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Diabetes Mellitus, Aortic Stiffness, and Cardiovascular Mortality in End-Stage Renal Disease

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Abstract. Cardiovascular mortality is elevated in patients with end-stage renal disease (ESRD), especially in those with diabetes mellitus. Although the higher cardiovascular death rate in diabetic ESRD patients may be the result of more advanced atherosclerotic changes of the arterial wall, this has not been documented previously. Aortic stiffness was compared between ESRD patients with and without diabetes, and the impact of aortic stiffness on cardiovascular mortality was examined in a prospective, observational cohort study. The cohort consisted of 265 ESRD patients on hemodialysis, including 50 diabetic patients studied between June 1992 and December 1998. At baseline, the diabetic ESRD patients had significantly higher aortic pulse wave velocity (PWV), a noninvasive measure of aortic stiffness, than the nondiabetic patients. During a mean follow-up period of 63 mo, 81 deaths, including 36 cardiovascular deaths, were recorded. Kaplan-Meier analysis revealed higher all-cause or cardiovascular mortality rates in the diabetic as compared with the nondiabetic patients and also in those with higher aortic PWV than those with lower aortic PWV. The effect of diabetes on cardiovascular death was significant in the Cox model, including age, years on hemodialysis, gender, smoking, C-reactive protein, hematocrit, and body mass index as covariates. However, when aortic PWV was included as a covariate, the impact of diabetes was no longer significant, whereas aortic PWV was a significant predictor. In a model including 13 covariates, aortic PWV remained a significant predictor for cardiovascular and overall mortality but not for non-cardiovascular death. These results demonstrate that the increased aortic stiffness of the ESRD patients with diabetes mellitus contributed to the higher all-cause and cardiovascular mortality rates.

Diabetic nephropathy is the leading cause of end-stage renal disease (ESRD) in the United States, Europe, and Japan. The cardiovascular mortality rate is elevated in those with ESRD (1,2), diabetes mellitus (3,4), and especially in those with both diabetes and ESRD (5–8). Although the higher cardiovascular mortality in diabetic patients with ESRD is presumably the result of more advanced atherosclerosis in this population, there has been no direct documentation for this hypothesis.

Atherosclerosis has two important features, namely thickening and stiffening of arterial wall (9). Previous studies revealed that carotid artery intima-media thickness is increased in diabetes (10–12) and in ESRD (13). We recently reported that diabetic ESRD patients have greater carotid artery intima-media thickness than those with diabetes or ESRD alone (14). O'Leary *et al.* (15) have shown that carotid artery thickness predicted myocardial infarction in a large cohort of the elderly. Thus, arterial wall thickening appears to parallel cardiovascular disease, but none of these studies directly examined a potential relationship between arterial wall thickness and cardiovascular mortality.

With regard to arterial wall stiffening, stiffness of carotid artery (16) and aorta (12) is increased in diabetes. Aortic stiffness is also increased in ESRD (17,18). According to London *et al.* (17), aortic stiffness was associated with left ventricular hypertrophy in patients with ESRD. Recently, Blacher *et al.* (19) reported that aortic stiffness predicted all-cause and cardiovascular mortality in French ESRD patients. This indicates that arterial wall stiffness is a good predictor for cardiovascular mortality, although this needs to be confirmed in other ethnic groups. So far, no study is available that compared aortic stiffness between ESRD patients with and without diabetes. In addition, it is not known whether more pronounced aortic stiffness explains the higher cardiovascular mortality rate in diabetic ESRD patients.

We, therefore, examined the impact of aortic stiffness on outcome in a cohort of 265 ESRD patients including 50 subjects with type 2 diabetes. This study was part of the MAP ESRD study that was started in 1992 to evaluate the effects of metabolic changes on arteriosclerosis and prognosis in ESRD patients. We confirmed that aortic stiffness was an independent predictor for overall and cardiovascular fatal events in the

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Japanese cohort. Furthermore, we demonstrated that the increased aortic stiffness in diabetic ESRD patients contributed to the higher cardiovascular mortality rate of this group.

Materials and Methods

Study Design and Patients

We performed a prospective, observational cohort study. The cohort consisted of 265 ESRD patients who had been treated by regular hemodialysis for more than 3 mo at Inoue Hospital, Suita, Japan, and who gave informed consent. The subjects were recruited from those who were dialyzed in morning sessions, so that blood tests were done after an overnight fast. We excluded patients when they had severe illness or apparent acute inflammatory symptoms. The patients corresponded to 90% of those who received hemodialysis in morning sessions or 53% of the total hemodialysis patients of this hospital. The subjects were registered between June 1992 and June 1995. Mean (± SD) age at entry was 55.4 ± 10.5 yr, which was close to the mean age of the entire dialysis population in Japan at the end of 1992 (56.0 ± 13.5 yr; $n = 123{,}926$). Duration of hemodialysis before inclusion was 6.9 ± 5.2 yr. Fifty patients (19%) had type 2 diabetes mellitus, and their mean duration of diabetes was 20 ± 7 yr at inclusion. Table 1 summarizes characteristics of the subjects at inclusion. After baseline studies, including PWV and other clinical and biochemical measurements, they were followed up to December 1998. This study was approved by the institutional ethical committee (Inoue Hospital Approval No. 101).

