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Different Ankle Brachial Index Levels in Asymptomatic Hemodialysis Patients

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Abstract

Resting ankle brachial systolic pressure index (ABI) level of 0.90 is 95% sensitive in detecting angiogram-positive peripheral arterial disease (PAD) and that falsely elevated pressures or incompressible arteries at the ankle level and ABI > 1.30 is caused by mediosclerosis. We evaluated 94 hemodialysis (HD) patients for the presence of PAD and mediosclerosis using ABI measurement, and the presence of atherosclerotic lesions using high resolution B-mode ultrasonography of the common carotid (CCA) and femoral arteries (FA). Asymptomatic HD patients with high ABI (mediosclerosis) and low ABI (PAD) levels were common. Patients with normal and high ABI levels had high percentage of atherosclerotic lesions. Older age, diabetes and low serum albumin, and higher doses of prescribed calcium carbonate were associated ($p<0.05$) with low levels of ABI in our HD patients. Male gender, higher blood pressure and presence of diabetes were associated ($p<0.05$) with high ABI levels. Low and high ABI levels were not associated with the specific risks such as elevated serum phosphate, calcium phosphate product and intact parathyroid hormone levels. Arterial disease in asymptomatic HD patients is frequent. Screening for atherosclerotic lesions in HD patients should be recommended even if they had no symptoms.

Introduction

Cardiovascular disease is a major cause of morbidity and death among hemodialysis (HD) patients (1). Many studies have demonstrated that damage of large arteries due to atherosclerosis is a major contributory factor to the high cardiovascular morbidity and mortality of HD patients (2). The most prevalent arterial complication is occlusion and / or stiffening caused to a large part by extensive calcifications (3,4). Arterial intima calcification represents an advanced stage of atherosclerosis and is associated with development of plaques and occlusive lesions (5). Unlike arterial intima calcification, mediosclerosis, or arterial media calcifications in its typical form does not obstruct the arterial lumen (5), but few studies have recently shown that mediosclerosis in HD patients can be associated with atherosclerosis, intimal plaques, occlusive lesions and future cardiovascular risk (6). High resolution B-mode ultrasonography of the common carotid arteries (CCA) and femoral arteries (FA) is

a fundamental technique for the investigation of atherosclerosis in HD patients (7). Ankle brachial systolic pressure index (ABI) measurement using Doppler techniques is an established method to study the presence of lower limb atherosclerosis or peripheral arterial disease (PAD) (8). It has been suggested that a resting ABI level of 0.90 is 95% sensitive in detecting angiogram-positive PAD and almost 100% specific in identifying apparently healthy individuals (9). Falsely elevated pressures or incompressible arteries at the ankle level and ABI > 1.30 is caused by mediosclerosis (6,9).

Among a variety of pathophysiological conditions, older age, male gender, longer history of smoking, higher body mass index (BMI) and pulse pressure, hypertension, diabetes, chronic inflammation, malnutrition, abnormalities in lipid composition, HD duration, elevated serum calcium (Ca) and phosphate (PO_4) levels, higher Ca-PO_4 product (CaxPO_4) and calcium carbonate ($CaCO_3$) intake, as well as intact parathyroid hormone (iPTH) concentrations (7,10-22), have been closely associated with general atherosclerotic changes in HD populations. Mediosclerosis is common in HD patients and it is commonly associated with the presence and duration of diabetes, HD treatment and its duration, serum lipids, serum C reactive protein (CRP), higher serum PO_4 and CaxPO_4 levels, higher doses of prescribed $CaCO_3$ and lower serum albumin levels (6,23). Patients with mediosclerosis are younger than those with atherosclerotic intimal calcifications and also differed with less diabetes, hypertensive vascular disease, and clinical history of cardiovascular disease due to fewer atherosclerotic lesions (5,6). However, the pathogenesis and clinical significance of mediosclerosis in HD patients remains uncertain (6,23).

The aim of this study was to evaluate the presence of PAD and mediosclerosis using ABI measurement in our asymptomatic HD patients.

Subjects and Methods

Patients

In a cross-sectional study we examined 94 patients (62 men, 32 women; mean age 55.24±12.55 years, range 26-85 years). They were all more than 12 months on hemodialysis (86.36±50,08 months, range 14-223 months), and had been free of symptoms for cardiovascular disease or peripheral artery disease for at least six months prior to inclusion.

