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Vascular and valvular calcifications in dialysis patients: the same pathogenesis?

Teresa Adragão, Ana Pires, Carlos Lucas, Rita Birne, Luís Magalhães, Margarida Gonçalves, Acácio Pita Negrão

Gambro-Healthcare, Nefroclinica. Estoril, Portugal

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ABSTRACT

Osteoblastic bone formation has been described in cardiac valves resembling the active calcification process already demonstrated in arteries, in relation to osteoblastic transformation of vascular smooth muscle cells. The aim of our study was to evaluate the mortality risk of cardiac valvular calcification in haemodialysis patients and to analyse the association of valvular calcification with arterial vascular calcification. Valvular calcification (VC) was diagnosed by B-Mode echocardiography. A simple vascular calcification score (SVCS) was evaluated in plain X-ray of hands and pelvis (0-8). We studied 127 prevalent HD patients (75 males and 52 females) with a mean HD duration of 48±53 months. Aortic VC (AVC) was diagnosed in 19 patients (15%), mitral VC (MVC) in 37 patients (29%) and AVC or MVC in 39 patients (31%); SVCS › 0 was diagnosed in 91 patients (71%) and SVCS ≥ 3 in 63 patients (50%). After 48 months follow-up there were 43 all cause deaths and 21 cardiovascular deaths. Vascular and all valvular calcifications were associated with lower cumulative survival. The adjusted risk of all cause death was 3.7 fold higher in AVC (p‹0.001). For each unit increment of the SVCS there was 56% increase in cardiovascular death risk (p‹0.001). SVCS was associated with aortic (p=0.002) and mitral (p‹0.001) valvular calcification. In conclusion, in these patients valvular and vascular calcifications were independent predictors of mortality. Vascular calcification was independently associated with cardiac valvular calcification, suggesting that these two types of calcification may share common characteristics.

Key-Words:
Haemodialysis; mortality; valvular calcification; vascular calcification.

INTRODUCTION

Vascular calcifications are highly prevalent in dialysis patients and have been associated with an increased risk of total and cardiovascular death[1]. Some mechanisms linking vascular calcifications with cardiovascular risk, such as the association between vascular calcifications and arterial stiffness, have already been recognised[2]. Loss of arterial distensibility is associated with increased pulse pressure[3], left ventricular hypertrophy and decrease of coronary perfusion during diastole. It has been demonstrated that vascular calcification in dialysis and non-dialysis patients is an active cellular process, similar to bone formation[4-6]. Vascular smooth muscle cells can differentiate into osteoblasts due to different stimuli, which, in dialysis patients, may be hyperphosphataemia and hypercalcaemia[7]. Reduction of calcification inhibitors, such as fetuin-A or matrix-Gla protein, may be another factor associated with the development of calcification[8]. Valvular calcification is an independent predictor of cardiovascular death in the general population[9] and ectopic bone

formation has been also identified, most likely originating from differentiated myofibroblasts[10], resembling the active calcification process already demonstrated in arteries. It has already been demonstrated that valvular calcification is also a predictor of cardiovascular mortality in peritoneal dialysis patients[11]. The aim of this study was to evaluate in a group of haemodialysis patients the risk of all cause death and of cardiovascular death related to cardiac valvular calcification and to analyse the association of cardiac valvular calcification with arterial vascular calcification.

PATIENTS AND METHODS

Study design

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

Population

One hundred and twenty seven patients, 75 males and 52 females, without previous parathyroidectomy were evaluated. Twenty six patients (21%) were diabetic. At baseline, mean age was 62±15 years (24-91) and mean haemodialysis duration was 47±56 months (4-271). During an observational period of 48 months, 43 patients (34%) died. The diagnosis of vascular disease at baseline was based on previous clinical manifestations and test results. Coronary artery disease was diagnosed if the patient had typical angina pectoris, 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 stroke or transient ischaemic attack or the detection of an old cerebral infarction in computed tomography. Peripheral arterial disease was diagnosed if there was claudication, ischaemic ulcers, lower limbs amputation, revascularisation or diagnosis of obstruction by Doppler or angiography. Coronary artery disease was diagnosed in 33 patients (25%). Peripheral artery disease was present in 17 patients (13%) and 6 patients (5%) had had a previous stroke.

