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Arterial stiffness in predialysis patients with uremia

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Arterial stiffness in predialysis patients with uremia.

Background. Hemodialysis patients have advanced arterial wall stiffening as shown by increased aortic pulse wave velocity (PWV), an independent predictor of cardiovascular mortality. We compared aortic PWV of uremic patients before starting hemodialysis treatment with that of patients on maintenance hemodialysis.

Methods. The subjects were 71 patients with end-stage renal disease (ESRD) before starting hemodialysis (predialysis group), 144 patients on maintenance hemodialysis, and 140 healthy control subjects. These three groups were all nondiabetic and comparable in age and gender.

Results. The hemodialysis group had greater aortic PWV than the healthy subjects, and the predialysis patients showed a still higher value than the hemodialysis group. Multiple regression analysis in the total subjects revealed that the presence of renal failure was significantly associated with increased aortic PWV independent of age, gender, blood pressure, body mass index, smoking, high-density lipoprotein (HDL) and nonhigh-density lipoprotein (non-HDL) cholesterol levels. In contrast, hemodialysis was associated with decreased aortic PWV independent of renal failure and the other factors. Further analyses in the combined uremic patients again indicated the favorable impact of hemodialysis on aortic PWV independent of the classical risk factors, use of antihypertensive medications, including angiotensin-converting enzyme inhibitors and calcium channel blockers, hematocrit, serum calcium, phosphorus, parathyroid hormone levels, and the use of calcium carbonate. Insulin resistance using homeostasis model assessment (HOMA-IR) was associated with increased aortic PWV.

Conclusion. Aortic stiffening was present in uremic patients before starting hemodialysis treatment and no adverse effect of hemodialysis was observed, suggesting the important roles of renal failure and/or metabolic alterations secondary to renal failure in arterial stiffness in patients with uremia.

Key words: arterial stiffness, chronic kidney disease, dyslipidemia, insulin resistance, atherosclerosis.

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Cardiovascular disease is a major cause of death in patients with end-stage renal disease (ESRD) treated with hemodialysis, and their risk relative to the general population exceeds 10 for death from cardiovascular disease [1]. Also, hemodialysis patients have advanced arterial wall changes as shown by increased thickness of carotid artery [2] and increased stiffness of aorta [3, 4]. Recent studies showed that these morphologic [5, 6] and functional properties [7,8] of arterial wall are predictors of death from cardiovascular disease in hemodialysis populations independent of the classical risk factors.

So far, it is not established whether hemodialysis treatment promotes these arterial wall changes, although Lindner et al [9] speculated that long-term hemodialysis accelerated atherosclerosis. Most of previous cross-sectional studies showed no significant relationship of duration of hemodialysis with histologic grading [10], thickness [2, 11], or stiffness [3, 4] of arterial wall of patients on maintenance hemodialysis. In addition, hemodialysis duration did not associate with the risk of death from cardiovascular disease [7, 8]. Recently, Joki et al [12] reported that significant stenosis of coronary arteries is frequently found in uremic patients at the time of starting hemodialysis. Muntner et al [13] showed that the risk of cardiovascular mortality is elevated in patients with chronic renal insufficiency. Mourad et al [14] found that increased arterial stiffness is significantly associated with reduced creatinine clearance in subjects with mild-to-moderate renal failure. These studies indicate that arterial wall change is advanced and the risk of cardiovascular death is elevated before starting hemodialysis, although these studies did not examine the possible effects of hemodialysis. We [11] recently found that carotid artery intima-media thickness of predialysis patients was as great as that of maintenance hemodialysis patients, and that the presence of renal failure, but not hemodialysis, was a significant risk factor for the arterial thickening. To date, no previous study performed comparison of arterial

Table 1. Subjects

	Healthy	Predialysis	Hemodialysis	*P* value
Number	140	71	144	—
Male gender	59 (42%)	41(58%)	69 (47%)	0.100
Age *years*	60 ± 10	61 ± 13	60 ± 9	0.590
Smoker	44 (31%)	31 (44%)	40 (28%)	0.062
Body mass index kg/m^2	22.6 ± 2.7	21.7 ± 3.4	21.4 ± 2.5[a]	0.001
Systolic blood pressure *mm Hg*	128 ± 17	143 ± 23[a]	153 ± 26[a,b]	<0.0001
Diastolic blood pressure *mm Hg*	79 ± 11	81 ± 13	84 ± 14[a]	0.005
Total cholesterol *mg/dL*	211 ± 29	162 ± 43[a]	168 ± 40[a]	<0.0001
HDL cholesterol *mg/dL*	62 ± 20	39 ± 12[a]	40 ± 13[a]	<0.0001
Non-HDL cholesterol *mg/dL*	149 ± 31	122 ± 42[a]	128 ± 40[a]	<0.0001
Triglycerides *mg/dL*	97 (45–424)	97 (27–248)	113 (33–378)	0.062
Fasting glucose *mg/dL*	96 ± 12	88 ± 10[a]	79 ± 12[a,b]	<0.0001
Insulin μ*U/mL*	5.0 (2.0–26)	8.6 (1.0–25)	6.8 (2–20)	<0.0001
HOMA-IR	0.97(0.39–6.93)	1.62 (0.18–6.17)	1.23 (0.34–4.59)	<0.0001
Serum creatinine *mg/dL*	0.9 ± 0.2	10.0 ± 3.4[a]	11.5 ± 1.8[a,b]	<0.0001
Serum calcium *mg/dL*	—	8.7 ± 1.2	9.4 ± 0.9	<0.0001
Serum phosphorus *mg/dL*	—	6.6 ± 1.8	6.0 ± 1.4	0.0125
Calcium × phosphorus	—	52.3 ± 16	55.6 ± 14	0.125
Intact parathyroid hormone *pg/mL*	—	282 (10–788)	132 (10–1900)	0.0003
C-reactive protein *mg/dL*	—	0.4 (0.1–5.2)	0.4 (0.1–5.4)	0.641
Hematocrit %	—	24.9 ± 4.6	27.3 ± 4.2	0.0002
Serum albumin *g/dL*		3.2 ± 0.5	3.7 ± 0.6	<0.0001
Medication for hypertension	—	61 (86%)	64 (54%)	<0.0001
Use of ACE inhibitors	—	9 (13%)	21 (15%)	0.468
Use of calcium channel blockers	—	56 (79%)	53 (37%)	<0.0001
Use of calcium carbonate	—	16 (23%)	109 (76%)	<0.0001
Presence of vascular complications	—	8 (11%)	28 (19%)	0.131
Duration of hemodialysis *years*	—	—	7.5 ± 5.4	—

Abbreviations are: HDL, high-density lipoprotein; non-HDL, non-high-density lipoprotein; HOMA-IR, insulin resistance index by homeostasis model assessment; ACE, angiotensin-converting enzyme.

Data are percentage, mean ± SD, and median (range). *P* values are by chi-square test, analyses of variance (ANOVA), and Kruskal-Wallis test, respectively.

[a] $P < 0.05$ vs. healthy control subjects; [b] $P < 0.05$ vs. predialysis group by Scheffe-type multiple comparison.

stiffness between predialysis and hemodialysis patients with ESRD.

The purpose of the present study was to compare arterial stiffness between predialysis and hemodialysis patients, and to evaluate the factors affecting arterial stiffness in patients with uremia.

METHODS

Subjects

This study consisted of 355 subjects including 71 patients with chronic renal failure just before starting hemodialysis treatment (predialysis group), 144 patients with ESRD treated with maintenance hemodialysis (hemodialysis group), and 140 healthy control subjects. We randomly selected these subjects from our database after categorizing by age and gender, so that the three groups were comparable in age and gender. Information was compiled from the questionnaire about smoking habits and past history of vascular diseases, including coronary artery, cerebrovascular, and peripheral artery diseases. Clinical characteristics of the subjects were given in Table 1. Informed consent was obtained from all study participants. This study was approved by the Institutional Ethical Committee.

