Prevalence and Risk Factors of Valvular Calcification in Hemodialysis Patients

Hayriye Sayarlioglu,[1] Gurkan Acar,[2] Murat Sahin,[3]
Orcun Altunoren,[1] Yasemin Coskun Yavuz,[1] Alper Bugra Nacar,[2]
Ekrem Dogan[1]

[1]Department of Internal Medicine, Division of Nephrology, Kahramanmaras Sutcu Imam University, Kahramanmaras, Turkey
[2]Department of Cardiology, Kahramanmaras Sutcu Imam University, Kahramanmaras, Turkey
[3]Department of Internal Medicine, Kahramanmaras Sutcu Imam University, Kahramanmaras, Turkey

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Introduction. Valvular abnormalities frequently occur in patients with chronic kidney failure. This study evaluated the prevalence of heart valve calcification (HVC) in hemodialysis patients and factors associated with it.

Materials and Methods. Medical charts of 129 hemodialysis patients were reviewed retrospectively. Demographic features and laboratory analysis of the patients were systematically recorded. Echocardiographic findings were collected, including ejection fraction, aortic valve calcification (AVC), mitral valve calcification (MVC), left ventricle mass, left ventricle mass index, and pulmonary artery pressure.

Results. Valvular abnormalities were found in 43 patients (33.3%); 30 patients (23.3%) had MVC, 28 (21.7%) had AVC, and 15 (11.6%) had both MVC and AVC. Patients with HVC were older than other patients ($P < .001$). On echocardiography, higher left ventricle mass, left ventricle mass index, and pulmonary artery pressure levels were found in patients with HVC. Regarding the lipid profile, serum calcium, serum phosphorus, calcium-phosphorus product, and parathyroid hormone concentrations, there were no significant differences between patients with and without HVC. Ejection fraction levels were significantly lower in patients with HVC ($P = .002$) and serum albumin level of patients with HVC was significantly diminished.

Conclusions. This study failed to show an association between HVC in hemodialysis patients and calcium-phosphorus product and parathyroid hormone levels; however, age and diabetes mellitus could be regarded as risk factors. In addition, HVC may lead to increased left ventricle mass index and pulmonary artery pressure and decreased ejection fraction, and low albumin levels may be attributable to inflammation.

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INTRODUCTION

Dialysis patients present a significantly increased total and cardiovascular mortality when compared with the normal population.[1,2] Valvular abnormalities occur in patients with chronic kidney failure.[3] Dystrophic calcification may cause valvular heart disease in these patients. In some studies, heart valve calcifications (HVCs) were found in about half of hemodialysis patients.[4,5] Patients with hemodialysis may frequently have comorbid

diseases, including heart valve calcification due to systemic atherosclerosis and cardiovascular complication, even in young adults. Previous studies demonstrated the association between age, diabetes mellitus, dialysis duration, higher serum calcium and phosphorus, and HVC in hemodialysis patients. In addition to these complications, there are potential risks of valve dysfunction, myocardial ischemia, conduction defects, infective endocarditis, and heart failure in hemodialysis patients with HVC.[6] Wang and colleagues demonstrated that cardiac valve calcification is as a strong independent predictor for all-cause mortality and cardiovascular deaths among the chronic kidney failure patients.[7] This study attempts to evaluate the prevalence of HVC in hemodialysis patients and potential risk factors associated with it.

MATERIALS AND METHODS

We retrospectively analyzed the hospital records of 129 hemodialysis patients from Kahramanmaras Sutcu Imam University Hemodialysis Center and two other hemodialysis centers in Kahramanmaras between December 2007 and December 2008. Patients having hemodialysis three times a week for at least since 6 months were included into the study, and those with terminal diseases, stage 3 to 4 heart failure and heart valve diseases, hospitalization due to acute coronary syndrome, potential risk of acute coronary syndrome, and a history of parathyroidectomy were excluded.

We collected data on patient's age and sex; duration on hemodialysis; hemodialysis adequacy (Kt/V urea); the presence of diabetes mellitus; systolic and diastolic blood pressure; serum levels of albumin, calcium, and phosphorus; calcium-phosphorus product; serum intact parathyroid hormone (PTH), and serum levels of total cholesterol, triglyceride, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol. In addition, ejection fraction (EF), aortic valve calcification (AVC) and mitral valve calcification (MVC), left ventricle mass (LVM), left ventricle mass index (LVMI), and pulmonary artery pressure (PAP) were recorded from patients' medical charts. For the further analysis, blood sampling was performed before the first dialysis session in the week after an overnight fast. Kt/V was calculated according to the National Kidney Foundation Dialysis Outcomes Quality Initiative recommendation.[8] Systolic blood pressure and diastolic blood pressure were measured before hemodialysis session using a sphygmomanometer in a sitting position after 15 minutes of rest.

