Original Article

Pulse Pressure and Chronic Kidney Disease in Patients with Type 2 Diabetes

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To determine the association between both age and degree of albuminuria and pulse pressure in patients with type 2 diabetes, we conducted this study consisting of two cross-sectional observations. A total of 833 ambulatory and 107 hospitalized type 2 diabetic patients with serum creatinine <2.00 mg/dl were studied. Systolic blood pressure (SBP), diastolic blood pressure (DBP), and pulse pressure (PP) were compared among ambulatory patients stratified according to the degree of albuminuria, as well as according to age at 10-year intervals. In the hospitalized patients, 24-h blood pressure was monitored, and 24-h SBP, DBP, and PP were correlated with aortic pulse wave velocity (PWV) and mean intima-media thickness (IMT) of the carotid arteries. In the ambulatory patients, SBP and PP were greater in patients with microalbuminuria and clinical albuminuria, as well as in the older groups, whereas DBP tended to be lower in the older age groups. Multiple regression analysis adjusted for covariates including age indicated that increased albuminuria was independently associated with greater PP (p<0.001). In the hospitalized patients, stepwise increases were observed in SBP and PP (daytime, nighttime and overall 24-h), but not in DBP, in microalbuminuric and albuminuric patients. SBP and PP were positively and DBP was negatively associated with aortic PWV; however, no association was found with IMT. In conclusion, PP is closely associated with higher age, degree of albuminuria, and large artery stiffness in patients with type 2 diabetes. (*Hypertens Res* 2006; 29: 345–352)

***Key Words*: diabetic nephropathy, pulse pressure, arterial stiffness**

Introduction

Pulse pressure (PP), the difference between the systolic and diastolic blood pressures (SBP/DBP), has recently emerged as a potentially independent risk factor for cardiovascular disease in individuals with and without diabetes (*1–4*). Widened PP is an indicator of increased stiffness of the large arteries, which is frequently associated with diabetes (*5–7*). In individuals with type 1 diabetes, age-associated increases in PP were more pronounced than in subjects without diabetes (*8*). On the other hand, information is scarce concerning age-related alterations in the blood pressure patterns of patients with type 2 diabetes (*9*). In addition, although chronic kidney disease or albuminuria is also associated with arterial stiffness (*6*, *7*, *10*, *11*), the relationship between progression of kidney disease and PP in patients with diabetes is unknown.

To address these issues, we conducted this study consisting of two cross-sectional observations. First, we determined associations between both age and degree of albuminuria and blood pressure variables in a large-scale population with type 2 diabetes. Second, in a small portion of patients with type 2 diabetes, blood pressure variables determined during 24-h, in-center monitoring were compared with the degree of albuminuria. We also sought to quantify the association between these variables and clinical indices of arterial stiffness.

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Table 1. Clinical Characteristics of 833 Ambulatory Patients with Type 2 Diabetes Classified According to the Stage of Kidney Disease

	Stage of nephropathy		
	Normoalbuminuria (n=611)	Microalbuminuria (n=154)	Clinical albuminuria (n=68)
Age (years)	55±13	59±12[†]	58±13
Men (%)	67.6	64.9	66.2
BMI (kg/m^2)	24.1±3.9	24.4±4.1	23.5±4.4
Diabetes duration (years)[a]	2.3 (0.2–8.3)	4.9 (0.8–11.0)[†]	10.4 (5.0–19.4)[†,‡]
HbA_{1C} (%)	8.1±2.0	8.5±1.9	8.5±2.3
Serum Cr (mg/dl)	0.93±0.18	0.94±0.18	1.23±0.42[†,‡]
GFR (ml/min/1.73 m^2)	75.3±15.4	73.0±14.9	59.3±19.0[†,‡]
Urine ACR (mg/g Cr)[b]	7.1 (4.4–12.5)	73.2 (46.1–129.3)[†]	799.6 (489.8–1,934.8)[†,‡]
Medication for diabetes (%)			
None	57.1	42.9	20.6*
Oral medication	11.1	12.3	33.8*
Insulin	31.8	44.8	45.6*
Antihypertensive medications (%)			
None	80.9	62.9	44.8*
ACEI	5.9	12.6	25.4*
ARB	0.7	0.7	4.5*
CCB	13.7	31.8	31.3*
β-Blockers	3.0	3.3	6.0
Diuretics	3.0	2.0	11.9*
Others	1.2	3.3	13.4*
Any antihypertensives	19.1	37.1	55.2*

