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Cardiac valve calcification in haemodialysis patients: role of calcium–phosphate metabolism

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Abstract

Background. Cardiac valve calcification (VC) has been detected with increased frequency in haemodialysis (HD) patients, making it necessary to determine the potential pathogenic factors in uraemic patients.

Methods. A total of 92 chronic HD patients (39 female, 53 male) and 92 age and gender-matched non-dialysis control subjects were evaluated by echocardiography and a severity score for VC was determined. Calcium–phosphate metabolism was evaluated at the beginning of haemodialysis.

Results. We found a greater prevalence of VC in dialysis patients than in normal patients (mitral annulus 44.5% *vs* 10%, $P=0.02$; aortic annulus 52% *vs* 4.3%, $P=0.01$). HD patients with mitral calcification were found to be older than patients without calcification, were on long-term renal replacement therapy, had longer duration of predialysis arterial hypertension, had greater values of the highest value of mean calcium–phosphate product in 6 successive months (CaxP) and the highest absolute value of calcium–phosphate product ($CaxP_{max}$). We also found a positive correlation between calcification score, age, and CaxP. No correlation was found between actual VC and arterial hypertension or parathyroid hormone. Multiple stepwise regression analysis selected age and CaxP as the most predictive parameters for mitral calcification ($r=0.47$). Mitral calcification was associated more frequently with rhythm and cardiac conduction defects, valvular insufficiency and with peripheral vascular calcification. Aortic calcification was correlated with age ($r=0.42$) and longer duration of predialysis arterial hypertension.

Conclusion. Our study confirmed an increased prevalence of VC in HD patients and selected age and calcium–phosphate product as the most predictive parameters. These findings support careful monitoring of calcium metabolism beginning at the early stages of end-stage renal failure to reduce the risk of heart disease.

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Key words: calcium; echocardiography; haemodialysis; mitral annulus calcification; parathyroid hormone; valvular calcification

Introduction

Mortality in end-stage renal disease is about 15-fold greater than in aged-matched controls [1]. Cardiovascular mortality is the leading cause of these deaths, accounting for more than 40% of all mortality in several reports [2]. The identification of factors that lead to ischaemic cardiopathy in these patients is of outmost interest.

Autopsy studies consistently show an association between calcification of the coronary arteries and atherosclerosis. Such studies [3] also verify an association between coronary artery calcification and valvular calcification (VC). Moreover, coronary artery calcification was shown to be of value to predict coronary artery disease in individuals with and without renal failure [4]. Haemodialysis (HD) patients are exposed to a much greater risk of calcific heart disease involving all the cardiac structures. Such features may be due to disturbances of calcium–phosphate metabolism as is suggested in several reports [5–9]. However, until now most reports aimed at the detection of pathogenic factors of VC in HD patients failed to prove a clear relationship with high levels of iPTH or calcium–phosphate product.

In the present study, we evaluate the prevalence of valvular calcification in HD patients and in a control group of a non-dialysis population. Our purpose was to identify eventual risk factors for valvular calcification in uraemic patients and determine whether those calcifications were associated with rhythm and cardiac conduction defects.

Subjects and methods

Patients

We studied 92 HD patients (39 female, 53 male; aged 60 ± 16 years) for the presence of VC and valvular dysfunction using

echocardiography and Doppler echocardiography. Ninety-two age-and gender-matched non-dialysis control subjects (45 female, 47 male; age 59 ± 17 years) were also evaluated by the same examiners in the same period. The 92 patients with end-stage renal disease were treated with HD for 53 ± 46 months. Mitral and aortic valve calcification were measured and scored. A severity score for VC was determined according to annulus thickness in B-mode evaluation (score 0 < 3 mm, score 1 = 3–5 mm, score 2 = 6–7 mm, score 3 > 8 mm).