Vascular and valvular calcifications

Vascular calcifications were evaluated in plain X-ray of pelvis and hands by a method previously described[12]. Pelvis 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 (Fig. 1). Hand films were divided for each

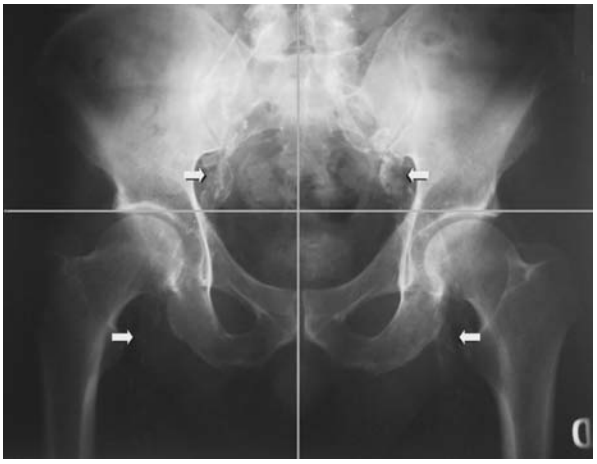

Figure 1

Ileo-femoral score evaluates the presence of vascular calcifications in iliac and femoral arteries. Calcification score is the sum of the presence (1) or absence (0) of vascular calcifications. In this example, pelvis score (1+1+1+1) = 4

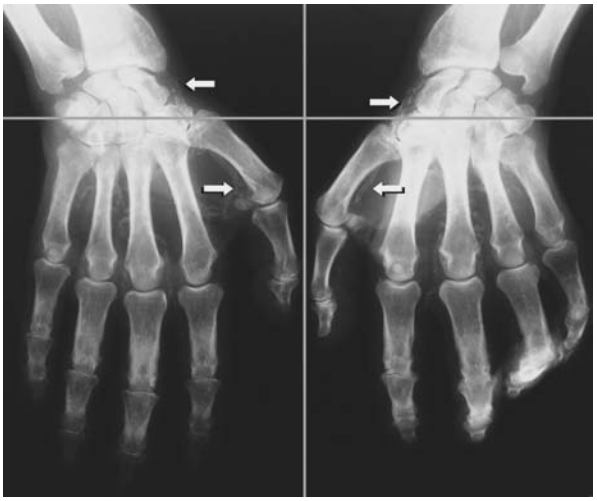

Figure 2

Hand score evaluates the presence of vascular calcifications in radial and digital arteries. In this example hand score (1+1+1+1) = 4. Total score is the sum of pelvis and hand score (8)

hand by a horizontal line over the upper limit of the metacarpal bones (Fig. 2). Pelvis films evaluated iliac and femoral arteries (ileo-femoral score) and hand films evaluated radial and digital arteries (hand score). Any vascular calcification lining the vessel walls either in an irregular pattern or in a linear pattern was considered. The presence of vascular calcifications in each section was rated as 1 and its absence as 0. Final score was the sum of all sections and ranged from 0 to 8.

Valvular calcifications of mitral and aortic valve were assessed with B-mode Echocardiography

Biochemical analysis

Serum levels of the following biochemical parameters were evaluated and time averaged for the 6 months preceding the evaluation of vascular and valvular calcifications: Ca, P, CaxP product, alkaline phosphatase, albumin, total iPTH. Total iPTH was evaluated every three months by immunochemiluminescence using a second generation assay.

Statistical analysis

Data are expressed as frequencies for categorical variables, mean values with SD for normally distributed variables. Comparison between groups was performed by Mann-Whitney U and chi-square tests. Multivariate analysis was performed by Binary logistic Regression Models. Survival evaluation was performed with Cox regression models. Survival curves were performed using Kaplan Meyer with evaluation of log rank. Variables entered in multivariate analysis were age, gender, haemodialysis duration, diabetes, CaxP, iPTH, albumin, cardiovascular disease at baseline and vascular and valvular calcifications. Statistical analyses were performed with the SPSS system 14.0 (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 48 months there were 43 all-cause deaths (34%) and 21 (17%) cardiovascular deaths and 34 patients (27%) needed cardiovascular hospitalisations. Demographic and biochemical values of the whole group are shown in Table 1. Aortic and mitral valvular calcification were detected in 19 (15%) and in 37 (29%) patients respectively. Aortic or mitral calcifications were detected in 39 patients (31%). Presence of vascular calcifications was identified in 91 patients (72%). A simple vascular calcification score (svcs) ≥ 3 was observed in 63 patients (49.6%). Mean calcium carbonate dose was 2.1±1.01 g/day. Thirty three patients (26%) were treated with calcitriol and the mean dose was 1.54±1.01 µg / week.

