ORIGINAL ARTICLE

A difference in systolic blood pressure between arms and between lower limbs is a novel risk marker for diabetic nephropathy in patients with Type 2 diabetes

Hiroshi Okada, Michiaki Fukui, Muhei Tanaka, Shinobu Matsumoto, Yusuke Mineoka, Naoko Nakanishi, Mai Asano, Masahiro Yamazaki, Goji Hasegawa and Naoto Nakamura

Recent studies have demonstrated 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 between lower limbs and the degree of albuminuria, which is an established marker for cardiovascular disease and diabetic nephropathy in patients with Type 2 diabetes. We measured blood pressure in the arms and lower limbs of 314 consecutive patients with Type 2 diabetes, and we calculated a difference in SBP between arms and between lower limbs. We then evaluated the relationship of the difference in SBP between arms and between lower limbs to the degree of urinary albumin excretion (UAE). The average difference in SBP between arms and between lower limbs was 3.52 ± 3.94 and 9.66 ± 14.1 mm Hg, respectively. Multiple regression analyses demonstrated that a difference in SBP between arms ($\beta = 0.172$, $P = 0.0239$) and between lower limbs ($\beta = 0.238$, $P = 0.0033$) independently correlated with the logarithm of the UAE. Multiple logistic regression analyses showed that a difference in SBP of ≥ 10 mm Hg between arms (odds ratio 12.23 (95% CI 1.130–132.35), $P < 0.0393$) and a difference in SBP of ≥ 15 mm Hg between lower limbs (odds ratio 4.291 (95% CI 1.403–13.123), $P < 0.0106$) correlated with the risk of albuminuria. A difference in SBP between arms and between lower limbs, therefore, could be a novel risk marker for diabetic nephropathy in patients with Type 2 diabetes.

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INTRODUCTION

Cardiovascular disease 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 cardiovascular disease.^{1,2} Microalbuminuria is considered as a predictor of cardiovascular disease and a surrogate marker for early kidney damage among patients with both Type 2 diabetes and hypertension.^{3,4} Hypertension is known to accelerate the progression of microalbuminuria, but the most recent guidelines do not mention inter-arm blood pressure difference. Recently, research has suggested that a difference in SBP between arms is associated with vascular disease and mortality.⁵ However, a relationship between a difference in SBP and albuminuria has not been investigated. Therefore, we evaluated the relationship between a difference in SBP between arms and between lower limbs and the degree of the urinary albumin excretion (UAE) in patients with Type 2 diabetes.

METHODS

Patients and study design

We measured blood pressure in 314 consecutive patients with Type 2 diabetes recruited from the outpatient clinic at the Kyoto Prefectural University of Medicine. TYPE 2 diabetes was diagnosed according to the Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus.⁶ Body mass index was calculated as weight in kilograms divided by height in meters squared. Average SBP is the average of right and left limb blood pressures. Patients were classified as nonsmokers, past smokers and current smokers according to a self-administered questionnaire. Retinopathy was assessed by ophthalmoscope and was graded and placed within the following categories: no diabetic retinopathy, simple diabetic retinopathy and proliferative diabetic retinopathy. Nephropathy was graded as follows: normoalbuminuria, $\text{UAE} < 30 \text{ mg g}^{-1}$ of creatinine ($\text{mg g}^{-1} \text{Cr}$); microalbuminuria, $30\text{--}300 \text{ mg g}^{-1} \text{Cr}$; and macroalbuminuria, $> 300 \text{ mg g}^{-1} \text{Cr}$. Albuminuria was defined as $\text{UAE} \geq 30 \text{ mg g}^{-1} \text{Cr}$. Patients with advanced renal dysfunction (defined as serum $\text{Cr} > 2.0 \text{ mg dl}^{-1}$) or malignancy were excluded from this study. We then evaluated the relationship between a difference in SBP between arms and between lower limbs to the degree of UAE. This study was approved by the local Research Ethics Committee and was

Department of Endocrinology and Metabolism, Kyoto Prefectural University of Medicine, Graduate School of Medical Science, 465 Kajji-cho, Kawaramachi-Hirokoji, Kamigyo-ku, Kyoto 602-8566, Japan

Correspondence: Dr M Fukui, Department of Endocrinology and Metabolism, Kyoto Prefectural University of Medicine, Graduate School of Medical Science, 465 Kajji-cho, Kawaramachi-Hirokoji, Kamigyo-ku, Kyoto 602-8566, Japan.

