Different Ankle Brachial Index Levels in Asymptomatic Hemodialysis Patients

S. Gelev [1], G. Spasovski [1], S. Dzikova [1], S. Tosev [2], M. Bosevski [2], Gj. Selim [1], P. Dzekova[1], A. Asani[1], V. Amitov [1] and A. Sikole [1]

Department of Nephrology [1], Department of Cardiology [2], University Clinical Center, Skopje, R Macedonia

Abstract

Background. It has been suggested that a resting ankle brachial systolic pressure index (ABI) level of ≤ 0.90 is 95% sensitive in detecting an angiogram-positive peripheral arterial disease (PAD) and that falsely elevated pressures or incompressible arteries at the ankle level and ABI ≥ 1.30 might be caused by mediosclerosis.

Methods. In a cross-sectional study on 117 asymptomatic hemodialysis (HD) patients, we evaluated the presence of PAD and mediosclerosis assessed by ABI measurement, and the presence of atherosclerotic lesions in patients with different ABI levels on high resolution B-mode ultrasonography (US) of the common carotid (CCA) and femoral arteries (FA). Finally, we compared various groups of patients according to the ABI levels for a number of clinical and biochemical parameters which might be responsible for those conditions.

Results. Our results showed frequent presence of high ABI (33.3%) and low ABI (23.1%) levels in asymptomatic HD patients. The low ABI group of patients were older, presented with more diabetics, lower dialysis adequacy, a higher dose of prescribed calcium carbonate and a number of documented cardiovascular and peripheral arterial diseases, as well as an increased CCA intima media thickness and a higher frequency of atherosclerotic and calcified intimal plaques. The high ABI group characterised by the prevalence of male gender and an increased level of all blood pressure parameters. In addition, patients with high ABI presented with higher internal diameter on CCA and FA.

Conclusions. Arterial disease in asymptomatic HD patients is a frequent finding. Screening for atherosclerotic lesions in HD patients could be recommended even if they are symptom free. The participation of a small number of patients in this study needs further confirmation in additional large scale trials.

Key words: hemodialysis, peripheral arterial disease, mediosclerosis, ankle brachial index

Introduction

Increased atherosclerotic damage of large arteries is a major contributor to the 20-fold time higher cardiovascular morbidity and mortality of the hemodialiysis (HD) patients than in the general population (1,2,3). The most prevalent arterial complication is an occlusion of the lumen and/or stiffening of the vessel wall largely caused by the extensive calcifications (4). Arterial intima calcification represents an advanced stage of atherosclerosis and is associated with development of plaques and occlusive lesions (5). Mediosclerosis (arterial media calcification) in its typical form does not obstruct the arterial lumen (5). A few studies have recently shown that mediosclerosis in HD patients may be associated with atherosclerosis, intimal plaques and occlusive lesions (5). HD patients are particularly prone to the development of atherosclerosis of lower limbs, so the peripheral arterial disease (PAD) is observed in a considerable percentage of HD patients (6). Knowledge of the prevalence of atherosclerotic PAD in HD patients is limited and is not yet sufficiently clarified. The ankle brachial systolic pressure index (ABI) measurement using Doppler techniques is an established method to evaluate the presence of PAD (7). It was suggested that a resting ABI level of ≤ 0.90 is 95% sensitive in detecting an angiogram-positive PAD and almost 100% specific in identifying apparently healthy individuals (7). In addition, it is known that falsely elevated pressures or incompressible arteries at the ankle level and ABI ≧ 1.30 might be caused by mediosclerosis (5,7).

While PAD is apparently associated with general atherosclerotic factors which are not specifically attributed to HD (8,9), mediosclerosis tend to be closely associated with HD and its duration (5). Recently, the mediosclerosis was demonstrated to be an active cellular process similar to the bone formation, and not only as a result of the passive extraskeletal calcification (10). The pathogenesis and clinical significance of mediosclerosis in HD patients remains uncertain (5,10).