Compared with nondiabetic ESRD patients, diabetic ESRD patients had higher body mass index, higher fasting plasma glucose, higher systolic BP, lower HDL cholesterol, lower serum creatinine, and shorter duration of hemodialysis treatment. The difference in age or gender between the two groups was not statistically significant.

Aortic Pulse Wave Velocity and BP Measurement

Aortic PWV and BP were measured as described previously (18). Briefly, these measurements were made with the patient in a supine position after 5-min bed rest. Arterial BP was measured with a mercury sphygmomanometer and a standard cuff in the arm. The average of two BP measurements was recorded. Aortic PWV was measured by the method of Hasegawa (20), using a PWV meter (model PWV-200, Fukuda Denshi, Tokyo, Japan). Pulse waves were recorded by using sensors that were placed on the skin at left carotid and right femoral arteries. Heart sounds S1 and S2 were detected by a microphone on the right edge of the sternum at the level of the second intercostal space. Electrocardiograms were obtained with electrodes placed at both arms and right leg. The PWV meter measures time intervals between pulse waves at the carotid and femoral probes (T) and between S2 and the notch of carotid pulse wave (Tc). PWV of the aorta is calculated as follows:

$$\text{PWV (m/s)} = 1.3 \times L/(T + Tc)$$

where L is the measured distance between the heart sound microphone and the femoral probe. The actual distance between the aortic orifice and the femoral site was estimated to be 1.3 × L (20). T + Tc indicates the time for the pulse wave to travel from the aortic orifice to the femoral artery. PWV increases as a function of the diastolic BP at the time of measurement in normal subjects (21). Therefore, the PWV meter automatically reports raw and BP-standardized PWV values. The latter represents a pressure-independent elastic property of the aorta. Aortic PWV was measured for 5 consecutive pulses, and the average was used for analysis. The coefficient of variation of PWV was less than 5%. In the present study, we used raw PWV data because a recent report by Guerin *et al.* (22) demonstrated that aortic PWV was BP-independent in a great proportion of ESRD patients. In the baseline study of our cohort, the raw (X) and BP-corrected PWV (Y) values showed a tight correlation ($r = 0.932$; $P < 0.0001$); the fitting line had a slope of 0.986 ± 0.024 and an intercept of −0.019 ± 0.211.

Other Measurements

Blood was drawn in the morning after an overnight fast of at least 12 h before starting a dialysis session. Whole blood was used for

Table 1. Characteristics of the ESRD cohort

Characteristic	Total	Nondiabetic Patients	Diabetic Patients
Number of patients	265	215	50
Age (yr)	55.4 ± 10.5	54.9 ± 10.4	57.9 ± 11.0[a]
Male (%)	41	39	52[a]
Smoker (%)	23	21	28
Duration of hemodialysis (yr)	6.9 ± 5.2	7.5 ± 5.3	3.7 ± 3.2[b]
Body mass index (kg/m^2)	21.5 ± 2.7	21.1 ± 2.5	22.9 ± 3.2[b]
Systolic BP (mmHg)	153 ± 27	150 ± 26	166 ± 27[b]
Diastolic BP (mmHg)	85 ± 14	86 ± 14	82 ± 12
Non-HDL cholesterol (mmol/l)	3.34 ± 1.00	3.32 ± 0.98	3.40 ± 1.09
HDL cholesterol (mmol/l)	1.01 ± 0.29	1.03 ± 0.28	0.93 ± 0.30[c]
Fasting plasma glucose (mmol/l)	4.84 ± 1.95	4.25 ± 0.53	7.32 ± 3.36[b]
Serum creatinine (μmol/l)	1016 ± 177	1028 ± 171	959 ± 197[c]
Total protein (g/l)	64.9 ± 4.6	65.0 ± 4.5	64.3 ± 4.86
C-reactive protein (mg/l)	5.4 ± 6.4	5.6 ± 7.4	4.5 ± 3.2
Hematocrit (%)	27.3 ± 4.0	27.2 ± 4.0	27.5 ± 4.0
Aortic pulse wave velocity (m/sec)	8.64 ± 2.16	8.35 ± 2.05	9.87 ± 2.31[b]

Mean ± SD. ESRD, end-stage renal disease; HDL, high-density lipoprotein. [a] $P = 0.06$–0.09; [b] $P < 0.005$; [c] $P < 0.05$ *versus* the nondiabetic group by ANOVA.

hematocrit, EDTA-plasma for lipids, and serum for other biochemical assays, including creatinine, total protein, and C-reactive protein (CRP). Total cholesterol was measured enzymatically (23). HDL cholesterol was measured after precipitating apolipoproteinB-containing lipoproteins with dextran sulfate and magnesium (24). Other measurements were by routine methods.

Outcome Data Collection

During the follow-up, one patient underwent renal transplantation. He was censored at the time of transplantation. Forty-seven patients moved away from Inoue Hospital. The outcome data of 34 out of the 47 patients could be obtained, although the remaining 13 patients were censored when they left the hospital. At the end of the follow-up, 170 patients were confirmed to be alive on hemodialysis and 81 to be dead. The mean follow-up period was 63 ± 23 mo.

