


Diabetic nephropathy ameliorated in patients with normal home blood pressure compared to those with isolated high home systolic blood pressure: A 5-year prospective cohort study among patients with type 2 diabetes mellitus

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Abstract

Background: Using normal home blood pressure (home BP) as a reference, isolated high home systolic blood pressure (IH-home SBP) increases the risk of diabetic nephropathy. However, whether diabetic nephropathy would improve among diabetic patients without IH-home SBP has not been previously assessed.

Methods: This prospective 5-year cohort study of 264 patients with moderate or severe albuminuria investigated the effect of IH-home SBP or normal home BP on the risk of diabetic nephropathy in patients with type 2 diabetes mellitus. Improvement of diabetic nephropathy was defined as remission or regression from moderate or severe albuminuria to normal or mildly increased albuminuria.

Results: Improvement of diabetic nephropathy was shown in 59 out of 264 patients during 5 years. The adjusted odds ratio (95% confidence interval) of normal home BP for improving diabetic nephropathy was 2.52 (1.01–5.99, $p = 0.05$).

Conclusion: Normal home BP had relation to an improvement in diabetic nephropathy among type 2 diabetic patients with moderate and severe increased albuminuria in the observation period of 5 years. Good home BP control might be valuable to ameliorate diabetic nephropathy.

Keywords

albuminuria, diabetes mellitus, diabetic nephropathy, IH-home SBP, normal home BP

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Introduction

Controlling home blood pressure (home BP) is of paramount importance in preventing diabetic nephropathy¹ because high home BP is associated with the progression of diabetic nephropathy.^{2,3}

When systolic blood pressure (SBP) is hypertensive while diastolic blood pressure (DBP) is normotensive, isolated systolic hypertension (ISH) is diagnosed.⁴ ISH is a frequent form of hypertension, which increases the risk of premature cardiovascular deaths.^{5–7} ISH, assessed by home BP (home ISH), has also been shown to associate with the risk for the development of diabetic nephropathy. Isolated high home systolic blood pressure (IH-home SBP) is a valuable predictor of diabetic nephropathy progression, based on results from our previous cohort study.^{8,9}

In contrast, rigorous control of SBP is associated with remission or regression of diabetic nephropathy.^{10–13} The optimal home SBP for remission induction or regression of microalbuminuria might be below 130 mmHg.¹⁴ Using an angiotensin II receptor blocker (ARB) reduced microalbuminuria in Japanese with patients type 2 diabetes mellitus (DM) regardless of with or without hypertension.¹⁵

Nevertheless, whether diabetic nephropathy would improve in diabetic patients without IH-home SBP has not been previously assessed. Then, we changed the viewpoints and performed a further assessment aiming to provide the impact of preventing ISH on the improvement of diabetic nephropathy in the patient group with type 2 DM through the observation period of 5 years.

Methods

The resources investigated in this study was the same as in our previous research based on data from KAMOGAWA-HBP study, which was the home BP cohort of patients type 2 diabetic patients who regularly went to the clinic at the Kyoto Prefectural University of Medicine Hospital or some other general hospitals existed in Japan as an outpatient.¹ The patients regular care physicians are the principal investigator of the study.

The current research involved patients with type 2 DM and assessed a prognostic significance of home BP for progression of diabetic nephropathy. Nephropathy was classified as follows: normal or mild albuminuria, described as urinary albumin/creatinine ratio (UACR) less than 30 mg per gram of creatinine (mg/g Cr); moderately increased albuminuria (microalbuminuria), described as UACR 30–300 mg/g Cr, or severely increased albuminuria (macroalbuminuria), described as UACR more than 300 mg/g Cr.^{16–21} Improvement of diabetic nephropathy was described as remission or regression from moderate or severe albuminuria to normal or mildly increased

albuminuria within the confines of the observation period. The local research ethics committee had recognition of the research methods (RBMR-E-349). Adherence to the general rules of the Declaration of Helsinki was kept by the research, and all patients who participated in the research prior to enrollment provided informed consent.

