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Cardiac valve calcifications and predictive parameters in hemodialysis patients

Yusuf Selcoki[1*], Faruk Turgut[2], Mehmet Kanbay[2], Adem Ozkara[3], Oguz Tekin[3], Burak Uz[2], Ali Akcay[2]

[1] *Department of Cardiology, School of Medicine, Fatih University, 06540 Ankara, Turkey*
[2] *Department of Internal Medicine, Division of Nephrology, School of Medicine, Fatih University, 06540 Ankara, Turkey*
[3] *Department of Family Medicine, School of Medicine, Fatih University, 06540 Ankara, Turkey*

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Abstract: Cardiac valvular calcification is frequent among hemodialysis (HD) patients. The presence of valvular calcification can help identify HD patients with a higher risk for cardiovascular diseases. Our aim was to determine the prevalence of valvular calcification (VC) in our maintenance hemodialysis (HD) population and to examine some possible etiologic factors for its occurrence. We studied forty-four patients on hemodialysis (23 women and 21 men; mean age 57 ± 18 year; mean HD duration 34 ± 28 months). Valvular calcification (VC) was observed in 21 patients (48%). Of these patients, 6 patients (13%) had mitral valvular calcification, 9 patients (20%) had aortic valvular calcification, and 6 patients (13%) had calcification of both valves. The patients with VC were older than patients without VC (66 ± 14 vs. 50 ± 18). The patients with aortic calcification had longer HD duration than others (48 ± 29 vs. 27 ± 24 months). Patients with VC had higher systolic and diastolic blood pressures than patients without VC. The patients with mitral calcification had higher C-reactive protein (CRP) levels (14 ± 13 vs. 7 ± 7). No significant differences were found with respect to calcium, phosphorus, parathyroid hormone, alkaline phosphatase and mean Ca $\times$ P product. Our study confirmed that there is an increased prevalence of VC in HD patients. Age is a risk factor for cardiac VC in HD patients. Longer HD duration was associated with aortic valve calcification. In addition, elevated level of CRP is associated with mitral valve calcification in HD patients.

Keywords: Cardiac valve calcification, hemodialysis, echocardiography

* E-mail: yussel1971@hotmail.com

1 Introduction

Patients with chronic kidney disease, especially the hemodialysis patients, frequently develop widespread cardiac and vascular calcifications [1]. Incidence of atherosclerotic cardiovascular accidents was higher in uremic patients than general population [2]. Cardiac valve calcification was observed in more than half the dialysis population [3]. Mitral annular calcification occurs in a proportion of patients with ESRD and is associated with increased mortality [4, 5]. Wang *et al.* has been reported that cardiac calcification predicts cardiac and all-cause mortality in long term peritoneal dialysis patients [6].

Increased serum phosphorus level and high calcium-phosphorus (Ca × P) product are responsible for all-cause and cardiovascular mortality in dialysis patients [7]. However, it has also been reported that there is no association between calcified valve and a high Ca × P product [3–5]. Vascular calcification mechanism is not fully understood. Recent studies suggest that it also involves inflammation, active cell-mediated and low concentrations of glycoprotein such as fetuin-A [8]. Some studies have revealed the importance of a number of inhibitors of calcification of cardiovascular structures, like fetuin-A, Osteopontin and Osteoprotegerin [1].

The aim of this study is to find a predictive factor for valvular calcification in hemodialysis patients by assessing the relationships between valvular calcification and calcium-phosphorus metabolism, inflammation, age, duration of hemodialysis, and echocardiography findings.

2 Statistical methods and Experimental Procedures

2.1 Patients

Forty-four patients recruited were undergoing regular HD (23 women and 21 men; mean age, 57 ± 18 year, age range $24 - 89$) at Fatih University Hemodialysis Center in Ankara. Exclusion criteria included malignancy, chronic inflammatory disease and acute infection. Patients were being dialyzed with standard bicarbonate dialysis three times weekly with each lasting 4 to 5 hours. 46 age-matched patients as a control group were included in the study to exclude valve calcification due to aging. The study was approved by the local ethics committee.