E-mail: sayarinapm@hotmail.com

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conducted in accordance with the Declaration of Helsinki. Informed consent was obtained from all participants.

Data collection and measurements

Blood samples were collected in the morning. 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 concentrations were determined using early morning spot urine samples. UAE was measured with an immunoturbidimetric assay. A mean value for UAE was determined from three urine collections.

Measurement of blood pressure

Blood pressure was measured using a Colin Waveform Analyzer (form pulse wave velocity; Colin Medical Technology, Komaki, Japan), which simultaneously measures pulse volumes in the brachial and ankle arteries together with bilateral arm and ankle blood pressure using an oscillometric method. The results obtained from the analyzer corresponded to the highest pressure between the three ankle arteries. Blood pressure was measured after allowing the patient to rest in the supine position for at least 5 min. A difference in SBP between arms and between lower limbs was expressed as the absolute difference, and these differences were determined for each subject. We calculated the BP difference as the absolute value of right–left ($|\text{right} - \text{left}|$).

Statistical analysis

The means and frequencies of potential confounding variables were calculated. As triglycerides and UAE showed skewed distributions, log transformation was conducted before performing correlation and regression analyses. The correlation between a difference in SBP between arms and between lower limbs and logarithm of UAE (log UAE), as well as the correlation between a difference in SBP between arms and between lower limbs and age, glycemic control or other variables were examined by Pearson's correlation analyses. To examine the effects of various factors on log UAE or albuminuria defined as $\text{UAE} \geq 30 \text{ mg g}^{-1} \text{ Cr}$, the following factors were considered simultaneously as independent variables for multiple regression analyses or multiple logistic regression analyses: age, sex, duration of diabetes, body mass index, average SBP, a difference in SBP, hemoglobin A1c, total cholesterol, logarithm of triglycerides, serum uric acid, smoking status, and status of antihypertensive drug and statin therapy. All continuous variables are presented as the mean $\pm$ s.d. or absolute number. A *P*-value < 0.05 was considered statistically significant. The size, direction, and statistical significance of relationships were estimated by the odds ratio with 95% CIs.

RESULTS

Characteristics of the 314 patients with Type 2 diabetes enrolled in this study are shown in Table 1. The average difference in SBP between arms and between lower limbs was 3.52 ± 3.94 and 9.66 ± 14.1 mm Hg, respectively. The relationships between a difference in SBP between arms and between lower limbs and other variables are shown in Table 2. A difference in SBP between arms positively correlated with log UAE, and no significant correlations were found between a difference in SBP between arms and age, duration of diabetes, body mass index, average SBP, hemoglobin A1c, total cholesterol, logarithm of triglycerides or serum uric acid level. A difference in SBP between lower limbs positively correlated with age, duration of diabetes, logarithm of triglycerides, serum uric acid level or log UAE. Finally, no significant correlations were found between a difference in SBP between lower limbs and body mass index, average SBP, hemoglobin A1c or total cholesterol. Multiple regression analyses on log UAE are shown in Table 3. Multiple regression analyses demonstrated that duration of diabetes, average brachial SBP, a difference in SBP between arms, serum uric acid levels or the use or non-use of antihypertensive drugs independently correlated with

