

Arterial Stiffness Is Associated With Incident Albuminuria and Decreased Glomerular Filtration Rate in Type 2 Diabetic Patients

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OBJECTIVE—To investigate the association between aortic stiffness and incident albuminuria and the decline in estimated glomerular filtration rate (eGFR) in patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS—We investigated 461 Japanese type 2 diabetic patients, comprising 199 women and 262 men, with a mean age of 59 ± 11 years. Patients were divided into two groups according to the median value of carotid-femoral pulse wave velocity (cf-PWV), which was used to evaluate aortic stiffness. The end point was defined as the transition from normo- to microalbuminuria or micro- to macroalbuminuria. The Cox proportional hazard model was used to calculate the hazard ratio (HR) and 95% CI. The correlation between cf-PWV and rate of change in eGFR was also determined by linear regression analysis.

RESULTS—The baseline mean (\pm SD) cf-PWV was 9.6 ± 2.4 m/s. During a median follow-up period of 5.9 years (range 0.3–8.6), progression of albuminuria was observed in 85 patients. The 5-year cumulative incidence of the end point in patients with cf-PWV below and above the median was 8.5 and 19.4%, respectively ($P = 0.002$, log-rank test). cf-PWV was significantly associated with incident albuminuria (HR 1.23, 95% CI 1.13–1.33, $P < 0.001$) by multivariate Cox regression analysis. A significant association between cf-PWV and annual change in eGFR was also suggested by multiple linear regression analysis (standardized estimate -0.095 , $P = 0.031$).

CONCLUSIONS—Aortic stiffness is associated with incident albuminuria and the rate of decline in glomerular filtration rate in type 2 diabetic patients.

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Patients with increased aortic stiffness and patients with chronic kidney disease (CKD) share many risk factors (1) and are at increased risk of incident cardiovascular disease (CVD) and cardiovascular mortality (2). A recent large cross-sectional population-based study revealed a significant association of CKD components, albuminuria and reduced glomerular filtration rate (GFR) with arterial stiffness (3). However, the association between arterial stiffness and

decline in renal function is controversial in longitudinal studies. Aortic pulse wave velocity (PWV), the gold standard for measuring aortic stiffness, was reported to be independently associated with a decline in renal function in patients with CKD from the Arterial Compliance and Oxidant Stress as Predictors of Loss of Renal Function, Morbidity and Mortality in Chronic Kidney Disease study (ACADEMIC) (4) but not in those from the Framingham Heart Study (5).

In type 2 diabetic patients, age and duration of diabetes were previously reported to be associated with aortic PWV (6). With regard to CKD components, albuminuria was recently reported to be associated with aortic PWV (7). However, a longitudinal analysis to reveal whether increased arterial stiffness predicts the progression of albuminuria and/or a rapid decline in renal function has never been determined in diabetic patients. We, therefore, conducted this observational cohort study to highlight the relationship between carotid-femoral PWV (cf-PWV) and change of albuminuria and GFR in type 2 diabetic patients.

RESEARCH DESIGN AND METHODS

Study population

This study was conducted in accordance with the Declaration of Helsinki. We examined the datasets of our earlier cohort study of Japanese type 2 diabetic patients with respect to the relationship between CKD and incident CVD as described previously (8). In brief, patients were aged >20 years, had type 2 diabetes according to World Health Organization criteria (9) with an estimated GFR (eGFR) of ≥ 15 mL/min per 1.73 m², and were admitted for glycemic control and evaluation of diabetes complications between 1 January 2002 and 31 December 2003. Patients undergoing renal replacement therapy, pregnant women, and patients with infectious and malignant diseases were excluded. In this study, we selected patients with normo- or microalbuminuria who had been examined by cf-PWV.

Participants underwent a routine medical history and physical examination as well as blood sampling. Information regarding smoking was obtained using a standard questionnaire. Smoking habits were classified as current or not. Physical examination included blood pressure measurement and anthropometry; laboratory tests included measurement of HbA_{1c}, serum lipids, creatinine, and urinary albumin

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levels in the first morning urine specimen. Ophthalmoscopic examinations were performed by ophthalmologists in our center, and diabetic retinopathy was evaluated by the international clinical diabetic retinopathy disease severity scale, proposed by the American Academy of Ophthalmology (10).