Echocardiography was performed in compliance with the American Society of Echocardiography's standard M-mode measurement after a hemodialysis session using a Vivid 7 device with a 2 MHz to 4 MHz phased array transducer (General Electric, Horten, Norway). All echocardiographies were done by the same cardiologist. Diagnosis of valve calcification (VC) was based on echocardiographic criteria of dense echoes in MVC or AVC. Interventricular septum thickness, left ventricular internal diameter, and posterior wall thickness were measured in end diastole. Left ventricular end-diastolic volume, left ventricular end-systolic volume, and left ventricular ejection fraction were calculated from 2-dimensional recordings using the modified biplane Simpson method. Left ventricle mass was calculated with the Devereux formula and was indexed to body surface area. The definition of left ventricle hypertrophy was gender related: an LVMI greater than 110 g/m^2 in women and an LVMI greater than 134 g/m^2 in men.[9,11]

All continuous data were expressed as mean ± standard deviation. Statistical analysis was performed using the Student *t* test. Qualitative data were compared using the chi squared test. A *P* value less than .05 was considered significant.

RESULTS

Of the total 129 hemodialysis patients, 43 had VC (33.3%), 30 had MVC (23.3%), 28 had AVC (21.7%), and 15 had both MVC and AVC (11.6%). The clinical characteristic of patients with and without VC is shown in Table 1. Patients with VC were older ($P = .001$). There were no significant differences between the patients with and without VC concerning the total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglyceride calcium, phosphorus, calcium-phosphorus product, and PTH concentrations. Dialysis duration of both MVC and AVC patients was significantly longer than that of other groups (19.6 ± 40.6 months versus 7.1 ± 5.8 months, $P = .01$).

On echocardiography, higher LVM, LVMI, and PAP were found in patients with VC. The LVMI was 137.6 ± 37.4 g/m^2 in patients without VC,

Table 1. Clinical and Echocardiographic Parameters of Patients With and Without Valve Calcification*

Parameter	Hemodialysis Patients		*P*
	No VC (n = 86)	VC (n = 43)	
Age, y	48. 2 ± 16.8	60.3 ± 13.5	< .001
Sex (%)			
Female	41 (47.7)	23 (53.5)	
Male	45 (52.3)	20 (46.5)	.50
Diabetes mellitus (%)	27 (31.4)	18 (41.9)	.24
Duration of hemodialysis, mo	7.1 ± 6.5	10.4 ± 20.6	.30
Kt/V	1.33	1.34	.95
Systolic BP, mm Hg	123.6 ± 16.1	129.3 ± 14.6	.06
Diastolic BP, mm Hg	78.3 ± 8.6	80.7 ± 6.0	.10
Serum calcium, mg/dL	8.3 ± 0.9	8.6 ± 0.7	.13
Serum phosphorus, mg/dL	4.3 ± 1.4	4.6 ± 4.4	.56
Calcium-phosphorus product	33.7 ± 13.5	32.4 ± 14.0	.62
Serum PTH, pg/mL	357.6 ± 298.0	338.3 ± 274.2	.73
Serum albumin, g/dL	4.1 ± 0.4	3.9 ± 0.5	.009
Serum cholesterol, mg/dL	160.7 ± 37.1	169.4 ± 40.4	.74
Serum LDLC, mg/dL	88.0 ± 29.3	93.7 ± 30.4	.33
Serum HDLC, mg/dL	38.8 ± 26.4	37.1 ± 14.8	.70
Serum triglyceride, mg/dL	180.7 ± 108.4	187.6 ± 100.8	.74
LVMI	137.5 ± 37.4	162.2 ± 34.9	.001
EF	64.0 ± 9.0	58.9 ± 9.4	.002
PAP	28.2 ± 5.7	31.1 ± 6.8	.01

*VC indicates valve calcification; BP, blood pressure; PTH, parathyroid hormone; LDLC, low-density lipoprotein cholesterol; HDLC, high-density lipoprotein cholesterol; LVMI, left ventricle mass index; EF, ejection fraction; and PAP, pulmonary artery pressure.