Table 1 Characteristics of patients

n	314
Age (years)	66.2 (8.5)
Sex (male/female)	193/121
Duration of diabetes (years)	14.6 (10.1)
Body mass index (kg m^{-2})	23.6 (3.7)
Average arms SBP (mm Hg)	135.4 (17.4)
Average arms DBP (mm Hg)	76.2 (9.9)
Average lower limbs SBP (mm Hg)	150.3 (24.5)
Average lower limbs DBP (mm Hg)	71.1 (10.4)
A difference in SBP between arms (mm Hg)	3.52 (3.94)
A difference in DBP between arms (mm Hg)	2.58 (2.25)
A difference in SBP between lower limbs (mm Hg)	9.66 (14.1)
A difference in DBP between lower limbs (mm Hg)	3.94 (5.63)
Hemoglobin A1c (%)	7.4 (1.5)
Total cholesterol (mmol l^{-1})	4.94 (0.83)
Triglycerides (mmol l^{-1})	1.53 (1.17)
Uric acid ($\mu\text{mol l}^{-1}$)	320.7 (91.6)
Creatinine ($\mu\text{mol l}^{-1}$)	73.3 (42.0)
Smoking (none/past/current)	233/54/27
Retinopathy (NDR/SDR/PDR)	223/36/55
Nephropathy (normo-/micro-/macroalbuminuria)	181/90/43
Antidiabetic treatment (diet/OHA/insulin)	39/173/102
Antihypertensive drug (–/+)	131/183
Statin (–/+)	166/148
Urinary albumin excretion (mg g^{-1} creatinine)	328.7 (1243.2)

Abbreviations: DBP, diastolic blood pressure; NDR, no diabetic retinopathy; OHA, oral hypoglycemic agent; PDR, proliferative diabetic retinopathy; SBP, systolic blood pressure; SDR, simple diabetic retinopathy.
Data are expressed as mean (s.d.) or absolute number.

Table 2 Correlation between a difference in systolic blood pressure and other variables

	Arms		Lower limbs	
	r	P	r	P
Age	0.028	0.6842	0.137	0.0445
Duration of diabetes	0.014	0.8358	0.143	0.0391
Body mass index	0.062	0.3702	0.073	0.2921
Average arms systolic blood pressure	0.051	0.4609	—	—
Average lower limbs systolic blood pressure	—	—	0.012	0.8587
Hemoglobin A1c	–0.026	0.7062	–0.009	0.8929
Total cholesterol	0.143	0.0563	0.072	0.3369
Logarithm of triglyceride	0.080	0.2429	0.135	0.0474
Uric acid	0.112	0.1443	0.160	0.0369
Logarithm of urinary albumin excretion	0.170	0.0142	0.311	< 0.0001

log UAE. In addition, a difference in SBP between lower limbs, serum uric acid levels or the use or non-use of antihypertensive drugs independently correlated with log UAE (Table 3). Multiple logistic regression analyses demonstrated that a difference in SBP ≥ 10 mm Hg between arms or a difference in SBP ≥ 15 mm Hg between lower limbs correlated with an increased risk of albuminuria (Table 4). The sensitivity and specificity of the difference in SBP between arms or between legs to predict albuminuria were 75.0% and 59.3% or 68.8 and 62.4%, respectively. The distributions for the inter-arm and inter-leg SBP differences are shown in Figures 1a and b,

respectively. We found a significant correlation between the inter-arm and inter-leg SBP differences ($r = 0.369$, $P < 0.0001$; Figure 2).

DISCUSSION

Although recent studies have found that a difference in SBP ≥ 10 mmHg between arms was associated with vascular disease and mortality,⁵ the relationships of a difference in SBP between arms and the degree of albuminuria, and a difference in SBP between lower limbs and the degree of albuminuria have not been investigated. Therefore, we evaluated the relationships between the difference in SBP between arms and between lower limbs and the degree of albuminuria in patients with Type 2 diabetes in this study. A positive correlation was found between a difference in SBP between arms and

between lower limbs and log UAE. Furthermore, a difference in SBP between arms and between lower limbs independently correlated with log UAE even after the adjustment for known risk factors for albuminuria including average SBP. A difference in SBP of ≥ 10 mmHg between arms or in SBP ≥ 15 mmHg between lower limbs correlated with a risk of albuminuria.