2.2 Laboratory Measurements

Blood samples were drawn before the first dialysis session of the week. Laboratory parameters from 3 consecutive months were averaged. Hemoglobin, blood urea nitrogen, creatinine, calcium, phosphorus, albumin, alkaline phosphatase, intact parathyroid hormone (iPTH), lipid profile (total cholesterol, high-density lipoprotein, low-density lipoprotein and triglyceride), serum iron, serum C-reactive protein (CRP) were measured using standard methods in the routine clinical laboratory and Ca × P product was calculated.

Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured before HD sessions with mercury sphygmomanometer in a seated position after 15 minutes of rest.

2.3 Echocardiography

Two-dimensional echocardiography was performed in each case using a *Toshiba corevision-pro* machine with a 2.5 MHz probe. Cardiac valve calcification is defined by bright echoes of more than 1 mm and more cups of the mitral valve, mitral annulus or aortic valve. Interventricular septum thickness (IVS), left ventricular internal diameter (LVID), and posterior wall thickness (PW) were measured in end diastole. Ejection fraction (EF) was calculated with Teicholz method from parasternal long axis.

2.4 Statistical analyses

Data were analyzed using SPSS software (Statistical Package for the Social Sciences, version 10.0, SSPS, Inc, Chicago, IL, USA). All values are expressed as mean ± SD. Statistical analysis was performed using Student's t-test, the Mann-Whitney U test, or chi-square test. P value < 0.05 was considered to be statistically significant.

3 Results

Twenty one (48%) of the 44 HD patients had valvular calcification. Of these patients, 6 patients (13%) had mitral valvular calcification (MVC), 9 patients (20%) had aortic valvular calcification (AVC) and 6 patients (13%) had calcification of both valves.

The baseline demographic characteristics of the patients are shown in table 1. The prevalence of VC in male and female patients was similar. The patients with VC were significantly older than the patients without VC (66 ± 14 vs. 50 ± 18; $p = 0.02$). There was no difference between the mean ages of HD patients and control group (57 ± 18 vs. 59 ± 14, $p = 0.68$). Eleven (25%) subjects have valve calcification in the control group and this is significantly lower than HD patients (21/44 vs. 11/46, $p = 0.027$). The duration of HD therapy was longer in patients with VC than patients without VC, but the difference was not significant statistically (41 ± 29 vs. 28 ± 26; $p = 0.11$). Patients with aortic valve calcification have significantly longer HD duration than others (48 ± 29 vs. 27 ± 24; $p = 0.01$).

As for the results, the hemodynamic and biochemical parameters are shown in Table 2. The patients with VC had significantly higher mean systolic and diastolic BP values than patients without VC (systolic BP 140 ± 13 vs. 126 ± 23 mmHg, respectively; $p = 0.02$ and diastolic BP 86 ± 7 vs. 78 ± 14 mmHg, respectively; $p = 0.03$). The patients with VC had higher mean serum levels of HDL than the patients without VC (46 ± 11 vs. 37 ± 9; respectively, $p = 0.01$). No significant differences were found with respect to calcium, phosphorus, mean Ca × P product, serum iron, albumin, alkaline phosphatase, total

Table 1 Demographic data for the groups of HD patients with and without cardiac valve calcification (VC).

	VC	No VC	P value
Patients number, (%)	21(48)	23(52)	
Gender (F/M)	14/7	9/14	0.08
Age (years)	66 ± 14	50 ± 18	0.02
Duration of HD (month)	41 ± 29	28 ± 26	0.11

cholesterol, LDL cholesterol, serum CRP level and iPTH concentrations. Mitral valve calcification patients had higher serum levels of CRP than the other patients (14 ± 13 vs. 7 ± 7 $p = 0.05$).

Table 2 Hemodynamic and biochemical parameters for the groups with and without cardiac valve calcification.