History of CVD was defined as a history of stroke/transient ischemic attack and coronary artery disease. Clinical evidence of coronary artery disease was defined as the presence of any of the following conditions: angina pectoris diagnosed by clinical symptoms and the presence of coronary artery stenosis evaluated by coronary angiography, a history of myocardial infarction, or previous coronary revascularization.

Measurements

Urinary albumin was measured by a latex agglutination test and normalized by urinary creatinine levels (11). The category of albuminuria was defined as normoalbuminuria if the albumin-to-creatinine ratio (ACR) was <30 mg/g, microalbuminuria if the ACR was 30–299 mg/g, and macroalbuminuria if the ACR was ≥300 mg/g (12). Serum creatinine was initially measured using Jaffé method in the hospital laboratory. From January 2003, this method was replaced by an enzymatic method, and measurements using Jaffé method were adjusted using a regression equation obtained from the correlation analysis of measurements of serum creatinine analysis by both methods in 10,132 samples from diabetic patients as follows: serum creatinine (enzymatic method, mg/dL) = $[0.972 \times \text{serum creatinine (Jaffé method, mg/dL)}] - 0.224$ ($r = 0.9992$, $P < 0.001$). GFR was estimated using the following modified three-variable equation for Japanese, as recently proposed by the Japanese Society for Nephrology: $eGFR$ (mL/min per 1.73 m^2) = $194 \times \text{serum creatinine (} [\mu\text{mol/L}] \text{ divided by } 88.4)^{-1.094} \times \text{age (years)}^{-0.287}$ ([if female] $\times 0.739$) (13).

cf-PWV was measured using a pulse wave velocimeter (model PWV-200; Fukuda Denshi, Tokyo, Japan), as described previously (6). Briefly, two different pressure waves were obtained using a pressure-sensitive transducer placed at the base of the neck for the left common carotid artery and over the right femoral artery. cf-PWV was calculated automatically as the ratio (m/s) of the distance traveled by the pulse wave, which was obtained from the measured distance between the carotid and femoral probes to transit time

that was determined from the latency between the corresponding upstroke of the carotid and femoral pulse waveforms. The effects of diastolic blood pressure on the PWV values were automatically calibrated using the software preinstalled on the PWV-200, and PWV values were reported at a diastolic blood pressure of 80 mmHg. PWV was conducted for screening of arterial stiffness in our hospital, and there were no significant differences of age and sex between patients who had PWV measured and those who had not.

In Japan, HbA_{1c} was measured by high-performance liquid chromatography using a set of calibrators assigned by the Japan Diabetes Society (normal range 4.3–5.8%). According to correlation analysis, HbA_{1c} values in Japan were estimated to be 0.4% lower than those measured by the National Glycohemoglobin Standardization Program (NGSP) (14). To standardize HbA_{1c} values to NGSP units, 0.4% was added to the measured values and expressed as HbA_{1c}-equivalent NGSP units in the current study. HDL cholesterol was determined enzymatically. LDL cholesterol was measured by a direct method or calculated using the Friedewald equation when the serum triglycerides level was <4.48 mmol/L (15).

Outcomes

The end point with regard to albuminuria was defined as the transition from normo- to microalbuminuria or micro- to macroalbuminuria and confirmed on at least two consecutive urinary ACR measurements to reduce misclassification. In addition, we evaluated the regression of albuminuria defined as the transition from micro- to normoalbuminuria, confirmed on at least two consecutive urinary ACR measurements. We further evaluated the association between cf-PWV and an annual change in logarithmically transformed urinary ACR when these two variables were treated as continuous variables. Patients with a follow-up period of urinary ACR of >1 year were included in the analysis. Changes in urinary ACR were defined as logarithmically transformed ACR at study end minus the value at baseline, divided by the follow-up period (years).

The end point with regard to renal function was the rate of change in eGFR. For each individual, the rate was determined by parameter estimates using a simple regression analysis, with eGFR as a function of time in years applied to all eGFR values obtained during the follow-up

period. Subjects were included to contribute to the GFR end point if they had undergone ≥2.0 years of follow-up observation since enrolling in the study, regardless of number of serum creatinine measurements and having information on albuminuria during the follow-up period. This minimum observation period was selected on the basis of a previous recommendation for an observation period of ≥2 years for valid determination of the rate of decline in GFR (16).