Table 3 Multiple regression analyses on logarithm of urinary albumin excretion

	Arms		Lower limbs	
	β	P	β	P
Age	0.068	0.4031	0.045	0.5885
Sex	0.044	0.6136	0.050	0.5679
Duration of diabetes	0.182	0.0298	0.159	0.0617
Body mass index	-0.088	0.3154	-0.104	0.2384
Average arms SBP	0.174	0.0234	—	—
Average lower limbs SBP	—	—	-0.015	0.8393
A difference in arms SBP	0.172	0.0239	—	—
A difference in lower limbs SBP	—	—	0.238	0.0033
Hemoglobin A1c	0.110	0.1952	0.126	0.1416
Total cholesterol	-0.080	0.3208	-0.071	0.3772
Logarithm of triglycerides	0.068	0.4168	0.056	0.5096
Uric acid	0.229	0.0076	0.232	0.0073
Smoking status	-0.009	0.9153	-0.035	0.6667
Antihypertensive drug	0.217	0.0078	0.222	0.0069
Statin	-0.035	0.6423	-0.024	0.7522

Abbreviation: SBP, systolic blood pressure.

Sex was defined as female (= 0) or male (= 1), smoking status was defined as nonsmoker (= 0), past smoker (= 1), or current smoker (= 2) and medication for hypertension or dyslipidemia was defined as without (= 0) or with (= 1).

Figure 1 The distributions for the inter-arm (a) and inter-leg (b) systolic blood pressure (SBP) difference (right-left).

Table 4 Multivariate adjusted odds ratios for albuminuria

	Odds ratio (95% CI)	P	Odds ratio (95% CI)	P
Age	1.030 (0.979–1.084)	0.2533	1.018 (0.968–1.071)	0.4840
Sex	1.726 (0.685–4.348)	0.2470	2.011 (0.786–5.142)	0.1446
Duration of diabetes	1.041 (0.997–1.087)	0.0706	1.035 (0.991–1.081)	0.1208
Body mass index	0.933 (0.813–1.070)	0.3193	0.922 (0.808–1.053)	0.2309
Average arms SBP	1.013 (0.986–1.040)	0.3580	—	—
Average lower limbs SBP	—	—	0.997 (0.970–1.024)	0.8281
A difference in arms SBP ≥ 10 mmHg	12.23 (1.130–132.35)	0.0393	—	—
A difference in lower limbs SBP ≥ 15 mmHg	—	—	4.291 (1.403–13.123)	0.0106
Hemoglobin A1c	1.241 (0.854–1.803)	0.2572	1.398 (0.977–1.999)	0.0666
Total cholesterol	0.989 (0.976–1.002)	0.0984	0.992 (0.979–1.004)	0.1973
Logarithm of triglycerides	3.094 (0.471–20.332)	0.2397	3.500 (0.511–23.953)	0.2017
Uric acid	1.175 (0.886–1.557)	0.2626	1.118 (0.836–1.496)	0.4526
Smoking status	1.255 (0.629–2.503)	0.5190	1.120 (0.559–2.244)	0.7498
Antihypertensive drug	3.226 (1.341–7.762)	0.0089	2.953 (1.237–7.048)	0.0147
Statin	0.784 (0.355–1.731)	0.5462	0.803 (0.363–1.777)	0.5883

Abbreviation: SBP, systolic blood pressure.

Sex was defined as female (= 0) or male (= 1), smoking status was defined as nonsmoker (= 0), past smoker (= 1), or current smoker (= 2) and medication for hypertension or dyslipidemia was defined as without (= 0) or with (= 1).

Figure 2 Correlation between the inter-arm and inter-leg systolic blood pressure (SBP) difference.

