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ORIGINAL ARTICLE

Risk factors of accelerated progression of peripheral artery disease in hemodialysis

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Abstract Ankle-brachial index (ABI) and brachial-ankle pulse wave velocity (baPWV) are markers for peripheral artery occlusive disease (PAOD) and arterial stiffness, respectively. The aims of this study were to assess whether PAOD and arterial stiffness progressed and to determine the risk factors for ABI and baPWV progression in patients on hemodialysis. This study enrolled 173 routine patients on hemodialysis. Both ABI and baPWV were measured by an ABI-form device at baseline and at 1 year of follow-up. Progression in ABI was defined as reduction in ABI exceeding 0.3, while baPWV measured at 1 year of follow-up exceeding that at baseline indicated baPWV progression. Comparison with baseline data showed increase in both prevalence of ABI < 0.9 ($p = 0.045$) and baPWV ($p = 0.028$) at 1 year of follow-up. Multiple linear regression analyses identified high fasting glucose and old age as independent factors of annual change in ABI and baPWV, respectively. Good control of blood sugar may contribute to delay the progression of peripheral artery disease in patients on hemodialysis.

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Introduction

A high prevalence of peripheral artery occlusive disease (PAOD) and increased artery stiffness have been reported in the end-stage renal disease (ESRD) population and are associated with increased morbidity and mortality [1—4]. There is growing evidence that uremia may predispose sufferers to PAOD progression and increased arterial stiffness with multiple pathogenic mechanisms involved, including deranged calcium/phosphate balance, secondary hyperparathyroidism, homocysteine, lipoprotein(a) metabolism, fluid overload, alterations in the angiotensin and endothelin systems, malnutrition, uremic toxins, oxidative stress, insulin resistance, and alterations in inflammatory and coagulation pathways [4,5].

A clinical device has been developed to automatically and simultaneously record the pulse waves of the brachial and posterior tibial arteries, using an automated oscillometric method. Using this device, we can easily and automatically calculate the ankle-brachial index (ABI) and brachial-ankle pulse wave velocity (baPWV) [6,7]. ABI has been reported to be a good marker for atherosclerosis and an ABI of <0.9 was useful in the diagnosis of PAOD [8—10], while baPWV has been taken as a good marker for arterial stiffness [11,12]. Previous cross-sectional studies have identified the risk factors of PAOD and increased artery stiffness in advanced chronic kidney disease and patients on hemodialysis, including old age, hypertension, diabetes mellitus (DM), previous coronary artery disease, previous cerebrovascular disease, wider pulse pressure, hyperlipidemia, malnutrition, and smoking [4,13,14]. However, there have been few studies evaluating the progression of PAOD and arterial stiffness longitudinally, or determining the risk factors of ABI and baPWV progression in patients on hemodialysis in Taiwan, an area with the highest prevalence of ESRD [15]. The aims of the present study were to assess the progression in PAOD and arterial stiffness and to determine the risk factors for ABI and baPWV progression in patients on hemodialysis.

Methods

Study design and participants

This is a prospective and observational study conducted at a single dialysis clinic in a regional hospital in Taiwan. All routine patients on hemodialysis in this hospital were included, except two patients who refused to be examined by an ABI-form device, four patients with atrial fibrillation, and six patients with both legs amputated due to complications of DM. Initially, 196 patients (91 men and 105 women) were included in this study. The ABI was measured twice within 1 year. During the follow-up period, 11 deaths were recorded in these 196 patients (5.6%), 10 patients were transferred to other hospitals, and two patients refused further examinations. Finally, 173 patients (80 men and 93 women) completed the study. The protocol was approved by our Institutional Review Board and all enrolled patients gave written, informed consent.

Hemodialysis

All patients underwent routine hemodialysis three times a week using a Toray 321 machine (Toray Medical Company, Tokyo, Japan). Each hemodialysis session lasting 3—4 hours was performed using a dialyzer with a blood flow rate of 250-300 mL/minute and a dialysate flow rate of 500 mL/minute.

Assessment of ABI and baPWV

Both ABI and baPWV might be influenced by hemodialysis [16]; hence, all measurements were made 10—30 minutes before hemodialysis. The measurements were taken using an ABI-form device (VP1000; Colin Co. Ltd., Komaki, Japan) [6,7,17] in a room with a temperature of around 25°C following a 5-minute rest upon arrival at the clinic. Occlusion and monitoring cuffs were placed tightly around the upper arms without blood access and with both sides of the lower extremities in the supine position. Dividing the ankle systolic blood pressure by the arm systolic blood pressure gave the ABI and the lower value of the ankle systolic blood pressure was used in the calculation. For measuring baPWV, pulse waves obtained from the brachial and tibial arteries were recorded simultaneously, and the transmission time, defined as the time interval between the initial increase in brachial and tibial waveforms, was determined. The transmission distance from the arm to each ankle was calculated according to body height. The baPWV value was automatically computed as the transmission distance divided by the transmission time. After obtaining bilateral baPWV values, the highest one was taken as the representative value for each participant. Both ABI and baPWV measurements were made at baseline and at the 1 year of follow-up. The automatic device and its reproducibility have been validated in previous research [17].