Data collection

Morning fasting blood samples were collected for biochemical measurements. Serum lipid profile (including levels of low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglycerides), hemoglobin A_{1c} (HbA_{1c}), creatinine and some other biochemical markers were evaluated by common laboratory process. The data collection of urinary samples was performed simultaneously with the beginning of the home BP measurements. Urinary albumin and creatinine concentrations were measured in second morning urine samples. An immunoturbidimetric assay was used to measure UACR, and the mean value of three consecutive urinary measurements was evaluated, which corresponded to the UACR. As recommended by the Japan Diabetes Society, levels of HbA_{1c} were categorized and reported according to the National Glycohemoglobin Standardization Program guidelines.²² We collected analysis of the data about patient demographics and clinical characteristics, including sex, age, duration of DM, smoking status, alcohol consumption, and use of antihypertensive medication at the same time as home BP measurements began. We used the volume plethysmographic method in order to measure the brachial-ankle pulse wave velocity (baPWV), which was made use of our previous cohort study also.²³ We made a diagnosis for diabetic nephropathy on the basis of the Nephropathy Study Group criteria.²⁴ Alcohol drinking behavior (everyday, social, or never) and smoking behavior (current, past, or never) were evaluated through interviews for patients. We made a diagnosis for Type 2 DM when the fasting plasma glucose level was more than 126 mg/dl (7.0 mmol/L) or random plasma glucose level more than or equal to 200 mg/dl (11.1 mmol/L) on the basis of the American Diabetes Association criteria.²⁵

Home BP measurements

In this study, a single baseline BP measurement was performed at entry for this study. Participants were provided instructions on how to measure their SBP/DBP at home three times each morning and evening for 14 consecutive days. And then, the 14-day average of the three morning and three evening mean values were calculated. Participants were provided instructions on measuring method of their morning SBP/DBP within 1h of waking up, before breakfast or, taking drugs, and sat and rested for at least 5 minutes.²⁶ We applied

to similarly instructions for evening SBP/DBP measurements before sleeping. In addition, eating was prohibited for over 1 hour before the evening measurement. Furthermore, we instructed patients that the cuff of the measuring device should be put around the contralateral side of the dominant arm, with its position maintained at heart level. Home BP measurements were performed using an automated device, HEM-70801C (Omron Healthcare Co. Ltd, Kyoto, Japan), which utilizes a digital display to present values of SBP/DBP and heart rate, measured using the cuff-oscillometric method. HEM-70801C utilizes the same components and BP-determining algorithm as those of another device, HEM-705IT, which was previously approved the criteria of the British Hypertension Society protocol.²⁷

In accordance with the Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH 2019),²⁸ the target level of home BP control is under 125/75 mmHg in hypertensive patients with type2 DM. Participants were categorized into four groups based on home BP levels: normal home BP (morning SBP less than 125 mmHg and morning DBP less than 75 mmHg), IH-home SBP (morning SBP more than or equal to 125 mmHg and morning DBP less than 75 mmHg, isolated high home DBP (IH-home DBP) (morning SBP less than 125 mmHg and morning DBP more than or equal to 75 mmHg), and high home BP (morning SBP more than or equal to 125 mmHg and morning DBP more than or equal to 75 mmHg).²⁹

Statistical analysis

The characteristics of patients who participated in our study were reported as medians with interquartile ranges or numbers. Logistic regression analysis was used to assess the relationship between IH-home SBP, IH-home DBP, and high home BP, and the risk of diabetic nephropathy, with “normal home BP” set as a reference. The following factors were considered as covariates among the adjusted models: sex, body mass index (BMI), duration of diabetes, HbA1c levels, total cholesterol, creatinine, smoking status, Clinical SBP and use of antihypertensive drugs (Model 2). In addition, adjustments were carried out the use of renin-angiotensin-aldosterone system inhibitors instead of other antihypertensive drugs (Model 3).

Moreover, we performed subgroup analyses according to age (more than or equal to 65 years vs. less than 65 years) and the use of antihypertensive medications (with vs. without antihypertensive drugs). *Statistical significance was set at $p < 0.05$.* Statistical analyses had been performed using JMP version 13.2 software (SAS Institute Inc., Cary, NC, USA). Two-tailed t test were used to determine statistical significance.

Results

Patients with type 2 DM were recruited 1,372 in the study. They were aged 20–90 years. Excluded patients were 115

and 422 because of insufficient home BP and data of UACR, respectively. Additionally, 148 patients were excluded as they freshly prescribed angiotensin-converting-enzyme inhibitor (ACE-I) or ARB or stopped them during follow-up. And then, 423 patients were excluded, who were with normal and mildly increased albuminuria.

Finally, 264 patients with moderate or severe albuminuria included (Figure 1). During the observation period of 5 years, among 218 participants with moderately increased albuminuria, 44 patients showed improvement to normal or mildly increased albuminuria. Among 46 patients with severely increased albuminuria, 12 patients improved to moderately increased albuminuria, and 3 patients improved to normal or mildly increased albuminuria (Figure 2).

The mean of SBP among 218 participants with moderate increased albuminuria was 138.4mmHg, and the mean of SBP among 44 participants with severe increased albuminuria was 148.3mmHg.