Date and cause of death were obtained by reviewing the hospital record forms. In the cases that moved away to other dialysis units, we reviewed the questionnaire forms filled by the attending physicians at the units. The 81 deaths during the follow-up included 36 fatal cardiovascular events: 8 deaths attributable to coronary heart disease, 6 to cerebrovascular disease, 13 to congestive heart failure, and 9 to sudden death. Sudden death was defined as a witnessed death that occurred within 1 h after the onset of acute symptoms and without evidence of accident or violence. The 45 fatal non-cardiovascular causes were cancer ($n = 7$), infectious disease ($n = 20$), and others ($n = 18$).

Statistical Analyses

Data were summarized as mean ± SD. Difference between mean values was assessed by ANOVA. Difference in distribution was evaluated by chi-squared test. Survival curves were estimated by the Kaplan-Meier method followed by log rank test. Prognostic variables for survival were examined by using the Cox proportional hazards regression models. Multiple regression analysis was used to assess independent associations between one dependent and two or more independent variables. In these analyses, dummy variables were used for gender (female = 1, male = 2), diabetes (nondiabetic patient = 1, diabetic patient = 2), and smoking (nonsmoker = 1, smoker = 2). Significance was defined as $P < 0.05$.

Results

Comparison of Aortic Pulse Wave Velocity between ESRD Patients with and without Diabetes Mellitus

The group of diabetic patients had a significantly greater aortic PWV than the group of nondiabetic patients (Figure 1). This difference remained significant in the age-stratified comparison except in the subgroup of 70 yr of age or older.

Effect of Diabetes Mellitus on Outcome

During the follow-up, 81 deaths, including 36 fatal cardiovascular events, were recorded for the total cohort. The survival curves of the diabetic and nondiabetic patient groups were compared by the Kaplan-Meier method followed by log-rank test (Figure 2). The diabetic group had significantly higher mortality, including a higher rate of fatal cardiovascular events.

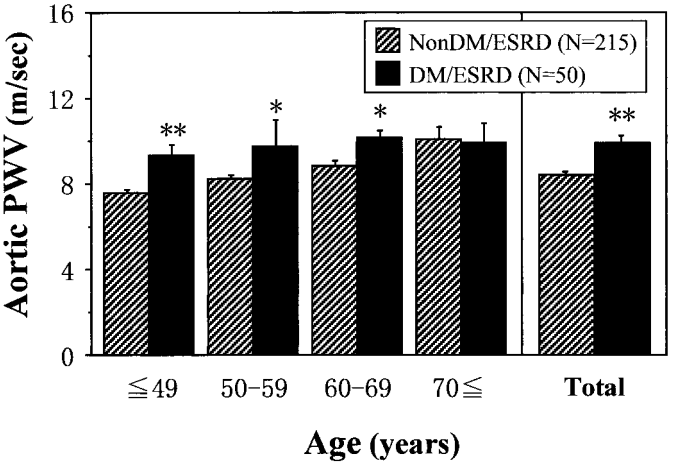

Figure 1. Comparison of aortic pulse wave velocity (PWV) between end-stage renal disease (ESRD) patients with and without diabetes mellitus. *$P < 0.05$; **$P < 0.01$; ***$P < 0.005$ by ANOVA.

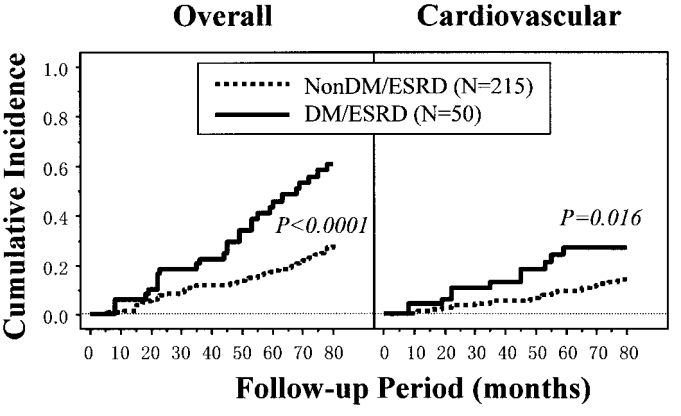

Figure 2. Comparison of cumulative overall mortality between ESRD patients with and without diabetes mellitus by the Kaplan-Meier analysis. *P*-values by log-rank test.

Effect of Aortic Pulse Wave Velocity on Outcome

The median of aortic PWV at entry was 8.2 m/s in the total group of subjects. We compared the survival curve between the subgroup with aortic PWV of 8.2 m/s or greater ($n = 136$) and the subgroup with aortic PWV lower than 8.0 m/s ($n = 129$). As shown in Figure 3, the overall mortality rate was significantly greater in those with greater aortic PWV values according to the Kaplan-Meier estimation. The same is true in the comparison of cardiovascular mortality rates.

