

## Prevalence and Correlates of Vascular Disease at Ultrasound Examination in Patients on Hemodialysis

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### Abstract

**Background:** Patients on hemodialysis present an increased risk of cardiovascular death. Intimal media thickness (IMT) and presence of arterial calcifications are well-known risk factors for cardiovascular death in hemodialysis patients.

**Objective:** To assess the prevalence of IMT and arterial calcifications in HD patients and to correlate image findings with clinical and laboratory data.

**Methods:** Cross-sectional study involving 75 patients on dialysis for > 12 months. Patients underwent B-mode ultrasound scan (US) for determination of IMT of the distal third of the common carotid arteries. Arterial calcifications were assessed by US of carotids, femoral and tibial arteries, and labeled positive if calcification was found in any arterial site.

**Results:** Patients were  $52 \pm 13$  years old, 57% were males and 16% were diabetics. IMT  $\geq 0.9$  mm was found in 57% of cases and arterial calcifications at US in 48%. Aging (decades) and smoking were associated with both increased IMT (adjusted odds ratio [aOR] = 3.4,  $p < 0.001$ ; aOR = 4.4,  $p = 0.045$ , respectively) and presence of vascular calcifications (aOR = 3.0,  $p < 0.001$ ; aOR = 6.8,  $p = 0.011$ , respectively). High intact parathyroid hormone levels (per each 100 pg/ml) were significantly associated with increased IMT (aOR = 1.7,  $p = 0.021$ ), but not with vascular calcification. In contrast, Diabetes and time on dialysis (years) were significant determinants for calcifications at US (aOR = 15.0,  $p = 0.009$ ; aOR = 1.39,  $p = 0.020$ ), but not for increased IMT.

**Conclusion:** Increased IMT and calcifications at US are common findings in hemodialysis patients. Aging and smoking are consistent determinants for both image alterations. Parathyroid hormone elevation is associated with increased IMT. Diabetes and time on dialysis substantially increase the risk for arterial calcification. (Arq Bras Cardiol 2011;96(4):260-265)

**Keywords:** Hemodialysis, vascular diseases, calcinosis, Doppler ultrasonography.

### Introduction

End-stage renal disease (ESRD) patients have a high mortality rate, mainly related to cardiovascular disease<sup>1</sup>. The development of non-invasive strategies for early detection of vascular disease could provide opportunities for an early patient approach. B-mode ultrasonography (US), which carries the potential for detection of early stages of vascular disease, can be used for the measurement of intimal-media thickness (IMT), considered a marker of atherosclerosis, and for detection of arterial calcifications<sup>2</sup>, which have been shown to be associated with a poorer survival rate on dialysis<sup>3,4</sup>. Currently, other diagnostic methods are available for the identification of arterial calcification in the clinical setting, including x-rays, echocardiography and electron-beam

computer tomography<sup>5-7</sup>. However, B-mode ultrasonography is a low-cost and easy-to-perform technique.

The objectives of the present study were to assess the prevalence of increased IMT and vascular calcifications using B-mode US and to correlate the findings with clinical and laboratory data.

### Methods

This is a cross-sectional, single-center study in which patients from a single dialysis center aged between 18 and 75 years, who had been on hemodialysis for at least 12 months, were approached for enrollment. The study was approved by the local Ethics Committee and all patients signed the informed consent form. Evaluation was accomplished between March 2006 and September 2007.

### Imaging studies

B-mode US was always performed by the same experienced physician, using high resolution B-mode (7.5-MHz transducer)

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ultrasonography devices (Medison 8000, and Esaote Caris Plus). IMT measurements were performed in the distal third of the common carotid arteries as previously suggested<sup>2</sup>. Cases with any value  $\geq 0.9$  mm, a cutoff previously associated with elevated incidence of cardiovascular events in a non-dialysis population<sup>6,9</sup>, were labeled positive. At the ultrasonographic evaluation of vascular calcification, a highly echogenic vascular wall or intraluminal structure producing bright echoes with shadowing were considered to be calcifications<sup>10</sup>. The sites investigated were: the distal third of the common carotid arteries; carotid and proximal third of the internal and external branches; the whole length of common femoral arteries; proximal third of superficial and deep femoral arteries; and distal half of posterior tibial arteries<sup>10</sup>. If a calcification was found in any arterial site, the case was labeled positive<sup>11</sup>.

