Association of Ankle-Arm Index with Inflammation and Mineral Bone Disorder in Hemodialysis Patients

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Abstract

Background: Reduced ankle-arm index (AAI), inflammation and mineral bone disorder (MBD) are all associated with increased risk of death and cardiovascular complications in patients on hemodialysis (HD), but the association between them deserves clarification.

Objective: To evaluate the association between abnormal AAI with MBD and inflammation in patients on HD.

Methods: This was a cross-sectional analysis of 478 patients on hemodialysis for at least one year. The AAI was evaluated using a portable Doppler and mercury column manometer. Patients were divided into 3 groups, according to AAI (low: < 0.9, normal: 0.9 to 1.3, and high: > 1.3). C-reactive protein measurement was used as an inflammatory marker, whereas MBD was evaluated by calcium, phosphorus and intact parathyroid hormone levels.

Results: Participants were 54 (18 to 75) years old, 56% males, 17% diabetics, and had been on hemodialysis for 5 (1 to 35) years. The prevalence of low, normal and high AAI was 26.8%, 64.6% and 8.6%, respectively. Using a backward conditional logistic regression model, age ($p < 0.001$), diabetes ($p = 0.001$), and C-reactive protein levels ≥ 6 mg/l ($p = 0.006$) were associated with the presence of low AAI, whereas male gender ($p < 0.001$), diabetes ($p = 0.001$) and elevated calcium x phosphorus product ($p = 0.026$) were associated with high AAI.

Conclusion: In patients on hemodialysis, the presence of diabetes was associated with both low and high AAI. The risk of having low AAI seems to be increased by aging and inflammation, whereas BMD was associated with high AAI. (Arq Bras Cardiol 2011;96(5):405-410)

Keywords: Ankle brachial index; inflammation; calcinosis; renal dialysis.

Introduction

The mortality rate among end-stage renal disease (ESRD) patients is excessively high and the main cause of death is cardiovascular disease (CVD)[1]. This burden of CVD has been attributed to both traditional and nontraditional risk factors, which are related to chronic kidney disease and/or dialysis procedure. Age, diabetes mellitus and smoking are traditional factors also applicable to dialysis patients[2]. Among nontraditional risk factors, mineral bone disorder (MBD), including high serum phosphorus, high calcium × phosphorus product and extreme intact parathyroid hormone (i-PTH) serum levels have all been associated with increased cardiovascular mortality risk[3-5]. Another nontraditional risk factor for cardiovascular death is microinflammation, usually assessed by C-reactive protein (CRP) serum levels.[6]

In addition to coronary artery disease and cerebrovascular disease, peripheral arterial disease (PAD) is also highly prevalent among dialysis patients and its presence has been associated with high mortality[7-10]. The ankle-arm index (AAI) has been used as a diagnostic tool for PAD[11]. This index is based on the fact that systolic blood pressure in the legs is usually equal to or slightly higher than in the upper limbs in healthy individuals. In the presence of an arterial stenosis, a reduction in pressure occurs distal to the lesion[12]. When angiography was used as a gold standard, AAI ratio < 0.9 was found to have high sensitivity and specificity when diagnosing PAD[11]. In addition, low AAI has a strong correlation with arterial disease in other sites and has been found to be a good predictor of mortality in the general population[7-10,13,14].

Both low and high AAI have been found to be strong predictors of death among hemodialysis patients[7-10,13,14] and it is plausible to think that high AAI in ESRD patients could be due to vascular calcification and arterial wall stiffness associated with MBD.

The aim of this study was to evaluate the association of low and high AAI values in patients on hemodialysis with

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several nontraditional cardiovascular risk factors, namely, inflammation and MBD.

Materials and methods

This is a cross-sectional multicenter study, performed at six dialysis facilities in Rio de Janeiro state, Brazil. The study was approved by the local Ethics Committee and all the patients signed the informed consent. The imaging studies and AAI measurements were taken between March 2006 and September 2007. All patients aged 18 to 75 years, who had been on hemodialysis for at least 12 months, were approached for enrollment. Exclusion criteria were: neoplasia diagnosis, presence of a positive anti-HIV test, atrial fibrillation, bilateral lower-limb amputation and dementia.