Independent Predictors for Cardiovascular Mortality

The Kaplan-Meier analysis gives only univariate comparison of survival curves. We, therefore, performed further analyses by using the Cox proportional hazards models to identify independent predictors for cardiovascular mortality (Table 2). In model 1, age, CRP, and diabetes were the significant predictors. In model 2, that included aortic PWV; however, the statistical impact of diabetes on cardiovascular mortality was no longer significant ($P = 0.090$), whereas aortic PWV was a

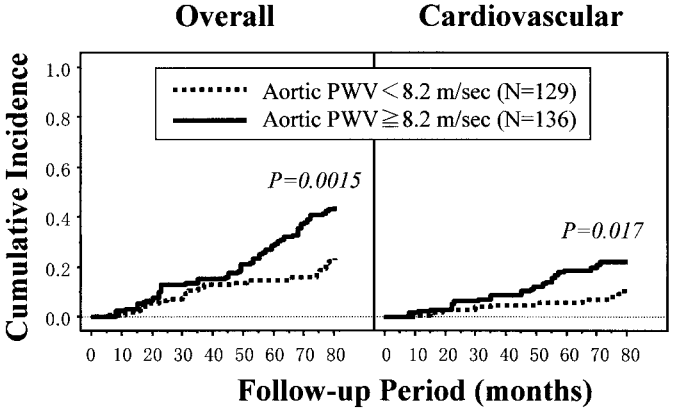

Figure 3. Comparison of cumulative cardiovascular mortality rates between ESRD patients with higher and lower aortic PWV values by the Kaplan-Meier analysis. *P* values by log-rank test.

significant predictor, suggesting correlations between diabetes, aortic PWV, and cardiovascular mortality. The impact of aortic PWV on cardiovascular mortality remained significant in model 3 that included serum creatinine, total protein, and systolic and diastolic BP as additional covariates. However, when HDL and non-HDL cholesterol levels were added to the model (model 4), the predictive power of aortic PWV was decreased to a borderline level ($P = 0.079$), suggesting correlations between plasma lipids, aortic PWV, and cardiovascular mortality. Also, male gender, higher CRP, and lower serum creatinine, were significant predictors for fatal cardiovascular events in the model.

Independent Predictors for Overall Mortality

Similar analyses were performed to identify independent predictors of overall mortality (Table 3). In the first model, diabetes was shown to be a significant predictor independent of age, years on hemodialysis, gender, smoking, body mass index, CRP, and hematocrit. When aortic PWV was added as another covariate to the model (model 2), the impacts of diabetes and aortic PWV on overall mortality were both significant. In model 3 that included serum creatinine, total protein, and systolic and diastolic BP as additional covariates, diabetes lost the predictive power, whereas lower serum creatinine, lower total protein, and lower diastolic pressure were significant factors in predicting a higher overall mortality rate. In the final model (model 4), including HDL and non-HDL cholesterol levels, aortic PWV remained significant as a prognostic factor. Also, male gender, higher CRP, lower serum creatinine, lower total protein, and lower diastolic BP were significant predictors of all-cause mortality in the model.

Independent Predictors of Non-Cardiovascular Mortality

The effects of diabetes and aortic stiffness on non-cardiovascular mortality were also analyzed by using the four Cox models. Diabetes and age at entry were significant predictors of non-cardiovascular death independent of gender, smoking, CRP, hematocrit, body mass index, and hemodialysis duration (model 1). Diabetes remained significant even when aortic PWV was included as an additional covariate, whereas aortic PWV was not a significant predictor (model 2), suggesting that increased aortic stiffness in patients with diabetes did not contribute to the diabetes-associated increase in non-cardiovascular mortality to a significant extent. PWV was not a significant predictor of non-cardiovascular mortality in the Cox models, including four and six additional covariates (model 3 and model 4).

Factors Associated with Aortic Pulse Wave Velocity

Factors associated with aortic PWV were evaluated by multiple regression analysis (Table 4). Increased aortic PWV was associated positively with systolic BP and negatively with diastolic pressure (model 1). In model 2, which included 13 variables, age, diabetes, systolic BP, and non-HDL cholesterol were significant factors, whereas others were not. CRP did not associate with aortic PWV.

Discussion

It is well established that diabetic ESRD patients have higher cardiovascular mortality than nondiabetic ESRD patients (5–8). Although the higher death rate in diabetic ESRD is presumably the result of more advanced atherosclerotic changes of arteries, this speculation is not directly supported by prospective studies. The aims of this study were to compare aortic stiffness between ESRD patients with and without diabetes mellitus and to examine the impact of aortic stiffness on cardiovascular mortality in a cohort of hemodialysis patients. We showed that the diabetic ESRD patients had higher aortic stiffness and higher cardiovascular mortality rates than nondiabetic ESRD patients. Aortic stiffness was an independent predictor of cardiovascular mortality in the total group of subjects. Furthermore, the impact of diabetes on cardiovascular mortality was replaced at least partly by the effect of aortic stiffness in the Cox model that included 13 covariates. These results provide the first evidence that more advanced atherosclerotic changes in diabetic ESRD contribute to the higher cardiovascular mortality rate of this population.

Except for this study, the report by Blacher *et al.* (19) is the only one that directly examined the power of aortic PWV in predicting mortality. Their and our studies are comparable in subject selection (ESRD patients were selected in the both studies), sample size ($n = 241$ *versus* $n = 265$), follow-up period (72 ± 41 *versus* 63 ± 23 mo), overall mortality (73 *versus* 81 fatal events), and definition of cardiovascular death. The proportion of cardiovascular events was slightly higher in the French patients (48 out of 73 overall events; 66%) than in our Japanese cohort (36 out of 81 overall events; 44%). The important difference was that our cohort included more diabetic patients (19%) than the Blacher's study (7%). We have confirmed the observation by Blacher *et al.* (19) that arterial stiffness as measured by aortic PWV was an independent predictor of cardiovascular and overall mortality, indicating that measurement of aortic PWV could serve as a noninvasive tool in the assessment of cardiovascular risk regardless of ethnic groups. Unfortunately, Blacher *et al.* did not examine