Data are expressed as mean±SD, percent of patients, [a]median (interquartile range), and [b]geometric mean (95% confidence interval). BMI, body mass index; GFR, glomerular filtration rate; ACR, albumin-to-creatinine ratio; Cr, creatinine; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; CCB, calcium-channel blockers. [†]$p<0.05$ *vs.* normoalbuminuria, [‡]$p<0.05$ *vs.* microalbuminuria by Tukey's studentized range test, *$p<0.05$ by Cochran-Armitage trend test.

Methods

Study Population

The cross-sectional study comparing blood pressure in ambulatory patients included Japanese individuals with type 2 diabetes, 20 years or older, who were consecutively referred to the outpatient clinic of the Department of Medicine, Diabetes Center, Tokyo Women's Medical University Hospital in Tokyo, Japan during 1999. Type 2 diabetes was diagnosed according to the criteria of the World Health Organization definition (*12*). Patients with serum creatinine concentrations equal to or higher than 2.00 mg/dl were excluded.

To compare 24-h ambulatory blood pressure among patients stratified by degree of albuminuria, adults with type 2 diabetes were recruited from hospitalized patients who were admitted to the Department of Medicine, Diabetes Center, Tokyo Women's Medical University Hospital for the purpose of glycemic control and evaluation of diabetic complications between April 2001 and May 2002.

The study protocol was designed in adherence to the declaration of Helsinki and informed consent was obtained from all subjects.

Blood Pressure Measurement

After the first visit, ambulatory patients underwent regular medical check-ups, separated by intervals of at least 14 days. Blood pressure was measured at each visit, while the subject was seated, using an oscillometric Omron HEM-707 device (Omron Inc., Kyoto, Japan). Three components of blood pressure, SBP, DBP, and PP were averaged from at least three and up to five visits. In patients who had been treated with antihypertensives, the medications were continued throughout the study period.

For hospitalized patients, blood pressure was recorded over a 24-h period with the use of properly validated monitors (*13*) and without withdrawal of antihypertensive medications in cases in which they were being taken. Fixed-clock intervals were used, defining daytime as 800 to 2200 h and nighttime as 2200 to 800 h. Blood pressure was recorded every 30 min during the daytime and every 60 min during the nighttime.

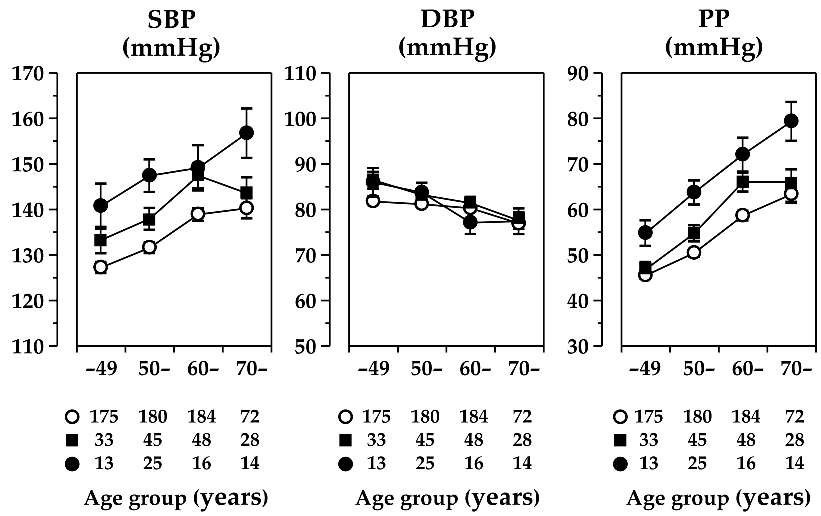

Fig. 1. *Comparison of systolic blood pressure (SBP, left), diastolic blood pressure (DBP, middle), and pulse pressure (PP, right) in patients with type 2 diabetes stratified by age and stage of kidney disease. The three blood pressure components were adjusted for gender, body mass index, diabetes duration, HbA_{1C}, and the use of any type of antihypertensive medication using ANCOVA, and expressed as the mean±SEM. Open circles, closed squares, and closed circles denote patients with normoalbuminuria, microalbuminuria, and clinical albuminuria, respectively. Numbers of patients stratified by age and degree of albuminuria are indicated.*

