolled BP when self-measured at home. The SHT group included subjects with uncontrolled BP measured in the medical setting and at home. These classifications are consistent with those used in

Table 1. Characteristics of the Subjects Divided According to Their Home and Casual Blood Pressure Values

Variable	Total (n=1,365)	SNBP (n=823)	WCHT (n=203)	MHT (n=175)	SHT (n=164)
CCr (mL/min)	60.9	61.7	61.8	59.6*,†	57.3*,†
Prevalence of proteinuria (%)	6.7	4.2	8.9	10.3*	12.8*
CCr<60 mL/min (%)	51.9	51.1	47.8	57.7*,†	56.8*,†
With proteinuria (%)	7.3	2.3	3.0	6.3*	9.8*,†
Without proteinuria (%)	44.6	48.8	44.8	51.4	47.0
CCr≥60 mL/min (%)	48.1	48.9	52.2	42.3*,†	43.2*,†
With proteinuria (%)	5.6	1.9	5.9*	4.0	3.0
Without proteinuria (%)	42.5	46.9	46.3	38.3	40.2
Gender (% male)	32.5	25.5	31.0	48.6*	51.8*,†
Age (years)	63.0	61.4	63.7*	65.5*	67.7*,†
BMI (kg/m^2)	23.4	23.0	24.1*	24.0*	24.1*
CBP systolic (mmHg)	130	121	148*	127*,†	153*
Diastolic (mmHg)	72	68	82*	71*,†	83*
Pulse (mmHg)	58	53	66*	56*,†	70*
HBP systolic (mmHg)	124	117	123*	141*,†	145*,†
Diastolic (mmHg)	75	71	73*	86*,†	85*,†
Pulse (mmHg)	49	46	50*	55*	60*,†
Current smoker (%)	12.5	10.7	12.8	14.3	18.9*
Diabetes mellitus (%)	10.4	10.3	9.4	10.3	12.2
Hypercholestrolemia (%)	31.6	28.3	37.4	34.3	37.8
Hypertension on treatment (%)	31.0	16.9	41.9*	60.6*	56.7*
History of cardiovascular disease (%)	5.3	3.8	4.9	8.0	11.0*

*$p<0.05$ *vs*. SNBP group, †$p<0.05$ *vs*. WCHT group (Tukey test). SNBP, sustained normal blood pressure; WCHT, white-coat hypertension; MHT, masked hypertension; SHT, sustained hypertension; CCr, creatinine clearance; BMI, body mass index; CBP, casual blood pressure; HBP, home blood pressure.

previous studies (*6*, *7*).

Background and Laboratory Data Collection

At the time of the annual health checkup, blood and urine samples were collected. The following biochemical tests were performed: creatinine, total cholesterol, glucose, and HbA1c. Serum creatinine was measured using the Jaffe assay. Other biochemical tests were measured with standard laboratory techniques. GFR was calculated using the Cockcroft-Gault formula as endogenous creatinine clearance (CCr) (*17*). The presence of proteinuria was diagnosed by a positive protein screen as measured by a semi-quantitative dipstick test for spot-urine (Urohemobonbix 5G08C; Bayer Medical, Sendai, Japan) for which a urinary protein level ≥30 mg/dL indicated a positive result (*18*).

Participants were questioned about their smoking habits, medications for hypertension, and their history of CVD, hypercholesterolemia, or diabetes mellitus. Subjects with a history of hypercholesterolemia, defined as the presence of a total cholesterol measurement ≥5.68 mmol/L (220 mg/dL) or the use of medication for the treatment of hypercholesterolemia were considered to have hypercholesterolemia. Subjects with a history of diabetes mellitus, defined as a fasting glucose concentration ≥7.0 mmol/L (126 mg/dL), a non-fasting glucose concentration ≥11.1 mmol/L (200 mg/dL), and an HbA1c concentration ≥6.5% or the use of medication for the treatment of diabetes were defined as having diabetes mellitus. BMI was calculated as weight (kg) divided by height squared (m^2).