Table 2. Cox proportional hazards models for cardiovascular mortality in ESRD patients

Parameter	Model 1	Model 2	Model 3	Model 4
Age at entry	1.059[a]	1.046[b]	1.027	1.030
(per 1 yr)	(1.021–1.099)	(1.006–1.087)	(0.980–1.077)	(0.982–1.080)
Male *versus* female	1.495	1.448	2.228	2.423[b]
	(0.704–3.177)	(0.681–3.079)	(0.965–5.142)	(1.021–5.748)
Smoker *versus* nonsmoker	0.623	0.617	0.587	0.603
	(0.257–1.509)	(0.257–1.486)	(0.235–1.463)	(0.243–1.500)
C-reactive protein	1.037[b]	1.043[c]	1.044[b]	1.044[b]
(per 1 mg/l)	(1.006–1.069)	(1.011–1.076)	(1.010–1.080)	(1.009–1.080)
Hematocrit	0.993	1.001	1.016	1.005
(per 1%)	(0.904–1.091)	(0.911–1.100)	(0.920–1.122)	(0.910–1.110)
Body mass index	1.022	1.031	1.059	1.059
(per 1 kg/m^2)	(0.901–1.159)	(0.908–1.170)	(0.926–1.212)	(0.909–1.233)
Hemodialysis duration before entry	0.982	0.988	0.976	0.974
(per 1 yr)	(0.907–1.062)	(0.913–1.069)	(0.901–1.057)	(0.894–1.062)
Diabetic *versus* nondiabetic patient	2.320[b]	2.092[d]	1.523	1.498
	(1.024–5.258)	(0.918–4.770)	(0.593–3.909)	(0.571–3.932)
Aortic pulse wave velocity	—	1.162[b]	1.183[b]	1.152[d]
(per 1 m/s)		(1.000–1.356)	(1.007–1.390)	(0.978–1.359)
Serum creatinine	—	—	0.998[b]	0.998[b]
(per 1 μmol/l)			(0.995–1.000)	(0.995–1.000)
Systolic BP	—	—	0.999	0.997
(per 1 mmHg)			(0.980–1.018)	(0.979–1.016)
Diastolic BP	—	—	0.984	0.986
(per 1 mmHg)			(0.945–1.024)	(0.947–1.026)
Serum total protein	—	—	0.986	0.979
(per 1 g/l)			(0.913–1.065)	(0.904–1.060)
Non-HDL cholesterol	—	—	—	1.215
(per 1 mmol/l)				(0.834–1.770)
HDL cholesterol	—	—	—	0.545
(per 1 mmol/l)				(0.090–3.302)

This table gives hazard ratios (95% CI). [a] $P < 0.005$; [b] $P < 0.05$; [c] $P < 0.01$; [d] $P = 0.079–0.090$ by the Cox analysis.

the effect of diabetes mellitus on aortic stiffness or on mortality.

Stiffening of the aorta impairs the cushioning function of the arteries and results in increased systolic BP, decreased diastolic pressure, and increased pulse pressure (25). Therefore, several explanations were possible for the observed relationship between aortic stiffness and cardiovascular mortality. First, the elevated systolic pressure may result in increased cardiac afterload, left ventricular hypertrophy, increased oxygen consumption, and myocardial ischemia. London *et al.* (17) demonstrated that left ventricular mass correlated positively with aortic PWV in hemodialysis patients. Second, lower diastolic pressure could impair coronary perfusion, which occurs only during diastole. Third, increased pulse pressure is an independent predictor of cardiovascular mortality in the general population (26). Finally, changes in blood flow pattern might cause end-organ damage by adversely affecting arterioles and endothelial function downstream and impairing peripheral microcirculation.

The diabetic ESRD group in our study had a higher mean aortic PWV than the nondiabetic ESRD patients, although the two groups were not statistically different with respect to age and gender. This difference in aortic stiffness remained significant in the age-stratified comparisons except in the subgroup of 70 yr of age or older. Furthermore, multiple regression analysis indicated that diabetes was an independent factor associated with increased aortic PWV in the total subjects. Previous studies showed that aortic PWV was higher in those with ESRD (17,18) or with diabetes (27). To the best of our knowledge, this study is the first one showing that diabetes further increased aortic stiffness in an ESRD population.

There are several risk factors peculiar to ESRD populations, such as lower serum creatinine (28), lower serum albumin (29), lower body weight-for-height (30), and lower hematocrit (31). These data in ESRD patients have been interpreted to indicate that protein-energy malnutrition, reduced muscle mass, and renal anemia predict a poor prognosis in ESRD patients. In our cohort, the impact of serum creatinine was also significant, whereas the impact of body mass index, hematocrit, and total protein (not albumin) was not. Selective measurement of fat

