

Valvular Calcification in Chronic Kidney Disease

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ABSTRACT

Background and objectives : Chronic kidney disease (CKD) is a risk factor for cardiovascular disease and is associated with increased all-cause mortality. Valvular calcification results from the deposition of calcium-phosphate crystals on the annulus and the leaflets of the valves, at sites of inflammation or mechanical stress. Use of a simple and noninvasive tool - 2D echocardiography identifies valvular calcification. This study was conducted to determine the frequency of Valvular calcification in chronic kidney disease patients compared to people with normal kidney function and to classify severity of valvular calcification according to stage of Chronic kidney disease.

Materials and Method : The study, a Hospital based, Observational, Case control study consisting of 50 cases and 50 controls was conducted from January 2017 to September 2018. After fulfilling eligibility criteria, cases and controls were enrolled in the study. Thorough physical examination and serum creatinine, serum calcium and phosphorus, urine albumin, ultrasonography of abdomen, electrocardiogram and echocardiography was performed in all cases and controls. Collected data were entered into Microsoft excel spreadsheet. $p < 0.05$ was considered as statistical significance. Statistical software STATA version was used for data analysis.

Results : Valvular calcification was observed in 62 % of cases as compared to 18% of controls. Frequency of valvular calcification was significantly increased in cases of chronic kidney disease on dialysis.

Mitral valve was the most common valve which was affected.

Age, Estimated glomerular filtration rate (severity of chronic kidney disease) and calcium phosphorus product were independent predictors of valvular calcification and found to be statistically significant.

Key-words : chronic kidney disease (CKD), valvularcalcification , dialysis, calcium phosphorus product, eGFR (estimated glomerular filtration rate).

Introduction :

Chronic kidney disease is defined as abnormality of kidney structure or function present for more than 3 months with implication of health.¹ Valvular calcification results from the deposition of calcium-phosphate crystals on the annulus and the leaflets of the valves, at sites of inflammation or mechanical stress². Valvular calcification is also an active process that involves de-differentiation of matrix cells into cells with osteoblastic potential. In the early stages of renal impairment, the complex balance between promoters and inhibitors of osteogenesis begins to breakdown, resulting in the deposition of calcium in extraskeletal organs.

Valvular calcification amongst dialysis patients is associated with subclinical measures of atherosclerosis³ and is a powerful predictor of cardiovascular disease events^{3,4} and all cause mortality. 2D echocardiography is a simple non invasive tool for assessing valvular calcification.

Mechanism of Valvular Calcification :

1. Mechanical-cardiac valves are subjected to cyclic mechanical stress which is related to pressure gradients and turbulent blood flow resulting from high rates of acceleration and high peak velocities.
2. The presence of **anemia, volume overload and hypertension** produces a high cardiac output state. Repetitive mechanical stress causes fatigue and rearrangement of bioelastomers leading to microfractures and fibrillar alteration of the collagen ultrastructure. This eventually leads to fibrosis and calcification.
3. **Lipid deposition** usually follows microfracture injury. This process involves the accumulation of

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oxidized low density lipoprotein cholesterol and the presence of chronic inflammation mediated by T lymphocytes and macrophages. Since oxidised LDL-C promotes inflammation and causes oxidative stress and is often a result of the inflammatory process, chronic inflammation may be the ultimate mediator of calcification in chronic kidney disease.

4. **ALTERED CALCIUM and PHOSPHORUS** metabolism particularly an increase in calcium phosphorus product and drugs that promotes hypercalcemia are all thought to contribute to the pathogenesis of valvular calcification.

- Valvular calcification is associated with a significantly increased risk for all-cause mortality in CKD patients.
- Kidney Disease Improving Global Outcomes guidelines have recommended use of echocardiography for risk stratification in CKD.

Aims and Objectives :

1. To determine the frequency of Valvular calcification in chronic kidney disease patients, compared to people with normal kidney function using 2D Echocardiography.
2. To correlate severity of Valvular calcification with stages of Chronic kidney disease as determined by GFR.
3. To identify the predictors of Valvular calcification in chronic kidney disease.

Material and Method :

This Hospital based, Observational, Case control study was conducted after approval by the Institutional Ethics Committee (IEC). 50 Cases and 50 controls who satisfied the eligibility criteria were enrolled after obtaining written informed consent from the inpatient and outpatient Department of Medicine.