Data Analysis

SAS software, version 9.1 (SAS Institute, Cary, USA), was used for all statistical analyses. Data are presented as means±SD, unless otherwise specified. Values among the four groups, including CKD markers, were compared by analysis of variance or χ^2-test. Analysis of covariance or a logistic regression model was used to adjust for between-group differences in the following confounding factors: gender, age, BMI, current smoking, diabetes mellitus, hypercholesterolemia, antihypertensive treatment, and history of cardiovascular disease. To quantify the magnitude of the correlation, we used Pearson's correlation coefficient (r). For all analyses, a two-tailed $p<0.05$ was considered statistically significant. The authors had full access to the data and take responsibility for its integrity.

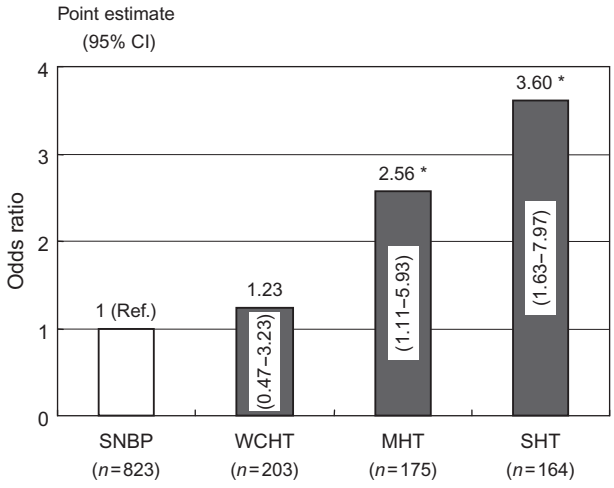

Fig. 1. *Odds ratios (ORs) and 95% confidence intervals for the presence of CCr < 60 mL/min with proteinuria in the four groups. This figure shows the values of the four groups classified by blood pressure threshold. Values were adjusted for age, gender, body mass index, current smoking, diabetes mellitus, hypercholesterolemia, antihypertensive treatment, and history of cardiovascular disease. SNBP, sustained normal blood pressure; WCHT, white-coat hypertension; MHT, masked hypertension; SHT, sustained hypertension. *p < 0.05 (maximum likelihood estimates).*

Results

The mean age of the 1,365 subjects was 63.0±8.9 years, and 32.5% were male. The mean BMI was 23.4±3.1 kg/m^2. Ninety-two subjects (6.7%) had a positive test for urinary protein. The mean estimated CCr was 60.9±16.4 mL/min (range, 15.4–132.0). The average HBP was 124/75 mmHg and the average CBP was 130/72 mmHg. A total of 12.5% of subjects were classified as current smokers, 31.0% were treated with antihypertensive medication, and 5.3%, 10.4%, and 31.6% of subjects were classified as having a history of cardiovascular disease, diabetes mellitus, and hypercholesterolemia, respectively.

We obtained a total of 26.0±4.6 measurements for HBP in each subject in the present study. A total of 60.3% of subjects were classified as having SNBP, 14.9% were classified as having WCHT, 12.8% were classified as having MHT, and 12.0% were classified as having SHT. Characteristics of the respective groups are shown in Table 1. Mean estimated CCr was significantly lower in the MHT and SHT groups (59.6 and 57.3 mL/min, respectively) than in the SNBP group (61.7 mL/min). The prevalence of CCr<60 mL/min was significantly higher in the MHT and SHT groups (57.7% and 56.8%, respectively) than in the SNBP group (51.1%). The percentage of subjects with proteinuria was significantly higher in the MHT and SHT groups (10.3% and 12.8%, respectively) than in the SNBP group (4.2%). Moreover, the prevalence of CCr<60 mL/min with proteinuria was significantly higher in the MHT and SHT groups (6.3% and 9.8%, respectively) than in the SNBP group (2.3%). This significant difference in CCr and proteinuria was not observed between the SNBP and WCHT groups.

The adjusted odds ratios (ORs) calculated by multiple logistic regression for the subjects with CCr<60 mL/min and proteinuria in each of the four groups are shown in Fig. 1. The likelihood of having a CCr<60 mL/min and proteinuria was significantly higher for subjects in the MHT group (OR 2.56, 95% CI 1.11 to 5.93) and SHT group (OR 3.60, 95% CI 1.63 to 7.97) than in the SNBP group (Fig. 1). A similar trend was also observed irrespective of antihypertensive treatment: The likelihood of having a CCr<60 mL/min and proteinuria was significantly higher in the MHT and SHT groups, both with and without antihypertensive treatment (Fig. 2). On the other hand, the likelihood of having a CCr<60 mL/min and proteinuria was not significant for the WCHT group (Fig. 1), irrespective of the presence of antihypertensive treatment (Fig. 2). HBP and CBP values were significantly correlated ($p<0.0001$, $r^2=0.26$).