Table 2. Clinical and Echocardiographic Parameters of Patients With and Without Mitral Valve Calcification*

Parameter	Hemodialysis Patients		*P*
	No MVC (n = 99)	MVC (n = 30)	
Age, y	49. 1 ± 17.2	62.6 ± 9.6	< .001
Sex (%)			
Female	46 (46.5)	18 (60.0)	
Male	53 (53.5)	12 (40.0)	.20
Diabetes mellitus (%)	29 (29.3)	16 (53.3)	.02
Duration of hemodialysis, mo	7.1 ± 6.1	12.2 ± 25.6	.13
Kt/V	1.33 ± 0.35	1.34 ± 0.35	.98
Systolic BP, mm Hg	123.6 ± 15.7	131.3 ± 14.8	.02
Diastolic BP, mm Hg	78.6 ± 8.3	80.8 ± 6.3	.18
Serum calcium, mg/dL	8.4 ± 0.9	8.6 ± 0.7	.21
Serum phosphorus, mg/dL	4.6 ± 3.1	3.8 ± 1.2	.20
Calcium-phosphorus product	33.8 ± 13.9	31.6 ± 12.6	.44
Serum PTH, pg/mL	367.7 ± 303.6	292.3 ± 227.2	.24
Serum albumin, g/dL	4.1 ± 0.4	3.8 ± 0.5	.002
Serum cholesterol, mg/dL	162.8 ± 37.3	166.2 ± 41.9	.68
Serum LDLC, mg/dL	89.8 ± 29.2	90 ± 31.5	.98
Serum HDLC, mg/dL	38.6 ± 24.7	37. ± 17.5	.75
Serum triglyceride, mg/dL	181.4 ± 105.6	188.4 ± 107.5	.75
LVMI	141.2 ± 39.2	161.7 ± 30.8	.02
EF	63.2 ± 9	58.9 ± 10.4	.03
PAP	28.4 ± 5.5	31.8 ± 7.6	.01

*MVC indicates mitral valve calcification; BP, blood pressure; PTH, parathyroid hormone; LDLC, low-density lipoprotein cholesterol; HDLC, high-density lipoprotein cholesterol; LVMI, left ventricle mass index; EF, ejection fraction; and PAP, pulmonary artery pressure.

Table 3. Clinical and Echocardiographic Parameters of Patients With and Without Both Aortic and Mitral Valve Calcifications*

Parameter	Hemodialysis Patients		*P*
	No AVC + MVC (n = 113)	AVC + MVC (n = 15)	
Age, y	50.5 ± 17.0	65 ± 7.3	.001
Sex (%)			
Female	55 (48.7)	6 (40.0)	
Male	58 (51.3)	9 (60.0)	
Diabetes mellitus (%)	39 (34.5)	8 (53.3)	
Duration of hemodialysis, mo	7.1 ± 5.8	19.6 ± 40.6	.01
Kt/V	1.34 ± 0.37	1.30 ± 0.19	.78
Systolic BP, mm Hg	124.5 ± 15.7	131.4 ± 15.6	.12
Diastolic BP, mm Hg	78.8 ± 8.1	81 ± 6	.31
Serum calcium, mg/dL	8.4 ± 0.9	8.5 ± 0.6	.73
Serum phosphorus, mg/dL	4.4 ± 2.9	3.9 ± 1.1	.50
Calcium-phosphorus product	33.5 ± 13.7	33.4 ± 10.7	.90
Serum PTH, pg/mL	354.8 ± 292.2	322.5 ± 274.6	.70
Serum albumin, g/dL	4 ± 0.4	3.7 ± 0.6	.002
Serum cholesterol, mg/dL	162 ± 38.2	173.6 ± 38.7	.28
Serum LDLC, mg/dL	89.1 ± 29.1	95.8 ± 34	.43
Serum HDLC, mg/dL	38.3 ± 23.2	38.1 ± 23.9	.98
Serum triglyceride, mg/dL	182.4 ± 106.5	187.1 ± 102.6	.87
LVMI	143.3 ± 38	168.9 ± 35.1	.03
EF	62.6 ± 9.6	58.3 ± 8	.09
PAP	28.6 ± 5.7	32.8 ± 8.5	.02

*AVC indicates aortic valve calcification; MVC, mitral valve calcification; BP, blood pressure; PTH, parathyroid hormone; LDLC, low-density lipoprotein cholesterol; HDLC, high-density lipoprotein cholesterol; LVMI, left ventricle mass index; EF, ejection fraction; and PAP, pulmonary artery pressure.

166 ± 39 g/m^2 in patients with AVC, 161.7 ± 30.8 g/m^2 in patients with MVC, and 168.9 ± 35.1 g/m^2 in patients with both MVC and AVC. Lower EFs were found in patients with VC than in patients without VC (58.9% ± 9.4% versus 64.0% ± 9.0%, respectively; P = .002), but EF ranges were normal. Significant differences were found with respect to serum albumin levels between the VC-negative and VC-positive groups. Data of patients with calcification of the aortic and mitral valves are shown in Tables 1 to 3.