Measurement of Albuminuria and Estimation of Glomerular Filtration Rate

Classification of the degree of urine albumin excretion was assessed according to the American Diabetes Association (ADA) criteria, on the basis of the albumin-to-creatinine ratio (ACR) in the first-morning urine specimen (*14*). ACR was calculated from urinary albumin and creatinine concentrations, determined using latex agglutination and Jaffe's method. Subjects were classified into one of the following three categories: 1) normoalbuminuria if ACR was less than 30 mg/g creatinine; 2) microalbuminuria if ACR was 30–299 mg/g creatinine; and 3) clinical albuminuria if ACR was equal to or greater than 300 mg/g creatinine.

Serum creatinine was measured by Jaffe's method. Glomerular filtration rate (GFR) was estimated using the following equation, originating from the Modification of Diet in Renal Disease (MDRD) Study group (*15*), and refitted for Japanese individuals, as recently proposed by the Working Group of Japan Chronic Kidney Disease Initiative (JCKDI):

$$\mathrm{GFR} = 186 \times \mathrm{SCr}^{-1.154} \times \mathrm{Age}^{-0.203} \times 0.742\ (\text{if female}) \times 0.881,$$

where SCr, serum creatinine (unpublished).

Measurements of Arterial Stiffness and Arterial Wall Thickness

Aortic pulse wave velocity (PWV), as an index of aortic stiffness and a possible risk factor for atherosclerosis (*16*), was measured using a pulse wave velocimeter (model PWV-200; Fukuda Denshi, Tokyo, Japan) as described elsewhere (*17*). Intima-media thickness (IMT) of the carotid arteries, a validated marker of generalized atherosclerosis, was determined by ultrasonographical B-mode imaging of the carotid artery performed using a high resolution real-time ultrasonograph with a 12-MHz in-line Sectascanner (SSA-390A; Toshiba, Tokyo, Japan). For each patient, three longitudinal measurements were performed on the bilateral carotid arteries and the averaged values were considered for analysis. All measurements were made during the hospital stay by the same examiner under blind conditions.

Statistical Analyses

Data were expressed as the arithmetic mean±SD, geometric mean and 95% confidence interval (CI), or median and interquartile range, as appropriate according to data distribution. Numerical data were compared using one-way analysis of variance (ANOVA) followed by multiple comparison by Tukey's studentized range test. Data were also compared by means of analysis of covariance (ANCOVA) adjusting for covariates, and were expressed as the adjusted mean±SEM. Categorical data were compared by Fisher's exact probability test. Trends in the frequency among groups were examined by the Cochran-Armitage trend test. In univariate correlation analyses, Spearman's correlation coefficients (r_s) were calculated. Multiple regression analysis with a stepwise selection procedure was utilized to identify factors affecting blood pressure components. All statistical analyses were performed

Table 2. Results of Multiple Regression Analyses with Stepwise Variable Selection to Determine Potent Factors Associated with Each Blood Pressure Component in 833 Ambulatory Patients with Type 2 Diabetes