We assessed another correlation between a difference in SBP between lower limbs and markers of atherosclerosis such as ankle brachial index and pulse wave velocity. A difference in SBP between lower limbs inversely correlated with ankle brachial index ($r = -0.482$, $P < 0.0001$), whereas a difference in SBP between lower limbs positively correlated with pulse wave velocity ($r = 0.256$, $P = 0.0002$). We also assessed the rates of albuminuria in four groups: a difference in SBP between arms of < 10 mm Hg and in SBP between lower limbs of < 15 mm Hg; < 10 mm Hg and ≥ 15 mm Hg; ≥ 10 mm Hg and < 15 mm Hg; and ≥ 10 mm Hg and SBP ≥ 15 mm Hg. The resulting albuminuria rates were 36.2% (92 of 254), 65.9% (29 of 44), 66.7% (8 of 12) and 100% (4 of 4), respectively, and we found a significant difference between four groups using the χ^2 -test ($P = 0.0002$).

It has long been recognized that hypertension or variability of SBP affects the progression of cardiovascular disease and renal damage.^{7–10} However, a difference in SBP between arms has historically been dismissed as a normal variant.⁷ O'Shea *et al.*¹¹ proposed an anatomical explanation with regard to a difference in SBP between arms. Frank *et al.*¹² suggested that normal anatomy alone cannot explain the higher left-arm pressures. A difference in SBP between arms has been described as a sign of aortic aneurysm or vascular disease; however, the earliest report dismissed the import of this difference as negligible.⁷ Orme *et al.*¹³ suggested that the prevalence of a difference in SBP between arms was significantly higher in patients with coronary artery disease compared with patients without coronary artery disease. In addition, an asymmetrical atheromatous narrowing of the subclavian or brachial arteries may be related to a large difference in SBP between arms.¹⁴ Moll *et al.*¹⁵ proposed that 83% of patients with a difference in SBP between arms had evidence of innominate or subclavian artery stenosis and Aboyans *et al.*¹⁶ reported that subclavian artery stenosis was significantly associated with peripheral artery disease (PAD), the common carotid artery intima-media thickness and the coronary artery calcium score. Clark *et al.*¹⁷ suggested that a difference in SBP between arms may be a marker of PAD. Thus, there is some evidence to support the association of a difference in SBP between arms with PAD. It is well known that PAD is associated with renal damage; Norgren *et al.*¹⁸ reported that 23–42% patients with PAD have renal artery stenosis of 50% or greater, and the management of patients with PAD should be

focused on the preservation of renal function. We also evaluated the relationship between ankle brachial index and albuminuria. We found a statistically significant negative correlation between ankle brachial index and log UAE ($r = -0.223$, $P = 0.0012$), which confirmed the possibility that there was a positive correlation between PAD and albuminuria.

We have many patients who have a difference in BP between arms and between lower limbs. In general, however, little attention is paid to a difference in SBP between arms and between lower limbs as a risk marker for diabetic nephropathy. Therefore, if our hypothesis is correct, it is important to clarify the role of a difference in BP between arms and between lower limbs in the progression of diabetic nephropathy. Although some studies have shown a correlation between a difference in SBP between arms and vascular disease or mortality, to the best of our knowledge, this is the first study to investigate the relationship between a difference in SBP between arms and between lower limbs and degree of UAE in patients with Type 2 diabetes.

The major strength of our study is the use of a simultaneous measurement technique to measure blood pressure. A recent meta-analysis has suggested that a simultaneous, automated, repeated measurement method is ideal because it prevents the erroneous diagnosis of a BP difference because of short-term fluctuations between measurements and also avoids intra-observer bias.^{19,20}

There are some limitations to our study. First, our cross-sectional data do not show the precise demonstration of a cause-effect nature of the relationship. Second, results in this study may not be applicable to the general population or to the patients with diabetes in a primary care clinic because the patients in this study were selected from the university hospital. Finally, we were unable to determine the SBP difference between the same ankle arteries because we used the oscillometric method rather than the doppler. Large, prospective trials, as well as another population study including patients with both Type 1 and Type 2 diabetes, are needed to better assess the relationship between a difference in BP between arms and between lower limbs and the degree of UAE in patients with diabetes.

CONCLUSION

In summary, a difference in SBP between arms and between lower limbs could be a novel risk marker for diabetic nephropathy in patients with Type 2 diabetes.

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