### Demographic, clinical and laboratory data

Demographic and clinical data were derived from chart examination. Hypertension was defined as current pre-dialysis systolic BP  $\geq 140$  mmHg and/or diastolic BP  $\geq 90$  mmHg and/or use of antihypertensive medications. Patients were classified as diabetics if they had diabetes previously to renal replacement therapy. Hemoglobin, creatinine, and equilibrated Kt/V (eKt/V) values represent the mean of the last three determinations before evaluation. To better estimate the impact of mineral metabolism disturbances 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 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 ultrasensitive immunoturbidimetric assay for C-reactive protein (CRP) was specifically performed for the study and the values shown here correspond to a single determination by the time of study enrollment.

### Statistical analyses

Continuous variables are presented as mean  $\pm$  SD or median and range as appropriate. Categorical variables are shown as frequencies. Differences between frequencies were analyzed by the Chi-square test. Associations between variables were assessed by backward conditional logistic regression analysis, in which all potentially relevant variables are included in the first step. Only variables presenting P values lower than 0.10 persisted in the next step. In case of significant collinearity between two variables, only the more relevant persisted in the next step. The decision about which variables should be excluded from the analysis in each step was made by the software. P values lower than 0.05 were considered significant. The software SPSS, version 17.0 was used for all statistics.

## Results

Of 128 patients on hemodialysis, 75 were enrolled in this study. The main reasons for exclusions were: dialysis time

lower than one year (18 patients); age older than 75 years (14 patients); and refusal to participate in the study (12 patients). Patients enrolled in the study were  $52 \pm 13$  years old, 43 (57%) males,  $59 \pm 34$  months on hemodialysis, and 12 (16%) were diabetics. Demographic and clinical characteristics of patients are shown in Table 1. Patients presented a wide range of age (Figure 1) and time on dialysis. Forty patients (53%) were on hemodialysis for less than 5 years, 30 (40%) for 5 to 10 years and 5 (7%) for more than 10 years. Laboratory data are shown in Table 2.

B-mode US was performed in all 75 patients. Increased IMT was present in 43 (57%) and arterial calcifications were detected in 36 (48%), Table 3. Calcification was present in more than three arteries in 23 of these 36 patients and 33 of them also exhibited increased IMT. Ten patients (22%) with increased IMT did not have ultrasonographic calcifications.

In search for determinants of the image findings, two models of backward conditional regression analysis were developed, with each one using  $\text{IMT} \geq 0.9$  mm and calcifications at US as the dependent variables. Clinical and laboratory data were used as the independent variables. Age (adjusted odds ratio [aOR] = 3.36 per decade,  $p < 0.001$ ), smoking (aOR = 4.49,  $p = 0.046$ ), and high iPTH levels (1.67 per 100 pg/ml) were significantly associated with  $\text{IMT} \geq 0.9$  mm, Table 4. Age (aOR = 2.96 per decade,  $p < 0.001$ ) and smoking (aOR = 6.77,  $p = 0.011$ ) were also associated with calcifications at US, Table 5. Diabetes (aOR = 1.67,  $p = 0.021$ ) and time on dialysis (aOR = 1.39,  $p = 0.020$ ) were associated with a significant risk for calcifications at US (aOR = 1.67,  $p =$

**Table 1 - Demographic and clinical characteristics of patients**

Number	75
Gender (F/M)	32/43
Ethnicity (white/black)	46/29
Age (years)	$52 \pm 13^a$
Smoking, f (%)	20 (27%)
Time on hemodialysis (months)	$59 \pm 34$
Primary renal disease, f (%)	
Hypertensive nephrosclerosis	33 (44)
Diabetic nephropathy	12 (16)
Reflux nephropathy	2 (3)
Polycystic kidney disease	5 (7)
Chronic glomerulonephritis	5 (7)
Other	2 (3)
Unknown	16 (21)
Co-morbidities, f (%)	
Diabetes	15 (20)
Arterial hypertension	41 (55)
Coronary disease	10 (13)
Peripheral artery disease (amputated)	3 (4)
Positive serology hepatitis C	6 (8)

<sup>a</sup> Mean  $\pm$  standard deviation.

