


Maximum morning home systolic blood pressure is an indicator of the development of diabetic nephropathy: The KAMOGAWA-HBP study

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Keywords

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ABSTRACT

Aims/Introduction: The maximum value of home systolic blood pressure is correlated with damage to target organs, including diabetic nephropathy. However, the precise relationship between the development of diabetic nephropathy and maximum home systolic blood pressure has not been elucidated.

Materials and Methods: In this prospective 2-year cohort subanalysis of the KAMOGAWA-HBP study, the patient population was 477 Japanese patients with normoalbuminuria. We investigated the effects of mean and maximum home blood pressure on the development of diabetic nephropathy, which we defined as a urinary albumin excretion value ≥ 30 mg/g creatinine. Among the 477 patients, 67 developed diabetic nephropathy.

Results: In our multivariate logistic regression analyses, the maximum morning home systolic blood pressure was significantly positively associated with the development of diabetic nephropathy after adjusting for patient sex and age, smoking status, the diabetes mellitus duration, body mass index, creatinine, total cholesterol, hemoglobin A1c, and anti-hypertensive medication use (odds ratio 1.21, 95% confidence interval 1.03–1.42, $P = 0.021$).

Conclusions: Maximum home blood pressure can be identified at a glance, and its measurement would thus be helpful to healthcare providers who treat patients with diabetes and normoalbuminuria.

INTRODUCTION

One of the major complications of diabetes is diabetic nephropathy, and patients with type 2 diabetes mellitus and nephropathy are reported to be at greater risk of developing cardiovascular disease¹ and mortality². Diabetic nephropathy is reported to be the most common setting for end-stage renal disease, the prevalence of which is increasing worldwide³. The treatment and the prevention of diabetic nephropathy are thus important to the goal of preventing renal and cardiovascular events.

Hypertension⁴ is also a risk factor for diabetic nephropathy⁴, and antihypertensive therapy is therefore crucial for preventing incident diabetic nephropathy in individuals who have both diabetes and hypertension¹. Tracking a person's home blood pressure (HBP) is useful for predicting target organ damage, because its reliability is guaranteed without the white coat phenomenon⁵, which has also been shown in patients with diabetes⁶. The measurement of HBP is thus essential for the treatment of hypertension.

We have documented associations between HBP and diabetic complications, such as nephropathy^{7,8}, and arterial stiffness⁹. It was shown that the maximum value of home systolic blood

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pressure (HSBP) had a significant correlation with target organ damage in individuals with untreated hypertension¹⁰. We also showed that the maximum morning HSBP is related to diabetic nephropathy in type 2 diabetes mellitus patients in our previous cross-sectional study of the KAMOGAWA-HBP cohort¹¹. We carried out the present study using the same cohort to investigate the utility of maximum HBP (maxHBP) values for predicting the occurrence of diabetic nephropathy in individuals with normoalbuminuria.

METHODS

Study design and participants

This was a subanalysis of the study named KAMOGAWA-HBP at 2 year, which is a prospective cohort investigation that has been ongoing at the Kyoto Prefectural University of Medicine's hospital and four general hospitals in Japan's Kansai prefecture¹¹. All of the patients in the present subanalysis of the KAMOGAWA-HBP study provided their informed consent to participate. The present study was approved by each hospital's ethics committee.

We recruited patients with type 2 diabetes mellitus seen in the period March 2008 to October 2015 at any of the several outpatient clinics of Kyoto Prefectural University of Medicine and the four general hospitals. The details of the KAMOGAWA-HBP study are provided elsewhere^{8,9}. Type 2 diabetes mellitus was diagnosed at all of the participating institutions based on the criteria published by the American Diabetes Association¹².