Improvement of diabetic nephropathy was observed in 15 patients (34.1%) among normal home BP group, in 16 patients (17.6%) among IH-home SBP group, and 28

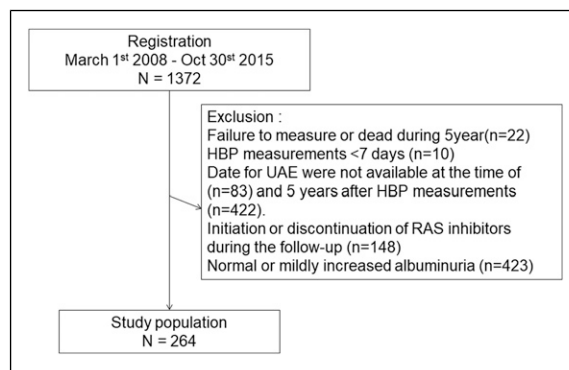


Figure 1. Flow diagram for the KAMOGAWA-HBP cohort.

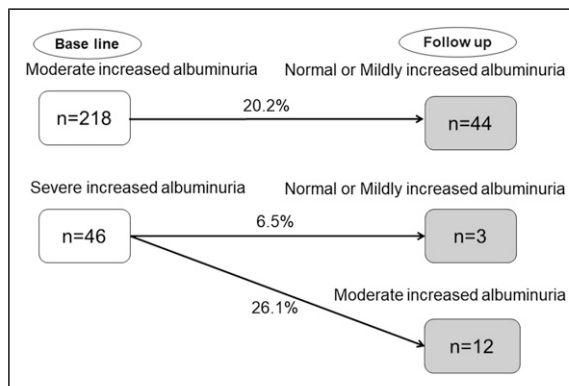


Figure 2. Transition of diabetic nephropathy remission or regression.

patients (22.4%) among high home BP group, respectively. In IH-home DBP group, there were no improvement of diabetic nephropathy.

Baseline number and clinical characteristics of the patients are shown in Table 1, which presented median (interquartile range) data. Age, diabetes duration, BMI, and

total cholesterol and HbA_{1c} were 67.0 (60.0–73.0) years, 11.0 (6.0–20.0) years, 24.1 (22.1–25.9) kg/m², 184 (164–210) mg/dL, and 6.8 (6.2–7.5) %, respectively. The unadjusted odds ratio (OR) with 95% confidence interval (CI) of normal home BP for improving diabetic nephropathy was 2.42 (1.06–5.53) using IH-home SBP as a reference

Table 1. Characteristics of patients.

Sex		
Male		147 (55.7)
Female		117 (44.3)
Age (y)		67.0 (60.0–73.0)
Duration of diabetes (y)		11.0 (6.0–20.0)
Body mass index (kg/m ²)		24.1 (22.1–25.9)
Mean morning systolic blood pressure (mmHg)		137.5 (128.1–151.3)
Mean morning diastolic blood pressure (mmHg)		74.5 (68.7–82.8)
Mean evening systolic blood pressure (mmHg)		133.1 (121.0–142.0)
Mean evening diastolic blood pressure (mmHg)		76.3 (67.8–85.0)
Clinic systolic blood pressure (mmHg)		140.8 (127.4–152.6)
Clinic diastolic blood pressure (mmHg)		76.3 (67.7–85.0)
Hemoglobin A _{1c} (%)		6.8 (6.2–7.5)
Hemoglobin A _{1c} (mmol/mol)		55 (48–90)
Total cholesterol (mg/dL)		184 (164–210)
Creatinine (mg/dL)		0.79 (0.61–0.93)
Smoking status		
Current smoker		55 (20.8)
Past smoker		79 (30.0)
Alcohol drinking		
everyday		69 (26.1)
Social		53 (20.1)
Diabetic complications		
Retinopathy		87 (33.0)
Neuropathy		101 (38.3)
Macrovascular complication		72 (27.3)
Use of antihypertensive medication		73 (27.7)
RAS (–/+)		93/171

For categorical variables, *n* (%) is presented. For continuous variables, median (interquartile range) is presented. RAS, renin-angiotensin-aldosterone system.

Table 2. Unadjusted and adjusted odds ratios for the remission or regression of diabetic nephropathy.

Hypertension status (<i>n</i>)	Model 1		* Model 2		* Model 3	
	Unadjusted OR (95%CI)	<i>p</i> value	Adjusted OR (95%CI)	<i>p</i> value	Adjusted OR (95%CI)	<i>p</i> value
Isolated high HSBP group (91)	1		1		1	
Normal HBP group (44)	2.42 (1.06–5.53)	0.035	2.52 (1.01–5.99)	0.05	2.52 (1.02–6.05)	0.05
High HBP group (125)	1		1		1	
Normal HBP group (44)	1.79 (0.84–3.80)	0.128	2.03 (0.78–5.17)	0.139	2.03 (0.80–5.15)	0.137

HBP, home blood pressure; HSBP, home systolic blood pressure.