Primary causes of chronic renal failure were chronic glomerulonephritis in 22 patients (23.4%), hypertensive nephropathy in 16 patients (17%), diabetic nephropathy in 13 patients (13.8%), polycystic kidney disease and chronic pyelonephritis in 12 patients (12.8%) each, obstructive nephropathy in 5 patients (5.3%), and in 14 patients (14.9%) the primary cause of chronic renal failure remained unknown.

The patients were dialyzed with low-flux synthetic membranes, bicarbonate dialysate with 1,75 mmol/l Ca, received epoietin to maintain hemoglobin between 100 and 120 g/l, and regularly took iron, vitamin supplements and $CaCO_3$ used to maintain serum PO_4 levels below 1.8 mmol/L. The duration of HD was individually tailored (4-5 hours thrice weekly) to control body fluids and blood chemistries.

All patients underwent careful interview and evaluation of patient history based on hospital and outpatient records. Systolic (SBP) and diastolic blood pressure (DBP) (recorded once a month before HD, on the day of the blood chemistry analyses, during 12 months preceding the ABI evaluations) were collected and averaged for statistical analysis. Brachial pulse pressure (PP) and mean arterial pressure (MAP) were calculated by the formula PP=SBP-DBP; MAP=DBP+(SBP-DBP)/3. Records for past cardiovascular, cerebrovascular disease and PAD, as well as levels of BMI, prescription for vitamin D_3 (μg/weekly) and $CaCO_3$ (g of elemental Ca/day) prescribed to each patient were taken from the patients files. Criteria for concomitant cardiovascular disease included abnormal electrocardiogram and history of documented cardiovascular disease like myocardial infarction, coronary angiogram showing significant occlusive disease, classic exercise angina, or arrhythmia. The definition of cerebrovascular and PAD included a history of a documented stroke or transient ischemic attack, and history of positive lower extremity angiogram and / or past presence of claudication (using the WHO/Rose questionnaire) (9). The influence of other potential traditional risk factors like age at the time of ultrasonographic examination, age at start of HD, gender, HD duration, cause of renal failure, smoking habits, dialysis adequacy (12 measurements of Kt/V) on ABI levels were also analyzed.

Blood Chemistries

Pre-dialysis hemoglobin, leukocyte, serum Ca, serum PO_4, serum albumin, triglycerides, total serum cholesterol, HDL cholesterol, LDL cholesterol and CRP were determined once monthly. Intact PTH and ferritin were determined every 4 months. The values of

the biochemical data considered in the present study were the averages of all above mentioned measurements over the 12 months period preceding the ABI measurements.

ABI measurement

All patients underwent lower limb Doppler analysis (Media-Sonics / Vasculab P-92A, 8 MHz) to confirm the presence or absence of occlusive lesions by measuring ABI. SBP in the ankles and arms of patients were measured at baseline by sphygmomanometer cuffs and Doppler flow detector (24). ABI was calculated by dividing the average ankle arterial pressure (mean of posterior and anterior tibial artery) with the arm pressure. Values of ABI of 0.95-1.30 were considered normal, whereas ABI > 1.30 indicated rigid arterial walls and presence of mediosclerosis (6,9). Subjects with ABI < 0.95 were considered to have PAD (6). ABI findings were analyzed by two observers blinded to clinical data, with inter-observer concordance of 94 %.

Ultrasonography

The presence of mediasclerosis in muscle-type arteries does not eliminate possible coexistence of atherosclerosis and plaque in large elastic-type vessels (6). So, in parallel with ABI measurements all patients underwent bilateral B-mode ultrasonography (Toshiba-HDI 3000 with 7,5 MHz transducer) of the CCA and FA for the evaluation of atherosclerotic lesions. CCA measurements were made 2 cm beneath the bifurcation and included approximately 4 cm of the CCA. FA was examined approximately 4 cm distal to the inguinal ligament at the site where the artery divides into the superficial and the profound FA. Intima media thickness (IMT) measurements were made on the far wall at the same level as the internal diameter measurements. IMT was defined as the distance between the leading edge of the lumen-intima interface to the leading edge of the media-adventitia interface of the far wall. A localized echo-structure encroaching into the vessel lumen was considered to be atherosclerotic plaque if the IMT was > 50% thicker than neighboring sites (7). Measurements of IMT and internal diameter were always made in plaque-free arterial segments. Ultrasonography findings of atherosclerotic parameters like IMT (mm), internal diameter (mm), atherosclerotic plaque detection and presence of calcified atherosclerotic plaque were compared between the groups.