Statistical analysis

Data were expressed as percentage, arithmetic means ± SD, or geometric means with 95% CI, as appropriate, according to data distribution. Triglycerides and ACR were logarithmically transformed to allow for the skewed distribution. For statistical analysis, the Student *t* test, χ^2 test, and linear regression analysis were used accordingly. Pearson correlation coefficients (*r*) and Spearman rank correlation coefficients were calculated in the univariate correlation analysis, and the cumulative incidence of the primary end point was estimated using the Kaplan-Meier analysis. We decided to use the median value of 9.1 m/s for cf-PWV as a cutoff in the current study because the relationship between aortic stiffness and CV events is continuous, and cf-PWV >8.2 m/s was reported to be significantly associated with not only all-cause mortality but also cardiovascular mortality (2). Risk estimates for reaching the end point were calculated using univariate and multivariate Cox proportional hazard model analysis. The following variables were incorporated as covariates in multivariate linear regression analysis and multivariate Cox regression analysis: age, sex, duration of diabetes, presence of proliferative diabetic retinopathy, history of CVD, smoking status, BMI, systolic and diastolic blood pressure, use of renin-angiotensin system (RAS) inhibitors (ACE inhibitors and angiotensin type 1 receptor blockers), antiplatelet agents, statins, HbA_{1c}, triglycerides, HDL cholesterol, LDL cholesterol, hemoglobin, uric acid, eGFR, urinary ACR, and cf-PWV at baseline. Starting of RAS inhibitors during the follow-up was included as a covariate in time-dependent Cox regression analysis. Prognostic factors were selected using the stepwise procedure, specifying the significant levels for entering an additional explanatory variable into the model as 0.25 and for removing an explanatory variable from the model as 0.15. To compare the impact of

coefficients for an indicator of the relative importance of the independent variables in multivariate linear regression analysis, we used a standardized estimate. The standardized estimate means the value multiplying the unstandardized partial regression coefficient by the SD of the predictor and dividing it by the SD of the criterion. The scores of standardized estimate vary from -1.00 to +1.00, respectively. All statistical analysis was performed using the Statistical Analysis System (SAS Institute, Cary, NC), version 9.2. A *P* value of <0.05 was considered significant.

RESULTS—A total of 461 type 2 diabetic patients (199 women, 262 men; age 59 ± 11 years [means ± SD]; range 20–86)

had sufficient baseline and follow-up data to qualify for inclusion of the end point with regard to albuminuria. Of the patients, 339 had normoalbuminuria and the other 122 had microalbuminuria. cf-PWV was 9.6 ± 2.4 m/s (means ± SD). Table 1 shows baseline demographic clinical characteristics and laboratory data of patients with type 2 diabetes according to the median cf-PWV value (9.1 m/s). Patients with higher cf-PWV were older, tended to be female, and exhibited a longer duration of diabetes and higher systolic, but lower diastolic, blood pressure, yielding higher pulse pressure than individuals with lower cf-PWV. They also had a higher prevalence of CVD and lower prevalence of smoking and were treated

more frequently with antiplatelet agents and statins than patients with lower cf-PWV. With regard to laboratory data, patients with a higher cf-PWV level had a higher urinary ACR level and lower HbA_{1c}, triglycerides, hemoglobin, and eGFR levels at baseline than patients with a lower cf-PWV.

During the median follow-up period of 5.9 years (range 0.3–8.6), 56 patients with normoalbuminuria and 29 with microalbuminuria progressed to a more advanced stage of albuminuria. As shown in Fig. 1, the 5-year cumulative incidence of the end point in patients with cf-PWV of <9.1 and ≥9.1 m/s was 8.5 and 19.4%, respectively (log-rank test, *P* = 0.002). In the univariate Cox regression analysis, cf-PWV was significantly associated with incident albuminuria (Table 2). The association between cf-PWV and incident albuminuria remained significant, even after adjustment for other covariates. When key potential confounding variables (age, sex, systolic blood pressure, HbA_{1c}, urinary ACR, eGFR, and use of RAS inhibitors) were forced to be included, cf-PWV remained a significant predictor of albuminuria progression (hazard ratio 1.24, 95% CI 1.13–1.37, *P* < 0.001). When starting of RAS inhibitors was included as a covariate in the time-dependent Cox regression analysis, we revealed the significant association between cf-PWV and incident albuminuria (hazard ratio 1.22, *P* < 0.001). In addition, PWV was not only associated with incident microalbuminuria in patients with normoalbuminuria (hazard ratio 1.26, 95% CI 1.13–1.41, *P* < 0.001) but also with incident clinical albuminuria in patients with microalbuminuria (1.25, 1.11–1.40, *P* < 0.001).