Methods

Duration of predialysis arterial hypertension, actual mean predialysis blood pressure and symptoms of coronary insufficiency were evaluated in dialysis patients. Standard electrocardiograms were analysed for rhythm and cardiac conduction disturbances. Calcium (mg/dl), phosphorus (mg/dl), and parathyroid hormone (iPTH) (ng/ml) were determined every month from the beginning of dialysis treatment in all HD patients. For purposes of the study we selected the highest value of mean calcium–phosphorus product for 6 successive months (CaxP) and the highest absolute value of calcium–phosphorus product ($CaxP_{max}$). A recent bone radiological study screening for reabsortive bone lesions, peripheral vascular calcification and ectopic calcification was performed in all patients. The aetiology of renal disease was distributed as follows: 19 chronic glomerulonephritis, 19 chronic interstitial nephritis, 18 diabetic nephropathy, 10 nephroangiosclerosis, 9 polycystic kidney disease, 2 amyloid nephropathy, and 10 unknown.

Eighty patients (87%) had long-standing hypertension (8.6 ± 6.8 years) before starting dialysis treatment and 23 (25%) were still hypertensive.

Echocardiographic evaluation of non-dialysis patients was made because they had non specified cardiac disease (55%), arterial hypertension (43%) or vascular cerebral disease (2%).

Statistics

All values are expressed as the mean ± standard deviation. Statistical evaluation included analysis of variance (ANOVA), χ^2 test and stepwise multiregression analysis. The P value was considered statistically significant when it was less than 0.05.

Results

Calcification of the mitral valve was present in 41 patients (44.5%) and calcification of the aortic valve in 48 patients (52%), while in the control population, the prevalence was 10% ($P = 0.02$) and 4.3% ($P = 0.01$) respectively. Fifty-four HD patients (58.7%) had calcification of both valves. The prevalence of VC was similar in males and females, and no correlation was found between aetiology of renal disease and VC.

In the control population, VC was more frequent in females (8% *vs* 4%) and in older patients (64 ± 16 *vs* 55 ± 13 years, $P = 0.0001$).

Clinical and laboratory parameters in HD patients with and without mitral calcification are compared in Table 1. Haemodialysis patients with mitral calcification were older (67 ± 12 *vs* 55 ± 17 years; $P = 0.0001$), had been on dialysis for a longer time (66 ± 53 *vs* 43 ± 36 months; $P = 0.01$), and had longer duration of predialysis arterial hypertension (11 ± 8 *vs* 7 ± 5 years; $P = 0.009$) than patients without mitral calcification. Actual arterial hypertension did not correlate with mitral calcification. The maximum calcium–phosphorus product ($CaxP_{max}$) and the highest mean calcium–phosphorus product in 6 successive months (CaxP) were significantly greater in patients with mitral valve calcification than patients without ($P = 0.002$ and 0.0007, $r = 0.20$ and 0.23 respectively). The value of iPTH was not significantly different between patients with and without mitral calcification.

Table 1. Clinical and laboratory parameters in HD patients with (MVC+) and without (MVC−) mitral calcification

	MVC+	MVC−	*P*
Age (years)	67 ± 12	55 ± 17	0.0001
Sex (male/female)	24/17	29/22	n.s.
pHT (years)	11 ± 8	7 ± 5	0.009
HD (months)	66 ± 53	43 ± 36	0.01
HT (yes/no)	7/6	34/35	n.s.
CaxP (mg/dl)	60 ± 13	51 ± 13	0.0007
$CaxP_{max}$ (mg/dl)	71 ± 19	67 ± 18	0.002
iPTH (ng/ml)	377 ± 296	343 ± 296	n.s.

MVC, mitral valve calcification; pHT, duration of predialysis arterial hypertension; HT, actual arterial hypertension.

Severity scores for valve calcification was higher in older patients. The correlation between this score and the calcium–phosphorus product was $r = 0.35$ (Figure 1).

In HD patients, multiple stepwise regression analysis with mitral valve calcification severity score as a dependent variable, selected age as the most predictive parameter ($P = 0.00001$) and CaxP ($P = 0.00001$) with a multiple r value of 0.47.