Statistical analysis

Variables were expressed as frequencies and percentages for discrete factors, and mean values ± standard deviation for normally distributed continuous factors. The patients were classified into three groups according to different ABI levels: patients with ABI < 0.95 as low ABI, patients with ABI 0.95-1.30 as normal ABI and patients with ABI > 1.30 as high ABI.

Analysis of variance (ANOVA) was used to compare clinical and biochemical parameters between these three groups. Comparisons of proportions were made using chi-square test. Gender (0 male, 1 female), smoking (0 no, 1 yes), presence of cardiovascular disease (0 no, 1 yes), cerebrovascular disease (0 no, 1 yes), PAD (0 no, 1 yes), diabetes (0 no, 1 yes), atherosclerotic plaque detection (0 no, 1 yes), presence of calcified plaque (0 no, 1 yes), were used as categorical variables.

Statistical analysis was performed with standard statistical package (SPSS for Windows version 9.0). *P*-values < 0.05 were considered to be statistically significant.

Results

Low ABI (< 0.95) was detected in 20 (21.3%) patients, high ABI (> 1.30) in 33 (35.1%) patients, and normal ABI (0.95-1.30) was found in 41 (43.6%) patients (table 1). The analyzed basic clinical characteristics of the study groups are presented in table 1.

Compared to patients with normal and high ABI, those with low ABI were older at inclusion and at start of HD, had higher frequency of diabetes and dose of prescribed $CaCO_3$. Patients with high ABI compared to the patients with normal ABI, had higher proportion of male gender and frequency of diabetes. Also, but not

Table 1: Basic clinical characteristics of the HD patients analyzed as a function of ABI status.

Variable	Low ABI	Normal ABI	High ABI	*P* value
Number of patients (%)	20 (21.3)	41 (43.6)	33 (35.1)	<0.004
Age at inclusion (years)	62.95±11.16	49.17±12.29	53.61±10.61	<0.0003
Age at start of HD (years)	56.5±11.43	43.63±16.19	45.48±6.36	<0.003
Duration of HD (months)	77±30.08	84.12±46.73	97.97±42.43	NS
Sex (male / female)	14 / 6	22 / 19	26 / 7	<0.03
Dialysis adequacy (Kt/V)	1.2±0.19	1.29±0.18	1.23±0.11	NS
Smoking (yes / no)	5 / 15	11 / 30	6 / 27	NS
BMI (kg/m^2)	23.48±3.13	23.92±4.48	23.32±7.15	NS
Dose of $CaCO_3$ (g elemental Ca / day)	3.49±1.23	2.67±1.33	3.31±1.18	<0.03
Dose of vitamin D_3 (μg/weekly)	0.39±0.56	0.2±0.5	0.21±0.1	NS
Diabetes (yes / no)	9 / 11	1 / 40	5 / 28	0.00006

significantly, high ABI patients had been on HD longer, and normal ABI patients had better dialysis adequacy and lower dose of prescribed vitamin D_3.

The relationship between carotid and femoral atherosclerosis and ABI measurements is presented in Table 2. Compared to patients with normal and high ABI, those with low ABI had higher frequency of cardiovascular disease and PAD, and higher frequency of cerebrovascular disease.

Table 2: Atherosclerotic complication of the HD patients analyzed as a function of ABI status.

Variable	Low ABI	Normal ABI	High ABI	*P* value
Cardiovascular disease (yes / no)	19 / 1	25 / 16	25 / 8	<0.006
Cerebrovascular disease (yes / no)	9 / 11	4 / 37	8 / 25	<0.002
PAD (yes / no)	12 / 8	11 / 30	7 / 26	<0.005

Table 3. presents the distribution of primary renal disease between the three groups with different ABI. Compared to patients with normal and high ABI, those with low ABI had higher frequency of diabetic nephropathy and low frequency of chronic glomerulonephritis. Patients with high ABI compared to the patients with normal ABI, had higher proportion of diabetic nephropathy and lower frequency of chronic glomerulonephritis. Also, but not significantly, high ABI patients had higher frequency of chronic pyelonephritis, and normal ABI patients had lower frequency of hypertensive nephropathy and higher frequency of polycystic kidney disease.