Demographic, biochemical parameters and calcifications (Table I)

Haemodialysis duration was longer in patients with aortic and mitral calcification (Table I). All cause death and cardiovascular death were more frequent in patients with valvular or vascular calcifications (Table I). Other demographic or biochemical parameters were not different in patients with or without valvular and vascular calcifications.

Mean Survival and Cumulative Survival

All cause death (Table II; Fig. 3) and cardiovascular death (Table III; Fig. 4) were responsible for significant lower mean survival and lower cumulative survival in patients with valvular and vascular calcifications.

Mortality risk of valvular and vascular calcifications (Table IV)

In separate Cox regression models, in all patients, adjusting for age, gender, HD duration, diabetes, iPTH, CaxP product, albumin and cardiovascular disease at baseline, the mortality risk for each type of valvular calcification and for the vascular calcification score was evaluated (Table IV). The adjusted risk of all cause death and of cardiovascular death was, respectively, 3.8 and 2.6 fold higher in patients with aortic valvular calcification. The adjusted risk of all cause death and of cardiovascular death was, respectively, 2.4 and 2.9 fold higher in patients with mitral valvular calcification. In non-diabetic patients, mitral valvular calcification and mitral or aortic valvular calcification were also associated with increase in all-cause mortality (Table IV).

Table I

Valvular Calcifications

	All Patients N=127	Aortic Valve		Mitral Valve		Aortic or Mitral Valve	
		AVC=0 N=108	AVC>0 N=19	MVC=0 N=89	MVC>0 N=38	AMVC=0 N=87	AMVC>0 N=40
Age	62±15	61±15	66±12	61±15	65±14	61±15	65±14
Male gender	75 (59%)	65 (60%)	10 (53%)	57 (63%)	18 (49%)	56 (64%)	19 (49%)
Diabetes	26 (21%)	23 (21%)	3 (16%)	18 (20%)	8 (22%)	18 (21%)	8 (21%)
HD duration (months)	48±53	44±52	**65±49***	**38±42**	**71±66****	**38±42**	**69±66***
Ca (mg/dL)	9.9±0.7	9.9±0.8	10±0.6	9.9±0.8	10.0±0.6	9.9±0.8	10.0±0.6
P (mg/dL)	4.9±1.4	4.8±1.4	5.3±1.3	4.8±1.4	5.2±1.4	4.8±1.4	5.2±1.4
CaXP (mg^2/dL^2)	49.3±15.6	48.6±15.7	53.6±14.0	47.7±15.6	53.2±15.0	47.8±15.6	52.7±15.1
iPTH (pg/mL)	302±380	272±313	476±624	315±394	273±347	287±320	337±492
AP (ng/mL)	30.0±22.4	30.1±23.3	29.2±17.4	30.9±22.3	28.1±23.1	30.9±22.3	28.1±23.1
Albumin (g/L)	3.7±0.3	3.7±0.3	3.7±0.3	3.7±0.3	3.7±0.3	3.7±0.3	3.7±0.3
$CaCO_3$ dose (g/day)	2.1±1.5	2.2±1.5	1.6±1.4	2.2±1.6	1.9±1.3	2.2±1.6	1.8±1.3
Ejection fraction (%)	38±7	38±6	38±7	37±6	38±7	38±6	38±7
LVPW (mm)	10.2±1.8	10.3±1.6	9.5±3.4	10.3±1.6	10±2.5	10.2±1.6	10.1±2.5
All cause death	43 (34%)	32 (30%)	**11 (58%)***	24 (27%)	**19 (51%)***	24 (27%)	**19 (49%)***
Cardiovascular death	21 (17%)	15 (14%)	6 (32%)	10 (11%)	**11 (30%)***	10 (11%)	**11 (28%)***
Cardiovascular hospitalisation	34 (27%)	26 (24%)	8 (42%)	17 (19%)	**17 (46%)****	17 (19%)	**17 (44%)****
SVCS > 0	91 (72%)	74 (69%)	17 (90%)	58 (64%)	**33 (89%)****	57 (65%)	**34 (87%)***
SVCS ≥ 3	63 (50%)	49 (45%)	**14 (74%)***	37 (41%)	**26 (70%)****	37 (42%)	**26 (67%)***