Collection of demographic, medical, and laboratory data

Demographic and medical data including age, sex, smoking history, and comorbidities were obtained from medical records and interviews with patients. Body mass index (BMI) was calculated as the ratio of weight in kilograms divided by the square of height in meters. Laboratory data were obtained from fasting blood samples using an autoanalyzer (Roche Diagnostics GmbH, D-68298 COBAS Integra 400, Mannheim, Germany). High-sensitivity C-reactive protein (Dade Behring Marburg GmbH, Germany) was measured using commercially available kits. Serum intact parathyroid hormone concentration was evaluated using a commercially available two-sided immunoradiometric assay (CIS Bio International, Gif Sur Yvette, France). Blood samples were centrifuged within 1 hour of collection and frozen at −20°C until analysis. Plasma homocysteine levels were determined by fluorescence polarization immunoassay using an IMx Homocysteine kit (Abbott Laboratories, Abbott Park, IL, USA). Blood samples were obtained within 1 month of enrollment. In addition, information regarding patient medications including aspirin, angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, β-blocker, calcium channel blocker, and HMG-CoA reductase

inhibitors (statins) during the study period was obtained from medical records.

Definitions of progression of ABI and baPWV

△ABI was defined as ABI measured at 1-year follow-up minus ABI measured at baseline. Reduction in ABI exceeding 0.3 was considered as progression of ABI [18]. △baPWV was defined as baPWV measured at 1-year follow-up minus baPWV measured at baseline. A positive △baPWV indicated progression of baPWV.

Statistical analysis

Statistical analysis was performed using SPSS 12.0 for windows (SPSS Inc., Chicago, IL, USA). Data are expressed as numbers and percentages, or mean ± standard deviation. The differences between groups were analyzed by Chi-square test for categorical variables or by independent *t*-test for continuous variables. Paired t-test was performed to compare the prevalence of ABI < 0.9 and baPWV values at baseline and 1-year follow-up. Linear regression analysis was employed to identify the factors associated with the ratio of △ABI to baseline ABI and △baPWV to baseline baPWV. Age, sex, and the independent variables with a $p < 0.2$ in the univariate analysis were selected in the multivariate analysis. A p value of less than 0.05 indicated significant difference.

Table 1 Baseline characteristics of the study patients.

Characteristics	Study patients (n = 173)
Age (yr)	57.3 ± 12.7
Male sex (%)	46.2
Smoking history (%)	24.9
Diabetes mellitus (%)	39.3
Hypertension (%)	70.5
Coronary artery disease (%)	24.3
Cerebrovascular disease (%)	9.2
Duration of hemodialysis (mo)	72.4 ± 53.4
Systolic blood pressure (mmHg)	148.8 ± 24.6
Diastolic blood pressure (mmHg)	80.4 ± 14.5
Pulse pressure (mmHg)	68.7 ± 16.9
Heart rate (beats/min)	82.1 ± 13.9
Body mass index (kg/m^2)	24.3 ± 3.7
ABI < 0.9 (%)	23.1
baPWV (cm/s)	1795.0 ± 458.5
Laboratory parameters	
Albumin (g/dL)	3.97 ± 0.25
Fasting glucose (mg/dL)	119.5 ± 57.9
Triglyceride (mg/dL)	152.9 ± 98.4
Total cholesterol (mg/dL)	180.1 ± 40.7
HDL-cholesterol (mg/dL)	41.1 ± 10.7
LDL-cholesterol (mg/dL)	90.6 ± 28.3
Hematocrit (%)	30.5 ± 3.7
Calcium-phosphorous product	47.1 ± 10.7
Uric acid (mg/dL)	7.7 ± 1.5
PTH (pg/mL)	425.6 ± 329.8
hsCRP (mg/L)	0.70 ± 1.00
Homocysteine (μmol/L)	29.4 ± 9.9
Cardio-thoracic ratio > 50%	36.4
Medications	
Aspirin use (%)	17.9
ACEI and/or ARB use (%)	26.0
β-blocker use (%)	16.8
Calcium channel blocker use (%)	35.3
Statins use (%)	32.9

ABI = ankle-brachial index; ACEI = angiotensin converting enzyme inhibitor; ARB = angiotensin II receptor blocker; baPWV = brachial-ankle pulse wave velocity; HDL = high-density lipoprotein; hsCRP = high-sensitivity C-reactive protein; LDL = low-density lipoprotein; PTH = parathyroid hormone.

