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Original Article

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A simple vascular calcification score predicts cardiovascular risk in haemodialysis patients

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Abstract

Background. Cardiovascular morbidity and mortality are highly prevalent in haemodialysis (HD) patients and have been recently associated with vascular calcifications. The objective of our study was to assess the value of a simple vascular calcification score for the prediction of cardiovascular death, cardiovascular hospitalizations and fatal and non-fatal cardiovascular events in HD patients, and to correlate this score with cardiovascular disease and with other known predictors of vascular disease.

Methods. In this observational, prospective study 123 chronic HD patients (75 males and 48 females; 20% diabetic) were included, who were on low-flux HD treatment for 46.6 ± 52 months (mean $\pm$ SD). We set up a simple vascular calcification score based on plain radiographic films of pelvis and hands. Brachial pulse pressure and mean arterial pressure (MAP) were measured and cardiovascular events and hospitalization episodes were assessed.

Results. During an observational period of 37 months there were 17 cardiovascular deaths; 28 patients needed cardiovascular hospitalizations and 32 patients suffered fatal and non-fatal cardiovascular events. Coronary artery disease was diagnosed in 43 patients (35%), peripheral arterial disease in 33 patients (26.8%), cerebrovascular disease in 16 patients (13%) and vascular disease (coronary artery disease or peripheral arterial disease or cerebral vascular disease) in 61 patients (49.6%). By binary logistic regression, diabetes ($P = 0.01$), male sex ($P < 0.001$), age ($P = 0.02$), HD duration ($P = 0.02$) and MAP ($P = 0.03$) were independently associated with a vascular score ≥ 3. This score ≥ 3 was independently associated with coronary artery disease ($P = 0.008$), peripheral arterial disease ($P < 0.001$) and vascular disease ($P = 0.001$). Patients with a vascular calcification score ≥ 3 had a 3.9-fold higher risk of cardiovascular mortality ($P = 0.03$), a 2.8-fold higher risk of cardiovascular hospitalizations ($P = 0.02$) and a 2.3-fold higher risk of fatal or non-fatal cardiovascular events ($P = 0.04$).

Conclusions. The present vascular calcification scoring represents a simple tool for the assessment of cardiovascular risk related with vascular calcifications in chronic HD patients.

Keywords: haemodialysis; mortality; vascular calcification; vascular disease

Introduction

Cardiovascular mortality is the main cause of death in haemodialysis (HD) patients and can be 20-fold higher than in the general population, with greater differences in the younger population [1,2].

There are two main types of vascular calcifications in HD patients: (i) common atherosclerosis, with intimal patchy calcifications of atherosclerotic plaques and (ii) mediasclerosis with medial linear calcifications that seem to be related to mineral metabolism disturbances [3,4]. It has been recently demonstrated that mediasclerosis is an active cellular process, similar to bone formation [4,5] and is not the result of a passive metastatic calcification. Vascular muscle cells can differentiate into osteoblasts due to different stimuli, one of which may be hyperphosphataemia [3,4,6]. Deposition of bone matrix proteins can precede vascular calcification [5]. Different vascular calcification scores have been evaluated in HD patients by various methods, mainly using B-mode ultrasonography [7] and electron beam computed tomography [8,9]. These scores have been related to oral calcium load [9], cardiovascular disease [9,10]

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and mortality [7,11] in HD patients. Medial artery calcifications have already been differentiated from intimal calcifications by plain radiography in non-insulin diabetic patients and have been associated with all-cause and cardiovascular mortality [12]. In HD patients, these different calcification patterns were both associated with cardiovascular and all-cause mortality and intimal artery calcifications were associated with a lower survival [13]. The early diagnosis of vascular calcifications and the identification of their cause raise the hope for a possible direct therapeutic intervention that might reduce cardiovascular disease in HD patients. It has already been demonstrated that calcium carbonate and calcium acetate are associated with the progression of vascular calcification, a phenomenon that can be attenuated or arrested by sevelamer, a phosphorus binder that does not increase calcium levels and also reduces LDL-cholesterol [14,15].

The main objective of this study was to evaluate the usefulness of a simple vascular calcification score based on plain radiographic films, for prediction of cardiovascular mortality in HD patients. Secondary objectives were to correlate this score with cardiovascular hospitalizations, fatal and non-fatal cardiovascular events, cardiovascular disease, with simple arterial properties [pulse pressure (PP) and mean arterial pressure (MAP)], and with calcium, phosphorus, calcium and phosphorus product and intact parathormone (iPTH) levels.

Patients and methods

Study design

An observational, prospective, single-centre study of a cohort of prevalent patients treated with HD was used.