We also evaluated the OR for the subjects with CCr<60 mL/min and proteinuria using the data of 2-d HBP values, which were calculated using the same number of measurements as the CBP, and observed a similar trend (Figs. 3 and 4). The 2-d HBP and CBP values were significantly correlated ($p<0.0001$, $r^2=0.21$).

Discussion

This community-based study demonstrated that MHT and SHT are closely associated with CKD in the Japanese general population and that there is a significantly higher probability of CKD in these hypertension types compared with SNBP or WCHT subjects. To our knowledge, this is the first report to suggest the clinical significance of MHT for CKD in a community-based cohort.

GFR decline is closely related to poor volume control and is linked with an elevation of oxidative stress, a non-traditional CVD risk (*19*). On the other hand, proteinuria, which is a risk of GFR decline (*20*) and cardiovascular events (*21*), is a marker of endothelial cell dysfunction or systemic vasculopathy (*22*). Based on this medical background information, it has been speculated that decreased GFR with proteinuria may exaggerate the risk of CVD events and poor patient outcomes. A recent report by Irie *et al*. suggested that the combination of proteinuria and hypercreatininemia or reduced GFR was a significant predictor of CVD and overall mortality (*23*).

In the present study, subjects with MHT and SHT, but not those with WCHT, were revealed to have this condition at a higher prevalence. Furthermore, the odds of having CCr<60 mL/min with proteinuria in the MHT and SHT groups were significantly higher than in the SNBP group, irrespective of