We conducted a further analysis to reveal the association between cf-PWV and an annual change in logarithmically transformed urinary ACR when these two variables were treated as continuous variables. Patients with a follow-up period of urinary ACR of >1 year (*n* = 418) were included in the analysis. PWV was significantly associated with a change in urinary ACR in the multivariate regression analysis (standardized estimate 0.12, *P* = 0.020) as well as in the univariate regression model (*r* = 0.11, *P* = 0.027). Other significant covariates were HbA_{1c} (standardized estimate 0.11, *P* = 0.020) and uric acid (standardized estimate 0.12, *P* = 0.018), respectively.

In contrast, the regression of microalbuminuria was also observed in 23

Table 1—Clinical characteristics and laboratory data in type 2 diabetic patients in relation to cf-PWV levels

| | cf-PWV (m/s) | | <i>P</i> † |
|--|------------------------|------------------------|------------|
| | <9.1 (<i>n</i> = 226) | ≥9.1 (<i>n</i> = 235) | |
| Age (years) | 54 ± 12 | 65 ± 8 | <0.001 |
| Sex (male, %) | 62.8 | 51.1 | 0.011 |
| Current smoker (%) | 30.1 | 18.3 | 0.003 |
| Diabetes duration (years) | 10 ± 8 | 14 ± 9 | <0.001 |
| History of CVD (%) | 9.7 | 20.9 | <0.001 |
| BMI (kg/m ²) | 25.1 ± 4.5 | 24.5 ± 4.6 | 0.145 |
| Systolic blood pressure (mmHg) | 126 ± 17 | 131 ± 19 | 0.003 |
| Diastolic blood pressure (mmHg) | 79 ± 11 | 74 ± 11 | <0.001 |
| Pulse pressure (mmHg) | 47 ± 15 | 57 ± 17 | <0.001 |
| Proliferative diabetic retinopathy (%) | 17.3 | 23.4 | 0.102 |
| Treatment for diabetes (%) | | | |
| Diet | 18.1 | 9.4 | 0.006 |
| Oral agents | 43.4 | 43.0 | 0.934 |
| Insulin | 38.5 | 47.2 | 0.058 |
| Antihypertensive agents (%) | | | |
| Calcium channel blockers | 25.7 | 30.6 | 0.235 |
| ACE inhibitors | 13.3 | 16.6 | 0.327 |
| Angiotensin type 1 receptor blockers | 15.5 | 21.7 | 0.087 |
| β-Blockers | 4.9 | 9.4 | 0.061 |
| α-Blockers | 0.9 | 1.7 | 0.439 |
| Diuretics | 2.7 | 5.1 | 0.174 |
| Antiplatelet agents (%) | 16.8 | 43.4 | <0.001 |
| Statins (%) | 18.6 | 32.3 | <0.001 |
| cf-PWV (m/s) | 7.8 ± 0.8 | 11.3 ± 2.2 | <0.001 |
| HbA _{1c} (%) | 9.1 ± 1.8 | 8.8 ± 1.6 | 0.042 |
| Triglycerides (mmol/L)‡ | 1.48 (1.37–1.59) | 1.34 (1.27–1.42) | 0.047 |
| HDL cholesterol (mmol/L) | 1.22 ± 0.35 | 1.26 ± 0.42 | 0.224 |
| LDL cholesterol (mmol/L) | 3.07 ± 0.82 | 3.13 ± 0.84 | 0.416 |
| Uric acid (mmol/L) | 0.31 ± 0.09 | 0.31 ± 0.10 | 0.856 |
| Hemoglobin (g/L) | 143 ± 13 | 137 ± 14 | <0.001 |
| Urinary ACR (mg/g)‡ | 14 (12–16) | 19 (17–22) | 0.002 |
| <30 (%) | 79.7 | 67.7 | 0.004 |
| 30–299 (%) | 20.3 | 32.3 | 0.004 |
| Creatinine (μmol/L) | 59.7 ± 17.0 | 66.3 ± 21.8 | <0.001 |
| eGFR (mL/min per 1.73 m ²) | 92.9 ± 26.6 | 75.6 ± 20.4 | <0.001 |

Data are means ± SD, geometric means, or percent. †*t* test or χ² test. ‡Geometric means (95% CI).