Population

One hundred and twenty-three patients, 75 males and 48 females, treated with low flux HD, without previous parathyroidectomy, constituted the study population (Table 1); 25 patients (20.3%) were diabetic. On the day of the vascular score evaluation, mean age was 62 ± 14 years (24–91) and mean HD duration was 46.6 ± 52 months (6–271). During an observational period of 37 months, 36 patients died and one patient received a renal transplant. Mean follow-up was 32 ± 9 months (4–37).

The primary endpoint after 37 months was cardiovascular mortality. Secondary endpoints were cardiovascular hospitalizations, fatal and non-fatal cardiovascular events, and the diagnosis of vascular disease (coronary artery disease and/or cerebral vascular disease and/or peripheral arterial disease). The diagnosis of vascular disease was based on a query answered by the attending physicians of the study patients and was dependent on clinical manifestations. Coronary artery disease was diagnosed if the patient had developed typical angina pectoris, had a positive stress test, suffered a myocardial infarction, or underwent a percutaneous coronary intervention or coronary bypass surgery; diagnosis of cerebral vascular disease was based on the occurrence of

Table 1. Univariate analysis

	All patients	Score ≥3	Score <3	Significance (*P*)
Number of patients	123	65 (53%)	58 (47%)	NS
Age (years)	62.9 (14.5)	64.5 (12.8)	61.3 (16.2)	NS
HD (months)	46.6 (52.)	53.0 (57.1.)	39.4 (44.1)	NS
Male gender (%)	75 (61%)	51 (79%)	24 (41%)	
Female gender (%)	48 (39%)	14 (22%)	34 (58%)	<0.001
Diabetes (%)	25 (20%)	18 (28%)	7 (12%)	0.02
Ca (mg/dl)	9.9 (0.7)	9.9 (0.7)	9.8 (0.9)	NS
P (mg/dl)	4.9 (1.4)	4.8 (1.5)	4.9 (1.3)	NS
CaXP $(mg/dl)^2$	48.8 (15.4)	49 (16)	49 (15)	NS
iPTH (pg/ml)	302 (379)	292 (354)	313(408)	NS
Al	18.6 (7.0)	18.8 (7.2)	18.1 (6.7)	NS
Albumin (g/dl)	3.72 (0.36)	3.76 (0.32)	3.68 (0.28)	NS
Haemoglobin (g/dl)	11.3 (1.2)	11.5 (1.4)	11.2 (1.1)	NS
Kt/v	1.38 (0.19)	1.37 (0.18)	1.42 (0.21)	NS
PP (mmHg)	67.3 (17)	69.0 (18)	65.4 (15.7)	NS
MAP (mmHg)	105.3 (14)	107.4 (14.9)	102.9 (12.4)	NS
Initial CAD (%)	32 (26%)	20 (31%)	12 (21%)	NS
Final CAD (%)	43 (35%)	28 (43%)	15 (26%)	0.03
Initial CVD (%)	6 (5%)	4 (6%)	2 (3%)	NS
Final CVD (%)	16 (13%)	11 (17%)	5 (9%)	NS
Initial PAD (%)	16 (13%)	12 (19%)	4 (7%)	0.06
Final PAD (%)	33 (27%)	28 (43%)	5 (9%)	<0.001
Initial VASCD (%)	36 (29%)	22 (34%)	14 (24%)	NS
Final VASCD (%)	61 (50%)	43 (66%)	18 (31%)	<0.001
CV deaths (%)	17 (14%)	14 (22%)	3 (5%)	0.008
CV hospitalizations (%)	28 (23%)	22 (34%)	6 (10%)	0.002
CV events (%)	32 (26%)	24 (37%)	8 (14%)	0.004

Results in mean values (SD); CAD, coronary arterial disease; CVD, cerebrovascular disease; PAD, peripheral arterial disease; VASCD, vascular disease; CV, cardiovascular; NS, not significant.

stroke or transient ischaemic attack or the detection of an old cerebral infarction using computed tomography; peripheral arterial disease was diagnosed if there was claudication, ischaemic ulcers, lower limbs amputation, revascularization or diagnosis of obstruction by Doppler or angiography. Vascular disease diagnosis was performed in two steps: at baseline and at the end of the follow-up. For each patient, hospitalizations during the observational period were classified as cardiovascular, non-cardiovascular or absent. Calcium, phosphorus, haemoglobin, albumin and Kt/V were evaluated every month and iPTH and aluminum every 3 months, in the 6 months that preceded vascular calcification score evaluation. Levels of iPTH were determined by a first generation immunochemiluminometric assay. PP and MAP were evaluated once a month, based on blood pressure (BP) measurement before HD, on the day of the blood chemistry analysis, during the same 6 months period. PP was calculated by the formula $PP = SBP - DBP$; $MAP = DBP + (SBP - DBP)/3$ (SBP, systolic blood pressure; DBP, diastolic blood pressure).

