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A difference in systolic blood pressure between arms is a novel predictor of the development and progression of diabetic nephropathy in patients with type 2 diabetes

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ABSTRACT

Objective: Recent studies have suggested that a difference in systolic blood pressure (SBP) between arms is associated with both vascular disease and mortality. The aim of this study was to investigate the relationship between a difference in SBP between arms and change in urinary albumin excretion or development of albuminuria in patients with type 2 diabetes.
Methods: We measured SBP in 408 consecutive patients with type 2 diabetes, and calculated a difference in SBP between arms. We performed follow-up study to assess change in urinary albumin excretion or development of albuminuria, mean interval of which was 4.6 ± 1.7 years. We then evaluated the relationship of a difference in SBP between arms to diabetic nephropathy using multiple regression analysis and multiple Cox regression model.
Results: Multiple regression analyses demonstrated that a difference in SBP between arms was independently associated with change in urinary albumin excretion ($\beta = 0.1869$, $P = 0.0010$). Adjusted Cox regression analyses demonstrated that a difference in SBP between arms was associated with an increased hazard of development of albuminuria; hazard ratio was 1.215 (95% confidence interval 1.077–1.376). Moreover, the risk of development of albuminuria was increased in patients with a difference in SBP of equal to or more than 10 mmHg between arms; hazard ratio was 4.168 (95% confidence interval 1.478–11.70).
Conclusion: A difference in SBP between arms could be a novel predictor of the development and progression of diabetic nephropathy in patients with type 2 diabetes.

1. Introduction

Cardiovascular disease (CVD) is the primary cause of mortality and morbidity in patients with type 2 diabetes, and several risk factors including smoking, hypertension and dyslipidemia have been shown to accelerate the progression of CVD [1,2]. Elevated albumin excretion rate, which is a useful marker for diabetic nephropathy, has been reported to be associated with increased risk of cardiovascular mortality, the progression of CVD [3,4] and all cause mortality [5].

We occasionally find a difference in blood pressure between arms in patients with type 2 diabetes [6], however, we dismiss it as a normal variant in general. Recent studies suggested that a difference in systolic blood pressure (SBP) between arms is associated with both vascular disease and mortality [7,8]. Although current diabetes guideline recognizes the need to control of hypertension for prevention of diabetic complication, a difference in blood pressure between arms is not featured [9]. We recently reported that a difference in SBP between arms is associated with albuminuria in a cross-sectional study [10]. However, a relationship between a difference in SBP and the progression or development of diabetic nephropathy has not been investigated. Therefore, we evaluated the relationship between a difference in SBP between arms and change in the urinary albumin excretion (UAE) or the development of albuminuria in patients with type 2 diabetes.

2. Methods

2.1. Patients and study design

We performed a retrospective cohort study in 408 patients recruited from the outpatient clinic at the Kyoto Prefectural

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University of Medicine from January 2006 to December 2012. Type 2 diabetes was diagnosed according to the Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus [11]. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Patients were classified as nonsmokers, past smokers, or current smokers according to a self-administered questionnaire. Nephropathy was graded as follows: normoalbuminuria, UAE less than 30 mg per gram of creatinine (mg/g Cr); microalbuminuria, 30–300 mg/g Cr; or macroalbuminuria, more than 300 mg/g Cr. Albuminuria was defined as UAE equal to or more than 30 mg/g Cr. Patients with advanced renal dysfunction (serum Cr more than 2.0 mg/dL; $n = 15$) or malignancy ($n = 7$) and patients with major cardiovascular event during a follow up ($n = 8$) were excluded from this study. Moreover, we excluded patients with newly prescribed angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker (ARB) during a follow up ($n = 62$) because antihypertensive drugs such as ARB could delay the development of albuminuria in patients with diabetes [12]. We then evaluated the relationship of a difference in SBP between arms to change in UAE in all patients ($n = 408$) and calculated the hazard ratio for development of albuminuria in patients with normoalbuminuria ($n = 256$). This study was approved by the local Research Ethics Committee and was conducted in accordance with the Declaration of Helsinki. Informed consent was obtained from all participants.

2.2. Measurement of blood pressure and data collection

Blood pressure was measured after allowing the patient to rest in the supine position for at least 5 min. One measurement was performed in each patient. Right and left blood pressure was measured using a simultaneous measurement technique. We measured blood pressure using a Colin Waveform Analyzer (from pulse wave velocity; Colin Medical Technology, Komaki, Japan) [13], which simultaneously measures pulse volumes in the brachial and ankle arteries together with bilateral arm and ankle blood pressure using an oscillometric method. A difference in SBP between arms was expressed as the absolute value of SBP of the right arm minus the left arm or of the left arm minus the right arm, whichever value is positive. Average SBP is the average of right and left blood pressure.