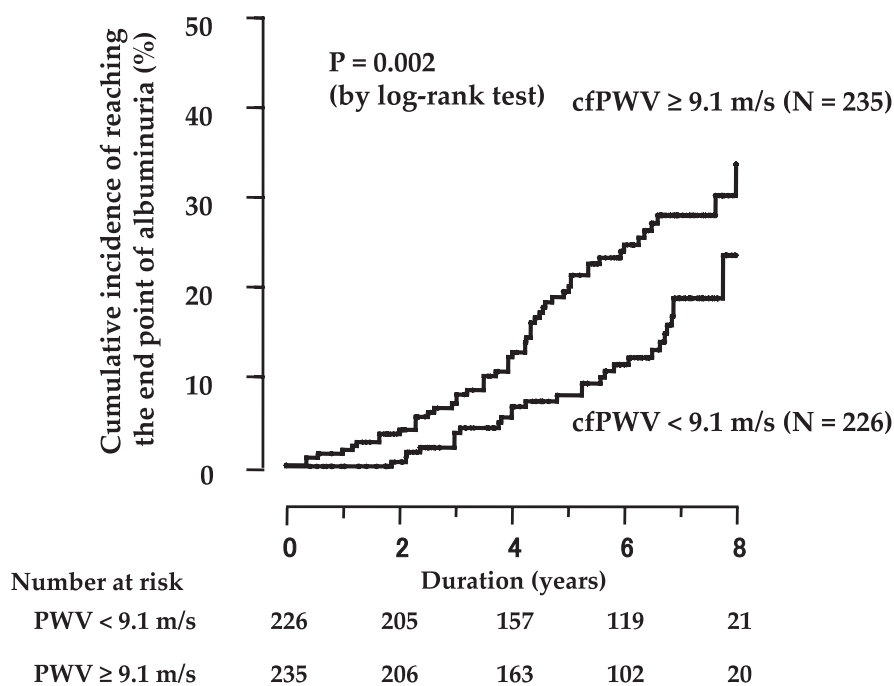


Figure 1—Cumulative incidence of the end point (transition to a more advanced stage of albuminuria) in type 2 diabetic patients with a cf-PWV level above and below the median value (9.1 m/s). The difference between Kaplan-Meier estimates for the two groups was statistically significant (log-rank test, $P = 0.002$).

(18.7%) of 122 microalbuminuric patients during the follow-up period (4.9 ± 2.3 years, range 0.4–8.6). Patients with regression of microalbuminuria had a significantly lower cf-PWV than patients without (9.0 ± 2.4 vs. 10.8 ± 2.8 m/s, $P = 0.005$). PWV was significantly associated with regression of albuminuria (hazard ratio 0.72, 95% CI 0.57–0.90, $P = 0.004$). Other significant covariates were systolic blood pressure (0.96, 0.94–0.99, $P = 0.012$), HbA_{1c} (0.58, 0.41–0.82, $P = 0.002$), and uric acid (0.48, 0.33–0.70, $P < 0.001$), respectively.

A total of 567 type 2 diabetic patients (238 women, 329 men; age 61 ± 12 years, range 20–88) had sufficient baseline and follow-up data to qualify for

inclusion of the end point of decline in renal function. cf-PWV was not significantly correlated with the annual decline of eGFR (Spearman rank correlation coefficient -0.06 , $P = 0.151$) by univariate correlation analysis. However, a significant association between cf-PWV and annual change in eGFR was observed by multiple linear regression analysis (Table 3). We conducted a sensitivity analysis to reveal whether starting RAS inhibitors could attenuate the association between PWV and the decline in GFR, especially in patients with CVD. Use of RAS inhibitors increased from 29.7% at baseline to 54.7% at the end of the study in patients without CVD and from 48.4 to 61.1% in patients with CVD. When

starting RAS inhibitors during the follow-up was included as a covariate in the multiple regression analysis, the association between cf-PWV and decline in eGFR remained statistically significant (standardized estimate -0.09 , $P = 0.038$).