HD duration was evaluated on the day of vascular calcification assessment. A simple vascular calcification score was evaluated in all patients during a 4 month period and marked the beginning of the study for each patient. This vascular calcification score was evaluated in plain radiographic films of pelvis and hands, performed in the same centre. The pelvis radiographic films were divided into four sections by two imaginary lines: a horizontal line over the upper limit of both femoral heads and a median vertical line over the vertebral column. The films of the hands were divided, for each hand, by a horizontal line over the upper limit of the metacarpal bones. The presence of linear calcifications in each section was counted as 1 and its absence as 0. The final score was the sum of all the sections, ranging from 0 to 8. Vascular calcifications were deliberately evaluated only in muscular arteries: iliac, femoral, radial and digital. Pelvis films evaluated iliac and femoral arteries (Figure 1); hand films evaluated radial and digital arteries (Figure 2). The analysis of all the radiographic films was performed by one single experienced clinician blinded to patient information. Only linear calcifications, with or without patchy calcifications, were considered for the final calcification score, because they outline the vessel wall and have undoubtedly vascular localization. Patchy isolated calcifications that may be associated with intimal calcifications were not considered in this score because they may be confused with other types of extra-vascular calcifications, for instance, phleboliths.

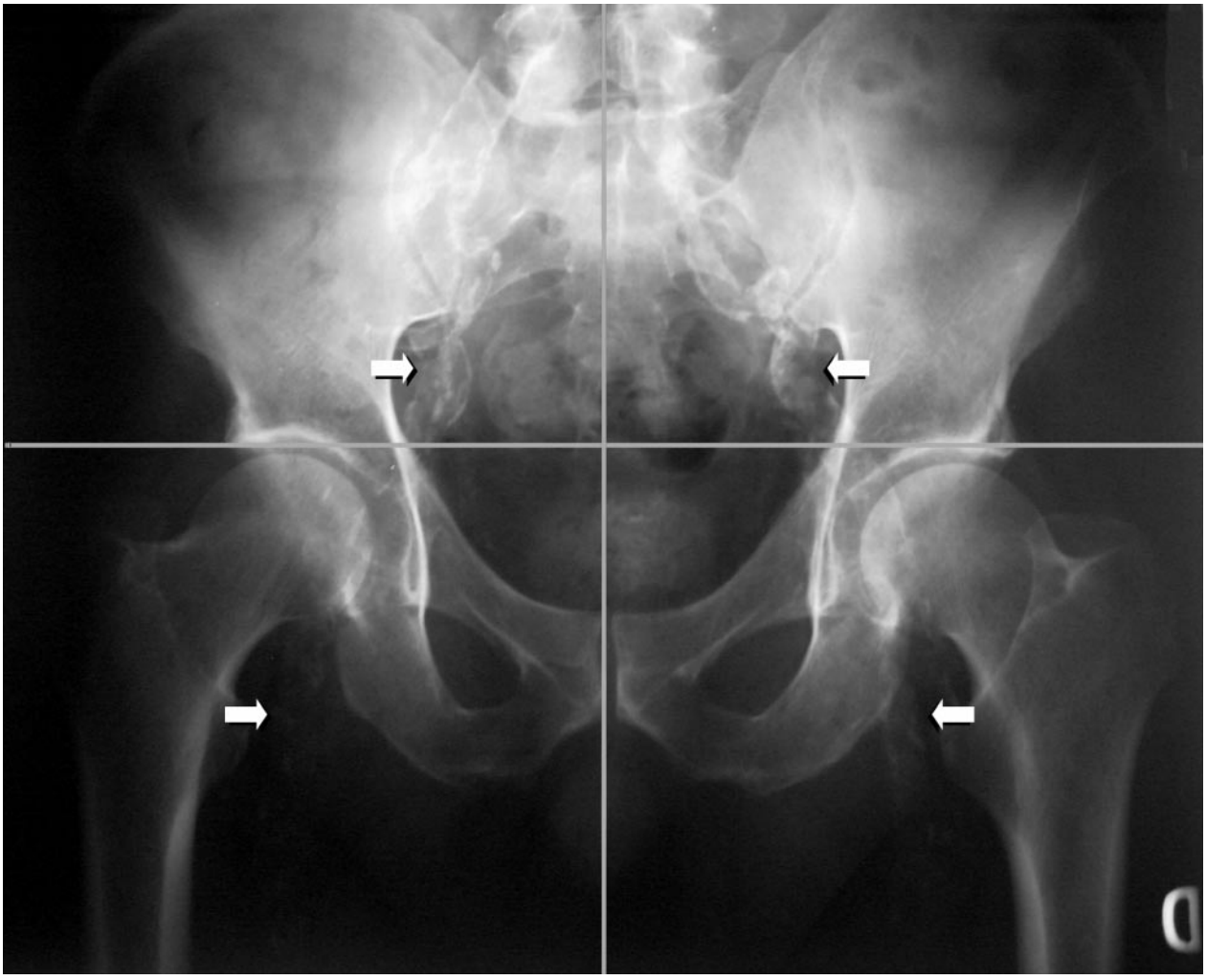

Fig. 1. Calcification score is the sum of the presence (1) or absence (0) of parallel linear calcifications in each section. In the example, pelvis score $= 1 + 1 + 1 + 1 = 4$.

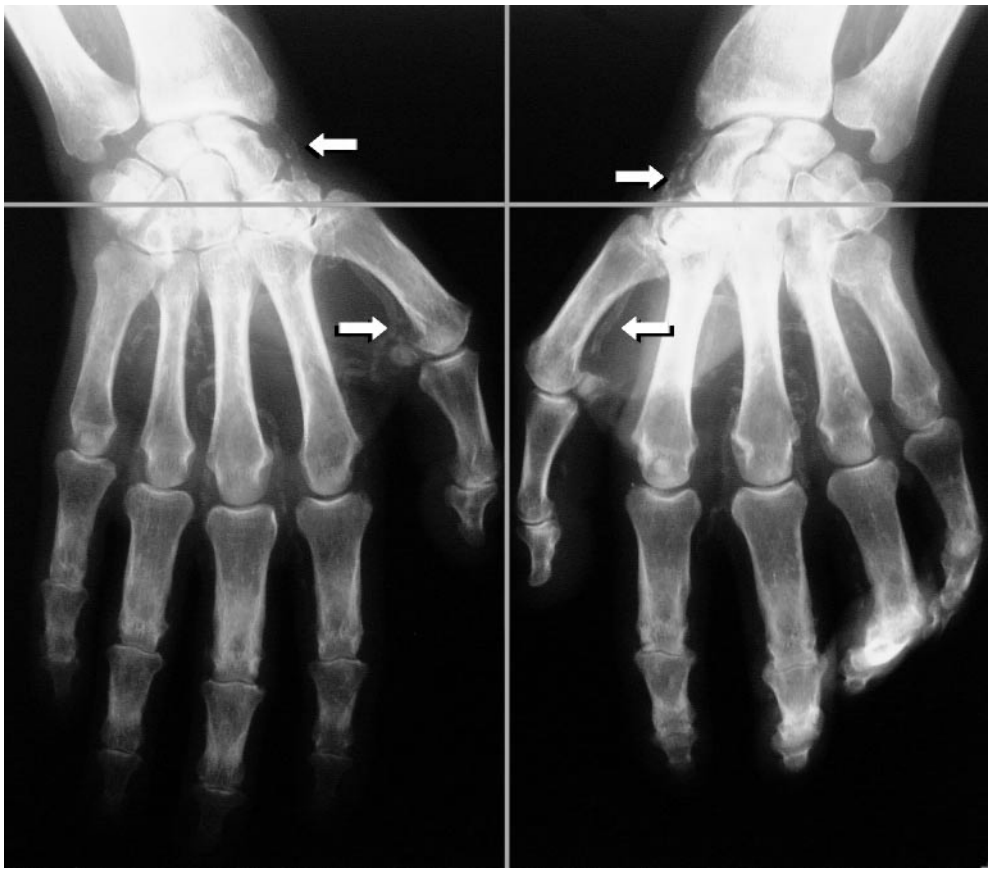

Fig. 2. Hands score in this example is 4; total score is the sum of pelvis and hands score [8].