The ankle-arm index

Patients were evaluated once to obtain the AAI. Measurement was accomplished before hemodialysis session, after 5 minutes in supine position. The AAI, defined as the ratio of ankle-to-arm systolic blood pressure, was measured by 3 trained observers (one physician and two medical students) based on the information that interobserver and intraobserver variability for Doppler blood pressure measurement is negligible[7,15]. In lower limbs, tibial posterior arteries were used, since the *dorsalis pedis* artery is congenitally absent in 4 to 12% of the population[11]. Systolic blood pressure was measured twice at each site, in rapid and alternate succession, to obtain a mean value. Standard blood pressure arm cuffs connected to a mercury column were applied to the arm and to each ankle (with the lower end of the bladder just above the malleoli). After palpation of the arteries, ultrasound gel was applied, and a Doppler stethoscope (10 MHz, Super Dupplex, Huntleigh Technology Inc., Manalapan NJ, USA) was used to assess systolic blood pressure. Systolic blood pressure in the upper limb was measured on the brachial artery of the arm contralateral to the vascular access. To calculate AAI, the lowest mean from the ankles was divided by the mean in the arm.[16]

To evaluate the relationship between AAI and demographics, clinical and laboratory data, the population was divided into three groups according to AAI values: low AAI group (< 0.9), normal AAI group (0.9 to 1.3) and high AAI group (> 1.3).

Demographic, clinical and laboratory data

Demographics and clinical data were derived from both a structured clinical interview and a database used in all six dialysis units. These data included gender, age, ethnicity, time on dialysis, primary renal disease, vascular access, current smoking (yes/no), and use of medications (calcium acetate, calcium carbonate, calcitriol, sevelamer and erythropoietin). Comorbidities were defined as follows: Hypertension (pre-dialysis systolic BP ≥ 140 mmHg and/or diastolic pressure ≥ 90 mmHg and/or use of antihypertensive medications); coronary artery disease (exertion angina, current use of coronary vasodilator, past myocardial infarction, and coronary artery bypass surgery or angioplasty); stroke sequelae; PAD (current use of peripheral vasodilator, past lower limb artery bypass surgery or angioplasty or nontraumatic lower limb amputation); diabetes mellitus (diabetic nephropathy as the primary renal disease or clinical diagnosis after renal replacement therapy start); parathyroidectomy; and hepatitis C seropositivity.

Hemoglobin, creatinine, and equilibrated Kt/V (eKt/V) values were defined by calculating the mean of the last three determinations nearest to the AAI measurement. To better estimate the impact of MBD on findings, cumulative exposure was assessed through calculation of the mean of all values for serum calcium, phosphorus and intact parathyroid hormone (i-PTH) measurements along a 36-month period, just before AAI evaluation or since hemodialysis initiation for patients on renal replacement therapy for less than 3 years. Calcium and phosphorus serum levels were measured on a monthly basis and i-PTH every six months. Routine blood analyses were performed in the same laboratory. An ultra-sensitive immunoturbidimetric assay for C-reactive protein (CRP) was specifically employed for the study and the values shown were determined by the time AAI was measured.

Statistical analysis

Continuous variables were presented as mean ± SD if data followed a normal distribution and as median and range if data distribution was non-Gaussian. Categorical variables were shown as frequencies. Differences among AAI groups were assessed by one-way ANOVA complemented by Bonferroni test or by Kruskal-Wallis ANOVA complemented by Dunn test as appropriate. Analysis of the frequencies was performed by Fisher's exact test. The association between variables and the risk of presenting low AAI was studied by backward conditional logistic regression. Age, gender, diabetes, smoking, time on dialysis, serum albumin, CRP, calcium, phosphorus, calcium x phosphorus product and i-PTH were included in the initial step. The same analysis was performed to assess the variables associated with the risk of having high AAI. $P < 0.05$ were considered significant. The software SPSS, version 17.0 was used for the statistical analysis.