The aim of our study was to: i) evaluate the presence of PAD and mediosclerosis using ABI measurement in asymptomatic HD patients; ii) evaluate the presence of atherosclerotic lesions using high resolution B-mode ultrasonography of the common carotid and femoral arteries especially in patients with normal and high ABI levels; iii) to compare the various groups of patients according to the ABI levels for a number of clinical and biochemical parameters that might be responsible for those conditions.

Patients and methods

Patients

In a cross-sectional study we examined 117 patients (72 male, 45 female; mean age 54.42±12.56, range 26-85 years) being at least 12 months on HD (87.98±56.13, range 14-287 months). The patients were symptoms free in the last 6 months in terms of cardiovascular disease and claudication as a hallmark of PAD (using the WHO/Rose questionnaire) (7) and signs for intercurrent infection.

Correspodence to: Saso Gelev, Department of Nephrology, University Clinical Center, Skopje, R. Macedonia; E-mail: lili@mp.com.mk

Primary cause of chronic renal failure was: chronic glomerulonephritis in 26 (22.2%), hypertensive nephropathy in 22 (18.8%), diabetic nephropathy in 17 (14.5%), polycystic kidney disease in 13 (11.1%), chronic interstitionephritis in 14 (11.9%), obstructive nephropathy in 6 (5.1%), and unknown cause in 19 patients (16.2%).

The standard care of our patients consisted of bicarbonate dialysis with 1.75 mmol/l calcium (Ca), a low-flux synthetic membranes, epoietin and regular iron and vitamin supplementation to maintain hemoglobin levels between 100 and 120 g/l, and a use of calcium carbonate ($CaCO_3$) as a solely phosphate (PO_4) binder in order to keep the serum PO_4 levels ≤1.8 mmol/L. The duration of HD was individualised to 4 - 5 hours thrice weekly as needed.

All patients underwent careful interview and evaluation of patient history based on the hospital and outpatient records. Systolic (SBP) and diastolic blood pressure (DBP) (from the records taken at the same day as the regular monthly blood analyses, during 12 months prior to the study) were collected and averaged for a statistical analysis. Brachial pulse pressure (PP) and mean arterial pressure (MAP) were calculated by the formula PP=SBP-DBP; MAP=DBP+(SBP-DBP)/3. Data on the previous atherosclerotic complications (cardiovascular, cerebrovascular disease and PAD), as well as levels of body mass index (BMI), prescription of vitamin D_3 (μg/weekly) and $CaCO_3$ (g of elemental Ca/day) were extracted from the patient files. The criteria for concomitant cardiovascular disease included abnormal electrocardiogram or coronary angiogram as a history of documented cardiovascular disease such as myocardial infarction, significant occlusive disease, classic exercise angina, or arrhythmia. The definition of cerebrovascular disease included a documented history of a stroke or transient ischemic attack with a computed tomography (CT), and a positive lower extremity angiogram for PAD. The association with other potential traditional risk factors like age at inclusion, age at the start of HD, gender, HD duration, cause of renal failure, smoking habits and dialysis adequacy were also analysed in various ABI groups.

Biochemistry

Pre-dialysis hemoglobin, leukocyte, serum Ca and PO_4, albumin, triglycerides, total cholesterol, HDL, LDL cholesterol and C-reactive protein (CRP) were assessed monthly. Serum intact parathyroid hormone (iPTH) and ferritin were measured every 4 months. Of note, the values of biochemical data considered in the present study were averaged for all above mentioned measurements over the 12 months period prior to the ABI evaluation.

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. Two observers blinded to the clinical data, analysed ABI findings with an inter-observer concordance of 93 %. Patient's SBP in the ankles and arms was measured by sphygmomanometer cuffs and Doppler flow detector (11). ABI was calculated by dividing the average ankle arterial pressure (mean of posterior and anterior tibial artery) with the arm pressure. ABI values of 0.95-1.30 were considered normal, whereas ABI > 1.30 indicated rigid arterial walls and a presence of mediosclerosis (5). Subjects with ABI < 0.95 were considered to have PAD (5).