	VC	No VC	P value
Patients number, (%)	21(48)	23(52)	
SBP (mmHg)	140 ± 13	126 ± 23	0.02
DPB (mmHg)	86 ± 7	78 ± 14	0.03
Hemoglobin (g/dL)	10 ± 1	11 ± 1	0.9
Iron (ug/dL)	64 ± 41	65 ± 33	0.9
Calcium (mg/dL)	8.9 ± 0.8	8.9 ± 0.8	0.9
Phosphate (mg/dL)	5.3 ± 1.3	5.5 ± 1.2	0.6
Ca × P product	48 ± 13	50 ± 13	0.64
PTH (pg/ml)	480 ± 462	603 ± 451	0.408
Albumin (g/dL)	3.8 ± 0.4	3.8 ± 0.4	0.89
T. cholesterol (mg/dL)	146 ± 29	145 ± 37	0.952
HDL (mg/dl)	46 ± 11	37 ± 9	0.01
LDL (mg/dL)	77 ± 25	76 ± 30	0.88
CRP (mg/l)	11 ± 11	8 ± 8	0.31
ALP (I/U)	125 ± 60	181 ± 139	0.1

On echocardiography evaluation, higher IVS and PW thickness were found in patients with VC, but the difference was not significant (Table 3). There were also no differences between left ventricular diameter, left atrial diameter and ejection fraction.

Table 3 Echocardiographic parameters of the patients with and without cardiac valve calcification.

	VC	No VC	P value
IVS (cm)	$1.2.0 \pm 0.1$	1.1 ± 0.1	0.07
LVID (cm)	4.7 ± 0.6	4.6 ± 0.1	0.64
PW (cm)	1.2 ± 0.1	1.1 ± 0.1	0.06
LA (cm)	3.9 ± 0.5	3.5 ± 0.7	0.09
EF (%)	57 ± 10	60 ± 8	0.34

4 Discussion

In this study, we have demonstrated that valvular calcification (VC) is a common finding in end-stage renal disease (ESRD) patients undergoing hemodialysis (HD). In accordance with medical literature, VC was found in 48% of our HD patients. Braun and co-workers reported that two-thirds of adult patients on HD had electron-beam computed tomography (EBCT) evidence of coronary artery calcification, and that more than one-half of these individuals also had cardiac VC [3]. The echocardiography results from this study indicate that the prevalence of VC is 46% in patients on HD. VC is potentially dangerous due to association with valve dysfunction, myocardial ischemia, conduction defects, infective endocarditic, and heart failure [9].

Previous studies based on imaging and echocardiography findings have revealed that the prevalence of calcification of the aortic and mitral valves in ESRD patients ranges from 30% to 50% [10, 11]. The reported prevalence of aortic valve calcification (AVC) in HD patients is 28% to 55%, and it is 10% to 40% in mitral valve [9, 12, 13]. This study revealed a higher prevalence of aortic valve alone (20%) than of mitral valve alone (13%) in this patient group. The prevalence of both aortic and mitral valve calcification was lower in our study than the previous studies (13%).

It was shown recently that VC is an independent predictor for all-cause and cardiovascular mortality in peritoneal dialysis patients [6]. In HD patients, VC was associated with all-cause and cardiovascular mortality, but after adjusting for other cardiovascular risk factors and complications, as well as left ventricular mass index, it lost significance [14]. In the study of Sharma *et al.* MVC predicted all-cause mortality, cardiovascular mortality and morbidity in ESRD patients [4]. MVC is common in the setting of ESRD [6, 11, 15, 16] and in patients with chronic kidney disease before the onset of ESRD [17]. More recently, Fox *et al.* have demonstrated that in the community, chronic kidney disease is associated with MVC before the onset of ESRD [17]. In these patients MVC did predict mortality.

In agreement with data from medical literature, we found association between VC and age and duration of hemodialysis therapy. Eleven (25%) subjects have valve calcification in the control group; this is significantly lower than HD patients. This finding indicates that valve calcification is more prevalent in HD patients than normal population because of aging. The duration of hemodialysis therapy was longer in patients with VC than patients without VC, but the difference was not significant. However, patients with aortic valve calcification have significantly longer HD duration than those without. Aging is the most important risk factor for VC [3, 9, 18]. Duration of hemodialysis therapy seems to be another risk factor for VC [9, 11, 18]. Such relation was also found for MVC, but not for AVC, in the study by Riberio *et al.* [16]. Nevertheless, in the study of Covic *et al.*, age and duration of HD did not differ between patients with or without MVC.