Dependent variable	Independent variable	Parameter estimate	Standard error	p value	Standarzized parameter estimate	r^2
Systolic blood pressure (mmHg)	Intercept	95.378	5.936	<0.001	0.000	0.284
	Age (years)	0.332	0.048	<0.001	0.223	
	Sex (man=1, woman=0)	−4.610	1.253	<0.001	−0.118	
	BMI (kg/m^2)	1.071	0.150	<0.001	0.220	
	log [ACR (mg/g Cr)]	7.099	0.875	<0.001	0.253	
	HbA_{1C} (%)	−1.349	0.299	<0.001	−0.138	
	Antihypertensive medication (yes=1, no=0)	7.204	1.459	<0.001	0.160	
Diastolic blood pressure (mmHg)	Intercept	65.351	2.643	<0.001	0.000	0.170
	Diabetes duration (years)	−0.255	0.048	<0.001	−1.784	
	BMI (kg/m^2)	0.825	0.086	<0.001	0.315	
	log [ACR (mg/g Cr)]	1.796	0.505	<0.001	0.119	
	HbA_{1C} (%)	−0.603	0.169	<0.001	−1.151	
Pulse pressure (mmHg)	Intercept	26.944	4.315	<0.001	0.000	0.375
	Age (years)	0.392	0.036	<0.001	0.339	
	Sex (man=1, woman=0)	−5.456	0.912	<0.001	−0.169	
	Diabetes duration (years)	0.166	0.063	0.008	0.080	
	BMI (kg/m^2)	0.271	0.110	0.014	0.071	
	log [ACR (mg/g Cr)]	5.624	0.655	<0.001	0.258	
	HbA_{1C} (%)	−0.715	0.217	<0.001	−0.094	
	Antihypertensive medication (yes=1, no=0)	5.553	1.061	<0.001	0.158	

BMI, body mass index; ACR, albumin-to-creatinine ratio; Cr, creatinine.

using the Statistical Analysis System (SAS Institute, Cary, USA) version 9.13. A p value less than 0.05 was considered significant.

Results

Comparison of Blood Pressure in Ambulatory Patients with Type 2 Diabetes by Age and Degree of Albuminuria

A total of 833 ambulatory individuals, 275 women and 558 men, with type 2 diabetes were studied. Mean±SD age was 56±13 years (range: 20–85 years). A majority of patients (611) were normoalbuminuric, and 154 and 68 patients were classified as having microalbuminuria and clinical albuminuria, respectively (Table 1). Patients with microalbuminuria were significantly older than those with normoalbuminuria; the gender ratio and body mass index (BMI) were comparable among the three groups. Patients with clinical albuminuria were more likely to be treated with medications for both diabetes and hypertension than those with normo- and microalbuminuria.

Blood pressure was measured on at least three occasions (4.8 occasions on average). SBP, DBP, and PP were compared among the following age intervals: less than 50 years (N=221), 50–59 years (N=250), 60–69 years (N=248), and 70 years or older (N=114), as well as according to the degree of albuminuria, using ANCOVA, adjusting for gender, BMI, diabetes duration, HbA_{1C}, and the use of any type of antihypertensive medication as confounding factors. As shown in Fig. 1, the adjusted mean SBP was higher in the older age-groups, as well as in patients with microalbuminuria and albuminuria, with statistically significant differences among all age groups ($p<0.05$ except for 60–69 years *vs*. 70 years or older [$p=0.999$]) and degrees of albuminuria ($p<0.001$) by ANCOVA. No significant differences were observed in adjusted mean DBP in patients with microalbuminuria and albuminuria, except for a significantly higher DBP in microalbuminuric than normoalbuminuric patients ($p=0.032$). DBP tended to be lower in the older age-groups; adjusted DBP was significantly lower in patients 70 years or older than those less than 50 years ($p=0.001$) and 50–59 years ($p=0.003$). The adjusted mean PP was markedly higher in older age-groups for all levels of albuminuria ($p<0.001$ except for 60–69 years *vs*. 70 years or older [$p=0.165$]). PP was also significantly greater for all age groups with clinical albuminuria than those with normoalbuminuria and/or microalbuminuria ($p<0.001$).

Table 3. Clinical Characteristics of 110 Hospitalized Patients with Type 2 Diabetes Classified by the Stage of Nephropathy