Ultrasonography

The presence of mediosclerosis in muscle-type arteries does not eliminate a possible coexistence of atherosclerosis and plaque in the large elastic-type vessels. High resolution B-mode ultrasonography of the common carotid arteries (CCA) and femoral arteries (FA) is a fundamental technique for the noninvasive investigation of atherosclerosis in HD patients (2). Along with the ABI measurements, all patients underwent bilateral B-mode ultrasonography (TOSHIBA - HDI 3000 with 7.5 MHz transducer) of the CCA and FA to evaluate the atherosclerotic lesions. CCA measurements were recorded at 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 profound FA. Intima media thickness (IMT) measurement was performed on the far wall at the same level as the internal diameter measurements. IMT was defined as a distance between the leading edge of the lumen-intima interface to the leading edge of the media-adventitia interface of the far wall. A localised echo-structure encroaching into the vessel lumen was considered to be atherosclerotic plaque if the IMT was > 50% thicker than the neighboring sites (2). Measurements of IMT and internal diameter were performed always on the plaque-free arterial segments. Ultrasonography findings of atherosclerotic parameters like IMT (mm), internal diameter (mm), atherosclerotic plaque detection and the presence of calcified atherosclerotic plaque were all compared among the groups. A single observer measured the aforementioned parameters twice per patient with an intra-observer reproducibility of 96%. The mean of the two values was then recorded as the patient result.

Statistical analysis

Variables were expressed as frequencies and percentages for discrete parameters, and mean values ± standard deviation (SD) for normally distributed continuous parameters. The patients were classified in three groups according to the different ABI levels: ABI < 0.95 as low ABI, ABI 0.95-1.30 as normal ABI and ABI > 1.30 as high ABI group.

Analysis of variance (ANOVA) was used to compare clinical and biochemical parameters between the groups. Chi-square test was used to compare the proportion of the categorical parameters. Gender (0-male, 1-female), smoking, history of cardiovascular and cerebrovascular disease, PAD, diabetes, atherosclerotic plaque detection and the presence of calcified plaque (0-no, 1-yes), were used as categorical variables.

Statistical analysis was performed with the standard statistical package (SPSS for Windows version 9.0). A p value < 0.05 was considered statistically significant at a two tailed level.

Results

Low ABI was detected in 27 (23.1%), high ABI in 39 (33.3%) and normal ABI was found in 51 (43.6%) of patients (Table 1). Differences between study groups for various clinical characteristics at baseline were listed in Table 1. Low ABI patients were older at inclusion and the start of HD, with lower dialysis adequacy, a higher number of documented cardiovascular disease and PAD, higher dose of prescribed calcium carbonate, and diabetic nephropathy as the most prevalent etiology of renal failure.

Table 1. Clinical characteristics of the HD patients analysed as a function of ABI status