Results

Of a total of 1,170 ESRD patients on maintenance hemodialysis in the six facilities, 478 patients were enrolled in the study. General characteristics of patients are listed in Table 1. Median age was 53.6 (18 to 75) years, 56% were males, 16.9% diabetics, and 50.6% had hypertension as the primary renal disease. Median time on dialysis was 59 (12 to 427) months, with 27% of patients on dialysis for less than 3 years. Values of selected laboratory parameters were: eKt/V 1.51 ± 0.40; hemoglobin 11.4 ± 1.6 g/dl; serum albumin 3.8 ± 0.3 g/ dl; CRP 4.7 (0.1 - 150) mg/l; ion calcium 4.6 ± 0.3 mg/dl; phosphorus 5.4 ± 1.2 mg/dl; and i-PTH 370 (10 to 2,500) pg/ml.

The prevalence of low, normal and high AAI was 26.8%, 64.6% and 8.6%, respectively. Table 2 shows the characteristics of each AAI group.

Patients in the low AAI group were significantly older than those in the normal and high AAI groups. Male gender prevailed in the high AAI group, when compared to the low and normal ones. The prevalence of diabetes, PAD

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Table 1 - Characteristics of the population (n = 478)

Male, f (%)	268 (56%)
Age (years)	53.6 (18.3 to 75)
Primary renal disease, f (%)	
Hypertensive nephrosclerosis	242 (50.6%)
Diabetic nephropathy	71 (14.9%)
Chronic glomerulonephritis	41 (8.6%)
Polycystic kidney disease	21 (4.4%)
Lupus nephropathy	8 (1.7%)
Others	33 (6.9%)
Unknown	62 (13.0%)
Comorbidities, f (%)	
DM	81 (16.9%)
Arterial hypertension	291 (60.9%)
Smoking	73 (15.3%)
Coronary artery disease	114 (23.9%)
Stroke sequelae	16 (3.3%)
PAD	86 (18%)
Time on dialysis (months)	59 (12 to 427)
Patients < 3 years of hemodialysis, f (%)	129 (27%)
Anti-HCV positive test, f (%)	101 (21.1%)
eKt/V	1.51 ± 0.40
Hemoglobin	11.4 ± 1.6 g/dl
Albumin	3.8 ± 0.3g/dl
Calcium	4.6 ± 0.3 mg/dl
Phosphorus	5.4 ± 1.2 mg/dl
i-PTH	370 (10 to 2,500) pg/ml

PAD -Peripheral artery disease ; eKt/V - equilibrated Kt/V; i- PTH - Intact parathyroid hormone.

Table 2 - Demographics according to AAI classification

n	Ankle-arm index		
	Low	Normal	High
	128	309	41
Male (%)	53.1	53.7	80.5*
Age (years)	62 (20 to 77)	49 (18 to 75)**	54 (27 to 71)**
Primary renal disease (%)			
Diabetic nephropathy	25.0	8.4**	31.7†
Hypertensive nephrosclerosis	51.6	52.1	36.6
Chronic glomerulonephritis	3.9	11.0**	4.9
Polycystic kidney disease	3.9	4.9	2.4
Lupus nephropathy	0	2.3	2.4
Others	8.6	6.5	4.9
Unknown	7.0	14.9	17.1
Comorbidities (%)			
Diabetes	30.5	9.4**	31.7†
Hypertension	65.6	60.5	48.8
Smoking	17.2	15.2	9.8
Coronary artery disease	25.0	15.2#	12.2
Stroke sequelae	8.6	1.6**	0
Peripheral artery disease	27.3	7.4**	24.4†
Nontraumatic amputation	7.8	1.3**	9.8†
Parathyroid gland surgery	4.7	6.5	7.3
Time on dialysis (months)	57 (13 to 321)	59 (12 to 292)	65 (13 to 427)
Positive Anti-HCV test (%)	20.3	19.4	36.6††

*Values are expressed by frequency and median (range); *p < 0.01 vs low and normal AAI; **p < 0.01 vs low AAI; # p <0.05 vs low AAI; † p <0.01 vs normal AAI; †† p < 0.05 vs normal AAI.*

and nontraumatic amputation was significantly lower in the normal AAI group, when compared to both the low and high AAI groups. Coronary artery disease and stroke sequelae were more frequent in the low AAI group than in the normal AAI group. No difference was observed regarding blood pressure or pulse pressure measurements among AAI groups (data not shown).

The laboratory findings by AAI group are shown in Table 3. The low AAI group presented higher CRP and lower serum albumin than the normal AAI group. Serum creatinine was lower in the low AAI group than in both the normal and high AAI groups. The high AAI group presented increased serum phosphorus levels and calcium × phosphorus product, when compared to the normal and low AAI groups. The high AAI group also presented increased i-PTH levels compared to the low AAI group.