Table 3. Cox proportional hazards models for overall mortality in ESRD patients

Parameter	Model 1	Model 2	Model 3	Model 4
Age at entry	1.061[a]	1.053[a]	1.016	1.016
(per 1 yr)	(1.035–1.088)	(1.025–1.081)	(0.986–1.047)	(0.986–1.047)
Male *versus* female	1.345	1.309	2.610[a]	2.590[a]
	(0.799–2.264)	(0.777–2.204)	(1.475–4.616)	(1.440–4.660)
Smoker *versus* nonsmoker	0.774	0.764	0.620	0.623
	(0.428–1.399)	(0.424–1.378)	(0.333–1.154)	(0.329–1.181)
C-reactive protein	1.031[b]	1.035[a]	1.041[a]	1.041[a]
(per 1 mg/l)	(1.008–1.054)	(1.012–1.058)	(1.016–1.066)	(1.016–1.066)
Hematocrit	0.995	1.001	1.030	1.033
(per 1%)	(0.934–1.061)	(0.938–1.067)	(0.963–1.103)	(0.964–1.108)
Body mass index	0.973	0.980	1.044	1.051
(per 1 kg/m^2)	(0.892–1.061)	(0.898–1.069)	(0.952–1.145)	(0.947–1.166)
Hemodialysis duration before entry	1.003	1.009	0.993	0.997
(per 1 yr)	(0.953–1.056)	(0.958–1.062)	(0.943–1.045)	(0.942–1.055)
Diabetic *versus* nondiabetic patient	2.566[a]	2.402[a]	1.558	1.561
	(1.460–4.511)	(1.363–4.233)	(0.810–2.997)	(0.798–3.052)
Aortic pulse wave velocity	—	1.100[c]	1.151[c]	1.156[c]
(per 1 m/s)		(1.000–1.236)	(1.031–1.285)	(1.032–1.295)
Serum creatinine	—	—	0.996[a]	0.996[a]
(per 1 μmol/l)			(0.995–0.998)	(0.995–0.998)
Systolic BP	—	—	1.002	1.003
(per 1 mmHg)			(0.990–1.015)	(0.990–1.016)
Diastolic BP	—	—	0.972[c]	0.971[c]
(per 1 mmHg)			(0.949–0.995)	(0.948–0.994)
Serum total protein	—	—	0.937[c]	0.941[c]
(per 1 g/l)			(0.887–0.991)	(0.889–0.997)
Non-HDL cholesterol	—	—	—	0.976
(per 1 mmol/l)				(0.738–1.292)
HDL cholesterol	—	—	—	1.294
(per 1 mmol/l)				(0.444–3.769)

This table gives hazard ratios (95% CI). [a] $P < 0.005$; [b] $P < 0.01$; [c] $P < 0.05$ by the Cox analysis.

mass and muscle mass might have provided more information than body mass index. Recombinant erythropoietin has been available for the treatment of renal anemia since 1990 in Japan, and such treatment might have reduced the predictive power of hematocrit. Also, serum albumin might be a better index of nutrition than serum total protein.

Increased CRP has been reported to be closely associated with cardiovascular disease in the general population (32,33) and in ESRD patients as well (34). In this study, we also observed a significant effect of CRP on cardiovascular and overall mortality. It is not known, however, whether inflammation in ESRD patients promotes arterial stiffening. This study did not find a significant relationship between CRP and aortic stiffness in the ESRD patients. The impact of CRP on either cardiovascular or overall mortality was independent of aortic PWV in our cohort. In addition, CRP did not have independent association with aortic PWV in the baseline study. In sharp contrast to our results, recent cross-sectional studies by Stenvinkel *et al.* (35) and Zoccali *et al.* (36) reported that CRP was an independent predictor for increased intimal thickening and the number of atherosclerotic plaques of carotid arteries in hemodialysis patients. Interestingly, Torzewski *et al.* (37) demonstrated co-localization of CRP, CRP receptor, and macrophage-specific CD68 in the intimal tissue of human carotid arteries, suggesting a role of CRP in the development of intimal lesions. Fichtlscherer *et al.* (38) revealed that an elevated CRP level was associated with impairment of endothelium-dependent, but not endothelium-independent, vasodilatation in patients with coronary artery disease. Taken together, these studies may indicate that CRP has greater effects on morphologic and functional changes of arterial intima than those of arterial media. Arterial stiffening largely results from changes in arterial media. Therefore, the lack of association between CRP and aortic PWV in our study is in line with these recent studies. In this context, the observed effects of CRP and PWV on cardiovascular mortality may indicate that changes in the intima and media independently contribute to poor long-term survival of ESRD patients. This possibility, however, needs to be explored in further studies in which thickness and stiffness of arterial wall are measured simultaneously.

Table 4. Multiple regression analysis of factors associated with aortic PWV in ESRD patients[a]

Parameter	Model 1		Model 2	
	β	P	β	P
Systolic BP	0.464	<0.0001	0.271	0.003
Diastolic BP	−0.248	<0.0001	−0.029	0.747
Age	—	—	0.333	<0.0001
Male gender	—	—	0.041	0.589
Diabetes mellitus	—	—	0.149	0.029
Smoker	—	—	0.019	0.773
Non-HDL cholesterol	—	—	0.167	0.009
HDL cholesterol	—	—	−0.035	0.585
Duration of hemodialysis	—	—	−0.045	0.489
Serum creatinine	—	—	0.085	0.254
Serum total protein	—	—	−0.005	0.937
Hematocrit	—	—	−0.032	0.605
C-reactive protein	—	—	−0.008	0.900
R^2	0.141 ($P < 0.001$)		0.267 ($P < 0.001$)	

[a] This table gives standard regression coefficients (β) and level of significance (P). R^2, multiple coefficient of determination.