*p<0.05; **p<0.01

Comparison between means: Mann-Whitney U; comparison between frequencies: chi-square. SVCS, simple vascular calcification score; AVC, aortic valve calcification; MVC, mitral VC; AMVC, aortic or mitral VC; LVPW left ventricular posterior wall

Table II

All cause mortality (Kaplan Meier)

	Aortic Valve		Mitral Valve		Aortic or Mitral Valve		Plain X-ray score	
	AVC=0 N=108	AVC>0 N=19	MVC=0 N=90	MVC>0 N=37	AMVC=0 N=88	AMVC>0 N=39	SVCS=0 N=36	SVCS>0 N=91
Number of events	32	11	24	19	24	19	6	37
Mean survival (SE), months	40.0 (1.2)	34.5 (3.2)	41.1 (1.2)	34.5 (2.3)	40.9 (1.3)	35.2 (2.3)	42.4 (1.9)	37.9 (1.4)
Cum. survival (%)	70%	42%	73%	49%	73%	51%	83%	59%
Log Rank 5.78	7.75	5.94	5.48					
Sig. 0.016	0.005	0.015	0.019					

AVC, aortic valve calcification; MVC, mitral VC; AMVC, aortic or mitral VC; SVCS, simple vascular calcification score

Table III

Cardiovascular mortality (Kaplan Meier)

	Aortic Valve		Mitral Valve		Aortic or Mitral Valve		Plain X-ray score		Plain X-ray score	
	AVC=0 N=108	AVC>0 N=19	MVC=0 N=90	MVC>0 N=37	AMVC=0 N=88	AMVC>0 N=39	SVCS=0 N=36	SVCS>0 N=91	SVCS<3 N=64	SVCS≥3 N=63
Number of events	15	6	10	11	10	11	20	1	4	17
Mean survival (SE), months	43.6 (0.8)	40.1 (2.8)	44.5 (0.8)	39.4 (2.1)	44.5 (0.8)	39.8 (2.0)	46.1 (0.8)	41.8 (1.1)	45.5 (0.8)	40.8 (1.5)
Cum. survival (%)	85%	61%	88%	65%	87%	68%	97%	75%	93%	71%
Log Rank	4.30		7.97		6.54		6.22		8.78	
Sig.	0.038		0.005		0.011		0.010		0.003	

AVC, aortic valve calcification; MVC, mitral VC; AMVC, aortic or mitral VC; SVCS, simple vascular calcification score

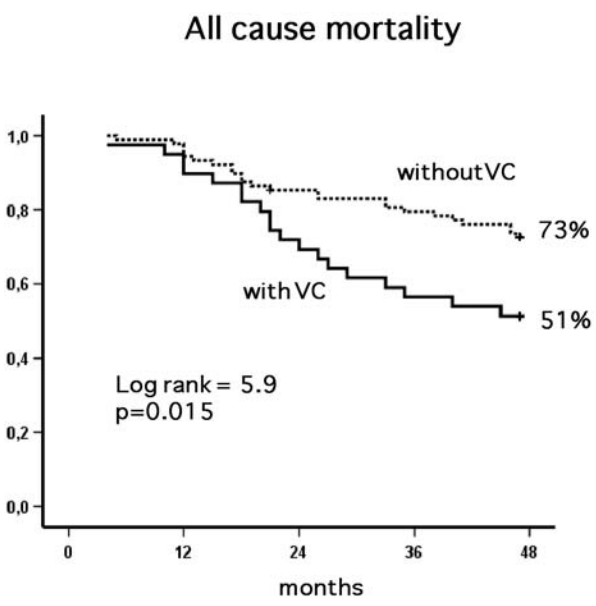

Figure 3

Lower survival in relation to all cause death in patients with valvular calcification (VC)