In the regression analysis, only age, diabetes and elevated CRP were significantly associated with the risk of presenting low AAI (Table 4), whereas the variables associated with the risk of presenting high AAI were male gender, diabetes and elevated calcium x phosphorus product (Table 5).

Discussion

In the present study, a high prevalence of abnormal AAI, mostly low AAI, was seen in patients on maintenance hemodialysis. AAI measurement is an easy, reliable and non-invasive test, which is a marker of atherosclerotic vascular disease as well as a predictor of mortality in the general population and patients on hemodialysis[9,10,13,14].

CVD has been identified as the main cause of death in dialysis patients[1]. Both, traditional and nontraditional risk factors related to chronic kidney disease and/or dialysis procedure are involved in this process. Among nontraditional CVD risk factors, BMD, inflammation and time on dialysis have been widely explored[3-6]. However, a link between abnormal AAI and such nontraditional risk factors is lacking.

Underscoring the role of AAI as a surrogate marker of generalized atherosclerosis, we found that the low AAI group had higher prevalence of CVD.

As expected, diabetes was found to be associated with increased risk of low AAI. In the present study, diabetes was

Table 3 - Laboratory findings

Parameters	Ankle-arm index		
	Low	Normal	High
CRP (mg/l)	6.4 (0.2-150)	3.9 (0.1-150)*	4.3 (0.2-41)
Albumin (g/dl)	3.74 ± 0.31	3.84 ± 0.30*	3.72 ± 0.36
BUN (mg/dl)	69 ± 22	68 ± 22	76 ± 22
Creatinine (mg/dl)	10.6 ± 2.8	11.9 ± 3.0*	12.2 ± 2.8*
eKt/V	1.51 ± 0.41	1.53 ± 0.42	1.36 ± 0.23†
Hemoglobin (g/dl)	11.6 ± 1.6	11.2 ± 1.7	12.2 ± 2.8
Ferritin (ng/ml)	584 (12 to 3,791)	491 (10 to 3,000)	581 (49 to 1,741)
Alkaline phosphatase (UI/ml)	127 (21 to 2,147)	121 (13 to 2,290)	119 (25 to 1,252)
i-PTH (pg/ml)	297 (28 to 2,202)	386 (4 to 2,500)	489 (10 to 2,160)**
Ion calcium (mg/dl)	4.6 ± 0.3	4.6 ± 0.3	4.6 ± 0.4
Phosphorus (mg/dl)	5.3 ± 1.2	5.4 ± 1.1	5.8 ± 1.4††
Ca´P product (mg^2/dl^2)	24.1 ± 5.7	24.7 ± 5.5	27.1 ± 6.3††

*CRP - C reactive protein; BUN - blood urea nitrogen; i-PTH - intact parathyroid hormone; Values are expressed by the median (limits) or by the mean ± SD; *p < 0.01 vs low AAI; **p < 0.05 vs low AAI; †p < 0.05 vs normal AAI; ††p < 0.05 vs low and normal AAI.*

Table 4 - Backward conditional regression analysis for the association of clinical and laboratory parameters with low AAI

	Odds ratio	95% confidence interval	p value
Age (decades)	1.95	1.58 to 2.41	< 0.001
Diabetes (y/n)	2.87	1.56 to 5.28	0.001
CRP (≥ 6 mg/l)	1.98	1.21 to 3.22	0.006

Variables entered on step 1: age, gender, diabetes, smoking, time on dialysis, serum albumin, C-reactive protein, calcium, phosphorus, calcium x phosphorus product and i-PTH.

Table 5 - Backward conditional regression analysis for the association of clinical and laboratory parameters with high AAI

	Odds ratio	95% confidence interval	p value
Gender (male)	4.40	1.85 to 10.46	0.001
Hypertension (y/n)	0.49	0.24 to 1.00	0.051
Diabetes (y/n)	6.51	2.78 to 15.25	< 0.001
Ca´ P product (each mg^2/dl^2)	1.08	1.01 to 1.15	0.026
iPTH (each 100 pg/ml)	1.06	0.99 to 1.13	0.078

Variables entered on step 1: age, gender, diabetes, smoking, time on dialysis, serum albumin, C-reactive protein, calcium, phosphorus, calcium x phosphorus product and i-PTH.

also associated with increased risk of high AAI. This could be accounted for by the greater prevalence of vascular calcification in such patients, which promotes arterial stiffness and higher blood pressure in lower limbs[10].