Results

The clinical characteristics of the study patients are shown in Table 1. The mean age of the 173 patients was 57.3 ± 12.7 years and there were 80 men and 93 women. Among our patients, 39.3% were diabetic and 70.5% received medications for high blood pressure. Pre-existing and documented coronary arterial and cerebrovascular diseases were noted in 24.3% and 9.2% of patients, respectively. Biochemical data were listed in the Table 1. At baseline, the prevalence of ABI < 0.9 was 23.1% and the average baPWV was 1795.0 ± 458.5 cm/s. The underlying etiologies of hemodialysis in our study patients included

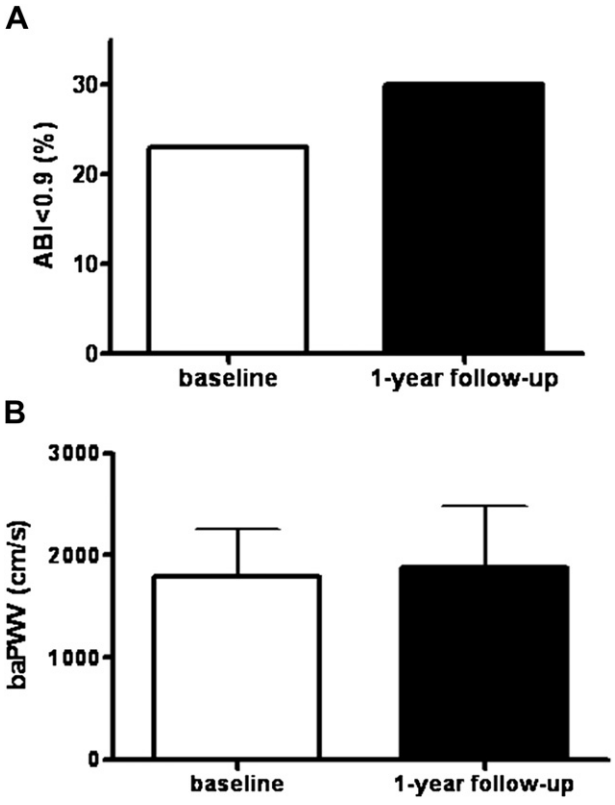

Figure 1. (A) The prevalence of ABI < 0.9 increased yearly during 1-year follow-up (23.1%, and 30.1%; $p = 0.045$); (B) values of baPWV increased yearly during 1-year follow-up (1795.0 ± 458.5, and 1880.7 ± 604.0; $p = 0.028$). ABI = ankle-brachial index; baPWV = brachial-ankle pulse wave velocity.

Table 2 Comparison of baseline characteristics between progressors and non-progressors of ABI.

Parameters	Progressors of ABI ($n = 10$)	Non-progressors of ABI ($n = 163$)	p
Age (yr)	59.5 ± 10.2	57.1 ± 12.9	0.567
Male sex (%)	50.0	46.0	0.806
Smoking history (%)	30.0	24.5	0.711
Diabetes mellitus (%)	60.0	38.0	0.194
Hypertension (%)	70.0	70.6	> 0.99
Coronary artery disease (%)	30.0	23.9	0.707
Cerebrovascular disease (%)	10.0	9.2	> 0.99
Duration of hemodialysis (mo)	71.0 ± 65.2	72.4 ± 52.8	0.933
Systolic blood pressure (mmHg)	147.8 ± 18.3	148.9 ± 25.0	0.891
Diastolic blood pressure (mmHg)	75.0 ± 11.4	80.7 ± 14.6	0.226
Pulse pressure (mmHg)	72.8 ± 19.0	68.4 ± 16.8	0.426
Heart rate (beats/min)	82.2 ± 8.1	82.1 ± 14.2	0.984
Body mass index (kg/m^2)	23.9 ± 4.0	24.3 ± 3.7	0.716
baPWV (cm/s)	1813.3 ± 498.0	1793.8 ± 457.6	0.897
Laboratory parameters			
Albumin (g/dL)	3.81 ± 0.22	4.00 ± 0.28	0.042
Fasting glucose (mg/dL)	156.6 ± 55.7	120.8 ± 62.5	0.079
Triglyceride (mg/dL)	161.3 ± 92.5	154.3 ± 103.1	0.833
Total cholesterol (mg/dL)	178.9 ± 40.2	177.9 ± 40.2	0.936
HDL-cholesterol (mg/dL)	40.6 ± 7.7	41.1 ± 10.9	0.897
LDL-cholesterol (mg/dL)	89.9 ± 24.8	90.7 ± 28.6	0.933
Creatinine (mg/dL)	10.1 ± 2.4	10.3 ± 2.3	0.690
Hematocrit (%)	31.7 ± 3.9	31.0 ± 3.8	0.547
Calcium-phosphorous product	41.9 ± 6.4	46.2 ± 12.8	0.300
Uric acid (mg/dL)	7.6 ± 1.3	7.7 ± 1.6	0.838
PTH (pg/mL)	531.4 ± 379.9	418.7 ± 360.9	0.341
hsCRP (mg/L)	0.55 ± 0.46	0.71 ± 1.01	0.667
Homocysteine (μmol/L)	33.9 ± 8.9	29.2 ± 9.9	0.189
Cardio-thoracic ratio > 50%	40.0	36.2	> 0.99
Medications			
Aspirin use (%)	30.0	17.2	0.388
ACEI and/or ARB use (%)	20.0	26.4	> 0.99
β-blocker use (%)	20.0	16.6	0.675
Calcium channel blocker use (%)	20.0	36.2	0.497
Statins use (%)	60.0	31.3	0.083