Table 3: Underlying renal diseases of the HD patients analyzed as a function of ABI status.

Variable	Low ABI	Normal ABI	High ABI	*P* value
Cardiovascular disease (yes / no)	19 / 1	25 / 16	25 / 8	<0.006
Cerebrovascular disease (yes / no)	9 / 11	4 / 37	8 / 25	<0.002
PAD (yes / no)	12 / 8	11 / 30	7 / 26	<0.005

The haemodynamic characteristics are listed in Table 4. Patients with high ABI levels had higher SBP, DBP, MBP and PP compared to patients with normal ABI. Increased CCA-IMT was found in patients with low ABI compared to the patients with normal ABI, but the values of FA-IMT were similar in the different groups of patients. Patients with high ABI had thicker CCA diameter compared with the normal ABI patients, and thicker FA diameter compared to the normal and low ABI patients. There was a high frequency of atherosclerotic plaques, as well as calcified intimal plaques on CCA and FA in high and normal ABI patients. However, compared with the normal and high ABI patients, the patients with low ABI had expectedly higher frequency of atherosclerotic plaque and calcified atherosclerotic plaque on both CCA and FA.

Table 4: Haemodynamic parameters of the HD patients analyzed as a function of ABI status.

Variable	Low ABI	Normal ABI	High ABI	*P* value
SBP (mmHg)	145.1±26.85	136.58±26.89	150.1±21.21	<0.03
DBP (mmHg)	85.3±16.7	79.39±14.5	85.91±7.5	<0.05
MBP (mmHg)	105.2±19.78	98.45±17.9	107.27±7.07	<0.03
PP (mmHg)	60.4±12.57	57.19±16.05	64.09±21.21	<0.05
CCA-IMT (mm)	1.64±0.37	1.44±0.26	1.5±0.11	<0.02
CCA diameter (mm)	7.45±1.04	7.09±0.93	7.75±0.32	<0.004
CCA plaques (%)	80	39	54.5	<0.0009
CCA calcified plaques (%)	70	19.5	24.2	<0.0002
FA-IMT (mm)	1.48±0.27	1.47±0.26	1.48±0.11	NS
FA diameter (mm)	7.32±1.11	6.93±0.95	7.89±0.46	<0.0002
FA plaques (%)	75	48.8	63.6	<0.05
FA calcified plaques (%)	40	14.6	15.1	<0.05

Blood chemistry results are listed in Table 5. There were no significant differences in blood hemoglobin, leukocyte, serum levels of CRP, lipids and ferritin between our patients with different levels of the ABI. Normal ABI patients had significantly higher serum albumin levels compared to the patients with low ABI levels. No significant differences were found in HD specific risks like serum levels of Ca, PO_4, Ca x PO_4 product and iPTH of normal ABI patients in comparison with the patients with low and high ABI levels.

Table 5: Blood chemistry of the HD patients analyzed as a function of ABI status.

Variable	Low ABI	Normal ABI	High ABI	*P* value
Blood hemoglobin (g/l)	113.02±14.39	115.69±10.41	115.99±11.55	NS
Blood leukocyte (x 10^9/l)	6.56±1.14	6.57±1.47	6.23±1.05	NS
Total serum Ca (mmol/l)	2.37±0.15	2.33±0.16	2.36±0.13	NS
Serum PO_4 (mmol/l)	1.62±0.35	1.46±0.13	1.51±0.08	NS
Ca x PO_4 product (mmol/l)	3.83±0.84	3.45±0.99	3.55±0.54	NS
Serum albumin (g/l)	37.5±2.99	39.39±2.75	38.98±1.82	<0.02
Serum CRP (mg/l)	6.73±7.79	4.82±0.53	6.02±6.17	NS
Serum triglycerides (mmol/l)	2.43±1.25	2.03±0.97	2.13±1.19	NS
Total serum cholesterol (mmol/l)	4.72±1.16	4.64±0.96	4.75±0.31	NS
Serum HDL cholesterol (mmol/l)	0.97±0.28	1.02±0.27	0.96±0.19	NS
Serum LDL cholesterol (mmol/l)	2.69±0.63	2.59±0.84	2.84±1.08	NS
Serum iPTH (pg/ml)	194.1±165.61	139.2±249.67	147.79±162.9	NS
Serum ferritin (mg/l)	724.8±355.5	601.8±263.7	700.8±145.7	NS