Blood pressure measurement

For all of the HBP measurements, an automated blood pressure (BP) device based on the cuff-oscillometric technique (HEM-7080IC; Omron Healthcare, Kyoto, Japan) was used. The HEM-7080IC automatically generates a digital display of the wearer's systolic BP (SBP)/diastolic BP (DBP) values and his/her heart rate. The HEM-705IT (Omron Healthcare), which is another automatic BP tool, has been shown to satisfy the British Hypertension Society protocol's criteria¹³. The same blood pressure-determination algorithm and components as the HEM-705IT are used in the HEM-7080IC.

Each of the study participants was taught how to measure his or her morning BP and evening BP three times at intervals of ≥ 1 min for 14 (consecutive) days. We calculated the mean of the three morning BP measurements and the mean of the evening BP measurements of each day, and then the level of HBP ("mean HBP" in this study) was computed from those 14 means. We defined the maximum HBP (maxHBP) as the highest readings among the 3×14 measurements each in the morning or evening. The patients measured their first morning BP values within 1 h of waking up, before their breakfast and before taking any medication, while seated after resting for ≥ 5 min¹⁴. The patients measured their evening BP values just before they went to bed.

For each BP measurement, the patient put the cuff of the HEM-7080IC around his or her non-dominant arm with the

cuff placed on the upper arm, at heart-level. We used the mean of the three readings (morning or evening) as the "clinic BP."

Data collection

The information about the patients' background factors (i.e., age, sex, smoking habit, alcohol habit/intake, duration of diabetes, hypoglycemic agent(s) and antihypertensive medication) was gathered from the patients and their medical records at the clinic BP measurement visit. After the patients had fasted overnight, venous blood samples were used to measure the concentrations of fasting plasma glucose, total cholesterol and triglycerides, and creatinine. Each patient's level of hemoglobin A1c (HbA1c) was determined by high-performance liquid chromatography. All HbA1c values are presented herein using National Glycohemoglobin Standardization Program units. Spot morning urine samples were obtained, and the patients' urinary albumin excretion (UAE) was evaluated by an immunoturbidimetric assay. The mean UAE was obtained with the use of three urinary measurements.

The Diagnostic Neuropathy Study Group¹⁴ criteria were used to diagnose neuropathy. Retinopathy was assessed by chart review for each patient, which identified the absence/presence and grade of retinopathy: no diabetic retinopathy, simple diabetic retinopathy or proliferative diabetic retinopathy. Macrovascular complication was defined as a medical history of cerebrovascular disease, cardiovascular disease or the occlusive arterial disease, arteriosclerosis obliterans.

Definition of nephropathy and the development of diabetic nephropathy

The following three grades were used for nephropathy (normoalbuminuria, microalbuminuria, macroalbuminuria): normoalbuminuria: a UAE value < 30 mg/g of creatinine (Cr; mg/gCr); microalbuminuria, 30–300 mg/gCr; and macroalbuminuria, > 300 mg/gCr¹⁵. We defined diabetic nephropathy as a UAE value ≥ 30 mg/gCr.

Statistical analysis

We used the JMP version 13.0 program (SAS Institute, Cary, NC, USA) for all of the analyses of the patients' data. Probability values < 0.05 were accepted as significant. Categorical variables are expressed as numbers, and continuous variables are presented as the mean \pm standard deviation.

The odds ratio (OR) and 95% confidence interval (CI) of the mean and maxHBP measurements (both of which were divided by 10) and other variables on the development of diabetic nephropathy were calculated by carrying out univariate and three different multivariate logistic regression analyses. We adjusted model 2 for the patient sex, patient age, smoking status, diabetes mellitus duration, body mass index (BMI), total cholesterol and creatinine, and HbA1c. Model 3 was adjusted for the model 2 variables and for antihypertensive medication use. We selected these covariants because they are factors in the amelioration or deterioration of diabetic nephropathy¹¹.

We also carried out subgroup analyses, using the subgroup factors of age (≥ 65 years, < 65 years) and the presence/absence of the use of antihypertensive medication.