ABI = ankle-brachial index; ACEI = angiotensin converting enzyme inhibitor; ARB = angiotensin II receptor blocker; baPWV = brachial-ankle pulse wave velocity; HDL = high-density lipoprotein; hsCRP = high-sensitivity C-reactive protein; LDL = low-density lipoprotein; PTH = parathyroid hormone.

nondiabetic glomerular diseases (42.2%), diabetic kidney disease (35.3%), hypertension (11.6%), tubulointerstitial diseases (8.7%), and other diseases (2.3%).

The incidence of *de novo* ABI < 0.9 is 18.0%. Fig. 1A shows increasing prevalence of ABI < 0.9 among the participants during the 1-year follow-up (23.1%, and 30.1%; $p = 0.045$); while Fig. 1B illustrates increasing baPWV in the same period (1795.0 ± 458.5, and 1880.7 ± 604.0; $p = 0.028$).

The comparison of baseline characteristics between study patients with and without ABI progression is shown in Table 2. As can be seen, patients with ABI progression were significantly associated with lower serum albumin levels than those without. Multiple linear regression analysis revealed that covariates in the model included age, sex, a history of DM, serum albumin level, fasting glucose, homocysteine level, and use of statins. In addition, the ratio of △ABI to baseline ABI were significantly and negatively associated with fasting glucose ($\beta = -0.222$, $p = 0.018$).

Table 3 shows the comparison of baseline characteristics between study patients with and without baPWV progression. As can be seen, patients with baPWV progression were significantly associated with a higher serum creatinine level than those without. Multiple linear regression analysis revealed that covariates in the model included age, sex, a history of coronary artery disease, serum triglyceride level, high-density lipoprotein cholesterol, creatinine level, and cardiothoracic ratio > 50%. In addition, the ratio of △baPWV to baseline baPWV was independently correlated with age ($\beta = 0.192$, $p = 0.045$).

Table 3 Comparison of baseline characteristics between progressors and non-progressors of baPWV.