CONCLUSIONS—Although CKD was reported to be cross-sectionally correlated with aortic stiffening (1,3), the association of aortic stiffness with kidney disease progression received less attention, especially in patients with diabetes. In this single-institutional observational cohort study of Japanese patients with type 2 diabetes, we observed for the first time an increased incidence of albuminuria in subjects with higher aortic stiffness, as assessed by cf-PWV. The association between cf-PWV and incident albuminuria remained significant even after adjustment for other renal risk factors, including HbA_{1c} and systolic and diastolic blood pressure. In addition, multivariate linear regression analysis revealed that cf-PWV had an independent association with a faster decline in kidney function. To the best of our knowledge, this is the first study to demonstrate the association of aortic stiffness with both incident albuminuria and decline in renal function in type 2 diabetic patients.

Several recent studies (17,18) support the significant association between cf-PWV and incident albuminuria in the current study. A population-based cross-sectional study from Taiwan (17) reported that albuminuria was more strongly associated with arterial stiffness (brachial-ankle PWV) in patients with diabetes than in patients without. Hypertensive patients with higher brachial-ankle PWV from the Japanese Trial of the Prognostic Implication of Pulse Wave Velocity (JTOPP) carried a significantly higher risk of incident albuminuria than patients with lower brachial-ankle PWV (18). Furthermore, we, for the first time, clarified that diabetic patients with lower cf-PWV are more likely to experience a regression of albuminuria than patients with higher cf-PWV. Aortic stiffness may be predictive of not only progression but also regression of albuminuria in patients with type 2 diabetes.

The significant inverse association of cf-PWV and GFR in a multivariate linear regression model is another noteworthy finding in the current study. These findings are in accordance with recent prospective data from ACADEMIC (4) and other studies (19,20); however, such

Table 2—Hazard ratios of the progression of albuminuria (transition to a more advanced stage of albuminuria) in type 2 diabetic patients

| | Hazard ratio | 95% CI | P |
|--------------------------|--------------|-----------|--------|
| Univariate analysis | | | |
| cf-PWV (m/s) | 1.23 | 1.11–1.32 | <0.001 |
| Multivariate analysis | | | |
| cf-PWV (m/s) | 1.23 | 1.13–1.33 | <0.001 |
| Other covariates | | | |
| Log ACR (mg/g) | 2.02 | 1.39–2.94 | <0.001 |
| HbA _{1c} (%) | 1.17 | 1.04–1.33 | 0.011 |
| LDL cholesterol (mmol/L) | 0.72 | 0.55–0.93 | 0.013 |

Table 3—Multiple regression analysis with stepwise variable selection to investigate the risk factors associated with GFR slope in type 2 diabetic patients

| | Standardized estimate | P† |
|--|-----------------------|--------|
| cf-PWV (m/s) | −0.095 | 0.031 |
| Log ACR (mg/g) | −0.225 | <0.001 |
| eGFR at baseline (mL/min per 1.73 m ²) | −0.250 | <0.001 |
| HbA _{1c} (%) | −0.161 | <0.001 |
| Hemoglobin (g/L) | 0.072 | 0.047 |

†Multiple regression analysis (stepwise method).