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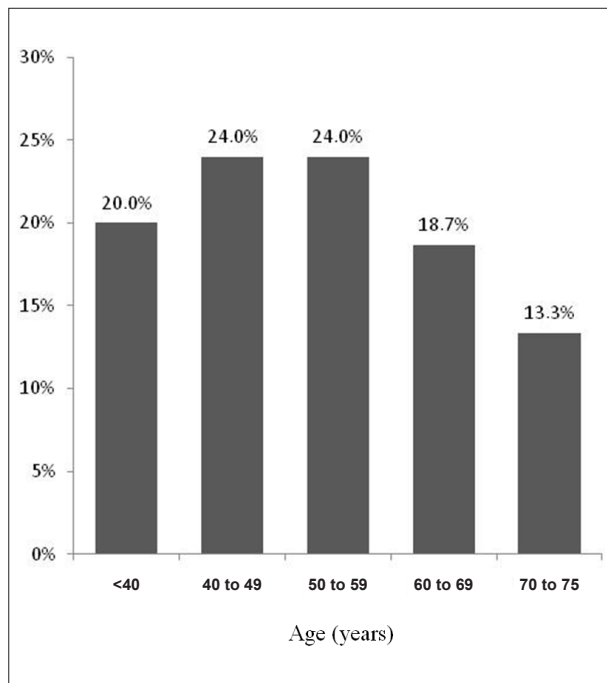


Figure 1 - Distribution of the patients according to age.

Table 2 - Laboratory data of patients

Hemoglobin (g/dl)	10.9 ± 1.5 <sup>a</sup>
Creatinine (mg/dl)	10.9 ± 3.4
Calcium (mg/dl)	9.4 ± 1.0
Phosphorus (mg/dl)	4.9 ± 1.1
CaxP (mg <sup>2</sup> x dl <sup>2</sup> )	46.2 ± 11.6
iPTH (pg/ml)	281 (43-1,759)
Equilibrated Kt/V	1.6 ± 0.2
C-reactive protein (mg/l)	6 (0 - 150)

<sup>a</sup> Mean ± standard deviation or median (range).

Table 3 - Findings on image studies

IMT ≥ 0.9 mm	43 (57%)
Calcification at US	36 (48%)

IMT - intimal media thickness; US - ultrasonography.

0.021 and aOR = 1.39, p = 0.020, respectively), but not for increased IMT. Phosphorus, calcium, Ca x P product and iPTH were not found to be risk factors for vascular calcification at US. C-reactive protein levels were not associated with IMT ≥ 0.9 mm or calcifications at US.

To better explore the relationship between i-PTH levels and IMT an additional multivariate regression analysis model was used, in which i-PTH levels were stratified in 3 categorical ranges: < 150 pg/ml, 150 to 300 pg/ml, and > 300 pg/ml. In this analysis, a significant elevated risk was restricted to the

Table 4 - Backward conditional regression analysis for association of clinical and laboratory parameters with increased IMT

	Odds ratio	95% confidence interval	p value
Age (decades)	3.36	1.81 - 6.21	<0.001
Smoking (y/n)	4.39	1.03 - 18.77	0.046
iPTH (each 100 pg/ml)	1.67	1.08 - 2.58	0.021

Variables entered on step 1 - gender, time on dialysis, smoking, age, diabetes, i-PTH, C-reactive protein.

Table 5 - Backward conditional regression analysis for association of clinical and laboratory parameters with vascular calcification

	Odds ratio	95% confidence interval	p value
Age (decades)	2.96	1.63 - 5.36	<0.001
Smoking (y/n)	6.77	1.56 - 29.3	0.011
Diabetes (y/n)	1.67	1.08 - 2.58	0.021
Time on dialysis (years)	1.39	1.05 - 1.82	0.020

Variables entered on step 1 - gender, time on dialysis, smoking, age, diabetes, calcium, phosphorus, Ca<sup>2+</sup> P, i-PTH, C-reactive protein.

highest band (> 300 pg/ml) in comparison to the middle band (aOR = 6.26 [1.05 - 37.50], p = 0.045).

## Discussion

It is well known that ESRD patients bear an elevated risk for cardiovascular diseases, which represent the leading cause of death in this population<sup>1</sup>. The arterial disease is generalized and the presence of carotid structural defects<sup>2,8</sup>, as well as peripheral vascular disease<sup>2,12</sup> are strongly correlated with coronary disease and mortality. The objective of this study was to assess vascular disease in ESRD patients using non-invasive imaging studies and to correlate the findings with clinical and laboratory data. The profile of our patients is roughly similar to the overall population on dialysis in Brazil<sup>13</sup>.