	Stage of nephropathy		
	Normoalbuminuria (n=60)	Microalbuminuria (n=27)	Macroalbuminuria (n=23)
Age (years)	61±12	63±11	61±11
Men (%)	55.0	48.2	82.6
BMI (kg/m^2)	24.6±3.3	23.8±3.6	24.9±4.4
Diabetes duration (years)[a]	6.3 (5.7–6.9)	6.4 (5.9–6.8)	6.6 (6.0–7.2)
HbA_{1C} (%)	9.0±1.9	8.2±7.9	7.9±1.9[†]
Serum Cr (mg/dl)	0.91±0.18	0.99±0.30	1.29±0.37[†,‡]
GFR (ml/min/1.73 m^2)	71.8±14.6	66.6±18.3	55.2±16.0[†,‡]
Urine ACR (mg/g Cr)[b]	7.7 (6.5–9.0)	74.6 (56.0–99.5)[†]	830.5 (629.3–1,096.0)[†,‡]
Medications for diabetes (%)			
None	25.0	14.8	4.3
Oral medication	36.6	29.7	21.8
Insulin	38.4	55.5	73.9
Antihypertensives (%)			
None	51.7	3.7	8.7*
ACEI	21.7	40.7	65.2*
ARB	3.3	40.7	21.7*
CCB	41.7	59.3	56.5
β-Blockers	10.0	14.8	4.4
Others	0.0	7.4	0.0
Any antihypertensives	48.3	96.3	91.3*

Data are expressed as mean±SD, percent of patients, [a]median (interquartile range), and [b]geometric mean (95% confidence interval). BMI, body mass index; GFR, glomerular filtration rate; ACR, albumin-to-creatinine ratio; Cr, creatinine; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; CCB, calcium-channel blockers. [†]$p<0.05$ *vs*. normoalbuminuria, [‡]$p<0.05$ *vs*. microalbuminuria by Tukey's studentized range test, *$p<0.05$ by Cochran-Armitage trend test.

Age-related changes in blood pressure variables in diabetic patients stratified by the degree of albuminuria and with the parameter estimates (±SEM) of age as an independent variable were determined using multiple regression analysis. In patients with normoalbuminuria, microalbuminuria, and clinical albuminuria, the 10-year increments in age were associated with an increase in SBP of 3.5±0.5 ($p<0.001$), 3.7±1.6 ($p<0.001$), and 2.0±1.4 mmHg ($p<0.001$), respectively. DBP decreased by 0.3±0.3 ($p=0.369$), 1.3±0.8 ($p=0.105$), and 3.0±1.0 mmHg ($p=0.005$), respectively, per 10-year age increment; and PP increased by 3.6±0.4 ($p<0.001$), 5.1±1.0 ($p<0.001$), and 4.9±1.3 mmHg ($p<0.001$), respectively, per 10-year age increment.

To determine factors associated with blood pressure, multiple regression analyses were conducted for the 833 ambulatory patients. In a model using each blood pressure variable as a dependent variable, age, sex, diabetes duration, BMI, HbA_{1C}, logarithmically transformed urinary ACR, estimated GFR, and administration of any type of antihypertensive medication were incorporated as explanatory variables, which were selected using a stepwise variable selection method. As summarized in Table 2, urinary ACR was selected as a predictive variable for increase in all three blood pressure variables. Estimated GFR was not included in either model as a statistically significant variable. Associations of other variables are listed in Table 2.

Comparison of 24-h Ambulatory Blood Pressure in Hospitalized Patients with Type 2 Diabetes by the Degree of Albuminuria

Twenty-four-hour blood pressure monitoring was performed for 110 subjects with type 2 diabetes (45 women and 65 men; mean age: 61±11 years). Among these patients, 60 were normoalbuminuric, 27 were microalbuminuric, and the other 23 had clinical albuminuria. Demographic and laboratory data classified according to urinary ACR are summarized in Table 3. Mean age, proportion of gender, and BMI were not significantly different among the three groups; HbA_{1C} values in patients with clinical albuminuria were significantly lower than those in patients with normoalbuminuria.

As illustrated in Fig. 2, both SBP and PP, adjusted for covariates, in daytime, nighttime, and overall 24-h, were significantly higher in patients with microalbuminuria and clinical albuminuria. On the other hand, there were no differences in adjusted DBP throughout the day.