Parameters	Progressors of baPWV ($n = 90$)	Non-progressors of baPWV ($n = 83$)	*P*
Age (yr)	56.4 ± 12.8	58.2 ± 12.7	0.360
Male sex (%)	46.7	45.8	0.907
Smoking history (%)	26.7	22.9	0.566
Diabetes mellitus (%)	40.0	38.6	0.846
Hypertension (%)	71.1	69.9	0.859
Coronary artery disease (%)	18.8	30.1	0.085
Cerebrovascular disease (%)	6.7	12.0	0.222
Duration of hemodialysis (mo)	68.6 ± 46.4	76.4 ± 60.1	0.338
Systolic blood pressure (mmHg)	149.2 ± 27.1	148.5 ± 21.8	0.841
Diastolic blood pressure (mmHg)	80.7 ± 15.0	80.0 ± 13.9	0.762
Pulse pressure (mmHg)	68.9 ± 19.1	68.4 ± 14.3	0.850
Heart rate (beats/min)	82.4 ± 15.4	81.8 ± 12.2	0.781
Body mass index (kg/m^2)	24.3 ± 3.6	24.2 ± 3.9	0.905
ABI < 0.9	23.3	22.9	0.945
Laboratory parameters			
Albumin (g/dL)	3.98 ± 0.26	3.95 ± 0.24	0.496
Fasting glucose (mg/dL)	122.5 ± 60.6	116.2 ± 55.0	0.475
Triglyceride (mg/dL)	139.9 ± 77.4	166.9 ± 115.9	0.071
Total cholesterol (mg/dL)	178.8 ± 39.1	181.4 ± 42.5	0.674
HDL-cholesterol (mg/dL)	42.3 ± 11.1	39.7 ± 10.3	0.122
LDL-cholesterol (mg/dL)	90.9 ± 29.5	90.4 ± 27.1	0.908
Creatinine (mg/dL)	10.6 ± 2.4	9.9 ± 2.2	0.047
Hematocrit (%)	30.6 ± 4.0	30.4 ± 3.2	0.800
Calcium-phosphorous product	46.1 ± 10.2	48.2 ± 13.1	0.248
Uric acid (mg/dL)	7.8 ± 1.6	7.6 ± 1.4	0.410
PTH (pg/mL)	406.3 ± 309.9	446.6 ± 350.8	0.423
hsCRP (mg/L)	0.62 ± 0.85	0.78 ± 1.12	0.299
Homocysteine (μmol/L)	30.1 ± 10.5	28.7 ± 9.2	0.375
Cardio-thoracic ratio >50%	30.0	43.4	0.068
Medications			
Aspirin use (%)	18.9	16.9	0.729
ACEI and/or ARB use (%)	28.9	22.9	0.369
β-blocker use (%)	14.4	19.3	0.395
Calcium channel blocker use (%)	36.7	33.7	0.687
Statins use (%)	34.4	31.3	0.663

ABI = ankle-brachial index; ACEI = angiotensin converting enzyme inhibitor; ARB = angiotensin II receptor blocker; baPWV = brachial-ankle pulse wave velocity; HDL = high-density lipoprotein; hsCRP = high-sensitivity C-reactive protein; LDL = low-density lipoprotein; PTH = parathyroid hormone.

Discussion

The present longitudinal study evaluated the progression of PAOD and arterial stiffness and the influence of atherosclerotic risk factors on ABI and baPWV progression in patients with hemodialysis. We found increase in both prevalence of ABI < 0.9 and baPWV during 1 year of follow-up. High fasting glucose and old age were identified as major factors responsible for the accelerated progression in ABI and baPWV, respectively.

We have reported the associated risk factors for abnormal ABI and baPWV in chronic kidney disease and patients on hemodialysis [13,14]. However, the reported results were from cross-sectional studies. There are some recent longitudinal studies examining the risk factors for PAOD and artery stiffness progression [19—21]. Ohnishi et al. [20] evaluated longitudinally the risk factors of *de novo* PAOD in 468 adult elderly men for 5 years. They found that older age, smoking, cerebrovascular disease, and coronary artery disease were the risk factors for PAOD. In our study, we examined the annual change in ABI, not *de novo* PAOD, and found that high fasting glucose was associated with accelerated progression of ABI. Uremia may worsen metabolic syndrome features including insulin resistance, glucose intolerance, and hyperglycemia, resulting in high cardiovascular morbidity and mortality [22]. Takenaka et al. [21] studied the associated factors of annual change in heart-tibial PWV in 72 patients on hemodialysis, and found that higher triglyceride levels and longer duration of dialysis were associated with greater increase in heart-tibial PWV. Jung et al. [19] also examined the factors associated with changes in heart-femoral PWV over one year in 67 peritoneal dialysis patients, and identified change in mean arterial pressure and triglyceride as risk

factors for heart-femoral PWV progression. In their studies, serum triglyceride levels were evaluated monthly or every 3 months during the observation period, and those measurements were averaged for analysis. In our study, only a single measurement of triglyceride level was made, which might explain the discrepancy between our results and those obtained by Takenaka and Jung [19,21]. Shinohara et al. [5] compared the aortic pulse wave velocity (PWV) of 71 uremic patients before initiation of hemodialysis with that of 144 patients on chronic hemodialysis, and found that the predialysis patients had greater aortic PWV than the patients on hemodialysis. They attributed their findings to good volume control and reversed insulin resistance in patients with hemodialysis, which might have favorable effects on arterial stiffness. The same reason may account for the lack of correlation between the duration of dialysis and arterial stiffness progression in our study patients.

In summary, the present study demonstrated increase in both prevalence of ABI < 0.9 and baPWV during 1 year of follow-up in patients on hemodialysis. High fasting glucose and old age were independent determinants of accelerated progression in ABI and baPWV, respectively. Good control of blood sugar may help delay the progression of peripheral artery disease in patients on hemodialysis.

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