Variable	Low ABI (n=27)	Normal ABI (n=51)	High ABI (n=39)	ANOVA P value
number of patients (%)	27 (23.1)	51 (43.6)	39 (33.3)	<0.0002
age at inclusion (years)	62.77±10.63 [c]	50.3±12.94	55.1±10.74 [e]	<0.0001
age at start of HD (years)	55.68±11.74 [c]	44.48±16.63	47.13±12.46 [e]	<0.005
duration of HD (months)	84.5±54.37	84.16±50.71	94.85±64.01	NS
sex (male / female)	16 / 11	27 / 24	29 / 10 [a]	<0.04
dialysis adequacy (Kt/V)	1.20±0.18 [a]	1.29±0.18	1.23±0.19	<0.04
smoking (yes / no)	10 / 17	12 / 39	8 / 31	NS
body mass index (kg/m^2)	24.41±5.57	23.83±4.22	23.21±3.57	NS
diabetes (yes / no)	10 / 17 [c]	1 / 50	8 / 31 [b]	<0.0006
prescribed $CaCO_3$ (g elemental Ca/day)	3.38±1.18 [a]	2.69±1.27	3.01±1.36	<0.02
prescribed vitamin D3 (µg/weekly)	0.38±0.59	0.18±0.48	0.20±0.48	NS
cardiovascular disease (yes / no)	26 / 1 [c]	32 / 19	31 / 8 [d]	<0.001
cerebrovascular disease (yes / no)	9 / 18 [b]	5 / 46	14 / 25 [b]	<0.002
peripheral arterial disese (yes / no)	3 / 24 [b]	0 / 51	1 / 38	<0.01
chronic glomerulonephritis (%)	7.41 [b]	33.33	17.95	<0.009
hypertensive nephropathy (%)	22.2	13.73	23.08	NS
polycystic kidney disease (%)	7.41	15.68	7.69	NS
chronic pyelonephritis (%)	11.1	7.84	17.95	NS
unknown renal disease (%)	14.81	21.57	10.26	NS
obstructive nephropathy (%)	0	5.88	7.69	NS
diabetic nephropathy (%)	37.04 [c]	1.96	15.38 [b]	<0.0001
systolic blood pressure (mmHg)	141.59±28.68	137.98±26.99	150.51±23.61 [a]	<0.02
diastolic blood pressure (mmHg)	83.41±17.14	80.54±14.78	86.54±13.14 [a]	<0.04
mean arterial pressure (mmHg)	102.81±20.69	99.68±18.31	107.86±15.84 [a]	<0.02
pulse pressure (mmHg)	58.18±13.68	57.44±15.53	63.97±15.01 [a]	<0.04

All values are expressed as mean ± SD; normal ABI vs low ABI or high ABI: [a]p<0.05, [b]p<0.01, [c]p<0.001; low ABI vs high ABI: [d]p<0.05; [e]p<0.001; NS (not significant); $CaCO_3$ (calcium carbonate)

Table 2. B-mode ultrasonography findings of CCA and FA analysed as a function of ABI status

Variable	Low ABI (n=27)	Normal ABI (n=51)	High ABI (n=39)	ANOVA P value
CCA-IMT (mm)	1.61±0.33 [a]	1.43±0.38	1.49±0.27	<0.05
CCA diameter (mm)	7.41±1.04	7.15±0.93	7.75±0.91 [b]	<0.003
CCA plaques (%)	88.89 [c]	45.09	61.54 [d]	<0.0006
CCA calcified plaques (%)	62.96 [c]	23.53	28.21 [e]	<0.0005
FA-IMT (mm)	1.47±0.25	1.43±0.25	1.47±0.28	NS
FA diameter (mm)	7.13±1.22	7.01±1.09	7.75±1.09 [c,d]	<0.0001
FA plaques (%)	81.48 [b]	50.98	69.23	<0.004
FA calcified plaques (%)	44.44 [a]	19.61	17.95 [e]	<0.01

All values are expressed as mean ± SD; normal ABI vs low ABI or high ABI: [a]p<0.05, [b]p<0.01, [c]p<0.001; low ABI vs high ABI: [d]p<0.05; [e]p<0.001; NS (not significant); CCA (common carotid artery); IMT (intima-media thickness); FA (femoral artery)