Discussion

The results of this study confirm frequent presence of low ABI (21.3%) and high ABI (35.1%) levels in our asymptomatic HD patients. According to the previous reports (6,9), these results suggest frequent presence of PAD (low ABI) and mediosclerosis (high ABI). As expected, low ABI levels were associated with atherosclerotic lesions including increased IMT on CCA, higher presence of atherosclerotic plaque and

calcified atherosclerotic plaque on both CCA and FA. Patients with low ABI had frequently documented atherosclerotic complications such as clinical history of cardiovascular disease, cerebrovacular disease and of course PAD. Our patients with low ABI were significantly older, had more frequently diabetes and lower serum albumin. These results are consistent with the data from previous reports on non-specific generalized atherosclerotic risks and PAD occurrence (9-12,15,19,25). But, our HD patients with low ABI levels in proportion with the other patients did not show significant differences in other non-specific atherosclerotic risk factors, e.g. smoking, BMI, BP, serum levels of CRP and lipids (10,11,13,16,18). Opposite of previous reports (18,20), low ABI levels in our patients were not associated with HD specific atherosclerotic risks such as elevated serum PO_4 and $CaxPO_4$ product. However, consistent with literature reports, low ABI levels were associated with higher dose of prescribed $CaCO_3$ (18,20,21). The report stating that oral vitamin D_3 doses prescribed to HD patients favours arterial intimal calcifications (22) was not supported by this study.

While low ABI is apparently associated with generalized atherosclerosis which is not specifically attributed to HD (10,25), it has been reported that high ABI seems to be much more closely associated with HD and its duration (6). Similar to previous investigations (6), our patients with high ABI were much younger than those with low ABI, and were of similar age as of the normal ABI patients. Also, they were frequently male and diabetic, and had significantly higher BP parameters compared to the patients with normal ABI. High ABI patients had high percentage of atherosclerotic damage such as plaques and intimal calcifications, and had significantly increased internal diameter on both, CCA and FA. According to previous reports (4,6,23), the presence of atherosclerotic plaque and intimal calcifications in the large elastic type arteries, such as CCA and FA, even in the high level of ABI of our patients indicated that HD patients with mediosclerosis also developed atherosclerotic lesions. The present study did not show any association between high ABI and blood chemistry specific risk factors in our HD patients.

Finally, our findings showed high percentage of atherosclerotic plaque and calcified plaque on CCA and FA in our normal ABI patients too. In addition, as we expected and in accordance with general atherosclerotic risks (7,9-11,13,15,19,25), younger age, lower BP parameters, doses of prescribed $CaCO_3$ and proportion of diabetes, higher female gender, frequency of chronic glomerulonephritis and serum albumin levels were associated with normal range ABI. Expectedly normal ABI patients had lower atherosclerotic lesions such as CCA-IMT and internal diameter on CCA and FA, lower frequency of atherosclerotic plaque and calcified intimal plaque on both, CCA and FA, as well as lower frequency of documented atherosclerotic complications.

In conclusion, asymptomatic HD patients with high ABI (mediosclerosis) and low ABI (PAD) levels are common. Also, asymptomatic HD patients with normal and high ABI levels have high percentage of atherosclerotic lesions. Screening for atherosclerotic lesions by ABI measurement and B-mode ultrasonography on CCA and FA in HD patients could be recommended even if they have no symptoms. Some of the previous reported non-specific atherosclerotic risk factor (older age, diabetes, low serum albumin), atherosclerotic lesions and higher doses of prescribed $CaCO_3$ were associated with low levels of ABI in our HD patients. The possibility that the oral Ca doses prescribed to HD patients favours arterial intimal calcifications was supported by this study. Some of the non-specific atherosclerotic risks (male gender, blood pressure, diabetes) were associated with high ABI levels in our patient too. Low and high ABI levels in our patients were not associated with some HD specific risks such as elevated serum PO_4 and Ca x PO_4 product. The small number of patients who participated in this study necessitates confirmation of our results in additional large scale studies.

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