Inclusion Criteria for Cases :

1. Age 21 - 60 years with 3 months' duration of deranged eGFR (< 60ML/MIN/1.73m²).
2. Chronic kidney disease due to anyetiology.
3. CKD cases on Maintenance hemodialysis.
4. CKD cases not on maintenance hemodialysis.

Exclusion Criteria of Cases :

1. Patient of Rheumatic heart disease.
2. Pregnant women.
3. Documented ischemic heart disease.
4. Documented congenital heart disease.
5. Patients with acute renal failure

Inclusion Criteria of Controls :

1. Age \pm 5 yrs. and gender matched with cases.
2. Non CKD Patients with GFR of > 90 ml / min /1.73 m².

Exclusion Criteria of Controls :

1. Patient of Rheumatic heart disease.
2. Pregnant women.
3. Documented ischemic heart disease.
4. Documented congenital heart disease.
5. Patients with acute renal failure

Detailed history and clinical examination and investigations was done

A) Blood investigations: Hemoglobin, blood sugar level, serum creatinine , serum calcium, serum phosphorus. B) Urine routine microscopy and albumin. C) USG abdomen. D) ECHOBy using Cockcroft Gault formula, eGFR was calculated and severity was classified as follows

GFR category	GFR (ml/min/1.73 m ²)	Terms
G1	≥ 90	Normal or high
G2	60-89	Mildly decreased*
G3a	45-59	Mildly to moderately decreased
G3b	30-44	Moderately to severely decreased
G4	15-29	Severely decreased
G5	<15	Kidney failure

Abbreviations: CKD, chronic kidney disease; GFR, glomerular filtration rate.

*Relative to young adult level

In the absence of evidence of kidney damage, neither GFR category G1 nor G2 fulfill the criteria for CKD.

Age restricted to 60 years to minimize age related calcification bias.

Mitral Annular Calcification (MAC) is the common degenerative process involving the fibrous annulus of mitral valve preferably posterior than anterior. MAC is most commonly visualized by echo as an echodense, irregular shelf like structure involving the mitral valve annulus.

Staging of Mitral Annular Calcification

MILD TO MODERATE	1-4 mm
SEVERE	> 4 mm

Aortic Calcification : calcification / sclerosis of aortic valve according to area.⁵ Aortic calcification classified as mildly calcified (isolated, small spots) involving 1/3rd of aortic valve area, moderately calcified (multiple bigger spots) involving 1/3rd to 2/3rd aortic valve area, heavily calcified (extensive thickening/calcification of all cusps) involving more than 2/3rd of aortic valve area.

Collected data were entered into Microsoft excel spreadsheet. Continuous variables were presented as Mean \pm SD. Categorical variables were expressed in frequency and percentages. Continuous variables were compared between cases and control by performing independent t-test. Categorical variables were compared by performing chi-square test. For small numbers, Fisher exact test was used wherever required. Multiple Logistic Regression analysis was performed to determine independent predictors of Valvular calcification in CKD patients. $p < 0.05$ was considered as statistical significance. Statistical software STATA version was used for data analysis.

Observations and Results :**Table 1 : Age Distribution in Cases and Controls**

Age in year	CASES n=50	CONTROLS n=50
21-30	6 (12%)	8 (16%)
31-40	11 (22%)	13 (26%)
41-50	18 (36%)	17 (34%)
51-60	15 (20%)	12 (20%)
TOTAL	50	50
AGE IN YEARS (MEAN \pm SD)	42.58 \pm 10.01	42.22 \pm 10.31
RANGE	(22-59)	(21-60)

The age variation of cases was from 22 to 59 years. Majority of the cases were in the age group of 41-50 years, which included 18 patients (36%). The mean age of the cases was 42.58 years.

Table 2 : Distribution of Cases According to Stages of CKD

STAGE OF CKD	CASES n=50	MALE	FEMALE
3	15 (30%)	2 (4%)	13 (26%)
4	14 (28%)	4 (8%)	10 (20%)
5	21 (42%)	14 (28%)	7 (14%)

21 (42%) cases were found in stage 5, followed by 15 (30%) cases in stage 3, followed by 14 (28%) cases in stage 4. Of the total 20 male 2 (4%) were in stage 3, 4 (8%) were in stage 4, and 14 (28%) were in stage 5. Out of total 30 females 13 (26%) were in stage 3, 10 (20%) in stage 4 and 7 (14%) in stage 5.