DISCUSSION

Heart valve calcification was first described a century ago. Its pathologic features were first described by Dewitsky in 1910. Later postmortem studies revealed that calcific valve lesions may occur without acute rheumatic fever.[11] Up to date, many necropsy and population studies have been carried out on HVC (showing, for example, that high rate of VC in elderly populations).[12]

More than 50% of deaths among patients with end-stage renal disease are caused by cardiovascular diseases. Valvular heart disease is common in end-stage renal disease patients. The incidence of valvular heart disease is 5 times greater in dialysis patients than in the general population.[13] In our study, we evaluated the prevalence of VC in hemodialysis patients and its related factors. We found VC in one-third of our hemodialysis patients. In other studies, MVC was found in 38.6% to 51.7% and AVC in 28% to 75%.[5,14,15]

It is well known that aging is an important factor for HVC. The incidence of VC increases progressively with advancing age. In the general population, the prevalence with echocardiography ranges between 2.8% and 6.3%, the majority which are determined in individuals older than 59 years.[16,17] Other suggested factors are female gender,[13] hypertension,[18] dyslipidaemia,[19] diabetes mellitus,[20] primary,[21] secondary hyperparathyroidism, and uremia.[22] In uremic patients, MVC occurs more frequently than in normal subjects.[23,24] In these patients, MVC prevalence ranges from 9.5% to 36%.[14,23] In our study, patients with MVC were older than those without MVC and more likely to have diabetes mellitus. Results of our study were consistent with other studies showing that aging

and diabetes mellitus are the predominant risk factors. In our study, MVC values of the patients were significantly higher but systolic blood pressure values were in normal range. In addition, LVMI and PAP values were higher in patients with MVC and these results may be indicating volume overload.

Left ventricular hypertension is highly prevalent in patients with earlier stages of kidney disease. Levin and colleagues have shown that the major correlates of LVH are systolic hypertension and anemia.[25] Blood pressures values in our patients with MVC were in normal range and the patients were not anemic. Contrary to many studies,[26-28] we did not find any association between VC and serum levels of calcium, phosphorus, or PTH. In parallel with our findings, there are previously held studies supporting our findings. Strozecki and colleagues showed that no significant differences were found with respect to calcium, phosphorus, PTH, and calcium-phosphorus product.[29] In hemodialysis patients, the pathogenesis of vascular calcification is complex and cannot be attributed to a simple passive process. This process includes certain factors that may promote or inhibit calcification. Tissue and vascular calcification in hemodialysis patients is influenced by other markers in the tissue (eg, fetuin A). Due to equipment shortage, we could not measure these markers. Ikee and coworkers showed that MVC was associated with increased age, higher high-sensitivity C-reactive protein, and higher serum β2-microglobulin, but not with higher serum calcium. In our study, serum albumin levels were significantly lower in patients with MVC.[14] Lower albumin levels may be a marker of inflammation. Because of the retrospective design of our study, we were unable to collect C-reactive protein values, but some studies provide evidence of association between low albumin and inflammation.[14]

Aortic valve calcification is the most common valvular abnormality in the general population as well as in patients with hemodialysis.[30] In the general population, AVC is increased with age, occurs mainly in those over the age of 65 years.[31,32] In our study, mean age of the patients with AVC was significantly higher. The LVMI and PAP was found to be higher in the AVC patients. There are some studies with similar findings.[29,33] Wang and colleagues have found that the albumin levels are significantly diminished in patients with HVC; however, they could not propose a concrete reason that may lead to such decrement.[7] Additionally, Ikee and coworkers have found decreased albumin levels in patients with AVC and it was attributed to the inflammatory process.[14] In the light of these findings, lower albumin levels may be a marker of inflammation.

Dialysis duration of patients with both MVC and AVC was significantly longer than other patients. In other studies, the duration of dialysis has been identified as a risk factor for HVC.[28,34,35] Blood studies, Kt/V, and blood pressure values in patients with AVC were in normal ranges. While there is not a sufficient data presenting the importance and potential role of these parameters, it is thought that hemodialysis sufficiency may improve the calcium, phosphorus, and PTH levels, and that will positively affect the HVC.

CONCLUSIONS

Our study confirmed that older age and diabetes mellitus are the most predictive parameters of VC in hemodialysis patients. Other markers were not associated with HVC. In addition, increased LVMI, increased PAP, and lower EF may be found due to volume overload. Low serum albumin levels may be attributed to inflammation.

CONFLICT OF INTEREST

None declared.

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Correspondence to:
Hayriye Sayarlioglu, MD
Sutcu Imam Universitesi Tip Fak, Arastirma Hastanesi
Kahramanmaras, Turkey
Tel: +90 532 296 7570
Fax: +90 344 221 2371
E-mail: hayriyesayarlioglu@yahoo.com

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