*Model 2: Odds ratios were adjusted for sex, duration of diabetes mellitus, body mass index, hemoglobin A_{1c}, total cholesterol, creatinine, smoking status, Clinical SBP and use of antihypertensive medications.

*Model 3: Odds ratios were adjusted for variables in model 2 and additional adjustment for use of renin angiotensin system inhibitors instead of use of antihypertensive medications.

and 1.79 (0.84–3.80) using high home BP as a reference (Table 2). Multivariate adjusted OR (95% CI) for improving diabetic nephropathy of normal home BP was 2.52 (1.01–5.99, $p=0.05$) (Model 2), and 2.52 (1.02–6.05, $p=0.05$) in Model 3 using IH-home SBP as a reference (Table 2). Using high home BP as a reference, the adjusted OR (95% CI) given normal home BP of improving diabetic nephropathy was 2.03 (0.78–5.17, $p=0.139$) (Model 2), and 2.03 (0.80–5.15, $p=0.137$) in Model 3 (Table 2).

An adjusted OR (95% CI) using IH-home SBP as a reference for improving nephropathy of normal home BP was 1.99 (0.54–7.30) in sub-group analyses of age more than or equal to 65 years (Table 3); meanwhile, among age less than 65 years, an adjusted OR (95% CI) was 3.96 (0.64–24.5) (Table 3).

An adjusted OR (95% CI) using IH-home SBP as a reference for improving nephropathy of normal home BP was 2.86 (1.13–7.21) in sub-group analyses of diabetic nephropathy in patients with moderate increased

albuminuria (Table 4); meanwhile, among diabetic nephropathy in patients with severe increased albuminuria, an adjusted OR (95% CI) was 1.16 (0.20–12.69) (Table 4).

Discussion

Normal home BP was associated with improvement of albuminuria in type 2 diabetic patients during an observation period of 5 years.

A mechanism likely to account for the association between good SBP control and remission or regression of diabetic nephropathy has been described elsewhere.^{10–15} Inadequately controlled SBP at baseline may induce hemodynamic changes in patients with type 2.¹⁴ The pathogenesis of ISH is enrolled increased arterial stiffness.³⁰ Furthermore, arterial aging might result in an additional progression in IH-home SBP, which is a risk factor for target-organ damage³¹ and diabetic nephropathy.³² In type

Table 3. Unadjusted and adjusted odds ratios for the remission or regression of diabetic nephropathy in patients equal to or more than 65 years old and less than 65 years old.

Hypertension status	Model 1		* Model 2		* Model 3	
	Unadjusted OR (95%CI)	<i>p</i> value	Adjusted OR (95%CI)	<i>p</i> value	Adjusted OR (95%CI)	<i>p</i> value
≥65 years old						
Isolated high HSBP group	1		1		1	
Normal HBP group	1.99 (0.64–6.22)	0.240	1.99 (0.54–7.30)	0.300	2.08 (0.57–7.63)	0.267
< 65 years old						
Isolated high HSBP group	1		1		1	
Normal HBP group	3.56 (0.82–15.4)	0.090	3.96 (0.64–24.5)	0.139	3.13 (0.48–20.3)	0.232

HBP, home blood pressure; HSBP, home systolic blood pressure.

*Model 2: Odds ratios were adjusted for sex, duration of diabetes mellitus, body mass index, hemoglobin A_{1c}, total cholesterol, creatinine and use of antihypertensive medications.

*Model 3: Odds ratios were adjusted for variables in model 2 and additional adjustment for use of renin angiotensin system inhibitors instead of use of antihypertensive medications.

Table 4. Unadjusted and adjusted odds ratios for the remission or regression of diabetic nephropathy in patients with moderate increased albuminuria and in patients with severe increased albuminuria.

Hypertension status	Model 1		* Model 2		* Model 3	
	Unadjusted OR (95%CI)	<i>p</i> value	Adjusted OR (95%CI)	<i>p</i> value	Adjusted OR (95%CI)	<i>p</i> value
Patients with moderate increased albuminuria (218)						
Isolated high HSBP group	1		1		1	
Normal HBP group	2.86 (1.13–7.21)	0.03	3.16 (1.13–8.84)	0.03	3.18 (1.14–8.85)	0.03
Patients with severe increased albuminuria (46)						
Isolated high HSBP group	1		1		1	
Normal HBP group	1.6 (0.20–12.69)	0.657	2.21 (0.16–30.71)	0.55	2.2 (0.15–35.53)	0.57

HBP, home blood pressure; HSBP, home systolic blood pressure.