Mitral calcification was associated more frequently with rhythm and cardiac conduction defects ($\chi^2 = 6.8$; $P = 0.002$) and with peripheral vascular calcification ($\chi^2 = 9.2$; $P = 0.009$). The incidence of valvular insufficiency was 29.3% in patients with mitral calcification and 5.8% in patients without calcification.

Clinical and laboratory parameters in HD patients with and without aortic calcification are compared in Table 2. No relationship was found between aortic calcification and aetiology of renal disease, gender, time on dialysis, actual arterial hypertension, CaxP, $CaxP_{max}$, and iPTH. Aortic calcification correlated with age ($r = 0.42$; $P = 0.00001$). Patients with aortic calcification had also longer duration of predialysis arterial hypertension (10 ± 7 *vs* 7 ± 6 years, P = n.s.) than patients without calcification. Aortic valvular calcification was associated with peripheral vascular calcification ($\chi^2 = 17.5$; $P = 0.0001$), but not with rhythm and cardiac conduction defects. The prevalence of valvular insufficiency was 22% in patients with aortic calcification and 6% in patients without calcification.

Discussion

Haemodialysis patients have an increased incidence of calcification of cardiac structures which may contribute

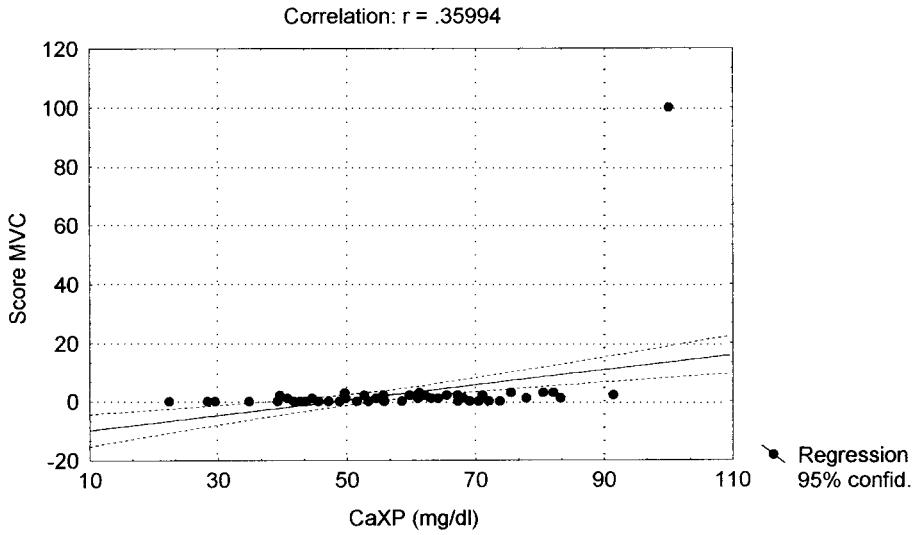

Fig. 1. Correlation of calcification score and CaxP.

Table 2. Clinical and laboratory parameters in HD patients with (AVC+) and without (AVC−) aortic calcification

	AVC+	AVC−	*P*
Age (years)	68±8	51±18	0.00001
Sex (male/female)	30/18	23/21	n.s.
pHT (years)	10±7	7±6	n.s.
HD (months)	55±47	52±44	n.s.
HT (yes/no)	5/43	18/26	n.s.
CaxP (mg/dl)	55±13	53±14	n.s.
$CaxP_{max}$ (mg/dl)	73±19	70±18	n.s.
iPTH (ng/ml)	276±180	257±148	n.s.

AVC, aortic valve calcification.

to the high cardiovascular mortality observed in these patients. Several studies suggest that coronary artery calcification is a predictor of coronary artery disease in patients with and without renal failure [3].

In our study the prevalence of calcified mitral and aortic valves in HD patients was very high. Several studies using echocardiography have found a prevalence ranging from 10 to 40% for mitral valve calcification [5,9,10,11] in HD patients. Our findings, like those from Braun *et al.* [12], suggest that this prevalence is even higher. Aortic valve calcification has been observed in 28–55% of HD patients [8,12]; our study supports the higher value.