RESULTS

Study participants

We enrolled 1,414 patients. The following patients were excluded: 39 patients who failed to adequately measure their HBP; 73 and 366 patients whose UAE data were not available at baseline and at 2 years after baseline, respectively; 121 patients who were newly prescribed an angiotensin II receptor blocker or angiotensin-converting enzyme inhibitor or stopped using them during the follow-up period; 315 patients whose UAE value were ≥ 30 mg/gCr at baseline; and 23 patients whose HBP measurements were for < 7 days. Thus, 477 patients (225 men, 252 women) were enrolled (Figure 1).

Baseline characteristics

A summary of the patients' baseline characteristics is given in Table 1. The patients' mean age was 63.7 ± 9.9 years, and their mean BMI was 23.7 ± 3.8 kg/m². Their mean HbA1c was $7.1 \pm 0.9\%$. Among the 477 patients, 223 (49.9%) received treatment with antihypertensive drugs.

Among the 477 patients with normoalbuminuria at baseline, at 2 years later, 65 patients (13.6%) had progressed to microalbuminuria, and two patients (0.4%) had developed macroalbuminuria.

Association between BP and the development of diabetic nephropathy

The unadjusted and adjusted ORs plus 95% CIs for the development of nephropathy are provided in Table 2. In the

univariate logistic regression analyses, maximum morning HSBP was positively and significantly associated with the development of diabetic nephropathy (model 1 OR 1.24, 95% CI 1.08–1.41, $P = 0.002$). The multivariate logistic regression analyses established that maximum morning HSBP was also positively and significantly associated with the development of diabetic nephropathy in model 2 (OR 1.24, 95% CI 1.06–1.45, $P = 0.007$) and model 3 (OR 1.21, 95% CI 1.03–1.42, $P = 0.021$). In contrast, the values of home DBP did not show a significant risk for the development of diabetic nephropathy. Furthermore, we checked the association between the development of diabetic nephropathy and clinic SBP or clinic DBP in multivariate analyses. Then, the adjusted ORs of the mean clinic SBP and clinic DBP were 1.09 (95% CI 0.94–1.29, $P = 0.243$) and 0.98 (95% CI 0.95–1.00, $P = 0.087$), both of which did not show a significant association.

Subgroup analyses according to age

The subgroup analyses according to age (≥ 65 vs < 65 years) showed that in the patients aged < 65 years, the maximum morning HSBP was significantly correlated with the development of diabetic nephropathy, even after adjusting for several variables (OR 1.60, 95% CI 1.20–2.14, $P = 0.001$), whereas no significant relationship was observed in our patients aged ≥ 65 years (OR 1.42, 95% CI 0.96–2.10, $P = 0.075$; Table S1). Additionally, the BMI values of the patients aged < 65 years were significantly greater compared with those of the patients aged ≥ 65 years (24.3 kg/m² vs 23.0 kg/m², $P < 0.001$), and the maximum morning HSBP values in the patients aged < 65 years were significantly higher than those of the patients aged ≥ 65 years (152.4 mmHg vs 145.2 mmHg, $P < 0.001$).