Overnight fasting blood and urine samples were taken in the morning at baseline. Serum total cholesterol and triglyceride concentrations were assessed using standard enzymatic methods. Hemoglobin A1c was assayed using high-performance liquid chromatography and expressed with the unit defined by the National Glycohemoglobin Standardization Program. Urinary albumin and Cr concentration were determined using an early morning spot urine samples. UAE was measured with an immunoturbidimetric assay. A mean value for UAE was determined from three urine collections. Change in UAE was calculated as follows; change in UAE = increase of UAE/follow up duration (year). Development of albuminuria was defined as UAE equal to or more than 30 mg/g Cr. As a follow-up study, we collected urine samples for calculation of UAE at the end of the follow-up.

2.3. Statistical analysis

The means and frequencies of potential confounding variables were calculated. Because triglycerides showed skewed distributions, log transformation was carried out before performing correlation and regression analysis. The relationships between a difference in SBP between arms and change in UAE as well as the relationships between a difference in SBP between arms and age or other variables were examined by Pearson's correlation analyses. To examine the effects of various factors on change in UAE or development of albuminuria defined as UAE equal to or more than 30 mg/g Cr, the following factors were considered simultaneously as independent variables for multiple regression analyses: age, sex, duration of diabetes, BMI, average SBP, a difference in SBP, hemoglobin A1c, total cholesterol, logarithm of triglycerides, uric acid, smoking status, antihypertensive drug and statin, or for multiple Cox regression model: age, sex, duration of diabetes, BMI, average SBP, a difference in SBP, hemoglobin A1c, total cholesterol, logarithm of triglyceride, uric acid, baseline UAE, smoking status, antihypertensive drug and statin. All continuous variables are presented as the mean ± standard deviation (SD) or absolute number. A P value <0.05 was considered statistically significant. The size, direction, and statistical significance of relationships were estimated by the hazard ratio with 95% confidence interval (CI).

3. Results

Characteristics of the 408 patients with type 2 diabetes enrolled in this study are shown in Table 1. Average difference in SBP between arms was 3.5 ± 3.2 mmHg. The average duration of follow up was 4.6 ± 1.7 years. Change in UAE was 20.6 ± 35.7 mg/g creatinine. There were 256 patients (62.7%) with normoalbuminuria at baseline. During the study period, 30 patients have developed albuminuria. A difference in SBP between arms positively correlated with age, BMI, average SBP, total cholesterol, logarithm of triglycerides or change in UAE, and no significant correlation was found between a difference in SBP between arms and duration of diabetes, hemoglobin A1c or serum uric acid level. Multiple regression analysis on change in UAE is shown in Table 2. Multiple regression analysis demonstrated that duration of diabetes, average SBP, a difference in SBP between arms or serum uric acid level was independently associated with change in UAE. Adjusted Cox regression analysis demonstrated that a difference in SBP between arms was associated with an increased hazard of development of albuminuria; hazard ratio of which was 1.215 (95% CI; 1.077–1.376) (Table 3). And, the risk of development of albuminuria was increased in patients with a difference in SBP of equal to or more

Table 1
Characteristics of patients.

n	408
Age (y)	66.0 (8.9)
Sex (male/female)	238/170
Duration of diabetes (y)	15.1 (10.4)
Body mass index (kg/m^2)	23.6 (3.7)
Average SBP (mmHg)	137.4 (18.9)
Average DBP (mmHg)	71.0 (9.9)
A difference in SBP between arms (mmHg)	3.5 (3.2)
A difference in DBP between arms (mmHg)	2.5 (2.1)
Hemoglobin A1c (%)	7.4 (1.4)
Total cholesterol (mmol/L)	4.8 (0.9)
Triglycerides (mmol/L)	1.5 (1.0)
Uric acid (μmol/L)	322.3 (83.9)
Creatinine (μmol/L)	72.9 (51.8)
Smoking (none/past/current)	285/71/52
Retinopathy (NDR/SDR/PDR)	282/58/68
Nephropathy (normo/micro/macroalbuminuria)	256/114/38
Antidiabetic treatment (diet/OHA/insulin)	40/311/128
Antihypertensive drug (calcium channel blocker/diuretic drug ACE inhibitor/ ARB/alpha blocker/beta blocker)	138/46/33/164/11/11
Statin (negative/positive)	210/198
Urinary albumin excretion (mg/g creatinine)	137.4 (722.5)

Data are expressed as mean (SD) or absolute number. SBP, systolic blood pressure; DBP, diastolic blood pressure; NDR, no diabetic retinopathy; SDR, simple diabetic retinopathy; PDR, proliferative diabetic retinopathy; OHA, oral hypoglycemic agent; ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker.