*Original Article*

# Determinants of Arterial Wall Stiffness and Peripheral Artery Occlusive Disease in Nondiabetic Hemodialysis Patients

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**Aortic pulse wave velocity (Ao-PWV) and ankle-brachial blood pressure index (ABPI) are significant prognostic factors in patients with end-stage renal disease (ESRD). Diabetes mellitus (DM) promotes changes in arterial walls, including marked increases in Ao-PWV and decreases in ABPI. To determine the prevalence of peripheral arterial occlusive disease (PAOD) as well as the clinical variables useful in predicting these changes in nondiabetic patients with ESRD undergoing hemodialysis (HD), we performed a cross-sectional study in a cohort of 143 patients. Ao-PWV and ABPI were measured simultaneously and compared with several annual biochemical measurements and other clinical variables. The prevalence of PAOD in our cohort was 30.5%. In univariate regression analysis, Ao-PWV correlated positively with age, heart rate (HR), blood pressure (BP), pulse pressure (PP) and HbA1c, and negatively with serum albumin and ABPI. ABPI correlated negatively with age, HD duration, systolic BP, PP, low-density lipoprotein (LDL) cholesterol and hypersensitive C-reactive protein (hs-CRP), and positively with serum albumin and bone mineral density. In a step-down multiple regression analysis, HbA1c was identified as an independent determinant of Ao-PWV along with age, HD duration, HR and mean BP, while hs-CRP was an independent contributor to ABPI along with age, HD duration, PP and LDL cholesterol. Our results suggest that HD promotes aortic wall stiffness and PAOD progression. We recommend the monitoring of HbA1c to allow the prediction of aortic wall stiffness in nondiabetic ESRD patients. Our results did not confirm the influence of insulin resistance on the development of arterial sclerosis lesions. (*Hypertens Res* 2007; 30: 377–385)**

***Key Words*: hemodialysis, arterial wall stiffness, end-stage renal disease, ankle-brachial blood pressure index, aortic pulse wave velocity**

## Introduction

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality among patients with end-stage renal disease (ESRD), leading to more than 50% of deaths in patients treated by renal replacement therapy (*1*, *2*). The risk of death from CVD is 30 times higher in patients with ESRD than in the general population (*3*). The epidemic of CVD in ESRD may be explained by a unique accumulation of risk factors for atherosclerosis (*4*). However, it remains a subject of controversy as to whether the high mortality is due to accelerated atherosclerosis promoted by ESRD *per se* or to pre-existing comorbidity from other causes. It is therefore important to define risk factors critical for overall and cardiovascular mortality in this patient population.

Recently, increased arterial wall stiffness, determined by pulse wave velocity (PWV) measurement, was identified as

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an independent marker of cardiovascular risk in the general population (*5*) and as a major contributor to mortality in ESRD, in that each aortic PWV (Ao-PWV) increase of 1 m/s was associated with a 39% increase in all-cause mortality (*6*). Moreover, peripheral arterial occlusive disease (PAOD) has recently attracted much attention as a risk factor for adverse outcomes. Ankle-brachial blood pressure (BP) index (ABPI; the ratio of ankle to brachial systolic BP [SBP]) is a simple, noninvasive, and reliable method to assess PAOD. ABPI is useful not only for the diagnosis of PAOD: large-scale studies have shown that it is a significant predictor of CVD and mortality (*7*, *8*). Limited available data also suggest that PAOD is prevalent in hemodialysis (HD) patients and is associated with poor outcome in this group (*9*, *10*). Hence, both ABPI and Ao-PWV have significant prognostic power for CVD and all-cause mortality in ESRD.

Individuals with clinically recognized diabetes mellitus (DM) are at increased risk of both CVD and PAOD. Diabetic patients with ESRD are predisposed to CVD and PAOD, presumably due to the more advanced atherosclerosis in this population (*11*, *12*); however, it is unclear whether or not the dialysis procedure itself promotes arteriosclerosis. Moreover, under conditions that exclude the specific milieu known to markedly exacerbate arteriosclerosis in diabetes, it is not clear what could be used to predict Ao-PWV and ABPI. HbA1c, an indicator of average glycemia over the previous 6 to 8 weeks, has been suggested as a diagnostic or screening tool for diabetes. Few studies, however, have examined the possible relationship between HbA1c and atherosclerosis in subjects not diagnosed with diabetes (*13–15*). Thus, whether or not HbA1c can predict aortic wall stiffness and the prevalence of PAOD in the nondiabetic ESRD population treated with HD is an issue of interest.

In this study, we performed cross-sectional analyses to clarify the prevalence of PAOD and predictive factors for both increased aortic wall stiffness and decreased ABPI in ESRD patients undergoing HD in the absence of the diabetic milieu. In addition, we reviewed HbA1c as a potential independent predictive variable of increases in aortic wall stiffness and decreases in ABPI.

## Methods

### Study Design and Patients

A total of 282 patients were treated with maintenance HD from June 2003 to May 2005 at Kyorinkai Murakami Memorial Hospital. Of these, 259 patients underwent HD regularly for more than 6 months. Patients in a critical state were excluded from the study; this included those with severe cerebrovascular disease (7 cases), severe PAOD with lower extremity amputation and/or active gangrene (5 cases), severe joint deformity due to rheumatoid arthritis (2 cases) or ankylosing spondylitis (1 case), complicating noncontrolled neoplasm (3 cases), decompensated liver cirrhosis (2 cases) and severe congestive heart failure (5 cases). One patient who changed treatment from HD to peritoneal dialysis and 9 patients who transferred to other institutions were also excluded. Informed consent could not be obtained from 7 other patients. Thus, 218 patients were analyzed. Of these, 64 were diagnosed with diabetic nephropathy as the cause of ESRD. HbA1c was measured every 3 months in nondiabetic patients. Repeat measurements of blood glucose at 2 h after a meal and/or a 75 g oral glucose tolerance test were performed in all patients whose HbA1c level exceeded 6.0%. Thus, 8 patients were considered to have developed DM after the introduction of HD. Since HbA1c is affected by severe anemia (*16*), 3 patients whose hematocrit levels were less than 25% were excluded from the study. Finally, a cohort of 143 patients diagnosed as nondiabetics became the main subjects of this study. Each subject provided informed written consent before participating in the study, which was approved by our institutional review board.

### Ao-PWV and ABPI Measurements

Ao-PWV, ABPI and BP measurements were performed on the morning before the midweek HD with the patient in a supine position after a 5 min bed rest. To avoid the effect of volume overload, these measurements were postponed on the scheduled day if weight gain relative to body weight after last HD was beyond 3% of dry weight. Arterial BP was measured with a mercury sphygmomanometer and a standard cuff in the arm. The average of two BP measurements was recorded. Ao-PWV was measured by the method of Hasegawa (*17*), using a PWV meter (VaSera VS-1000, Fukuda Denshi, Tokyo, Japan). Pulse waves were recorded by using sensors placed on the skin at the 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 on both arms and the 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 the carotid pulse wave ($T_c$). Ao-PWV was calculated as follows:

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

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 $1.3 \times L$ (*17*). $T + T_c$ indicates the time for a pulse wave to travel from the aortic orifice to the femoral artery. PWV increases as a function of diastolic BP (DBP) at the time of measurement in normal subjects (*18*). Therefore, the PWV meter automatically reports raw and BP-standardized PWV values. The latter represents the pressure-independent elastic property of the aorta. Ao-PWV was measured for 10 consecutive pulses, and the average was used for analysis. The PWV coefficient of variation was less than 5%.

ABPI measurements were conducted at the time of the Ao-

**Table 1. Clinical Features of 143 Nondiabetic Patients with End-Stage Renal Disease**

| Parameter | Value | Range |
|---|---|---|
| Male/Female | 86/57 | |
| Age (years) | 63.9 | 20–95 |
| Cause of end-stage renal disease | | |
| Chronic glomerulonephritis | 107 | |
| Hypertensive nephrosclerosis | 22 | |
| Polycystic kidney disease | 6 | |
| Others | 8 | |
| Current smoking (*n* (%)) | 37 (25.9) | |
| Duration of hemodialysis (m) | 88.8 | 6–379 |
| Body mass index (kg/m$^2$) | 21.5±3.0 | 15.3–34.8 |
| Systolic blood pressure (mmHg) | 146±27 | 74–228 |
| Diastolic blood pressure (mmHg) | 89±16 | 46–165 |
| Heart rate (bpm) | 69±11 | 49–118 |
| Total protein (g/dL) | 6.7±0.4 | 5.1–8.2 |
| Albumin (g/dL) | 4.1±0.3 | 3.3–4.9 |
| Calcium (mg/dL) | 9.2±0.8 | 7.6–11.0 |
| Phosphate (mg/dL) | 5.6±1.1 | 2.9–9.6 |
| Calcium-phosphate product | 51.5±11.0 | 24.7–81.0 |
| Total cholesterol (mg/dL) | 158±29 | 90–243 |
| Triglycerides (mg/dL) | 109±56 | 33–384 |
| LDL cholesterol (mg/dL) | 98±24 | 38–177 |
| HDL cholesterol (mg/dL) | 38±12 | 21–85 |
| Hypersensitive C-reactive protein (mg/dL) | 0.43±0.58 | 0.00–4.30 |
| Hemoglobin A1c (%) | 5.2±0.5 | 4.1–6.5 |
| HOMA-IR (mmol/L × μU/mL) | 1.26±0.93 | 0.29–4.64 |
| Intact-PTH (ng/mL) | 133±115 | 3–1,000 |
| Atrial natriuretic peptide | 106±60 | 18–310 |
| Brain atrial natriuretic peptide | 379±548 | 36–4,259 |
| Hematocrit (%) | 31.1±2.5 | 25–43 |
| β2-Microglobulin | 25.0±7.2 | 10.7–52.5 |
| Bone mineral density (g/cm$^2$) | 0.582±0.154 | 0.253–0.976 |
| Aortic pulse wave velocity (m/s) | 9.1±2.0 | 5.3–16.1 |
| Ankle-brachial blood pressure index | 1.00±0.18 | 0.44–1.44 |

Data are mean±SD. LDL, low-density lipoprotein; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment of insulin resistance; PTH, parathyroid hormone.

PWV measurements using the same device, which simultaneously measures arm and ankle (brachial and posterior tibial, respectively) artery BP, by oscillometry. ABPI was calculated as the ratio of the lower value of the ankle SBP divided by the SBP of the arm without vascular access.

## Collection of Other Data

Predialysis blood chemistry, determined twice per month, included serum creatinine, urea, uric acid, magnesium, calcium, phosphate, sodium, potassium, chloride and hematocrit. Serum albumin, blood lipids, hypersensitive C-reactive protein (hs-CRP) and β2-microglobulin were measured monthly. Intact parathyroid hormone (i-PTH) was measured every 3 months. Moreover, the bone mineral density (BMD) of the forearm was measured every 3 months by dual-energy X-ray absorptiometry (DEXA) using a DCS-600EX-III (Aloka, Tokyo, Japan). Overnight fasting blood glucose and lipids were measured within 1 month after Ao-PWV measurement. Both atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) were measured before the midweek HD. During measurement of ANP and BNP, volume overload and/or congestion were checked and excluded.

We used annual average blood biochemistry parameters of HD patients for analyses of prediction variables for Ao-PWV and ABPI, because seasonal changes among HD patients have been reported for such variables (*19*). (If the duration of HD was less than 12 months, we used average values from the start of HD to the examination.) In particular, serum levels of calcium, phosphate and i-PTH are labile to treatments includ-

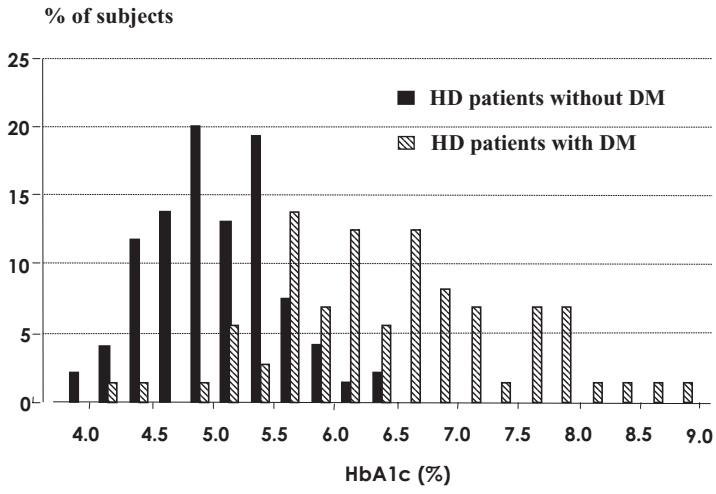


**Fig. 1.** *Bar graph showing frequency distribution of HbA1c in HD patients with or without DM.*

ing a dose of phosphate binder and vitamin-D analog; thus it seems that the mean value obtained from multiple samples is more useful than values obtained from a single sample for analysis. Moreover, blood samples were taken before dialysis under nonfasting conditions to obtain multiple samples for analysis. Desmeules *et al*. (*20*) demonstrated that non–high-density lipoprotein (HDL) cholesterol levels were equivalent in fasting and nonfasting samples. Indeed, the lipid profile values were highly correlated with the values obtained from overnight-fasting samples (total protein: $r=0.552$, $p<0.0001$; albumin: $r=0.667$, $p<0.0001$; total cholesterol: $r=0.776$, $p<0.0001$; triglycerides: $r=0.763$, $p<0.0001$; HDL cholesterol: $r=0.679$, $p<0.0001$; low-density lipoprotein [LDL] cholesterol: $r=0.765$, $p<0.0001$), and they were almost equivalent in our cohort. Therefore, we considered that the annual average values obtained from multiple samples were more useful than a single blood sample.

Insulin resistance was assessed using the homeostasis model assessment of insulin resistance (HOMA-IR) in 70 patients within 3 months before or after measurement of Ao-PWV and ABPI. HOMA-IR was calculated using the following equation:

$$\text{HOMA-IR (mmol/L} \times \mu\text{U/mL)} = \text{fasting blood glucose (mmol/L)} \times \text{fasting insulin } (\mu\text{U/mL})/22.5.$$

## Statistical Analysis

Data are presented as means±SD or actual numbers. Ages and HD duration are expressed by mean and range. Comparisons of HbA1c levels between nondiabetic and diabetic patients were analyzed by Student's unpaired *t*-test. Correlation analysis that was appropriate for the normal (Pearson's correlation) or non-normal (Spearman correlation) variable distributions was used to determine associations of both Ao-PWV and ABPI with a number of other parameters. The hs-CRP values were log-transformed before calculation. Correlations that were significant below the 10% level were entered in a multiple linear step-down regression model with both Ao-PWV and ABPI as dependent variables to determine the variables that best predicted both parameters. A step-up procedure was also used to cross-check results. A $p$ value less than 0.05 indicated statistical significance. All analyses were performed using statistical software (StatView 5; SAS Institute, Cary, USA) for the Windows operating system.

# Results

## Patient Characteristics

The characteristics of HD patients analyzed in this study are detailed in Table 1. The mean age was 64.0 years with a range of 20–95 years. The male/female ratio was 1.51. The causal diseases of ESRD were chronic glomerulonephritis in 107 cases (74.8%), hypertensive nephrosclerosis in 22 cases (15.3%), polycystic kidney disease in 6 cases (4.2%), reflux nephropathy in 3 cases (2.1%), gouty kidney in 3 cases (2.1%), and interstitial nephritis and amyloid kidney in 1 case each. Eighty-five patients (59.4%) were taking antihypertensive medications, including calcium-channel blockers (67 cases), angiotensin II receptor blocker (45 cases), β- or αβ-receptor blockers (27 cases) and angiotensin-converting enzyme inhibitor (11 cases).

The mean HbA1c level was significantly lower in nondiabetic HD patients (5.2±0.5) than in diabetic ESRD patients undergoing HD in our institution during the same period (6.5±1.2, $p<0.0001$, $n=72$). The frequency distribution of HbA1c in both HD patient groups is depicted graphically in Fig. 1. In contrast to diabetic HD patients, the values of the nondiabetic HD patients were distributed across a comparatively narrow range.

**Table 2. Univariate Correlations of Ao-PWV and ABPI with Other Variables in a Cohort of 143 Nondiabetic Patients with End-Stage Renal Disease**

| | Ao-PWV | | ABPI | |
|---|---|---|---|---|
| | *r* | *p* | *r* | *p* |
| Sex (male) | −0.015 | 0.863 | −0.045 | 0.596 |
| Age (years) | 0.423 | <0.001 | −0.389 | <0.001 |
| Current smoking | 0.088 | 0.282 | 0.029 | 0.729 |
| Duration of hemodialysis | 0.140 | 0.099 | −0.171 | 0.041 |
| Body mass index | −0.007 | 0.938 | 0.161 | 0.055 |
| Heart rate | 0.230 | 0.006 | 0.005 | 0.954 |
| Systolic blood pressure | 0.378 | <0.001 | −0.223 | 0.008 |
| Diastolic blood pressure | 0.245 | 0.003 | 0.105 | 0.211 |
| Mean blood pressure | 0.420 | <0.001 | 0.143 | 0.089 |
| Pulse pressure | 0.384 | <0.001 | −0.427 | <0.001 |
| ACEI/ARB use | 0.071 | 0.399 | −0.075 | 0.366 |
| No. of antihypertensive drugs | 0.026 | 0.753 | −0.026 | 0.752 |
| Total protein | −0.085 | 0.320 | 0.094 | 0.265 |
| Albumin | −0.163 | 0.046 | 0.376 | <0.001 |
| Calcium | 0.145 | 0.087 | 0.007 | 0.939 |
| Phosphate | −0.011 | 0.901 | 0.064 | 0.448 |
| Calcium-phosphate product | 0.035 | 0.678 | 0.069 | 0.412 |
| Total cholesterol | 0.042 | 0.619 | −0.117 | 0.165 |
| Triglycerides | −0.026 | 0.763 | 0.073 | 0.390 |
| LDL cholesterol | 0.132 | 0.119 | −0.245 | 0.003 |
| HDL cholesterol | −0.134 | 0.114 | 0.133 | 0.115 |
| Hemoglobin A1c | 0.191 | 0.023 | −0.021 | 0.808 |
| Intact parathyroid hormone | 0.099 | 0.244 | −0.029 | 0.728 |
| Hypersensitive C-reactive protein | −0.031 | 0.719 | −0.278 | <0.001 |
| Atrial natriuretic peptide | 0.071 | 0.499 | −0.119 | 0.183 |
| Brain atrial natriuretic peptide | 0.153 | 0.089 | −0.116 | 0.182 |
| Hematocrit | −0.045 | 0.599 | 0.134 | 0.112 |
| β2-Microglobulin | 0.023 | 0.791 | −0.089 | 0.291 |
| Bone mineral density | −0.131 | 0.126 | 0.176 | 0.0381 |
| HOMA-IR | −0.162 | 0.246 | 0.050 | 0.717 |
| ABPI | −0.286 | <0.001 | | |

ABPI, ankle-brachial blood pressure index; Ao-PWV, aortic pulse wave velocity; ACEI/ARB, angiotensin converting enzyme inhibitor and/or angiotensin receptor blocker; LDL, low-density lipoprotein; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment of insulin resistance.

## Prevalence of Peripheral Arterial Disease

Patients with an ABPI<0.9 were considered positive for PAOD. Forty-four patients (30.8%) in our cohort met this criterion for PAOD, of whom 25 (56.8%) were men, 10 (22.7%) were active smokers and 26 (59.1%) were taking antihypertensive agents. There were no differences in the male/female ratio, proportions of active smokers and patients taking antihypertensive agents between patients with PAOD and those without PAOD. Moreover, HOMA-IR did not differ between patients with PAOD (1.23±0.78 mmol/L × μU/mL) and those without (1.42±1.05 mmol/L × μU/mL). Age (72.1±11.0 *vs*. 60.5±12.0 years, $p<0.0001$), body mass index (BMI; 20.7±3.3 *vs*. 21.8±2.8 kg/m$^2$, $p<0.05$), pulse pressure (PP: 69±23 *vs*. 53±16 mmHg, $p<0.0001$), Ao-PWV (9.9±2.2 *vs*. 8.8±1.9 m/s, $p<0.01$), serum albumin (3.9±0.3 *vs*. 4.2±0.3 g/dL, $p<0.0001$), LDL cholesterol (107±19 *vs*. 94±25 mg/dL, $p<0.005$) and hs-CRP (0.73±0.84 *vs*. 0.31±0.36 mg/dL, $p<0.0005$) all differed between patients with PAOD and those without it (respective data are indicated in the parentheses). Furthermore, there were no differences in serum calcium, phosphate or i-PTH between patients with PAOD and those without it.

## Predictive Factors for Increased Ao-PWV and Decreased ABPI

Table 2 lists the univariate correlations of Ao-PWV and ABPI

**Table 3. Predictors of Ao-PWV and ABPI Identified by Multiple Regression Analysis in a Cohort of 146 Nondiabetic Patients with End-Stage Renal Disease**

| | Dependent variable=Ao-PWV | | | Dependent variable=Ao-PWV | |
|---|---|---|---|---|---|
| | Unstandardized coefficient $\beta$ | $p$ value | | Unstandardized coefficient $\beta$ | $p$ value |
| Age | 0.450 | <0.0001 | Duration of HD | −0.139 | 0.0456 |
| Duration of HD | 0.208 | 0.0017 | Pulse pressure | −0.402 | <0.0001 |
| Heart rate | 0.231 | 0.0004 | C-reactive protein | −0.221 | 0.0051 |
| Mean blood pressure | 0.377 | <0.0001 | LDL cholesterol | −0.159 | 0.0235 |
| Hemoglobin A1c | 0.222 | 0.0007 | Serum albumin | 0.191 | 0.0163 |

Ao-PWV, aortic pulse wave velocity; ABPI, ankle-brachial blood pressure index; HD, hemodialysis; LDL, low-density lipoprotein.

with other variables. Ao-PWV correlated positively with age, heart rate, SBP, DBP, mean BP, PP and HbA1c, and negatively with serum albumin and ABPI. The $p$ value for the correlation of Ao-PWV with HD duration was <0.10. On the other hand, ABPI correlated negatively with age, HD duration, SBP, PP, LDL cholesterol and hs-CRP, but positively with serum albumin and BMD. The $p$ value for the correlation of Ao-PWV with BMI and mean BP was <0.10 each. Unexpectedly, HOMA-IR did not correlate with Ao-PWV or ABPI.

To further explore the independent impact of Ao-PWV and ABPI, a step-down multiple regression analysis was performed (Table 3). HbA1c was found to be an independent contributor to Ao-PWV along with age, HD duration, heart rate and mean BP. For ABPI, hs-CRP was selected as an independent contributor along with age, HD duration, PP and LDL cholesterol. Both age and HD duration were independent factors that influenced both Ao-PWV and ABPI. The determination coefficients of these models were 0.685 for Ao-PWV and 0.609 for ABPI.

## Discussion

In this study, we analyzed putative predictive factors for both Ao-PWV and ABPI in nondiabetic patients treated with HD. As a feature of this study, enrolled patients were limited to those stably treated with HD for more than 6 months. No studies, to our knowledge, have examined these factors in nondiabetic ESRD patients undergoing HD. In the present cohort, the duration of HD was found to be an independent predictor for both Ao-PWV and ABPI. Moreover, HbA1c was identified as an independent predictive factor for Ao-PWV, while LDL cholesterol and hs-CRP were found to be independent predictors for ABPI.

Several studies have reported the factors associated with increased arterial wall stiffness in HD patients. SBP, age, prevalence of aortic calcification and complication with DM are independently associated with Ao-PWV (*21*). Another analysis of 24 patients treated with HD suggested that arterial wall elastic properties were influenced not only by hypertension and pressure constraints, but also by calcium and phosphorus metabolism and the duration of renal substitutional therapy (*22*). Nitta *et al*. demonstrated that left ventricular hypertrophy was associated with hypertension, increased arterial wall stiffness and the extent of vascular calcification in ESRD (*23*). Furthermore, they indicated that brachial-ankle PWV (baPWV) was an independent contributor to coronary artery calcification along with an aortic calcification index (*24*). In our study, univariate analysis revealed significant relations between Ao-PWV and age, heart rate and BP parameters including SBP, DBP, PP and mean BP. The importance of these relationships is consistent with the findings of previous reports (*21*, *22*), though we were not able to determine the relationship between Ao-PWV and serum calcium, phosphate or calcium-phosphate product, in disagreement with previous reports (*22*). In light of the relatively wide age range (20–95 years) and relatively high mean age (64 years) of our cohort, it could be speculated that elderly patients who were in a condition of relative malnutrition with insufficient intake of calcium or phosphate were more prevalent in our study cohort than in other study patients. This speculation also seems to explain why lipid-profile parameters, including total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides, were not associated with Ao-PWV. Serum albumin concentration was significantly associated with both Ao-PWV and ABPI, implicating the patient nutritional state in the atherogenic process. In a large cohort, serum levels of β2-microglobulin were found to be associated with baPWV (*25*); however, no such association with Ao-PWV or ABPI was identified in our cohort.

It is interesting that the HbA1c value was independently correlated with Ao-PWV, in spite of the narrow range of distribution of that value in our present cohort. It is known that the HbA1c value is influenced by the severity of anemia (*16*). Therefore, it is disputable whether the HbA1c value reflects the average blood glucose level in HD patients or not. To analyze this controversial point, we simultaneously measured the values of both HbA1c and glycated serum albumin (GSA) in patients treated with HD in our institution. Patients were classified into three groups according to hematocrit level (≥25 to <30%, ≥30 to <35% and >35%). The correlations between HbA1c and GSA were high and similar in all patients groups

(data not shown). Thus, we consider that the use of HbA1c provided a true evaluation of glycemic condition in this population. Cross-sectional studies in nondiabetic individuals revealed a relationship between HbA1c and both the prevalence of coronary artery disease and markers of subclinical atherosclerosis (*13–15*). In addition, Menon *et al*. (*26*) showed that glycosylated hemoglobin was correlated with increased mortality in patients with nondiabetic chronic kidney diseases. They also suggested that in patients with chronic kidney disease, hyperglycemia below currently defined thresholds is associated with adverse outcomes. Our results implicate "relative" hyperglycemia as an important risk factor for arteriosclerotic vascular damage in nondiabetic subjects. This theory is supported by the statistical power of HbA1c values for predicting Ao-PWV in nondiabetic ESRD patients, and emphasizes the importance of routine HbA1c measurements in nondiabetic ESRD patients.

Insulin resistance is known to play an important role in the progression of arteriosclerotic disorders. The Minoh study demonstrated that baPWV correlated with fasting serum insulin levels and HOMA-IR in the general population (*27*). A comparable association was found in a Korean population (*28*). A longitudinal study suggested that insulin resistance was an independent risk factor for coronary artery disease in Japanese subjects (*29*). Moreover, insulin resistance was found to be an independent predictor of cardiovascular mortality in a cohort of nondiabetic ESRD patients (*30*). In our study, HOMA-IR was evaluated in about half of the cohort. However, contrary to our expectation, we could not demonstrate any correlation between HOMA-IR and Ao-PWV or between HOMA-IR and ABPI. Although we cannot explain this contradiction, we speculate that the strict criteria used for selection of patients in this study, including exposure to HD procedure, uremic condition or malnutrition, counteracts the influence of insulin resistance on the development of arteriosclerosis.

The prevalence of PAOD in our cohort was comparable with that reported by other groups (*9*, *10*, *31*), although a large-scale analysis of HD patients in Japan (*32*) found a lower prevalence of PAOD. This difference is probably due to differences in age and duration of HD. The established risk factors for PAOD in the general population include increased age, hypertension, hyperlipidemia, smoking, DM and coronary heart disease, although there have been only a few attempts to identify PAOD risk factors among patients with ESRD. The HEMO study found that DM and smoking were associated with PAOD among HD patients (*33*). The current study demonstrated that age, BMI, PP, Ao-PWV, serum albumin, LDL cholesterol and hs-CRP were significantly different between patients with or without PAOD. Moreover, multiple regression analysis showed that age, duration of HD, PP, LDL cholesterol and hs-CRP were all independent contributors to ABPI. We speculate that the diabetic milieu exerts a powerful influence on atherosclerotic diseases that is sufficient to negate the influences of other risk factors. Thus, by excluding diabetics in the current study, relationships between the above-mentioned variables and ABPI were specific and therefore clearer.

There is growing evidence that chronic inflammation plays a role in the pathogenesis of atherosclerosis. Data from several prospective studies have demonstrated that elevated levels of the acute-phase reactant C-reactive protein (CRP) predicts an increased incidence of future cardiovascular events among a wide range of clinical populations (*34*, *35*). A study of the general United States adult population provided evidence of strong, graded, positive associations between inflammation and PAOD (*36*). In the ESRD population, CRP levels seem to be predictive of cardiovascular mortality rates in the ESRD population, as they are in the general population (*37*, *38*), however there are few studies documenting a link between PAOD and inflammation among renal patients. In the current study, we identified hs-CRP as an independent contributor to ABPI of nondiabetic ESRD patients treated with HD. Further studies are necessary to elucidate whether elevation of CRP is a cause of PAOD or a result thereof.

Only few studies have demonstrated that HD duration correlates either aortic wall stiffness or PAOD. Arterial compliance, evaluated by the ambulatory method of QK interval, which corresponds to the time between onset of the QRS complex and Korotkoff sound at diastolic pressure, was dependent on HD duration in 24 HD patients (*22*). The HEMO study also identified HD duration as a predictor of coronary heart disease and PAOD in univariate logistic regression analysis, but not in multivariate logistic regression analysis (*33*). Takenaka *et al*. (*39*) demonstrated that annual changes in PWV of HD patients showed strong correlation to HD duration, although the other authors could not find a relationship between HD duration and aortic wall stiffness (*6*, *40*) or ABPI (*32*). By excluding diabetic patients from the current study, we demonstrated that HD duration independently influences both aortic stiffness and PAOD. Thus, our study suggests that HD duration plays important roles in reduced aortic compliance and the progress of PAOD, however, further studies are needed to determine whether the duration of the uremic milieu of HD *per se* contributes to the arterial alterations.

In conclusion, the present study showed the following in nondiabetic ESRD patients treated with HD: 1) the duration of HD independently affected both increases in aortic wall stiffness and progression of PAOD; 2) HbA1c was an independent contributor to Ao-PWV along with age, duration of HD, heart rate, and mean BP; and, 3) hs-CRP was an independent contributor to ABPI along with age, duration of HD, PP and LDL cholesterol. Based on these data, we recommend monitoring HbA1c level as an important predictor of aortic wall stiffness, even in nondiabetic ESRD patients. Further studies are needed to establish whether HbA1c has a wider prognostic role for CVD and all-cause mortality in nondiabetic ESRD patients.

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