Patients in the predialysis group were those with ESRD entering hemodialysis treatment. All measurements were done 1 to 3 days before their first hemodialysis session. The primary renal diseases of the predialysis group were chronic glomerulonephritis (59%), hypertensive nephrosclerosis (14%), polycystic disease (8%), toxemia of pregnancy (3%), chronic pyelonephritis (1%), systemic lupus erythematodes (1%), and unknown (14%). We excluded patients who had been diagnosed to have diabetes mellitus on the basis of past history and/or presence of overt fasting hyperglycemia of 126 mg/dL or greater [15]. Medication for hypertension included calcium channel blockers (79%), angiotensin-converting enzyme (ACE) inhibitors (13%), α-, β- or αβ-receptor antagonists (30%), and loop diuretics (25%). Of the predialysis patients, 86% received antihypertensive medication. Statins were used for 3% of the predialysis patients for dyslipidemia. These patients were studied without washing out these medications.

Patients in the hemodialysis group were those who were on maintenance hemodialysis for more than three months. The hemodialysis patients received 3 to 5 hours of hemodialysis, three times a week, using bicarbonate dialysate. Dialyzer membranes were cuprophane (54%), polymethylmethacrylate (26%), cellulose triacetate (18%), and ethylenevinyl alcohol (3%).

The primary renal diseases of the hemodialysis group were chronic glomerulonephritis (72%), hypertensive nephrosclerosis (5%), polycystic disease (9%), toxemia of pregnancy (3%), chronic pyelonephritis (2%), gout (2%), systemic lupus erythematodes (2%), and unknown (7%). We excluded diabetic patients using the same criteria as above [15]. Medication for hypertension included calcium channel blockers (42%), ACE inhibitors (17%), α-, β- or αβ-receptor antagonists (6%), and loop diuretics (24%). Of the hemodialysis patients, 54% received antihypertensive medication. Statins were used for 3% of the hemodialysis patients for dyslipidemia. These patients were studied without washing out these medications.

The healthy control subjects were participants of a local health check program at the Osaka Municipal Health Promotion Center. We excluded subjects with overt hyperglycemia using the same criteria as above [15], overt proteinuria, and liver dysfunction as defined by increased serum alanine aminotransferase (ALT) >50 IU. Those on medication for diabetes mellitus, hypertension, and/or hyperlipidemia were also excluded. Therefore, the healthy control subjects included those who were hypertensive and/or hyperlipidemic without medication.

Blood pressure and aortic pulse wave velocity (PWV) measurement

Blood pressure and aortic PWV measurements were made with the patients in a supine position after a 5-minute bed rest. In hemodialysis patients, these measurements were performed 1 to 2 hours after hemodialysis to avoid possible effects of volume overload before dialysis and to reduce acute hemodynamic changes just after dialysis. Blood pressure was measured with a mercury sphygmomanometer and a standard cuff in the arm. The average of two blood pressure measurements was recorded.

Aortic PWV was measured as a noninvasive index of aortic sclerosis [16] by the method of Hasegawa [17], using a PWV meter (model PWV-200) (Fukuda Denshi, Tokyo, Japan) as previously described [4, 8]. Briefly, amorphous sensors were put on the skin at right femoral and left carotid arteries to record pulse waves. Heart sounds S1 and S2 were detected by a microphone set on the right edge of the sternum at the second intercostals space. Electrocardiogram was monitored with electrodes placed on the right and left arms and right leg. The PWV meter measures time intervals between pulse waves at the carotid and femoral sites (T) and between S2 and the notch of carotid pulse wave (Tc). PWV of the aorta was calculated as follows:

$$\mathrm{PWV[m/s]} = 1.3\mathrm{L}/(\mathrm{T} + \mathrm{Tc})$$

where L is the measured distance in meter between the heart sound microphone and the femoral probe. The actual distance between the aortic orifice and the femoral artery was estimated to be 1.3 L [17]. T + Tc indicates the time in second for the pulse waves to travel from the aortic orifice to the femoral artery. PWV measurements were done for five consecutive pulses, and the average was used for analysis. The interobservation variation (coefficient of variation) was less than 5%.