The high ABI group characterised by the prevalence of male gender and an increased level of all blood pressure (BP) parameters. Patients with normal ABI presented with highest dialysis adequacy, chronic glomerulonephritis as a predominant cause of renal failure, a fewer number of documented cerebrovascular complications and a lower dose of prescribed $CaCO_3$. The groups did not differ with regard to the duration of HD, smoking habits, BMI and the dose of prescribed vitamin D_3. The relationship between carotid and femoral atherosclerosis and ABI measurements are presented in Table 2. Expectedly, patients with low ABI had increased CCA-IMT and a higher frequency of atherosclerotic and calcified atherosclerotic plaque on both CCA and FA, whereas similar values of FA-IMT were found in either group of patients. In addition, the high ABI patients presented with a higher internal diameter on CCA and FA. Blood chemistry results are listed in Table 3. There were no significant differences in the hemoglobin and leukocyte, CRP, serum lipids and ferritin among the various ABI groups of patients. Normal ABI patients had significantly higher serum albumin levels in comparison with patients in the low ABI group. However, there was no difference in the specific parameters at risk for development of arterial disease such as total serum Ca, serum PO_4, calcium phosphate ($CaxPO_4$) product and iPTH when various ABI groups were compared.

Discussion

The results of our study confirm the frequent presence of low ABI (21.3%) and high ABI (35.1%) levels in asymptomatic HD patients. In line with the previous reports (5,7) these results suggest frequent presence of PAD (low ABI) and mediosclerosis (high ABI) in our patients.

Among a variety of pathophysiological conditions, older age, male gender, hypertension, diabetes, abnormalities in lipid composition, chronic inflammation, malnutrition, longer HD duration, elevated levels of serum Ca, PO_4 and $CaxPO_4$ product, as well as iPTH concentrations have been closely

associated with the atherosclerotic changes in HD populations (2,9,12-23). As expected, low ABI levels in our study went along with the increased IMT on CCA, a higher presence of atherosclerotic and calcified atherosclerotic plaque on both, CCA and FA, and frequently documented atherosclerotic complications in terms of cardiovascular and peripheral arterial disease. Our patients with low ABI were older at the time of inclusion and start of HD, predominantly diabetics, with low serum albumin, lower dialysis adequacy and a higher dose of prescribed $CaCO_3$. This data did not differ from the previous reports (7,8). Interestingly, our HD patients with low ABI did not show significant differences in any of the non specific atherosclerotic risk factors (9,12-18,21), e.g. smoking, BMI, BP, CRP and serum lipids in comparison with the other groups. In addition, there was no difference neither at the specific factors at risk for development of an arterial disease such as elevated serum PO_4 and $CaxPO_4$ product and doses of prescribed vitamin D_3 between the various ABI groups (21-23). The prescribed dose of vitamin D_3 in our study tended to be higher in the low ABI group although statistical significance was not reach. Hence, our study did not confirm previous reports on the increased presence of arterial intimal calcifications in patients receiving high doses of calcitriol (23,24). The small number of patients in low ABI group (underpowered study) might be one of the possible explanations about this result.

Table 3. Blood chemistry of the HD patients analyzed as a function of ABI status

Variable	Low ABI (n=27)	Normal ABI (n=51)	High ABI (n=39)	ANOVA (p value)
blood hemoglobin (g/l)	113.57±14.03	115.05±10.46	115.81±12.96	NS
blood leukocyte (x 10^9/l)	6.52±1.12	6.45±1.48	6.18±1.45	NS
total serum Ca (mmol/l)	2.37±0.16	2.30±0.12	2.33±0.19	NS
serum PO_4 (mmol/l)	1.59±0.37	1.46±0.37	1.48±0.42	NS
$CaxPO_4$ product (mmol/l)	3.73±0.89	3.43±0.99	3.48±0.96	NS
serum albumin (g/l)	37.61±2.98 [a]	39.21±2.81	38.73±3.18	<0.03
serum CRP (mg/l)	6.52±6.92	6.28±8.92	6.38±7.51	NS
serum triglycerides (mmol/l)	2.40±1.18	2.05±0.93	2.09±1.01	NS
total serum cholesterol (mmol/l)	4.67±1.08	4.63±0.94	4.65±1.08	NS
serum HDL cholesterol (mmol/l)	0.96±0.27	0.99±0.27	0.98±0.28	NS
serum LDL cholesterol (mmol/l)	2.77±0.86	2.57±0.81	2.72±0.64	NS
serum iPTH (pg/ml)	197.51±171.99	136.28±131.79	138.26±237.55	NS
serum ferritin (mg/l)	729.01±355.99	603.91±260.81	714.74±406.04	NS