In our study, patients with VC had significantly higher systolic and diastolic blood pressures (BP) than patients without VC. In accordance with our findings, Torun *et al.* have been demonstrated that, in patients on HD, compared with the group without

VC, the group with calcification had significantly higher systolic and diastolic blood pressures [19]. Hypertension is a major risk factor for atherosclerosis, and an association between hypertension and VC in HD patients has been established [3]. In addition, hypertension is a well-known pathogenic factor of left ventricular hypertrophy (LVH) [20]. It is also suggested that hypertension acts as pathogenic factor of VC due to mechanical stress [11, 21]. In the study by Riberio *et al.*, MVC was associated with longer duration of predialysis hypertension, but there was no correlation between actual BP and VC [16]. On the other hand, Salgueira *et al.* also did not find a relationship between hypertension and VC [18]. These results suggest that good control of BP in uremic patients during the predialysis period and during HD is important to reduce progression of chronic renal disease and may prevent progression of VC.

Disturbance of Ca × P product is a well-known contributor to the development of cardiac VC in patients on HD. In addition, uncontrolled hyperphosphatemia is an established risk factor for cardiovascular calcifications [22]. Elevated Ca × P product was predictive parameter for VC in studies of Maher *et al.*, and Salgueira *et al.* [11, 18]. It is of interest that increased Ca × P product was the risk factor for MVC, but not for AVC in the study of Ribeiro *et al.* [16]. Also, Ca × P product was correlated with MVC score in this study. In contrast, Pannucio *et al.* did not found association between Ca × P product and VC [5]. In the present study, no significant differences were found with respect to calcium, phosphorus, and mean Ca × P product. Despite many clinical studies the role of PTH in cardiac VC remains unclear. Soft-tissue calcifications may be correlated both with very high and low PTH concentration [21, 23]. An U-curve shape may represent the relationship between PTH and VC [14]. Our study indicates that serum levels of PTH were lower in patients with VC, but it was not statistically significant.

A previous study has demonstrated a close relationship between VC and increased atherosclerosis in ESRD patients [24]. In addition, an association between atherosclerosis and inflammation has been reported in patients on HD [25]. Sharma *et al.* reported that high sensitivity C-reactive protein was higher in patients with MVC than those without, but the difference was not significant [4]. Torun *et al.* have also demonstrated that the patients with VC had significantly higher fibrinogen and CRP levels [19]. In agreement with these findings, we found that the HD patients with MVC had significantly higher serum levels of CRP than the group without VC.

The prognostic value of cardiac VC and their relationship with LVH and background cardiovascular risk in HD patients is still unknown. VC coexists with LVH, particularly when both valves are calcified [14]. Sharma *et al.* has demonstrated that the patients with MVC have increased LV cavity size, poorer LV systolic function, higher LV filling pressures compared to patients without MVC [4]. In our study, IVS and PW thickness were found higher in patients with VC, but it was not statistically significant. In addition, LV diameter, left atrium diameter and EF were similar in the two groups.

The current study has some limitations. We performed echocardiography for defining cardiac VC. Although echocardiography is a sensitive and specific method for the detection of VC, it is much less sensitive than EBCT. Another important limitation of

this technique is that it does not allow precise quantification of calcium deposited in the valvular apparatus of the heart [5]).

In conclusion, the presence of cardiac valve calcification in HD patients was associated with old age, elevated BP, increased interventricular septum and posterior wall thickness. Longer HD duration was associated with AVC. In addition, MVC in HD patients was associated with elevated serum CRP levels. Early identification of factors that might be related to VC in HD patients may prevent or hinder the extent of cardiovascular events associated with valvular calcification.

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