Blood sampling and assays

Blood was drawn in the morning after an overnight fast of at least 12 hours. In patients with hemodialysis treatment, fasting blood was taken at least 44 hours after the previous dialysis session. Serum albumin, calcium, phosphorus, C-reactive protein, and intact parathyroid hormone (PTH) were measured in the predialysis and hemodialysis patients. Whole blood was used for hematocrit, ethylenediaminetetraacetic acid (EDTA)-plasma for glucose, insulin and lipids, and serum for other biochemical assays. Glucose was measured by a glucose oxidase method. Insulin was measured by radioimmunometric assay (RIA) (Dinabot Co., Tokyo, Japan). Total cholesterol was measured enzymatically. High-density lipoprotein (HDL) cholesterol was measured after precipitating apolipoprotein B-containing lipoproteins with dextran sulfate and magnesium. Non-high-density lipoprotein (non-HDL) cholesterol was calculated by subtracting HDL cholesterol from total cholesterol. Other measurements were by routine methods.

Assessment of insulin resistance using homeostasis model assessment (HOMA-IR) index

Insulin resistance was evaluated using the HOMA-IR index originally described by Matthews et al [18]. HOMA-IR was calculated using the following formula:

$$\begin{aligned}\text{HOMA-IR} = {} & \text{fasting glucose(mmol/L)} \\ & \times \text{fasting insulin}(\mu\text{U/mL})/22.5\end{aligned}$$

HOMA-IR correlated closely with the insulin sensitivity index by the standard euglycemic hyperinsulinemic clamp as shown by Matthews et al [18] and by us [19]. This index can be used in subjects with renal failure [20].

Statistical analysis

Data were summarized as percentage, mean ± SD, and median (range). Difference in prevalence was evaluated by chi-squared test. Difference between mean values was assessed by analysis of variance (ANOVA), and then post hoc test was performed by Scheffe-type multiple comparison. Median (range) was given for triglycerides, insulin, HOMA-IR, C-reactive protein, and intact PTH because of their skewed distribution. Difference in median values was assessed by Mann-Whitney test or Kruskal-Wallis test. These variables with skewed distribution were

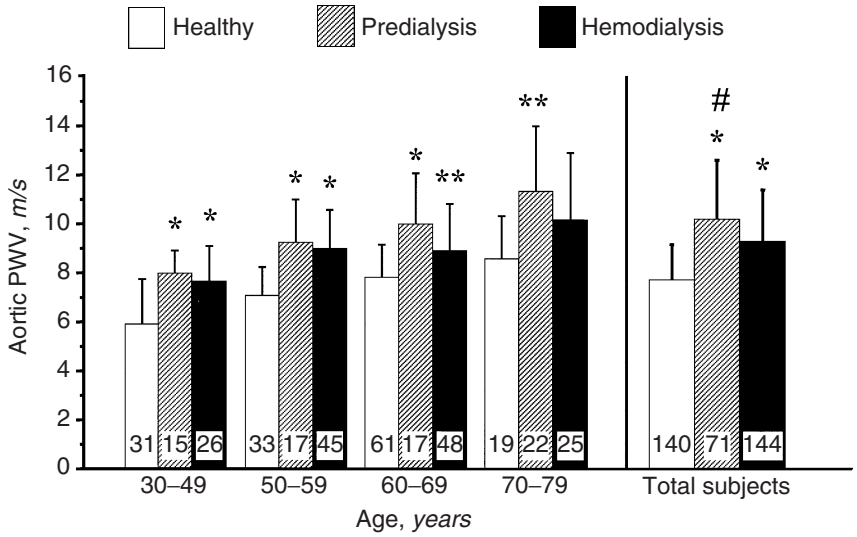

Fig. 1. Aortic pulse wave velocity (PWV) of the healthy, predialysis, and hemodialysis groups. Data are mean ± standard deviation. Numbers in each column indicate the number of subjects. $^{*}P < 0.01$ vs. healthy control group; $^{**}P < 0.001$ vs. healthy control group; $^{\#}P < 0.05$ vs. hemodialysis group by Scheffe-type multiple comparison. Difference between the predialysis and hemodialysis groups was significant in comparison where the subjects were not stratified by age.