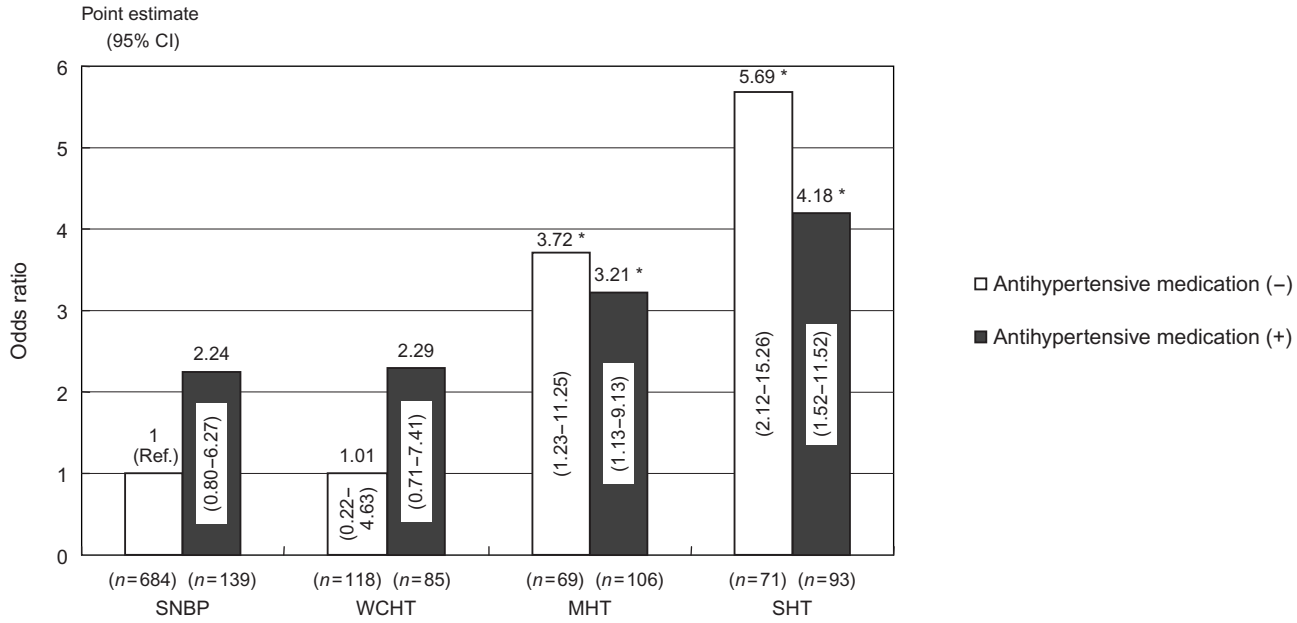

Fig. 2. *Odds ratios (ORs) and 95% confidence intervals for the presence of CCr < 60 mL/min with proteinuria in the presence or absence of antihypertensive medication. Participants were further divided into eight groups according to blood pressure threshold and the presence or absence of antihypertensive medication (each p value for interaction was > 0.14). Values were adjusted for age, gender, body mass index, current smoking, diabetes mellitus, hypercholesterolemia, antihypertensive treatment, and history of cardiovascular disease. SNBP, sustained normal blood pressure; WCHT, white-coat hypertension; MHT, masked hypertension; SHT, sustained hypertension. *p < 0.05 (maximum likelihood estimates).*

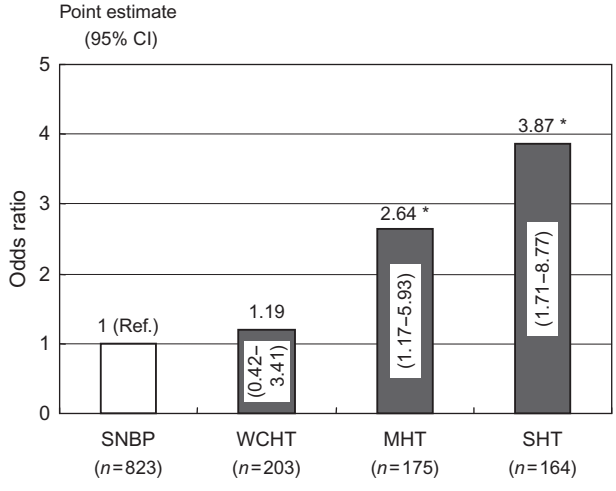

Fig. 3. *Odds ratios (ORs) and 95% confidence intervals for the presence of CCr < 60 mL/min with proteinuria in the four groups classified on the basis of 2-d HBP values. Values were adjusted for age, gender, body mass index, current smoking, diabetes mellitus, hypercholesterolemia, antihypertensive treatment, and history of cardiovascular disease. SNBP, sustained normal blood pressure; WCHT, white-coat hypertension; MHT, masked hypertension; SHT, sustained hypertension. *p < 0.05 (maximum likelihood estimates).*

the use of antihypertensive medications. These results suggest that, in addition to CBP, identification of MHT through the use of HBP could be an important screening strategy in the detection of CKD subjects.

The finding of the superior predictive value of HBP compared with CBP for CKD (Fig. 1) may be biased due to the method of the present study. We employed multiple measurements of HBP and a limited number of measurements of CBP (twice), which might have contributed to the results (Fig. 1). Therefore, we performed further analyses using the same number of measurements for HBP as for CBP (two measurements) and confirmed that HBP had retained a stronger predictive power than CBP (Fig. 3). In light of this, it is suggested that factors other than the number of measurements, such as the lack of the white-coat effect and the timing of BP measurement in the early morning, might be associated with the superior predictive power of HBP. With regard to the timing of BP measurements early in the morning, the effect of antihypertensive treatment should be considered, because a third of the study participants were regular users of antihypertensive medication. It is likely that the early-morning HBP of participants on antihypertensive treatment was affected by an insufficient duration of action of the antihypertensive drugs. Because the trough/peak ratios of most antihypertensive drugs are reported to be <50% (*24*), poor BP control late at night and early in the morning could be overlooked in BP