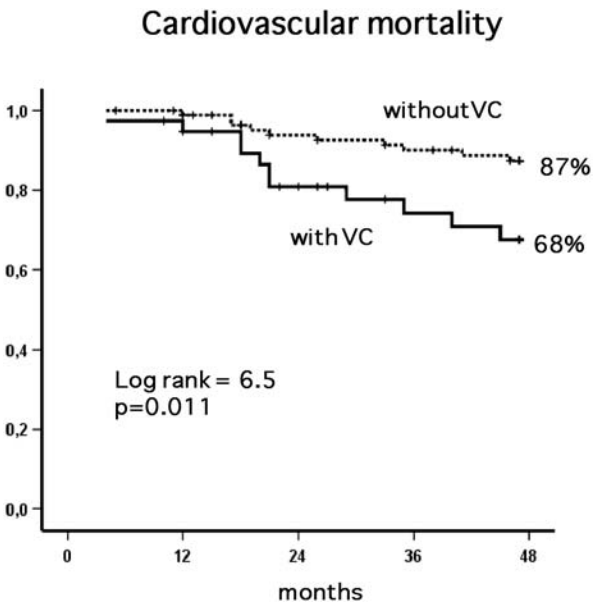

Figure 4

Lower survival in relation to cardiovascular death in patients with valvular calcification (VC)

Table IV

Mortality risk of each valvular calcification and vascular calcification score (Cox Regression)

	Dependent variable	Independent variables	B	Sig.	H.R.	95% CI
All patients	All cause mortality	Aortic valvular calcification	1.32	<0.001	3.8	1.83 to 7.76
		Mitral valvular calcification	0.89	0.004	2.4	1.32 to 4.50
		Aortic or Mitral valvular calcification	0.93	0.003	2.5	1.36 to 4.67
		Vascular calcification score	0.19	0.003	1.2	1.06 to 1.39
	Cardiovascular mortality	Aortic valvular calcification	0.96	0.047	2.6	1.01 to 6.77
		Mitral valvular calcification	1.17	0.008	3.2	1.36 to 7.58
		Aortic or Mitral valvular calcification	1.07	0.015	2.9	1.23 to 6.84
		Vascular calcification score	0.45	<0.001	1.6	1.26 to 1.95
Non- diabetic patients	All cause mortality	Mitral valvular calcification	0.92	0.009	2.5	1.22 to 5.04
		Aortic or Mitral valvular calcification	0.88	0.014	2.4	1.19 to 4.82
	Cardiovascular mortality	Vascular calcification score	0.64	<0.001	1.89	1.38 to 2.58

Results are adjusted for age, HD duration, diabetes, iPTH, Ca x P product, albumin and vascular disease at baseline. Vascular calcification score and each valvular calcification were evaluated in separate models.

Factors independently associated with mortality and morbidity (Table V)

In a Cox regression model adjusting also for all types of valvular calcification and simple vascular calcification score, factors associated with all cause mortality, cardiovascular mortality and cardiovascular hospitalisations were identified (Table V). Aortic valvular calcification was directly associated with all cause mortality (HR = 3.72, 95% CI = 1.81 to 7.66, p<0.001). The risk of all cause death was 3.7 fold higher in patients with aortic valvular calcification. Simple vascular calcification score was

Table V

Factors independently associated with mortality and morbidity (Cox Regression)

Dependent variable	Independent variables	B	Sig.	H.R.	95% CI
All cause mortality	PTH	-0.001	0.043	0.99	0.99 to 1.00
	albumin	-1.89	‹0.001	0.15	0.06 to 0.36
	aortic valvular calcification	1.32	**‹0.001**	3.72	1.83 to 7.76
Cardiovascular mortality	male gender	1.26	0.005	3.54	1.46 to 8.58
	simple vascular calcification score	0.45	**‹0.001**	1.56	1.25 to 1.94
Cardiovascular hospitalisations	diabetes	1.000	0.018	2.72	1.18 to 6.24
	albumin	-1.46	0.021	0.23	0.06 to 0.80
	Ca x P product	0.05	0.001	1.05	1.02 to 1.08
	simple vascular calcification score	0.09	**0.001**	1.34	1.13 to 1.59

Results are adjusted for age, HD duration, diabetes, iPTH, Ca x P product, albumin, vascular disease at baseline, vascular calcification score and all types of valvular calcifications.

directly associated with cardiovascular death (*HR=1.56, 95% CI = 1.25 to 1.94, p‹0.001*) and with cardiovascular hospitalizations (*HR=1.34, 95% CI = 1.13 to 1.59, p=0.001*). For each unit increment of the simple vascular calcification score there was a 56% increase of cardiovascular death risk. PTH (*p=0.04*) was a negative predictor of all-cause mortality. Albumin was a negative predictor of all-cause mortality (*p‹0.001*) and of cardiovascular hospitalisations (*p=0.02*). Diabetes (*p=0.018*) and CaxP product (*p=0.001*) were directly associated with cardiovascular hospitalisations.