The frequency of IMT ≥ 0.9 mm, a recognized marker of atherosclerosis, was very high, affecting 43 (57%) of patients. Although a number of studies had already addressed the issue of IMT determination in ESRD patients<sup>14,15</sup>, we could not find the incidence of IMT ≥ 0.9 mm in a non-selected hemodialysis sample for an appropriate prevalence comparison. It should be emphasized that the rate of 57% was obtained with a cutoff of 0.9 mm, which is associated with increased incidence of cardiovascular events<sup>8</sup>, but is, in some way, conservative. In a recent study, for instance, it was found that the upper limits (97.5 percentile) of IMT in a healthy population aged 50 to 59, and 60 to 75 years were 0.71 and 0.81 mm, respectively<sup>16</sup>.

Calcifications at US were also common, affecting 36 (48%) of patients, a proportion comparable to the ones reported in previous studies, which varied from 50 to 64%<sup>17-19</sup>. Thirty-three out of our 36 patients with calcifications also exhibited increased IMT, whereas 10 patients with increased IMT did not have ultrasonographic calcifications. These findings are

consistent with the present view that increased IMT can be seen as a preclinical marker of atherosclerosis that precedes plaque formation<sup>2,20</sup>.

To check for potential determinants of image findings in our study, we resorted to two models of logistic regression analysis, using selected clinical and laboratory data as independent variables against each one of the image findings. Age uniformly influenced image parameters, in a way that each decade of age was associated with approximately a three-fold increase in the chance of a positive finding in the studied image parameters. This finding is consistent with the extensive information available in the literature, highlighting the role of age on the development of vascular disease<sup>16,21</sup>. Similarly, smoking influenced both image parameters, with a four-fold increase in the chance of a positive IMT and an almost seven-fold increase in the chance of a calcification. Studies addressing smoking as a risk factor for vascular calcification in ESRD patients are scarce, but the smoking habit is a traditional risk factor for cardiovascular disease, with the risk being strongly dose-related<sup>22</sup>. The effects of time on dialysis, as well as of diabetes, however, were only seen towards the presence of calcifications. A recent study showed that patients on hemodialysis have roughly an eight-fold increased risk of having vascular calcification, when matched to subjects in general population<sup>23</sup>. Diabetes is a well-known risk factor for vascular calcifications<sup>24</sup> and the absence of its influence on increased IMT allows us to speculate whether the uremic environment can prevail upon glucose metabolism derangements during the early phase of vascular structural abnormalities in ESRD<sup>25</sup> patients. However, caution is advised in this regard, as the size of the sample may have contributed to the lack of impact of this factor upon IMT enlargement. High levels of i-PTH levels were associated with increased IMT. In an attempt to better clarify this issue, we resorted to an additional regression model employing i-PTH stratification. Significant association between i-PTH levels and increased IMT was restricted to the comparison between the group with PTH levels > 300 pg/ml and the one with i-PTH values between 150 and 300 pg/ml.

Interestingly, we did not find a correlation between vascular calcifications and cumulative mineral metabolism disturbances in our study. However, this finding cannot be seen as an argument against the reported role of phosphate overload in the development of vascular calcification<sup>26,27</sup>,

as phosphate serum levels may not be a precise marker of the oral phosphate load<sup>28</sup>. In addition, it does not refute the extensive literature placing mineral metabolism disturbances as pivotal risk factors for the high cardiovascular mortality among ESRD patients<sup>29,30</sup>, as mortality was not addressed in our study. It should be mentioned that, in agreement to our findings, absence of correlation between Ca x P product and IMT had already been reported<sup>15</sup>.

Our study carries limitations and the negative data should be interpreted with caution. The cross-sectional character of the design and the low number of patients may have contributed to the lack of significance in some statistics. However, the positive findings reinforce the role of some traditional risk factors such as aging, smoking, and diabetes as determinants of vascular disease in the ESRD population. They also show that some non-traditional factors, such as time on dialysis and elevated i-PTH levels can have an impact upon vascular abnormalities in such patients.

## Conclusions

Both increased IMT and calcifications at US are common findings in hemodialysis patients, but increased IMT was more frequent. Smoking was a consistent determinant for both image findings. The major impact was seen with age, so that each decade of age was associated with a three-fold increase in the chance of a positive finding in any of the imaging studies. Diabetes and time on dialysis substantially increase the risk for arterial calcification.

## 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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