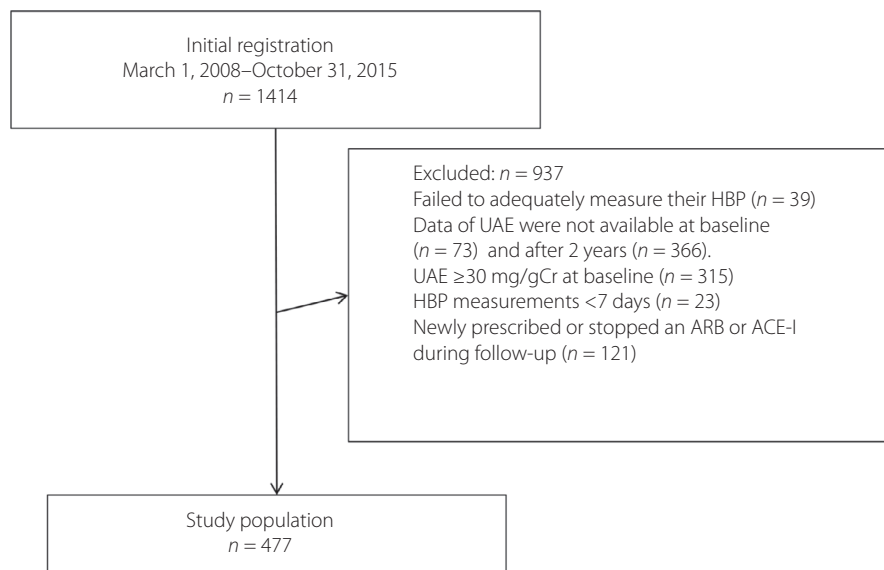


Figure 1 | The registration of patients. ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; Cr, creatinine; HBP, home blood pressure; UAE, urinary albumin excretion.

Table 1 | Clinical characteristics of the study patients

	Total (n = 477)
Sex (men/women)	225/252
Age (years)	63.7 ± 9.9
BMI (kg/m ²)	23.7 ± 3.8
Hemoglobin A1c, % (mmol/L)	7.1 ± 0.9/54.5 ± 10.3
Total cholesterol (mmol/L)	4.9 ± 0.8
Triglycerides (mmol/L)	1.4 ± 0.8
Creatinine (μmol/L)	63.5 ± 16.2
Pulse wave velocity (cm/s)	1,724.3 ± 349.9
Smoking status (current/ex/never)	287/125/65
Alcohol consumption status (everyday/social/never)	289/92/96
Duration of diabetes (years)	11.0 ± 8.9
Retinopathy (NDR/SDR/PDR)	383/61/33
Neuropathy (−/+)	367/110
Macrovascular complication (−/+)	391/86
Hypoglycemic treatment (diet/OHA/insulin/GLP-1)	92/284/99/2
Antihypertensive medication (−/+)	254/223
RAS inhibitors (−/+)	302/175
Calcium channel blockers (−/+)	352/125
Diuretics (−/+)	444/33
Clinic SBP	135.2 ± 18.0
Clinic DBP	76.9 ± 10.5
Mean morning home SBP	128.1 ± 15.4
Mean morning home DBP	73.3 ± 9.6
Mean evening home SBP	124.5 ± 13.9
Mean evening home DBP	68.5 ± 8.8
Max. morning home SBP	148.8 ± 19.0
Max. morning home DBP	86.0 ± 13.2
Max. evening home SBP	146.0 ± 18.5
Max. evening home DBP	81.6 ± 13.0

Data are number or mean ± standard deviation. All systolic blood pressure (SBP) and diastolic blood pressure (DBP) values are in mmHg. BMI, body mass index; GLP-1, glucagon-like peptide 1; Max., maximum; NDR, no diabetic retinopathy; OHA, oral hypoglycemic agent; PDR, no diabetic retinopathy; SDR, simple diabetic retinopathy; RAS, renin angiotensin aldosterone system.

Subgroup analyses based on the presence or absence of antihypertensive medication use

Our subgroup analyses based on the presence versus absence of antihypertensive medication use showed that in the patients who were not using antihypertensive medication, the maximum morning HSBP was significantly correlated with the development of diabetic nephropathy in both the univariate and multivariate analyses (model 1 OR 1.23, 95% CI 1.01–1.49, $P = 0.039$; model 2 OR 1.28, 95% CI 1.01–1.65, $P = 0.033$). In contrast, the maximum morning HSBP in the patients with antihypertensive medication use was not significantly related to the development of diabetic nephropathy (model 1 OR 1.09, 95% CI 0.95–1.26, $P = 0.203$; model 2, OR 1.23, 95% CI 0.97–1.55, $P = 0.081$; Table S2).