Factors independently associated with valvular or vascular calcifications (Table VI)

The simple vascular calcification score was an independent predictor of aortic valvular calcification (*p=0.002*), mitral valvular calcification (*p‹0.001*) or any valvular calcification (*p‹0.001*). For each unit increase in vascular score there was, respectively, a 46% and a 66% increase in aortic and mitral valvular calcification risk (Table VI). PTH was directly associated with aortic valvular calcification (*p=0.02*). HD duration was directly associated with mitral valvular calcification (*p=0.003*) or any valvular calcification (*p=0.01*). Male gender was directly associated with mitral valvular calcification (*p=0.005*) or any valvular calcification (*p=0.006*). Phosphorus levels were directly associated with mitral valvular calcification (*p=0.04*). Age (*p=0.001*), diabetes (*p=0.01*) and HD duration (*p=0.01*) were associated with simple vascular calcification score.

DISCUSSION

The first study to demonstrate an association between valvular calcification and mortality in dialysis patients was Wang *et al* [11]. In our group of haemodialysis patients we have also verified that aortic and mitral valvular

Table VI

Factors independently associated with valvular or vascular calcification

Dependent variable	Independent variables	B	Sig.	O.R.	95% CI
Aortic valve calcification	PTH	0.001	0.020	1.00	1.000 to 1.002
	vascular calcification score	0.380	**0.002**	1.46	1.145 to 1.866
Mitral valve calcification	male gender	1.565	0.005	4.78	1.599 to 14.316
	HD duration (months)	0.012	0.003	1.01	1.004 to 1.020
	Phosphorus	0.356	0.040	1.42	1.017 to 2.003
	vascular calcification score	0.504	**‹0.001**	1.66	1.295 to 2.114
Aortic or Mitral valve calcification	male gender	1.407	0.006	4.08	1.490 to 11.195
	HD duration (months)	0.010	0.011	1.01	1.002 to 1.017
	vascular calcification score	0.410	**‹0.001**	1.51	1.211 to 1.879
Vascular calcification score	diabetes	1.730	0.012	5.64	1.467 to 21.708
	age	0.049	0.001	1.05	1.020 to 1.027
	HD duration (months)	0.015	0.011	1.015	1.004 to 1.027

Simple vascular calcification score is an independent predictor of aortic and mitral calcification

calcifications and vascular calcifications were associated with all cause death and with cardiovascular death. When valvular and vascular calcifications were evaluated in the same model, aortic valvular calcification was an independent predictor of all cause death and the simple vascular calcification score was an independent predictor of cardiovascular death and cardiovascular hospitalisations. Factors associated with valvular calcifications were the simple vascular calcification score, male gender, PTH and phosphorus levels. Ribeiro S *et al* [13] were among the first authors to verify an association between calcium phosphate product and valvular calcification, pointing out the role of mineral metabolism in the pathogenesis of valvular calcification in dialysis patients.

Many factors may contribute to the development of vascular and valvular calcifications in dialysis patients and there is increasing evidence of a link between bone disease and vascular disease in these patients. Kidney Disease: Improving Global Outcomes (K/DIGO) has recommended a new classification for mineral and bone disorder of chronic kidney disease that includes the evaluation of biochemical abnormalities (Ca, P, PTH and vitamin D levels), diagnosis of renal osteodystrophy preferably by bone biopsy and evaluation of vascular calcifications[14].