Patients with mitral VC were older and had been on dialysis for a longer period than those without, as has been reported in other studies [5,12]. We found in multiple stepwise regression analysis that age and the highest value for mean calcium–phosphate product (CaxP) in 6 successive months were the most predictive values for mitral valve calcification. Moreover, we found a positive correlation between CaxP and the severity score for valvular calcification.

These data suggest that sustained derangement of calcium–phosphate metabolism may be implicated in calcific heart disease in HD patients.

In 87 HD patients studied by Maher *et al.* [8], VC was associated with an increased calcium–phosphate product and long-term HD. Rostand *et al.* [13] found in 43 HD patients a strong correlation between myocardial calcium content and calcium–phosphate product and suggested that increased myocardial calcium content results from poor calcium and phosphorus control. Morales *et al.* [14] evaluated interstitial calcium deposition by two-dimensional echocardiograms and concluded that abnormalities of myocardial structure are related to disorders of calcium–phosphate metabolism. In a recent work by Mazzaferro *et al.* [5], dialysis duration, age, and iPTH were selected as the most predictive parameters for mitral annulus calcification. The authors concluded that the pathogenic mechanism seemed to be different from that of other ectopic calcification while secondary hyperparathyroidism seems to play an ancillary role. Using electron-beam computed tomography, Braun *et al.* [12], did not find correlation between serum levels of calcium, phosphorus or iPTH, and cardiac calcification. The authors concluded that age and arterial hypertension are the most relevant risk factors for VC in HD patients just as they are for the normal population. While dialysis duration seems to be an important factor, the specific role played by disturbances of calcium–phosphate metabolism remains controversial.

In all the studies referred to above, assessments were based on the evaluation of calcium metabolism at the time of the study and, therefore past disturbances were not detected and chronic conditions were not differentiated from more recent ones. We believe that whatever metabolic derangement is responsible, it has to be a sustained one. In our study, all the values of serum calcium, phosphorus, and iPTH from the beginning of dialysis therapy were considered. Therefore we were able to identify chronic calcium metabolism derangements likely to cause effective damage.

It was suggested that non-dialysis patients with

valvular calcification have a higher mortality [15] related to rhythm and cardiac conduction defects. We confirmed an increased prevalence of rhythm and cardiac conduction defects, and valvular insufficiency in patients with mitral valve calcification. However, whether this correlates with an increased mortality rate deserves a follow-up study. Hypertension is a major risk factor for coronary artery disease and an association between hypertension and valvular calcification in HD patients has been identified [12]. Hypertension is also the most important risk factor for progression of chronic renal disease, and has a major impact on survival in dialysis patients [16]. We found a correlation between long-term hypertension and mitral valve calcification in our HD patients. Thus, control of arterial hypertension in haemodialysis patients is important to hinder progression of valve calcification and coronary disease.

Progression of valvular calcification and stenosis in HD patients deserves a follow-up study. Aortic VC was found to correlate only with age and arterial hypertension, the same factors found in the normal population by other authors. It seems that the specific role of calcium metabolism is more evident in mitral annulus calcification. Idiopathic calcification of the aortic valve occurs often in the elderly, and this pathological process is considered to be a degenerative one. Focal calcifications related to this process usually do not involve the mitral valve. It is possible that pathological processes refereed lead to aortic valve calcification have different pathological mechanisms, age being more important in aortic degenerative disease. Our data show that age more strongly correlates with aortic VC than mitral VC.

In conclusion, our results indicate that dialysis duration and calcium–phosphate metabolism play a role in mitral valve calcification of haemodialysis patients. Long-term arterial hypertension also seems to play an important role. Careful monitoring of calcium–phosphate metabolism, beginning in the early stages of chronic renal failure, may decrease the incidence of heart disease and cardiovascular mortality in HD patients.

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