Finally, association of 24-h blood pressure with aortic PWV or mean IMT of the carotid arteries was evaluated. In

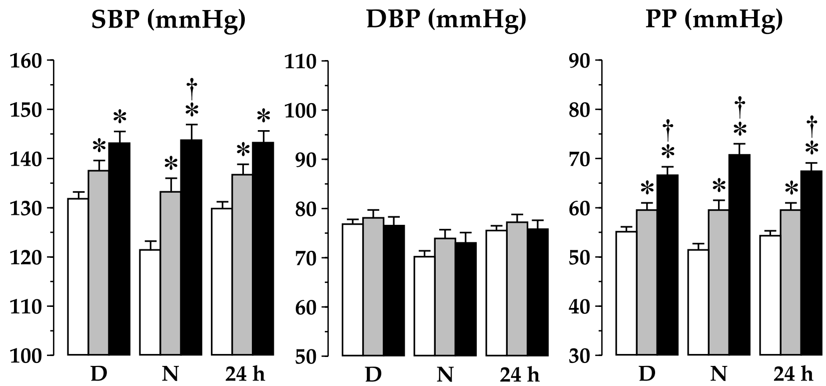

Fig. 2. *Comparison of systolic blood pressure (SBP, left), diastolic blood pressure (DBP, middle), and pulse pressure (PP, right) in patients with type 2 diabetes during daytime (D), nighttime (N), and 24-h. The blood pressure components were adjusted for gender, body mass index, diabetes duration, HbA_{1C}, and the use of any type of antihypertensive medication using ANCOVA, and expressed as the mean±SEM. White, gray, and black bars indicate patients with normoalbuminuria, microalbuminuria, and clinical albuminuria, respectively.* *$p<0.05$ vs. *microalbuminuria,* †$p<0.05$ vs. *clinical albuminuria.*

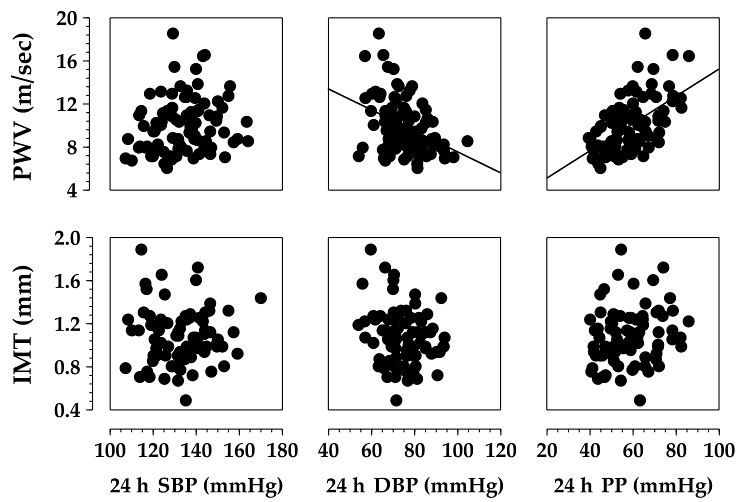

Fig. 3. *Simple correlation analysis between aortic PWV or carotid artery IMT and average 24-h systolic blood pressure (SBP), diastolic blood pressure (DBP), and pulse pressure (PP) in patients with type 2 diabetes.*

univariate correlation analyses, 24-h DBP was negatively ($r_s=-0.386$, $p<0.001$) and PP was positively ($r_s=0.565$, $p<0.001$) correlated with aortic PWV (Fig. 3). Twenty-four-hour SBP was weakly correlated with PWV with marginal significance ($r_s=0.194$, $p=0.063$). Although IMT showed a tendency similar to PWV, Spearman's correlation coefficients of SBP (0.014, $p=0.905$), DBP (−0.214, $p=0.057$) and PP (0.188, $p=0.094$) *vs*. IMT were not statistically significant. Multiple regression analyses demonstrated a significantly positive relationship between both SBP and PP, and aortic PWV, and an inverse relationship between DBP and aortic PWV, with parameter estimates (±SEM) of 0.071±0.020 ($p<0.001$) for SBP, 0.073±0.020 ($p<0.001$) for PP, and −0.067±0.023 ($p=0.004$) for DBP. No associations were found between carotid artery IMT and any of the three blood pressure variables.