Statistics

Variables were expressed as frequencies, percentages for discrete factors, and mean value for normally distributed continuous factors. Statistical comparison of baseline characteristics and endpoints was performed using the two-tailed chi-square test with Yates' correction or Fisher exact test when appropriate, for categorical variables, and the two-tailed Student *t*-test for continuous variables. Kaplan–Meier survival curves of patients with vascular calcification score ≥ 3 and <3 were compared by log-rank test. The independent variables associated with cardiovascular death, cardiovascular hospitalizations and fatal and non-fatal cardiovascular events were identified by Cox regression models. The covariates in Cox regression models were age, sex, HD duration, diabetes, CaXP, iPTH, albumin, vascular disease at baseline and vascular score. The independent variables associated with PP and MAP were identified by linear regression models. Variables included in these models were: age, sex, diabetes, HD duration, albumin, Ca, P, CaXP, iPTH and vascular calcification score. The independent variables associated with vascular calcifications, vascular disease at baseline and vascular disease at the end of follow-up were identified by binary logistic regression models. Covariates for vascular calcification analysis were: age, sex, diabetes, HD duration, albumin, Ca, P, CaXP and iPTH. Covariates for vascular disease analysis were the above plus PP, MAP and vascular calcification score. To identify those patients at highest risk for the study endpoint, the vascular calcification score values and the corresponding endpoint rates were related via a receiver operating characteristic (ROC) curve. The value associated with the highest accuracy was considered as the cut-off point for defining an elevated cardiovascular risk. The risk estimates for death, cardiovascular hospitalizations and fatal and non-fatal cardiovascular events were the adjusted hazard ratios (HRs) obtained by Cox regression. Statistical analyses were performed with the SPSS system 10.0 (SPSS Inc., Chicago, IL) and the Medcalc program version 6.0 (Medcalc software; Mariakerke, Belgium). For all comparisons, a *P*-value <0.05 was considered statistically significant.

Results

During an observational period of 37 months, there were 36 all-cause deaths and 17 cardiovascular deaths; 28 patients needed cardiovascular hospitalizations, and 32 patients suffered fatal or non-fatal cardiovascular events. At baseline, clinical vascular disease was diagnosed in 36 patients (29%): coronary artery disease in 32 patients (26%), peripheral arterial disease in 16 patients (13%) and cerebral vascular disease in six patients (5%); at the end of the follow-up coronary artery disease had been diagnosed in 43 patients (35%), peripheral arterial disease in 33 patients (27%), cerebral vascular disease in 16 patients (13%) and vascular disease in 61 patients (50%) (Table 1). Cardiovascular

death was associated with coronary artery disease in 12 patients, peripheral arterial disease in three patients and cerebral vascular disease in two patients. Coronary artery disease in 14 patients, peripheral arterial disease in 12 patients and cerebral vascular disease in three patients led to cardiovascular hospitalizations. One patient experienced two hospitalization episodes, one for coronary artery disease and one for cerebral vascular disease.

Vascular calcification score frequency

Anatomical calcification distribution was the following: iliac calcifications were present in 75 patients (61%), femoral calcifications in 74 patients (60%), radial calcifications in 45 patients (36.6%) and digital calcifications in six patients (5%). The distribution of vascular calcification score in the 123 patients was the following: score 0 in 31 patients (25.2%), score 1 in eight patients (6.5%), score 2 in 19 patients (15.4%), score 3 in two patients (1.6%), score 4 in 25 patients 20.3%, score 5 in eight patients (6.5%), score 6 in 26 patients (21.1%), score 7 in zero patients and score 8 in four patients (3.3%). This parameter does not present a normal distribution mainly due to the less frequent cases of unilateral vascular calcification: unilateral iliac calcifications in three patients, unilateral femoral calcifications in five patients, unilateral radial calcifications in 12 patients and unilateral digital calcifications in one patient.

By ROC curve analysis, the vascular calcification scores of the four anatomical regions (iliac, femoral, radial and digital) showed a similar relationship with cardiovascular mortality: iliac score >0 (AUC $=0.613$; 95% CI 0.522–0.699); femoral score >0 (AUC $=0.630$; 95% CI 0.539–0.715); radial score >0 (AUC $=0.604$; 95% CI 0.512–0.690); digital score >0 (AUC $=0.589$; 95% CI 0.498–0.677).

Univariate analysis

ROC curve analysis identified vascular calcification score ≥ 3 as the best cut-off value associated with cardiovascular mortality (AUC $=0.716$; 95% CI 0.629–0.793) and cardiovascular events (AUC $=0.687$; 95% CI 0.598–0.766). The vascular score ≥ 3 was measured in 65 patients (53%) (Table 1) and was more frequent among men and diabetic patients. Furthermore, a vascular score ≥ 3 was more frequently associated with cardiovascular hospitalizations, cardiovascular mortality and fatal and non-fatal cardiovascular events, coronary artery disease, peripheral arterial disease and vascular disease at the end of the follow-up period (Table 1). By univariate analysis, there were no significant differences between higher score and lower score patients with regards to age, HD duration, calcium, phosphorus and iPTH levels (Table 1). By Kaplan–Meier analysis, the cumulative hazard for cardiovascular death at 37 months was higher in patients with a vascular score ≥ 3: 23 *vs* 5%, log-rank $=5.7$; $P=0.01$ (Figure 3).