The predominance of older patients in the low AAI group in our study is in agreement with previous studies evaluating general and hemodialysis populations[9,10,13,14]. We found that the risk of having low AAI almost doubles for each additional decade. This finding reinforces age as a traditional risk factor for PAD in hemodialysis patients.

The patients with low AAI presented higher CRP levels and lower serum albumin and creatinine levels. These are not unexpected findings, as the association of malnutrition and inflammation with atherosclerotic disease and PAD, in general and hemodialysis populations, is well-known[17-19]. In the regression analysis, a CRP value ≥ 6 mg/l was the sole laboratory variable associated with the risk of presenting low AAI. Patients on hemodialysis usually present much higher CRP levels than those seen in general population. Thus, CRP level ≥ 6 mg/dl was a pre-specified definition of abnormality adopted by the dialysis facilities participating in the present study.

Serum phosphate levels were higher in patients with high AAI, probably reflecting its role in vascular calcification, as calcified arteries are stiffer and present a higher blood pressure[10]. No difference in serum calcium levels, according to AAI classification, was found. In the regression analysis, the only laboratory variable associated with the risk of presenting high AAI was the calcium x phosphorus product. No BMD marker was found to be associated with the risk of having low AAI. It should be stressed that in the current study, we used the means of calcium, phosphate and i-PTH measurements obtained throughout a 36-month period preceding AAI evaluation or since initiation of renal replacement therapy for those less than 3 years on hemodialysis. Vitamin D deficiency has been recognized as a nontraditional risk factor for atherosclerosis and adverse cardiovascular outcomes[20]. The deficiency of both 25-hydroxyvitamin D and its active form, 1,25-dihydroxyvitamin D, is highly prevalent in patients on hemodialysis[21,22]. We believe that some vascular abnormalities seen in our study could be at least partially attributed to vitamin D deficiency. As we could not measure serum vitamin D, this issue was not addressed in our study.

No association was detected between time on dialysis and the risk of presenting low or high AAI. Accordingly, PAD does not seem to be a complication of renal failure and/or the supportive therapy, but a consequence of other conditions, mainly aging and diabetes. Similar finding was demonstrated by Cheung et al[10], but not by Rajagopalan et al[23], who found a positive correlation between time on dialysis and PAD.

In our analysis, hypertension was not associated with low or high AAI, an observation also reported by Cheung et al[2] and Jaar et al[24], Hypertension is widely present among hemodialysis patients, with a prevalence that may reach 80% in some populations, making detection of its effect upon a specific subgroup hard to demonstrate[25]. It should be stressed that Rajagopalan et al[23] found a positive association between hypertension and PAD illustrating that data, in this regard, are not consensual.

Surprisingly, we found no association between smoking and the risk of abnormal AAI. Perhaps, the low prevalence of smoking in our population could have mitigated such effect.

The association between smoking and PAD in hemodialysis patients was demonstrated by Cheung et al[2] and Rajagopalan et al[23], but not by Ono et al[10].

We found a predominance of males among patients with high AAI. Similar finding was also described by Ono et al[10] and O'Hare et al[17]. In our study, the adjusted risk of presenting high AAI > 1.3 was 4.4-fold higher for males compared to females. The reasons for such difference are not clear and deserve further investigation.

Our study carries limitations. As it is an observational study, a causal relationship between inflammation and reduced AAI cannot be established. Another limitation is that we resorted to a single measurement of CRP despite previous information that this parameter may exhibit some instability along time, reflecting transient changes in inflammatory state[26].

In conclusion, the current study assessed a large number of patients on maintenance hemodialysis in order to evaluate the association between traditional and nontraditional risk factors for cardiovascular disease and ankle-arm index. Diabetes was associated with both low and high ankle-arm index. Aging and inflammation were associated with the risk of presenting low ankle-arm index, whereas bone metabolism disorder was associated with high ankle-arm index.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

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