Discussion

In this large scale cross-sectional study of Japanese patients with type 2 diabetes, we demonstrated that SBP was significantly greater in patients with microalbuminuria and clinical albuminuria, particularly among the older age-groups, whereas DBP tended to decrease with age. As a result, a striking relationship was found between PP, age, and the degree of albuminuria in type 2 diabetic patients in this study. This association between elevated PP and the level of albuminuria was confirmed in an analysis of hospitalized patients using

24-h blood pressure monitoring. We also found a close relationship between PP and aortic PWV, as a measure of large artery stiffness, but not between PP and IMT of the carotid arteries.

There has been rapidly growing interest in the relationship between chronic kidney disease and the risk of cardiovascular disease (*10*, *18*, *19*). The pathogenesis of cardiovascular diseases in patients with chronic kidney disease is multifactorial, and hypertension has been the single factor most frequently linked to progression of kidney disease. Although elevated SBP has long been accepted as a significant and independent risk factor for cardiovascular diseases in diabetic patients, PP is now receiving greater interest as a prognostic factor. In a recent case-control study involving almost 3,000 type 1 diabetic patients from Finland, the age-related rise in PP was most pronounced in patients with diabetic nephropathy, and PP was associated with age, male sex, duration of diabetes, and albuminuria (*8*). Our study extended these observations to type 2 diabetes, and suggests that elevated PP may be a marker of arterial aging or contribute to the pathogenesis of cardiovascular disease in these patients.

Increased PP arises from an interaction between cardiac stroke volume and the compliance of large conduit arteries. High cardiac output may widen PP; however, there has been no evidence of an increased stroke volume in diabetic compared to non-diabetic subjects (*20*) or in diabetic patients with clinical albuminuria compared to those with normo- and microalbuminuria (*21*). In addition, aging is associated with decreased stroke volume (*22*). Taken together, these observations suggest that decreased large artery compliance may be responsible for the greater PP in diabetic patients with nephropathy. Supporting this hypothesis are our findings of a strong and positive correlation between PP and aortic PWV (Fig. 3), which was also confirmed in the multiple regression analysis. In another recent study, PWV was also shown to be increased in diabetic patients with microalbuminuria, compared to diabetic patients with normoalbuminuria (*7*). A stepwise increase in arterial stiffness with increasing stages of chronic kidney disease has been also been reported recently (*10*).

In contrast to an earlier study employing type 1 diabetic patients (*8*), our study found that female gender was associated with a higher level of PP than male gender in patients with type 2 diabetes (Table 2). The discrepancy may arise from differences in the mean age associated with these types of diabetes (37.5 years in type 1 diabetic patients by Rönnback *et al*. (*8*) *vs*. 56 years in our type 2 diabetic patients). Several population studies, including the Third National Health and Nutrition Examination Survey, have demonstrated a greater age-related increase in SBP and greater age-related decrease in DBP in women than men, indicating that women exhibit a greater age-related increase in PP (*23*).

Our study has several limitations. This was a cross-sectional study; therefore, close associations of greater PP with higher age and the degree of albuminuria do not necessarily indicate that PP increases with age or the progression of diabetic kidney disease. To confirm these relationships, a longitudinal study will be needed. Secondly, blood pressure in hospitalized patients does not usually represent that in usual daily life, because bed rest and low-sodium diets administered during hospitalization may contribute to lower blood pressure. In addition, the results obtained from hospitalized patients in the present study should be interpreted with caution because of the small sample size. Finally, albuminuria was determined from a single measurement of urinary ACR, possibly leading to improper categorization because of marked day-to-day variability in albumin excretion. The ADA guideline recommends repeating measurements of urinary albumin for the classification of abnormalities in albumin excretion (*12*). Although we did not obtain multiple measurements of urinary ACR, we restricted the timing of urine collection to the first morning to minimize exercise-induced and diurnal variations (*24*).

In conclusion, these cross-sectional observations demonstrated that PP is closely associated with advanced age, the degree of albuminuria, and large artery stiffness in patients with type 2 diabetes. These results suggest that the excessive incidence of cardiovascular disease in patients with type 2 diabetes and advanced kidney disease may be attributable at least in part to increased PP. A cause-effect relationship between PP and age or degree of albuminuria remains to be clarified in longitudinal studies.

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