Non-HDL cholesterol was a significant and independent factor affecting aortic PWV in multiple regression models. This was consistent with our previous cross-sectional study (18) that demonstrated that non-HDL cholesterol, particularly cholesterol in the intermediate-density lipoprotein fraction, was an independent lipoprotein variable affecting aortic PWV in nondiabetic ESRD patients. However, although there were correlations between the lipid variables, aortic PWV, and cardiovascular mortality, neither the HDL nor the non-HDL cholesterol levels significantly predicted cardiovascular mortality in this cohort. Previous studies (39) showed that higher plasma total cholesterol was associated with lower mortality in hemodialysis patients. Thus, the relation between plasma lipids and mortality in ESRD patients is complex, presumably because a high plasma lipid level may be a marker of pro-atherogenic condition on one hand and an indicator of adequate nutrition and/or absence of microinflammation on the other (39).

In conclusion, our study demonstrates that aortic stiffness is more pronounced in diabetic compared with nondiabetic ESRD patients and that the increased aortic stiffness of the diabetic ESRD patients contributes to the higher cardiovascular mortality rate in this group. Further studies are needed to elucidate the factors affecting aortic stiffness and the reversibility of it to improve the prognosis of ESRD patients.

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References

1. Lindner A, Charra B, Sherrard DJ, Scribner BH: Accelerated atherosclerosis in prolonged maintenance hemodialysis. *N Engl J Med* 290: 697–701, 1974
2. Ma KW, Greene EL, Raij L: Cardiovascular risk factors in chronic renal failure and hemodialysis populations. *Am J Kidney Dis* 19: 505–513, 1992
3. Kannel WB, McGee DL: Diabetes and cardiovascular disease. The Framingham study. *JAMA* 241: 2035–2038, 1979
4. Pyorala K, Laakso M, Uusitupa M: Diabetes and atherosclerosis: An epidemiologic view. *Diabetes Metab Rev* 3: 463–524, 1987
5. Excerpts from United States Renal Data System 1999 Annual Data Report. *Am J Kidney Dis* 34: S1–S176, 1999
6. Brunner FP, Selwood NH: Profile of patients on RRT in Europe and death rates due to major causes of death groups. The EDTA Registration Committee. *Kidney Int Suppl* 38: S4–S15, 1992
7. Shinzato T, Nakai S, Akiba T, Yamagami S, Yamazaki C, Kitaoka T, Kubo K, Maeda K, Morii H: Report of the annual statistical survey of the Japanese Society for Dialysis Therapy in 1996. *Kidney Int* 55: 700–712, 1999
8. Johnson JG, Gore SM, Firth J: The effect of age, diabetes, and other comorbidity on the survival of patients on dialysis: A systematic quantitative overview of the literature. *Nephrol Dial Transplant* 14: 2156–2164, 1999
9. O'Rourke M: Mechanical principles in arterial disease. *Hypertension* 26: 2–9, 1995
10. Hosoi M, Nishizawa Y, Kogawa K, Kawagishi T, Konishi T, Maekawa K, Emoto M, Fukumoto S, Shioi A, Shoji T, Inaba M, Okuno Y, Morii H: Angiotensin-converting enzyme gene polymorphism is associated with carotid arterial wall thickness in non-insulin-dependent diabetic patients. *Circulation* 94: 704–707, 1996
11. Kogawa K, Nishizawa Y, Hosoi M, Kawagishi T, Maekawa K, Shoji T, Okuno Y, Morii H: Effect of polymorphism of apolipoprotein E and angiotensin-converting enzyme genes on arterial wall thickness. *Diabetes* 46: 682–687, 1997
12. Taniwaki H, Kawagishi T, Emoto M, Shoji T, Hosoi M, Kogawa K, Nishizawa Y, Morii H: Association of ACE gene polymorphism with arterial stiffness in patients with type 2 diabetes. *Diabetes Care* 22: 1858–1864, 1999
13. Kawagishi T, Nishizawa Y, Konishi T, Kawasaki K, Emoto M, Shoji T, Tabata T, Inoue T, Morii H: High-resolution B-mode