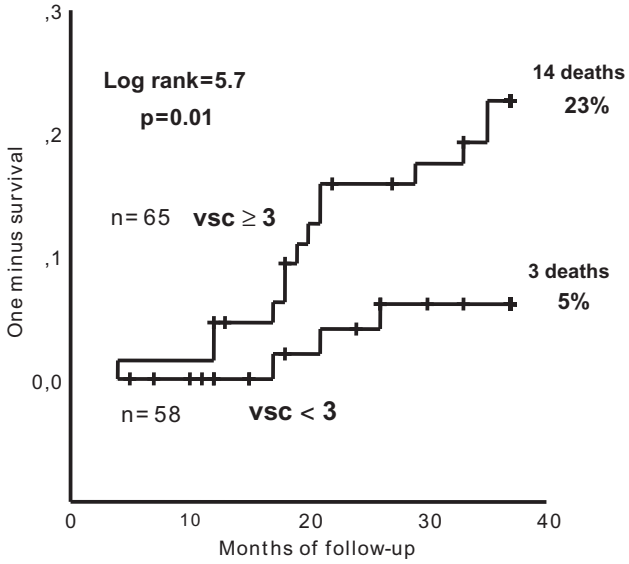

Fig. 3. Higher cardiovascular death risk in patients with vascular calcification score ≥ 3.

Multivariate analysis

Evaluation of the association of calcium, phosphorus and iPTH with vascular calcification score and vascular disease. Calcium, phosphorus and iPTH levels were evaluated during the 6 months that preceded the vascular calcification score assessment. Calcium levels were independently associated with iliac calcifications ($P=0.03$) (Table 2) and with PAD ($P=0.01$) (Table 3); phosphorus levels were independently associated with CAD ($P=0.01$) (Table 3). PTH levels were not correlated with vascular calcifications or with vascular disease in these patients.

Factors independently associated with PP and MAP. By multiple linear regression, PP was associated with diabetes ($B=12.8$; 95% CI $=5.8$–19.7; $P<0.001$) and correlated with age ($B=0.33$; 95% CI $=0.13$–0.52; $P=0.001$). MAP was associated with a vascular calcification score ≥ 3 (B $=5.6$; 95% CI $=0.8$–10.4; $P=0.02$). PP was an independent predictor of PAD ($P<0.001$) (Table 3).

Factors independently associated with vascular calcification score. Binary logistic regression (Table 2) showed that a vascular calcification score ≥ 3 was associated with diabetes ($P=0.01$), male sex ($P<0.001$), age ($P=0.02$), HD duration ($P=0.02$) and MAP ($P=0.03$). There was no correlation between final vascular score and calcium metabolism factors, but when analysing the different vascular calcification regions, in the same model, calcium levels were independently associated with iliac calcifications ($P=0.03$) (Table 2).

Factors independently associated with cardiovascular morbidity and mortality. By binary logistic regression (Table 3), vascular disease at the end of the follow-up was associated with vascular calcification score

Table 2. Vascular calcification score: multivariate analysis

Dependent variable	Independent variable	Risk	CI (95%)	Significance (*P*)
Vsc ≥3	Diabetes	4.2	1.4–13.1	0.01
	Male gender	7.47	2.9–19.1	0.000
	Age	1.04	1.008–1.077	0.02
	HD duration (months)	1.01	1.002–1.021	0.02
	MAP	1.04	1.004–1.074	0.03
Iliac score >0	Diabetes	4.6	1.4–14.7	0.01
	Male gender	3.5	1.5–8.3	0.004
	Age	1.04	1.012–1.072	0.005
	Calcium	1.8	1.050–3.143	0.03

Vsc, vascular calcification score.

Table 3. Cardiovascular morbidity and mortality: multivariate analysis

Dependent variable	Independent variable	Risk	CI (95%)	Significance (*P*)
Final CAD	Vsc >0	1.3	1.091–1.555	0.003
	Phosphorus	1.5	1.094–1.967	0.01
Final PAD	Vsc >0	1.7	1.278–2.259	0.000
	Diabetes	13.7	3.132–56.360	0.000
	PP	1.1	1.024–1.101	0.001
	Calcium	2.9	1.205–7.343	0.02
Final VASCD	Vsc >0	1.4	1.168–1.698	0.000
	Diabetes	3.3	1.071–10.044	0.04
	Age	1.04	1.008–1.074	0.01
CV hospitalizations	Vsc >0	1.3	1.093–1.554	0.003
CV events	Vsc >0	1.2	1.054–1.446	0.009
CV death	Vsc >0	1.4	1.107–1.803	0.01

Final, at the end of the follow-up; CAD, coronary artery disease; PAD, peripheral artery disease; VASCD, vascular disease; CV, cardiovascular; Vsc, vascular calcification score.