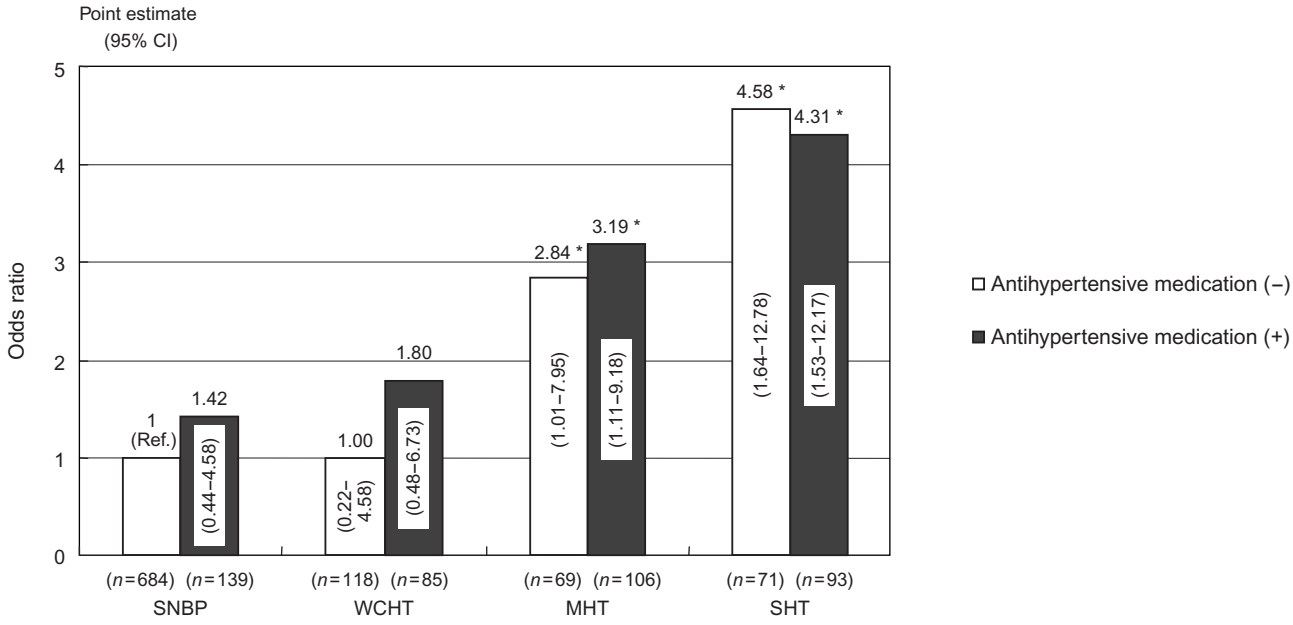

Fig. 4. *Odds ratios (ORs) and 95% confidence intervals for the presence of CCr < 60 mL/min with proteinuria in the presence or absence of antihypertensive medication based on 2-d HBP values. The eight groups were classified on the basis of 2-d HBP values (each p value for interaction was > 0.63). Values were adjusted for age, gender, body mass index, current smoking, diabetes mellitus, hypercholesterolemia, antihypertensive treatment, and history of cardiovascular disease. SNBP, sustained normal blood pressure; WCHT, white-coat hypertension; MHT, masked hypertension; SHT, sustained hypertension. *p < 0.05 (maximum likelihood estimates).*

measurements performed in the daytime (office BP measurement). This could be a reason why the OR of CKD risk is higher in the MHT group than in the WCHT group.

Recently, Agarwal and Andersen showed that HBP is a stronger predictor than CBP of progression to end-stage renal failure and mortality in CKD patients (*25*). Taking this finding together with our findings, control of HBP could be a therapeutic target in patients with CKD in terms of prevention of CVD events in CKD. This important issue could be a clinical challenge and should be addressed in future.

There are some limitations in this study. The first limitation involves the method of estimating renal function. We could not employ the recently recommended isotope dilution mass spectrometry–derived new modification of diet renal disease study (MDRD) equation to predict the estimated GFR (*26*) because serum creatinine levels were measured by the Jaffe assay and the accuracy of duBois' formula to estimate the body surface area (*27*) is not verified in the Japanese population. Thus, we used the Cockcroft-Gault equation to estimate GFR without normalization by body surface area (mL/min/1.73 m^2) and adjusted for body size afterward using BMI. The second limitation involves the method of quantifying proteinuria. In this study, the presence of proteinuria was diagnosed by a positive protein screen as measured by a semiquantitative dipstick test for spot-urine, where a urinary protein level ≥30 mg/dL indicated a positive result. This approach did not allow us to distinguish subjects with microalbuminuria from those with overt proteinuria. Studies should be conducted to investigate the important issue of albuminuria.

In conclusion, the present study demonstrated that MHT, like SHT, is closely related to CKD, and HBP measurement could be a useful screening strategy to detect CKD in the general population. Whether suppression of CKD by therapeutic intervention in patients with MHT should be attempted must be clarified.

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