entered to univariate and multivariate regression models after log-transformation. Correlation between two variables was examined by linear regression analysis. Multiple regression analysis was used to assess independent associations between one dependent and two or more independent variables. Dummy variables were used for gender (female = 0, male = 1), presence of renal failure (no = 0, yes = 1), hemodialysis (nonhemodialysis = 0, hemodialysis = 1), smoking (nonsmoker = 0, smoker = 1), and antihypertensive medications (no = 0, yes = 1). *P* values less than 0.05 were considered significant. All these analyses were performed using statistics software for Windows (StatView 5) (SAS Institute Inc., Cary, NC, USA) on personal computers.

RESULTS

Comparison of aortic PWV among the three groups

Figure 1 shows aortic PWV of the three groups. As compared with the healthy group (7.4 ± 1.4 m/second), the predialysis group (9.7 ± 2.4 m/second, $P = 0.001$) and the hemodialysis group (8.9 ± 2.0 m/second, $P < 0.0001$) had a significantly greater aortic PWV. In age-categorized comparison, the increased aortic PWV in the hemodialysis group remained significant in the 30 to 49, 50 to 59, and 60 to 69 years, but not in the 70 to 79 years. The increased aortic PWV of the predialysis group was significant in all age ranges.

When compared between the predialysis and hemodialysis groups, aortic PWV was significantly greater in the predialysis group ($P = 0.001$). The difference between the predialysis and the hemodialysis groups were not significant when the subjects were divided into age categories.

Correlation between aortic PWV and other factors

Factors affecting aortic PWV were examined by simple regression analysis (Table 2). In the total subjects, aortic PWV correlated positively with age, systolic blood pressure, diastolic blood pressure, insulin (log-transformed), and HOMA-IR (log-transformed), and negatively with HDL cholesterol. In the healthy control group, aortic PWV correlated positively with age, systolic blood pressure, diastolic blood pressure, non-HDL cholesterol, and fasting glucose. Aortic PWV correlated only with age in the predialysis group. In the hemodialysis group, it correlated positively with age, systolic blood pressure, and total cholesterol, negatively with serum calcium. In the combined group of patients with chronic renal failure (predialysis + hemodialysis), aortic PWV correlated positively with age and systolic blood pressure, and patients taking antihypertensive medications had a higher aortic PWV than the other patients.

Independent factors associated with aortic PWV

Factors independently associated with aortic PWV were examined by using multiple regression models in the total subjects (Table 3). In the first model, including classical risk factors, PWV was associated positively with age and systolic blood pressure and negatively with HDL cholesterol. In model 2, to which the presence of renal failure was added, the presence of renal failure was shown as a significant factor associated with aortic PWV independent of the above factors. In model 3, including hemodialysis as an additional variable, the association of renal failure with increased aortic PWV remained significant, while hemodialysis treatment had a significant association with decreased aortic PWV. In addition to these, aortic PWV had significant and independent

Table 2. Simple regression analysis of factors correlating with aortic pulse wave velocity (PWV)

Variables	Total	Healthy	Predialysis	Hemodialysis	Hemodialysis + Predialysis
Age	0.383[c]	0.471[c]	0.540[c]	0.286[c]	0.402[c]
Male gender	0.042	0.028	−0.024	−0.019	−0.003
Smoking	−0.022	−0.030	−0.055	−0.070	−0.033
Body mass index	−0.098	0.048	−0.099	−0.028	−0.049
Systolic blood pressure	0.356[c]	0.385[c]	0.176	0.236[b]	0.173[a]
Diastolic blood pressure	0.141[b]	0.270[b]	−0.083	0.103	0.021
Log (triglycerides)	0.063	0.106	−0.018	0.222	0.093
HDL cholesterol	−0.262[c]	−0.047	−0.135	0.015	−0.047
Non-HDL cholesterol	−0.003	0.267[b]	0.010	0.165	0.092
Fasting glucose	−0.067	0.307[c]	0.031	0.041	0.099
Log (insulin)	0.196[c]	0.078	−0.049	0.095	0.055
Log (HOMA-IR)	0.165[b]	0.125	−0.043	0.101	0.075
Serum creatinine	0.345[c]	0.079	−0.150	−0.002	−0.124
Serum calcium	—	—	0.069	−0.172[a]	−0.130
Serum phosphorus	—	—	0.021	−0.068	−0.014
Calcium × phosphorus	—	—	0.003	−0.128	−0.072
Log (intact parathyroid hormone)	—	—	−0.087	−0.002	0.009
Log (C-reactive protein)	—	—	0.159	0.098	0.131
Hematocrit	—	—	0.106	−0.096	−0.064
Medication for hypertension%	—	—	0.049	0.179	0.188[b]
Duration of hemodialysis	—	—	—	−0.113	—