All values are expressed as mean ± SD; normal ABI vs low ABI or high ABI: [a]$p<0.05$; NS (not significant); Ca (calcium); PO_4 (phosphate); CRP (C-reactive protein); iPTH (intact parathyroid hormone)

On the other hand, mediosclerosis is a common finding in HD patients, frequently associated with the presence and duration of diabetes and dialysis, BP, serum lipids, albumin, CRP, bone mineral metabolism parameters and doses of ingested $CaCO_3$ (5,10). In line with the previous reports, our patients with high ABI were younger than those with low ABI levels, with a male preponderance and higher BP parameters. Additionally, the characteristic of the high ABI group was the presence of an increased internal diameter on both, CCA and FA. According to the previous reports (4,5,10), we confirmed the presence of atherosclerotic plaque and intimal calcifications in the large elastic type arteries, such as CCA and FA. This indicates that even in the high ABI group of patients with mediosclerosis, some degree of atherosclerotic lesions may simultaneously occur, too. Hence, it should be underscored that our high ABI patients presented with a frequent history of documented cerebrovascular disease in comparison with the normal ABI patients. There were no differences between various groups in our study due to the blood chemistry parameters.

Our findings also showed a substantial percentage of atherosclerotic and somewhat lesser degree of calcified plaque on CCA and FA in our normal ABI, HD patients. We do not have a clear cut explanation of this phenomenon, although it may go along with the duration of dialysis, smoking habit and maybe a tendency towards lower PTH and insufficient handling of an exogenous calcium load. The serum levels of iPTH, PO_4 and $CaxPO_4$ product in our low ABI patients with frequent atherosclerotic changes, tended to be higher in comparison with the other groups. Hence, the present results might suggest that the calcium and phosphate metabolism is not the crucial factor which promotes development of the atherosclerotic damage. Indeed, all bone related parameters were within the referent range of the proposed K/DOQY guidelines for bone and mineral metabolism (25). In addition, the lower serum albumin levels in the low ABI group may confirm the hypothesis that malnutrition favors atherosclerosis (19). A permanent low grade inflammation or higher level of serum CRP is a typical finding in HD patients (20-21), but any connection between various ABI groups and the degree of inflammation was not observed in our study.

Finally, it should be pointed out that there is a need for further clinical trials with an appropriate control of the atherosclerotic risk factors like blood pressure, diabetes, and particularly, the amount of ingested calcium from $CaCO_3$ (26,27). The absence of any connection between our biochemical findings and the traditional atherosclerotic and mediosclerotic risk factors should not release us to maintain our interest in further control of the nutritional and inflammation markers, serum lipids, disorders of mineral and bone metabolism, intake of calcium salts and vitamin D, smoking and the blood pressure control.

Conclusion

Asymptomatic HD patients with high ABI (mediosclerosis) and low ABI (PAD) levels are common. Patients with low and a high ABI levels have a high percentage of atherosclerotic lesions and a frequent history of documented cardiovascular and cerebrovascular diseases. Reliable diagnosis of systemic atherosclerotic conditions in HD patients required use of both, ABI measurement and the B-mode ultrasonography on arteries. Screening for

atherosclerosis on CCA and FA in HD patients with these two diagnostic tools could be recommended even if patients are symptom free. Our results showed that older age, more diabetics, lower dialysis adequacy and a higher dose of prescribed $CaCO_3$ are frequently presented in patients with low ABI levels. A male preponderance and an increased BP were frequently found in patients with a high level of ABI. We need to maintain further control for both, HD specific and non specific atherosclerotic and mediosclerotic factors, in order to prevent the arterial disease in our HD patients. Further confirmation of our results in additional large scale clinical trials is needed.

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