($P<0.001$), age ($P=0.01$) and diabetes ($P=0.04$); coronary artery disease at the end of the follow-up was associated with phosphorus levels ($P=0.01$) and vascular calcification score ($P=0.003$); peripheral artery disease at the end of the follow-up was associated with diabetes ($P<0.001$), vascular calcification score ($P<0.001$), PP ($P=0.001$) and calcium levels ($P=0.02$). Vascular disease at baseline was not associated with any of these factors. Fatal and non-fatal cardiovascular events were associated with vascular calcification score ($P=0.009$); cardiovascular hospitalizations were associated with vascular calcification score ($P=0.003$); cardiovascular mortality was associated with vascular calcification score ($P=0.01$). All-cause mortality was inversely associated with albumin levels ($P<0.001$).

For a better evaluation of the cardiovascular risk, a vascular calcification score cut-off defined by ROC curve analysis was applied to the same statistical tests. The cardiovascular risk evaluation was the HR adjusted for sex, age, HD duration, diabetes, calcium and phosphorus product, iPTH levels and albumin. In patients with a vascular calcification score ≥3, the HR was 2.8 (95% CI 1.151–7.012; $P=0.02$) for cardiovascular hospitalizations, 2.3 (95% CI 1.044–5.182; $P=0.04$) for fatal and non-fatal cardiovascular events, and 3.9 (95% CI 1.108–13.422; $P=0.03$) for cardiovascular mortality (Figure 4). In patients with a vascular calcification score ≥3 the odds ratio was 3.2 (95% CI 1.358–7.448; $P=0.008$) for association with CAD, was 10.4 (95% CI 2.676–40.381; $P=0.001$) for association with PAD and was 4.3 (95% CI 1.884–9.929; $P=0.001$) for association with vascular disease (Figure 4).

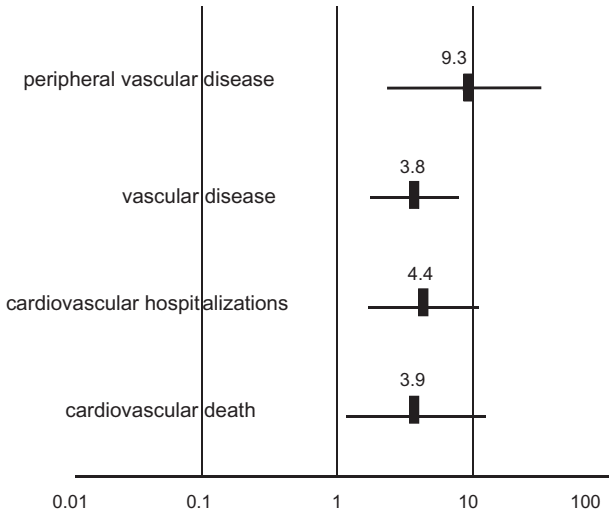

Fig. 4. Cardiovascular risk for vascular calcification score ≥3.

In summary, this simple vascular calcification score was independently associated with coronary artery disease, peripheral artery disease and vascular disease present at the end of the follow-up. A vascular calcification score ≥ 3 was an independent predictor of cardiovascular mortality, cardiovascular hospitalizations, and fatal or non-fatal cardiovascular events.

Discussion

Vascular calcifications in HD patients have already been related to arterial stiffness [7,11,16], cardiovascular disease [8,10] and cardiovascular mortality [7,11], and are more common than in the general population [8]. These extensive vascular calcifications, found even in young HD patients [9], may represent one of the factors contributing to the extremely high cardiovascular mortality for HD patients when compared with the general population [1].