Abbreviations are: HDL, high-density lipoprotein; Non-HDL, non-high-density lipoprotein; HOMA-IR, insulin resistance index by homeostasis model assessment.
[a]$P < 0.05$; [b]$P < 0.01$; [c]$P < 0.001$.

Table 3. Multiple regression analysis of factors affecting aortic pulse wave velocity (PWV) in the total subjects ($N = 355$)

	Model 1	Model 2	Model 3
Age	0.359[b]	0.386[b]	0.367[b]
Male gender	0.087	0.098	0.096
Smoking	−0.019	−0.018	−0.034
Systolic blood pressure	0.330[b]	0.202[a]	0.243[b]
Diastolic blood pressure	−0.026	0.013	−0.006
Non-HDL cholesterol	0.067	0.137[a]	0.150[a]
HDL cholesterol	−0.189[b]	0.005	0.007
Body mass index	−0.071	−0.020	−0.024
Presence of renal failure	—	0.357[b]	0.488[b]
Hemodialysis	—	—	−0.213[b]
R^2	0.320[b]	0.381[b]	0.405[b]

Abbreviations are: HDL, high-density lipoprotein; R^2, multiple coefficient of determination.
The table gives standard regression coefficients (β values).
[a]$P < 0.01$; [b]$P < 0.001$.

Table 4. Multiple regression analysis of factors affecting aortic pulse wave velocity (PWV) in patients with renal failure ($N = 215$)

	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6
Age	0.405[c]	0.416[c]	0.409[c]	0.418[c]	0.444[c]	0.417[c]
Male gender	0.033	0.072	0.038	0.028	−0.004	0.060
Smoking	−0.022	−0.017	−0.019	−0.021	−0.023	0.037
Systolic blood pressure	0.244[c]	0.219[c]	0.246[c]	0.229[c]	0.247[c]	0.280[c]
Non-HDL cholesterol	0.135[a]	0.148[a]	0.132[a]	0.115	0.140[a]	0.115
HDL cholesterol	−0.023	−0.039	−0.010	−0.024	−0.008	−0.049
Body mass index	−0.021	−0.027	−0.022	−0.031	−0.040	−0.070
Hemodialysis	−0.198[b]	−0.216[b]	−0.201[b]	−0.170[a]	−0.234[c]	−0.171[a]
Medication for hypertension	—	0.050	—	—	—	—
Hematocrit	—	—	−0.004	—	—	—
Serum calcium	—	—	—	0.001	—	—
Serum phosphorus	—	—	—	0.049	—	—
Log (intact parathyroid hormone)	—	—	—	0.002	—	—
Serum creatinine	—	—	—	—	0.118	—
Log (HOMA-IR)	—	—	—	—	—	0.147[a]
R^2	0.265[c]	0.288[c]	0.270[c]	0.241[c]	0.274[c]	0.291[c]

Abbreviations are: HDL, high-density lipoprotein; Non-HDL, non-high-density lipoprotein; HOMA-IR, insulin resistance index by homeostasis model assessment; R^2, multiple coefficient of determination.
The negative impact of hemodialysis on aortic PWV was significant in model 1. Then, possible confounding factors were evaluated in the subsequent models. The table gives standard regression coefficients (β values).
[a]$P < 0.05$; [b]$P < 0.01$; [c]$P < 0.001$.

associations with age, systolic blood pressure, and non-HDL cholesterol in this model.