*Model 2: Odds ratios were adjusted for sex, duration of diabetes mellitus, body mass index, hemoglobin A_{1c}, total cholesterol, creatinine and use of antihypertensive medications.

*Model 3: Odds ratios were adjusted for variables in model 2 and additional adjustment for use of renin angiotensin system inhibitors instead of use of antihypertensive medications.

2 diabetes, an association between proteinuria and high BP is strictly related to a higher risk of cardiovascular disease.^{33,34} Appropriate management is of great importance for advanced type 2 diabetic nephropathy.³⁵ Therefore, home SBP should be adequately managed (less than 125 mmHg). In home BP management, it is important to clarify that maintaining normal home BP is important for improving nephropathy.

Normal home BP was associated with remission or regression of diabetic nephropathy in this study. The patients in the normal home BP group were younger than those in the IH- home SBP group (64 vs 70 years old, $p=0.001$). Arterial stiffness was higher among patients in the IH- home SBP group than in the normal home BP group (1958 vs 1738. m/s, $p=0.006$) if comparing arterial stiffness using baPWV measurements between the normal home BP and IH- home SBP groups.^{22,33} Thus, arterial aging in normal home BP was not advanced, which might be associated with the improvement in diabetic nephropathy.

ISH among young to middle-aged Japanese people is associated with the risk of premature cardiovascular deaths.³⁴ In the current study, age-stratified subgroup analysis revealed that the adjusted OR was higher among patients aged less than 65 years than in those aged more than or equal to 65 years. Meanwhile, subgroup analyses stratified by use of antihypertensive medications revealed that the adjusted ORs were the same in spite of the presence or absence of ARB/ACE-I. Participants using ARB/ACE-I are at a lower risk of diabetic nephropathy and more frequently experience remission or regression of diabetic nephropathy.¹⁰⁻¹⁵ However, remission or regression of diabetic nephropathy was shown less frequently in patients using ARB/ACE-I than in patients not using ARB/ACE-I (17.5% vs. 31.2%) in our study. It should be attention to patients in this group had higher SBP (142.6 vs 135.3 mmHg, $p < 0.01$) than patients without ARB/ACE-I. Furthermore, they had a longer duration of diabetes (15.0 vs 13.0 years, $p < 0.01$) and poorer estimated glomerular filtration rate (69.1 vs 74.7 ml/min/1.73m², $p < 0.01$). To summarize these results, patients with ARB/ACE-I had remarkable hypertension and developed atherosclerosis and diabetic nephropathy, which consequently counteracted the effectiveness of ARB/ACE-I.

This is the first study to evaluate the impact of normal home BP in improving diabetic nephropathy among type 2 diabetic patients over the medium to long term compared with IH-home SBP to the best of our belief. These results support and strengthen previous reports. In addition, the importance of intensive home BP management among younger patients with diabetes was elucidated through an observation period of 5 years.

Despite, there are some considerable limitations in interpreting the findings. First, data on daily salt intake, protein intake, or exercise intensity, which would be

associated with diabetic nephropathy progression, were lack.^{35,36,37,38} We could not clearly identify the prognostic marker of home BP in the diabetic nephropathy progression even in a longer study in this regard. Second, the study included only Japanese people. Therefore, generalizability of these findings to other ethnic groups may not expect much. Third, we performed only a single baseline BP measurement. This would have resulted in a latent bias. Nevertheless, the association between BP at baseline or during follow-up and target organ damage was confirmed.²⁸ If the addition of subsequent values did not notably change the results, single BP assessments might be reliable. Fourth, another important issue is the lack of ultrasound findings on kidneys at baseline, particularly the size of kidneys, which should be hypertrophic or enlarged before the development of moderately increased albuminuria. Finally, a non-albuminuric phenotype has been reported in diabetic kidney disease (DKD) of type 2 DM.³⁹ Therefore, many patients with type 2 DM, despite being normoalbuminuric if they have a glomerular filtration rate (GFR) of less than 60 ml/min/1.73m², still have DKD. In the present study, we did not include patients with a GFR less than 60 ml/min/1.73m². Thus, we were not able to evaluate the decline in renal function according to in the definition of DKD in this study. Further studies will be conducted in the future.

In conclusion, normal home BP in type 2 diabetic patients was a prognostic marker for the improvement of diabetic nephropathy in a prospective cohort study of 5 years.

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