results should be interpreted with caution because of a lack of cf-PWV (19,20) and small sample size (4). In contrast, longitudinal analysis from the Framingham Heart Study (5) was unable to reveal the significant association of aortic stiffness when assessed by cf-PWV with a decline in GFR. Regarding the strength of the association between GFR and PWV, eGFR was cross-sectionally reported to be able to explain only 1% of PWV variability after adjusting for covariates including age, systolic blood pressure, and diabetes in patients with CKD (21). In contrast, we and others (4) reported that aortic PWV could explain ~10–30% of decline in GFR. Differences of the study design and populations among these studies may lead to contradictory results. We should also pay considerable attention to the discrepancy of the results between the univariate and multivariate analyses. This discrepancy may indicate the presence of confounding factors. We revealed the significant correlation between cf-PWV and eGFR at baseline ($r = -0.35$, $P < 0.001$) and interaction among these covariates on the eGFR decline ($P < 0.001$), tested by a multivariate regression analysis. Therefore, we conducted a further analysis to reveal whether cf-PWV was associated with rapid decline in eGFR in patients with eGFR ≥ 60 mL/min per 1.73 m² and/or in patients with eGFR < 60 mL/min per 1.73 m². In patients with eGFR ≥ 60 mL/min per 1.73 m², cf-PWV was significantly associated with a decline in eGFR (standardized estimate -0.087 , $P = 0.041$). In contrast, cf-PWV was not associated with a decline in eGFR (standardized estimate -0.043 , $P = 0.705$) in patients with eGFR < 60 mL/min per 1.73 m². These results may partially explain why cf-PWV was not correlated with decline in eGFR in the univariate analysis. Larger-scale studies, using cf-PWV to evaluate aortic stiffening, may be needed to clarify the association between aortic stiffness and decline in GFR.

The mechanisms linking increased albuminuria and/or decreased GFR in diabetic patients with higher arterial stiffness are not fully understood. Endothelial dysfunction and low-grade inflammation may be important mechanisms that link aortic stiffness to CKD and CVD. Furthermore, from the hemodynamic point of view, the juxtamedullary afferent arterioles of the kidneys are small and short vessels that are exposed to a high pressure and therefore have to maintain a strong vascular tone to provide a large pressure gradient in a short distance. These vessels might be directly influenced by hemodynamics of large arteries rather than other small vessels in peripheral circulation. Therefore, the stiffening of large arteries may directly increase pulsatile stress, especially in these vessels because of increased aortic characteristic impedance and early return of wave reflection and could cause glomerular and/or tubular damage via increased intrarenal pulse pressure (22), possibly leading to microvascular kidney damage (albuminuria and/or reduction of GFR).

Other findings in the current study included higher arterial stiffness in women than in men (Table 1). This study was compatible with previous studies from Sweden (23,24). Female sex was reported to affect the mechanical properties of elastic rather than muscular arteries in patients with type 1 diabetes, possibly explaining the reason why female patients with type 2 diabetes had a higher value of cf-PWV than male patients in the current study. In addition, patients with higher eGFR at baseline were at significantly increased risk of rapid decline in eGFR (Table 3). This result is compatible with results from a recent observational study from Japan (25). Although evidence is scarce whether high GFR estimated by serum creatinine could detect the glomerular hyperfiltration, which could explain why patients with higher eGFR at baseline were at increased risk of rapid decline in

eGFR in the current study. We should also consider the possibility that the association between high eGFR at baseline and greater decrease in eGFR was due to regression-to-the-mean principle.

The strength of the current study is the evaluation of aortic stiffness by cf-PWV, a standard method that is calculated from the tonometry waveform. Furthermore, we evaluated longitudinally the association of aortic stiffness while taking both components of CKD (albuminuria and reduced GFR) into account.

The limitations of the current study may include an ethnically and socially homogeneous population because the study was hospital based; therefore, generalization of our findings might be limited. Second, we were unable to evaluate longitudinally the association between changes in aortic stiffness and kidney disease during the follow-up period. Third, we did not restrict the interval between two consecutive results of testing for albuminuria. However, the minimum interval was > 1 month in the current study. Fourth, it is possible that lower muscle mass in the elderly patients with type 2 diabetes may have affected GFR levels, leading to misclassification of change in eGFR levels and underestimation of the association between aortic stiffness and GFR decline.

In conclusion, this hospital-based observational cohort study demonstrated for the first time that aortic stiffness is a potential predictor of incident albuminuria and decline in renal function, independent of other covariates, in patients with type 2 diabetes. The impact of aortic stiffening on the decline in GFR needs to be clarified in future larger studies.

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R.B. contributed to discussion, researched data, and wrote the manuscript. T.B., Y.U., and Y.I. contributed to discussion and reviewed and edited the manuscript. M.M., N.Y., I.N., K.T., K.H., N.T., and A.I. researched data.

As the corresponding author and guarantor of this manuscript, T.B. takes full responsibility for the work as a whole, including the study design, access to data, and the decision to submit and publish the manuscript.

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