Association of aortic PWV with uremia-related factors

The above results showed the associations of the presence of renal failure and hemodialysis treatment with increased and decreased aortic PWV, respectively. To examine a possibility that the latter finding was confounded by other factors relating renal failure and hemodialysis, we further analyzed the data using multivariate models in the predialysis and hemodialysis groups (Table 4). In model 1, containing classic risk factors and hemodialysis treatment, hemodialysis was again shown as a significant factor associated with decreased aortic PWV.

Because the predialysis and hemodialysis groups were significantly different in the use of antihypertensive medications, hematocrit, parameters of calcium homeostasis, serum creatinine, and the index of insulin resistance, these variables were added as uremia-related variables in the subsequent analyses (models 2 to 6). HOMA-IR was a significant and independent factor associated with

aortic PWV, whereas other uremia-related factors did not show significant association with aortic PWV. Importantly, hemodialysis treatment remained a significant factor associated with decreased aortic PWV in all of these models. Also, the positive associations of age and systolic blood pressure remained significant. The positive association between non-HDL cholesterol and aortic PWV was significant in models 1, 2, 3, and 5. Further analyses indicated that aortic PWV had no significant association with the use of ACE inhibitors, calcium channel blockers, or calcium carbonate. A phosphate binder sevelamer was not available in Japan at the time of this study. Also, aortic PWV did not have significant association with serum albumin or C-reactive protein levels (data not shown).

DISCUSSION

In the present study, we compared aortic PWV between predialysis and hemodialysis patients to evaluate the effects of renal failure and hemodialysis on artery wall stiffness. These two groups had a significantly greater aortic PWV than the healthy subjects. The mean aortic PWV of the predialysis group was higher than that of the hemodialysis group. Multiple regression analyses revealed that aortic PWV had a positive association with the presence of renal failure and a negative association with hemodialysis treatment independent of other factors. Further analyses indicated that blood pressure, non-HDL cholesterol, and HOMA-IR as independent factors associated with aortic PWV of the renal failure patients. These results suggest that it is not hemodialysis but renal failure and/or uremia-related metabolic abnormalities that have adverse effects on aortic stiffness.

Although, a recent study [13] has shown an increased risk of cardiovascular death in patients with chronic renal insufficiency, there is only limited amount of information about the arterial wall changes in predialysis patients with chronic renal failure. Bonomini et al [21] previously reported that the longer the duration of uremia on low protein diet, the worse were the clinical and metabolic problems of atherosclerosis, suggesting the role of renal failure in atherosclerosis. In our recent study [11], we found that predialysis patients had increased carotid artery intima-media thickness. Joki et al [12] reported a high prevalence of significant coronary artery stenosis in patients starting hemodialysis. These studies indicate the presence of morphologic alterations in arterial wall in predialysis patients. Mourad et al [14] found an inverse correlation between aortic PWV and creatinine clearance in subjects with mild-to-moderate renal failure. In the present study, we showed a remarkable increase in aortic PWV in uremic patients just before starting hemodialysis. Thus, this study provides further evidence that the functional property of arterial wall is impaired not only in hemodialysis patients but also in predialysis patients with renal failure.

Our results indicated the associations of renal failure and hemodialysis with increased and decreased aortic PWV, respectively. There are several possibilities that explain this finding. First, the result might have been confounded by some factors that differed between these two groups in the baseline comparison. To rule out this possibility, we reanalyzed the data by using multivariate models that included the use of antihypertensive medications, including ACE inhibitors [22] and calcium channel blockers [23], hematocrit, parameters of calcium homeostasis, the use of phosphate binders [24], and an index of insulin resistance HOMA-IR as covariates. However, the association between treatment with hemodialysis and decreased aortic PWV remained significant.