DISCUSSION

In the present study of a cohort of 477 Japanese individuals with normoalbuminuria, we investigated the association between maxHBP and the development of diabetic nephropathy. Diabetic nephropathy is the most common background for an individual's introduction to hemodialysis, the need for which is increasing worldwide³. The prevention of the development of diabetic nephropathy can therefore help reduce the number of people who need to undergo hemodialysis. The present investigation is the first to show that maximum morning HSBP is closely related to the development of diabetic nephropathy. HBP is reported to more accurately predict the risk of cardiovascular disease, compared with clinic BP^{5,16,17}; however, it can be difficult for physicians to accurately calculate a patient's mean HBP based on multiple self-measured HBP values in a record/log in clinical settings. In contrast, a patient's maxHBP can be identified at a glance, and its use thus makes it easy to evaluate the patient's BP levels.

The present findings obtained in a cross-sectional study showed that maximum morning HSBP is useful as an indicator of arterial stiffness and diabetic nephropathy^{9,11}. Other groups also reported that maximum morning HSBP is not only a useful indicator of target organ damage, but can also be used to predict stroke and cardiovascular events^{10,18,19}. Furthermore, a recent study showed that not only yearly elevated BP due to increased vascular resistance and decreased BP sensitivity, but also day-by-day, diurnal, seasonal and beat-by-beat BP instability lead to the morning BP surge, which triggers several cardiovascular events²⁰. These findings, including the present results, show that maxHSBP can be used as a risk factor for atherosclerosis.

In contrast, the patients' home DBP values were not shown to be a significant risk for the development of diabetic nephropathy. Possible explanations are as follows. First, the mean diastolic BP was reported to present a lower risk for cardiovascular events compared with the mean SBP²¹. Second, Kikuya *et al.*²² reported that instability of HSBP is related to a significant increase in the rate of cardiovascular mortality, whereas instability of home DBP was not.

Blood pressure instability was reported to be associated with endothelial cell dysfunction²³, which is caused by a decrease in the biological activity of nitric oxide (NO)²⁴ and related to diabetic nephropathy²⁵. Elevated maxHSBP was reported to be related to BP instability²⁶, and, in fact, maximum morning HSBP was also significantly associated with the coefficient variation of morning HSBP in the present study ($r = 0.282$, $P < 0.001$). Hypertension is reported to be related to progressive NO deficiency status²⁷, and NO production is known to decrease in patients with diabetic nephropathy²⁸. In an animal study, the NO production was increased by BP instability due to high sodium intake²⁹. In addition, the inhibition of NO synthase activates sympathetic nerves³⁰, which leads to BP instability. Taken together, these findings indicate that the interaction

Table 2 | Unadjusted and adjusted odds ratios of the development of diabetic nephropathy

	Model 1		Model 2 [†]		Model 3 [‡]	
	Unadjusted OR (95% CI)	<i>P</i>	Adjusted OR (95% CI)	<i>P</i>	Adjusted OR (95% CI)	<i>P</i>
Mean morning HSBP	1.31 (1.11–1.55)	0.002	1.31 (1.08–1.60)	0.007	1.26 (1.02–1.54)	0.029
Mean morning HDBP	0.92 (0.70–1.21)	0.559	1.07 (0.76–1.49)	0.702	1.02 (0.73–1.43)	0.919
Mean evening HSBP	1.20 (0.99–1.44)	0.055	1.18 (0.96–1.45)	0.127	1.13 (0.91–1.40)	0.268
Mean evening HDBP	0.76 (0.56–1.04)	0.079	0.88 (0.61–1.27)	0.497	0.86 (0.59–1.24)	0.419
Max. morning HSBP	1.24 (1.08–1.41)	0.002	1.24 (1.06–1.45)	0.007	1.21 (1.03–1.42)	0.021
Max. morning HDBP	0.98 (0.80–1.19)	0.802	1.02 (0.82–1.27)	0.846	1.01 (0.81–1.26)	0.952
Max. evening HSBP	1.05 (0.93–1.20)	0.423	1.09 (0.87–1.15)	0.993	0.98 (0.86–1.13)	0.817
Max. evening HDBP	0.87 (0.72–1.05)	0.143	0.85 (0.68–1.05)	0.122	0.85 (0.69–1.04)	0.112