The diagnosis of vascular calcification is usually made with very expensive and highly technical devices like electron beam computed tomography or multislice computed tomography [8,17,18]. The use of plain radiographic films of bone has already been suggested in the recent KDOQI clinical practice guidelines for bone metabolism and disease [19], not for bone disease evaluation but for vascular calcification assessment. In our score, vascular calcifications were deliberately evaluated only in muscular arteries: iliac, femoral, radial and digital, because muscular arteries are more prone to linear calcification in contrast with elastic arteries that are more prone to intimal calcification. Our objective was to have a simple tool for the evaluation of peripheral muscular arteries calcifications. Lower limb arteries were not chosen because of the high prevalence of amputations in HD patients. The radial artery was included in our score based on a previous evaluation by Mourad *et al.* [20] who demonstrated that the radial artery, a muscular artery devoid of atherosclerosis, had an increased stiffness that was independent of the BP level. Intimal calcifications have already been differentiated from medial calcifications by plain radiography and these different calcification patterns have been associated with different cardiovascular and all-cause mortality results [13]. In our score, only linear calcifications that outline the vessel wall, with or without patchy calcifications, were considered because they have an obvious vascular origin. Patchy isolated calcifications were not considered because of their possible non-vascular origin. These linear calcifications may correspond to the linear railroad calcifications described by Lehto *et al.* [12] and by London *et al.* [13] and identified by these authors as medial calcifications. However, vascular calcifications were evaluated in four vascular territories, and medial and intimal calcifications may coexist in the same patient and in the same vessel. Our vascular score does not exclude association of intimal and medial calcifications. This would explain why this score was a good predictor of cardiovascular mortality. In another study, this vascular calcification score was also correlated in univariate and multivariate analysis with pulse wave velocity measured by Complior® [21]. This finding confirms the value of this simple score, suggesting that linear calcifications identified by this method are associated with changes of the arterial wall properties. This calcification score that we have developed is a very simple tool, easy to use by the attending physician without assistance of a radiologist and may help identify patients at higher cardiovascular risk.

Changes of arterial wall properties with age are associated with SBP increase and DBP decrease. PP increase has been established as a cardiovascular disease risk factor in the general population [22] and in HD patients as well [23,24]. In our study, PP in multivariate analysis was not correlated with vascular calcification score but was correlated with age and diabetes and was independently associated with peripheral arterial disease. However, MAP, which is related to cardiac output and vascular resistance, was independently associated with a vascular calcification score ≥ 3. The fact that BP was evaluated immediately before an HD procedure, in a clinical situation of hypervolaemia, may have contributed to this result.

It has already been shown that PTH levels are overestimated with the common iPTH assays because they detect not only PTH (1–84), but also evaluate C-terminal fragments, which can have inhibitory activity. Newer 'whole PTH' assays can detect exclusively PTH (1–84), but the predictive power of these new assays is still unknown [19]. In the present study, vascular calcification score was independent of PTH values. This has already been demonstrated in other studies [8,16]. Hyperphosphataemia and high calcium phosphate product are predictors of mortality in HD patients [25]. In our study, there is some evidence for a relationship between calcium or phosphorus levels and vascular disease: phosphorus levels were correlated with coronary artery disease and calcium levels were correlated with peripheral arterial disease. The final vascular calcification score was not correlated with calcium, phosphorus or iPTH levels, but calcium levels were correlated with the presence of iliac calcifications. Similarly, Guérin *et al.* [16] did not find any association between a semi-quantitative vascular calcification score evaluated by B-mode ultrasonography and calcium, phosphorus and iPTH levels [16]. Previous hyperphosphataemia episodes that would have initiated this vascular calcification process may have been missed because of the time limited monitoring phase in these patients.

Vascular disease, present at the end of the follow-up, correlated with the vascular calcification score. Conversely, clinical vascular disease diagnosed at baseline did not predict vascular mortality or vascular events and did not correlate with the vascular calcification score. Vascular disease is oligosymptomatic in this population and sub-clinical vascular disease was not diagnosed at baseline, reflecting what happens in current practice. As many patients do not have a very

active life style, symptoms of cardiovascular disease may be delayed, explaining the absence of correlation of clinical vascular disease at baseline with cardiovascular death and cardiovascular events. Clinical evidence of vascular disease at the end of the follow-up, however, was strongly associated with the vascular calcification score. This association strongly supports the usefulness of this simple vascular tool at a stage of sub-clinical vascular disease.

Limitations of this vascular calcification score

This vascular calcification score is not quantitative and therefore is not adequate for accurately assessing the progression of calcifications, as opposed to the scores evaluated by electron beam computed tomography [14,15]. However, in a retrospective study of long-term HD patients where the authors also used a vascular calcification score based on radiographic films [26], it was possible to evaluate regression and aggravation of the calcifications over time.

Conclusion

Cardiovascular morbidity and mortality in this cohort of HD patients were related, among other factors, to a simple vascular calcification score evaluated by plain radiographic films of pelvis and hands. This simple vascular calcification score was independently associated with coronary artery disease, peripheral artery disease and vascular disease diagnosed at the end of the follow-up. Male sex, diabetes, age, HD duration and MAP were independently associated with a vascular calcification score ≥ 3. A vascular calcification score ≥ 3 was an independent predictor of cardiovascular mortality, cardiovascular hospitalizations, and fatal or non-fatal cardiovascular events. This vascular calcification score represents a simple and inexpensive tool for assessing the cardiovascular risk related to vascular calcifications in HD patients.

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Conflict of interest statement. We have had no involvements that might raise the question of bias in the work reported or in the conclusions, implications or opinions stated.

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