Second, volume overload may be an important factor for aortic PWV. Guerin et al [25] reported in maintenance hemodialysis patients treated for more than 3 months that aortic PWV was not always decreased after achieving blood pressure control by "dry weight" adjustment and antihypertensive medications in their long-term observation. Studies on an effect of acute volume control [22, 26] failed to find a significant change in aortic PWV following a single session of hemodialysis. However, the lack of change in aortic PWV may be the result of volume reduction and electrolyte changes counteracted by neural and hormonal responses. In the present study, we measured aortic PWV 1 to 2 hours after dialysis, when the conditions were expected to be more stable than just after hemodialysis, although such measurements may not be representative of steady state. Therefore, we cannot rule out a possibility that volume control by hemodialysis explains the seemingly favorable association between hemodialysis and aortic PWV found in this study.

Third, plasma lipids may explain the change in arterial stiffness. This study confirmed a positive link between aortic PWV and non-HDL cholesterol that was shown in our previous study [4]. Both aortic PWV [7, 8] and non-HDL cholesterol [27] are significant predictors of cardiovascular mortality in hemodialysis patients. However, non-HDL cholesterol was not different between the predialysis and hemodialysis groups in the present study, and the association between aortic PWV and non-HDL cholesterol was independent of the presence of renal failure and hemodialysis treatment. These results suggest that non-HDL lipoproteins have a significant role in arterial stiffness regardless of hemodialysis, but they are not likely to explain the negative association between aortic PWV and hemodialysis.

Fourth, the change in insulin resistance may account for the change in PWV in uremic patients. HOMA-IR is a surrogate index for insulin resistance measured by the euglycemic glucose clamp, the gold standard method for insulin resistance [18]. We previously showed that

HOMA-IR correlated closely with the measurement by glucose clamp in patients with type 2 diabetes mellitus [19] and in those with chronic renal failure [20]. We also showed an elevated HOMA-IR as an independent predictor of cardiovascular mortality in hemodialysis patients [28]. Insulin resistance is known to correlate with carotid artery stiffness in patients with type 2 diabetes mellitus [29]. Also, aortic PWV in elderly individuals correlates with plasma triglyceride and 2-hour post-load glucose levels [30]. These studies suggest the link among insulin resistance, arterial stiffness, and increased risk for cardiovascular mortality in these high-risk populations. In this study, HOMA-IR, in parallel with aortic PWV, was the highest in the predialysis group, the lowest in the healthy subjects, and intermediate in the hemodialysis patients. DeFronzo et al [31] showed that insulin resistance in uremic patients was partly reversed by hemodialysis. Therefore, insulin resistance appears to have an important role in arterial wall stiffening in uremia, although it may not fully explain the seemingly favorable effect of hemodialysis on aortic PWV.

Fifth, the association between hemodialysis and aortic PWV may be related to other factors not measured in this study such as advanced glycation end products (AGEs), homocysteine, and asymmetrical dimethyl arginine (ADMA). These substances are known to accumulate in uremic plasma [32–34], to affect vascular functions [35–37], and to be reduced by hemodialysis [32, 33, 37].

Finally, the cross-sectional design may have brought some bias in this study. Because we [8] and others [7] have shown that increased aortic PWV is a predictor of cardiovascular death in hemodialysis patients, it is possible that hemodialysis patients with very high PWV had already died and the hemodialysis patients of this study were "survivors." Such a possible selection bias can explain the seemingly favorable effect of hemodialysis on aortic PWV. However, this kind of bias would be present not only in the hemodialysis but also the predialysis patients with uremia. In addition, even a longitudinal observation of PWV change in the course of maintenance hemodialysis treatment will not be able to distinguish the effects of uremia, hemodialysis, and aging, because the subjects are exposed to these factors similarly. Therefore, it is quite difficult to clearly separate the effects of renal failure and hemodialysis on the vascular change. Nonetheless, it is a novel and important finding that uremic patients without hemodialysis had a comparable or even higher aortic PWV than those on maintenance hemodialysis.

CONCLUSION

We showed that uremic patients before starting hemodialysis had significantly increased aortic PWV as well as those on maintenance hemodialysis. The risk factor analyses indicated the important roles of renal failure and/or renal failure-related metabolic changes in arterial stiffening of uremic patients. Further studies are needed to determine whether hemodialysis treatment has favorable effects on arterial stiffness and how we can improve arterial stiffness to reduce the risk of cardiovascular death in patients with uremia.

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