All home diastolic blood pressure (HDBP) and home systolic blood pressure (HSBP) values are 10 mmHg. Smoking status was defined as non-smoker (0), ex-smoker (1) or current smoker (2). [†]Model 2: odds ratios (ORs) were adjusted for sex, age, smoking status, duration of diabetes mellitus, body mass index, hemoglobin A_{1c}, total cholesterol and creatinine. [‡]Model 3: ORs were adjusted for variables in model 2 and additional adjustment for use of antihypertensive medication.

between BP instability and a decrease in the production of NO might lead to the positive relationship between maximum morning HSBP and the development of diabetic nephropathy, which was reported to be associated with dysfunction of endothelial cells³¹.

In the present study's patients aged <65 years, maximum morning HSBP was closely related to the development of diabetic nephropathy, even after adjustment for several variables including the use of antihypertensive medications or renin–angiotensin system inhibitors; in contrast, the patients aged ≥65 years did not show a significant association. A possible explanation is that the BMI values of the patients aged <65 years were significantly greater compared with those of the patients aged ≥65 years. In addition, renin–angiotensin system activation and sympathetic nervous system activity caused by obesity might cause BP instability^{32,33}. Therefore, maximum morning HSBP affected the development of diabetic nephropathy in patients aged <65 years. In fact, the maximum morning HSBP values for the patients aged <65 years were significantly higher than those of the patients aged ≥65 years.

Most of the patients in the present cohort study were treated with antihypertensive medication (*n* = 223, 46.8%). Despite this medication, almost all of the BP measurements of the participants with antihypertensive medication were higher compared with those of the participants without such medication, and the crude proportion of the development of diabetic nephropathy in the participants who were using antihypertensive medication was much larger than that of the patients without (19.3% vs 9.5%).

In the present subgroup analysis based on the presence versus absence of antihypertensive medication use, the maximum morning HSBP in the patients without antihypertensive medication was significantly and positively related to the development of diabetic nephropathy, whereas the maximum morning HSBP in the patients using antihypertensive medication was not related to the development of diabetic nephropathy.

One of the possible reasons for this result is that treatment with antihypertensive medication might modify a patient's maxHSBP. The association between maxHSBP and the development of diabetic nephropathy in individuals taking antihypertensive medication might therefore be weaker than that in individuals not taking antihypertensive medication.

The present study's strengths include the use of a BP device that has the memory to store BP readings instead of the less-reliable patient logbooks, the accuracy of which is insufficient³⁴; in addition, we obtained HBP measurements for long consecutive periods. The study limitations include the following. First, the follow-up duration was only medium-long; the statistical power of our analyses might thus be limited. Second, dietary intake, especially sodium intake, is related to the prevalence of hypertension³⁵, and sodium restriction has an important role for the dietetic treatment of hypertension³⁶, as well as diabetic nephropathy³⁷. However, we did not have the patients' dietary intake data. With those data, we could more accurately investigate the association between maxHBP and diabetic nephropathy.

Third, the present study assessed the relationship between only a single baseline BP measurement and the development of diabetic nephropathy, which might have provided a potential bias. However, the association with cardiovascular disease risk was confirmed by BP at baseline in the patients or during their follow up, and this might indicate that single BP assessments are sufficient when subsequent values' inclusion does not significantly alter the results³⁸. The data including HBP during the observational period needs to be analyzed in future studies.

The results of the analyses carried out in the present prospective 2-year cohort study thus provide the first demonstration that the maxHSBP in individuals with type 2 diabetes mellitus and normoalbuminuria is positively associated with the development of diabetic nephropathy. A patient's maximum HSBP can be identified at a glance, and this measurement would therefore be helpful for healthcare providers who treat patients with diabetes and normoalbuminuria.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1 | Unadjusted and adjusted odds ratios of the development of diabetic nephropathy according to age <65 years or ≥65 years.

Table S2 | Unadjusted and adjusted odds ratios of the development of diabetic nephropathy according to use of antihypertensive medication.