ultrasonography in evaluation of atherosclerosis in uremia. *Kidney Int* 48: 820–826, 1995
14. Shoji T, Kawagishi T, Emoto M, Maekawa K, Taniwaki H, Kanda H, Tabata T, Nishizawa Y: Additive impacts of diabetes and renal failure on carotid atherosclerosis. *Atherosclerosis* 153: 257–258, 2000
15. O'Leary DH, Polak JF, Kronmal RA, Manolio TA, Burke GL, Wolfson SK, Jr: Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. Cardiovascular Health Study Collaborative Research Group. *N Engl J Med* 340: 14–22, 1999
16. Emoto M, Nishizawa Y, Kawagishi T, Maekawa K, Hiura Y, Kanda H, Izumotani K, Shoji T, Ishimura E, Inaba M, Okuno Y, Morii H: Stiffness indexes beta of the common carotid and femoral arteries are associated with insulin resistance in NIDDM. *Diabetes Care* 21: 1178–1182, 1998
17. London GM, Marchais SJ, Safar ME, Genest AF, Guerin AP, Metivier F, Chedid K, London AM: Aortic and large artery compliance in end-stage renal failure. *Kidney Int* 37: 137–142, 1990
18. Shoji T, Nishizawa Y, Kawagishi T, Kawasaki K, Taniwaki H, Tabata T, Inoue T, Morii H: Intermediate-density lipoprotein as an independent risk factor for aortic atherosclerosis in hemodialysis patients. *J Am Soc Nephrol* 9: 1277–1284, 1998
19. Blacher J, Guerin AP, Pannier B, Marchais SJ, Safar ME, London GM: Impact of aortic stiffness on survival in end-stage renal disease. *Circulation* 99: 2434–2439, 1999
20. Hasegawa M: Fundamental studies on pulse wave velocity of human aorta. *Jikei Med J* 85: 742–760, 1970
21. Nye E: The effect of pressure alteration on the pulse wave velocity. *Br Heart J* 26: 261–265, 1964
22. Guerin AP, Blacher J, Pannier B, Marchais SJ, Safar ME, London GM: Impact of aortic stiffness attenuation on survival of patients in end-stage renal failure. *Circulation* 103: 987–992, 2001
23. Shoji T, Nishizawa Y, Kawagishi T, Tanaka M, Kawasaki K, Tabata T, Inoue T, Morii H: Atherogenic lipoprotein changes in the absence of hyperlipidemia in patients with chronic renal failure treated by hemodialysis. *Atherosclerosis* 131: 229–236, 1997
24. Finley PR, Schifman RB, Williams RJ, Lichti DA: Cholesterol in high-density lipoprotein: Use of Mg^{2+}/dextran sulfate in its enzymic measurement. *Clin Chem* 24: 931–933, 1978
25. London GM, Drueke TB: Atherosclerosis and arteriosclerosis in chronic renal failure. *Kidney Int* 51: 1678–1695, 1997
26. Benetos A, Safar M, Rudnichi A, Smulyan H, Richard JL, Ducimetieere P, Guize L: Pulse pressure: A predictor of long-term cardiovascular mortality in a French male population. *Hypertension* 30: 1410–1415, 1997
27. Taniwaki H, Kawagishi T, Emoto M, Shoji T, Kanda H, Maekawa K, Nishizawa Y, Morii H: Correlation between the intima-media thickness of the carotid artery and aortic pulse-wave velocity in patients with type 2 diabetes. Vessel wall properties in type 2 diabetes. *Diabetes Care* 22: 1851–1857, 1999
28. United States Renal Data System. Comorbid conditions and correlations with mortality risk among 3,399 incident hemodialysis patients. *Am J Kidney Dis* 20: 32–38, 1992
29. Foley RN, Parfrey PS, Harnett JD, Kent GM, Murray DC, Barre PE: Hypoalbuminemia, cardiac morbidity, and mortality in end-stage renal disease. *J Am Soc Nephrol* 7: 728–736, 1996
30. Kopple JD, Zhu X, Lew NL, Lowrie EG: Body weight-for-height relationships predict mortality in maintenance hemodialysis patients. *Kidney Int* 56: 1136–1148, 1999
31. Ma JZ, Ebben J, Xia H, Collins AJ: Hematocrit level and associated mortality in hemodialysis patients. *J Am Soc Nephrol* 10: 610–619, 1999
32. Liuzzo G, Biasucci LM, Gallimore JR, Grillo RL, Rebuzzi AG, Pepys MB, Maseri A: The prognostic value of C-reactive protein and serum amyloid a protein in severe unstable angina. *N Engl J Med* 331: 417–424, 1994
33. Tracy RP, Lemaitre RN, Psaty BM, Ives DG, Evans RW, Cushman M, Meilahn EN, Kuller LH: Relationship of C-reactive protein to risk of cardiovascular disease in the elderly. Results from the Cardiovascular Health Study and the Rural Health Promotion Project. *Arterioscler Thromb Vasc Biol* 17: 1121–1127, 1997
34. Zimmermann J, Herrlinger S, Pruy A, Metzger T, Wanner C: Inflammation enhances cardiovascular risk and mortality in hemodialysis patients. *Kidney Int* 55: 648–658, 1999
35. Stenvinkel P, Heimburger O, Paultre F, Diczfalusy U, Wang T, Berglund L, Jogestrand T: Strong association between malnutrition, inflammation, and atherosclerosis in chronic renal failure. *Kidney Int* 55: 1899–1911, 1999
36. Zoccali C, Benedetto FA, Mallamaci F, Tripepi G, Fermo I, Foca A, Paroni R, Malatino LS: Inflammation is associated with carotid atherosclerosis in dialysis patients. Creed Investigators. Cardiovascular Risk Extended Evaluation in Dialysis Patients. *J Hypertens* 18: 1207–1213, 2000
37. Torzewski M, Rist C, Mortensen RF, Zwaka TP, Bienek M, Waltenberger J, Koenig W, Schmitz G, Hombach V, Torzewski J: C-reactive protein in the arterial intima: Role of C-reactive protein receptor-dependent monocyte recruitment in atherogenesis. *Arterioscler Thromb Vasc Biol* 20: 2094–2099, 2000
38. Fichtlscherer S, Rosenberger G, Walter DH, Breuer S, Dimmeler S, Zeiher AM: Elevated C-reactive protein levels and impaired endothelial vasoreactivity in patients with coronary artery disease. *Circulation* 102: 1000–1006, 2000
39. Ritz E: Why are lipids not predictive of cardiovascular death in the dialysis patient? *Miner Electrolyte Metab* 22: 9–12, 1996