The presence of hyperphosphataemia and increased CaxP product has been considered a major pathogenic factor leading to vascular and soft tissue calcification in uraemic patients. Hyperphosphataemia can occur either with hyperparathyroidism or with adynamic bone disease and this may explain the lack of correlation between vascular calcifications and PTH levels verified in many studies. In this study we have found, as described by Wang *et al* [11], a direct association between PTH levels and valvular calcification. Other studies have also verified an association between vascular calcifications and low PTH levels[15] or an absence of association between vascular calcifications and PTH levels[2,16,17]. Giacheli CM[7] has demonstrated, in an *in vitro* model with vascular smooth muscle cells from human aorta, that increase of phosphorus and calcium outside the cell, in the culture media, leads to deposition of calcium phosphate in the matrix. This happens via two different mechanisms: an extracellular passive mechanism of direct deposition but also by an active mechanism through activation of an intracellular transcription factor, the core binding factor α-1 (Cbfa-1). This factor upregulates osteogenic genes and increases the synthesis of osteocalcin, alkaline phosphatase, collagen-rich extracellular matrix and creates the conditions for deposition of calcium-phosphate. Under these conditions, the vascular smooth muscle cell in the vessels acquires the phenotypic characteristics of an osteoblast. Some studies have also associated vascular calcification with oral calcium dose[1,15,17,18]. However, hypercalcaemia and hyperphosphataemia are not the only factors associated with vascular calcification in dialysis patients.

A deficiency in inhibitor calcification factors such as fetuin-A or matrix-Gla protein have been also associated with the development of vascular calcification[8] and it is considered that vascular calcification is the final result of the balance between calcification inhibitors and inducers.

In our patients we have not verified any association between calcium levels or calcium carbonate dose with vascular or valvular calcifications but these parameters were averaged for the six months preceding the evaluation of vascular and valvular calcifications and this period of observation may not reflect the whole period of dialysis which really determines the exposure. Low levels of 25-hydroxivitamin D have also been associated with vascular calcifications[19] and treatment with native or active vitamin D may have an impact on the development of vascular calcifications[20]. We do not evaluate vitamin D levels routinely in our patients but it is possible that this information, in the future, will be useful in the management of bone disease in CKD patients.

In non renal patients with valvular calcification, ectopic bone formation has been identified in the valves[10]. This calcification, previously considered to be the result of a passive degenerative mechanism, seems to be the result of an active mechanism most likely originated from differentiated myofibroblasts[21]. Osteoblastic bone formation and osteoclastic bone resorption were identified in these calcified valves. Osteopontin, osteocalcin, BMP 2 and BMP 4, which are potent calcification inducers, were also identified in these areas. This active process of yet unclear origin resembles what has been also described for active calcification of arterial walls in dialysis[7] and non dialysis patients[4].

In this study we have verified that a simple vascular calcification score evaluated in plain X-ray of pelvis and hands was independently associated with valvular calcification. Wang AY *et al* [22] showed that valvular calcification was associated with an increase in carotid media-thickness and carotid calcification. These results suggest that calcification is a systemic disorder in dialysis patients and that vascular and valvular calcification may share common characteristics.

Computed tomography scans are more accurate for the quantitative assessment of vascular calcifications but may be inadequate for an initial screening of vascular calcifications because of its price and its limited availability in some areas[14]. K/DOKI guidelines recommend the utilisation of plain X-ray for identification of vascular calcifications in dialysis patients[23]. This simple vascular calcification score evaluated in plain X-ray was previously demonstrated to be associated with coronary artery disease, peripheral artery disease and to be a predictor of cardiovascular mortality and cardiovascular hospitalisations in dialysis patients[12]. This vascular calcification score is an inexpensive and valuable tool that can be used for screening for the presence of vascular calcifications in dialysis patients.

Limitations of this study

This is an observational study evaluating the association of valvular calcifications with mortality and the association of vascular calcifications with valvular calcifications. It is not possible to demonstrate a cause-effect relationship between these variables.

CONCLUSIONS

In summary, in these patients, male gender, HD duration, PTH, phosphorus levels and vascular calcifications were associated with cardiac valvular calcification. Valvular and vascular calcifications were independent predictors of all cause and cardiovascular mortality. Vascular calcification was independently associated with cardiac valvular calcification, suggesting that these two types of calcification may be the result of the same pathogenic process.

Conflicts of interest. None declared.

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Correspondence to:
Dr Teresa Adragão
Gambro-Healthcare, Nefroclinica-Estoril.
Rua Vale de S Rita, 19, 2765-293 Estoril, Portugal
tadragao@netcabo.pt