Table 3 : Valvular Calcification in Cases and Controls on Basis of Echocardiography

Echo Finding	Cases n=50	Control n=50
Normal	17 (34%)	34 (68%)
Mitral Valve / annular Calcification	13 (26%)	4 (8%)
Aortic Valve Calcification	10 (20%)	2 (4%)
Both Valve Involvement	8 (16%)	3 (6%)
Other Finding*	2 (4%)	7 (14%)

*other findings suggestive of ventricular hypertrophy, systolic dysfunction, diastolic dysfunction, pericardial effusion.

Echo was normal in 34 % cases and 68% controls. Valvular calcification was seen in 31 (62%) cases out of 50 cases and in control Valvular calcification was seen in 9 (18%) out of 50 controls. Mitral Valvular calcification seen in 26 % as compared to 8% in controls, aortic Valvular calcification seen in

20% of cases as compared to 4% in control, both valves involved in 16% cases as compared to 6% in controls. The prevalence of Valvular calcification was more in cases as compared with control group and was statistically significant with p value < 0.001.

Table 4 : Association of Valvular Calcification with Stages of CKD

Stages of CKD	STAGE 3	STAGE 4	STAGE 5	chi ² (X2) = 19.6687 p=0.003, HS
Mitral/MAC (n=13)	2 (6.46%)	6 (19.35%)	5 (16.12%)	
Aortic (n=10)	1 (3.22%)	3 (9.69%)	6 (19.35%)	
Both (n=8)	1 (3.22%)	0	7 (22.59%)	

Out of 13 cases in which mitral valve was calcified 6 cases were in stage 4, out of 10 cases of aortic valve calcification, 6 cases were in stage 5 and in 8 cases in which both valves were involved, 7 cases were in stage 5. This association was found to be statistically significant with chi2 value of 19.6687 and p value of 0.003

Table 5 : Association of Valvular Calcification in Dialysed and Non Dialysed Cases

Cases n=50	Mitral calcification /MAC n=13	Aortic calcification n=10	Both valvular involvement n=8	chi ² = 14.4620 P=0.003, HS
Hemodialysis n=32	10 (92.30%)	9 (90%)	7 (75%)	
Non dialysis n=18	3 (7.7%)	1 (10%)	1 (25%)	

In present study out of 50 cases, 32 were on maintenance hemodialysis. Mitral valve calcification was seen in 13 cases, 10 cases were on HD. Of the total 10 cases in which aortic valve was calcified, 9 cases were on HD and of the 8 cases in which both valves were calcified, 7 cases were on HD. This association between Valvular calcification with hemodialysis was significant with chi 2 value of 14.4620 and p value of 0.003.

Table 6 : Association of Calcium Phosphorus Product With Stages Of CKD

CaPO ₄ Product	STAGE 3 n=13	STAGE 4 n=14	STAGE 5 n=21	Rho value P-value
<40	4 (26.67%)	3 (21.43%)	2 (9.52%)	Rho=0.3258, p=0.0218,S
41-50	6 (40%)	3 (21.43%)	3 (14.28%)	
51-60	1 (6.67%)	3 (21.43%)	6 (28.57%)	
> 60	4 (26.66%)	5 (35.71%)	10 (47.63%)	

In stage 3, 6 cases had CaPO₄ product in range of 41-50, In stage 4, 5 cases had CaPO₄ product > 60. In stage 5, 10 cases had CaPO₄ product > 60. This was found to be statistically significant with Rho value of 0.3258 and p-value of 0.0218.

Table 7a : Association of Severity of Mitral Valve / Annular Calcification with Stage of CKD on Basis of Echocardiographic Findings.

Stages of CKD	STAGE 3	STAGE 4	STAGE 5	P-value=0.046 chi 2-6.1515, S
Mild to moderate Annular / Valvular Calcification n=9	4 (19.04%)	3 (14.28%)	2 (9.52%)	
Severe mitral Annular / Valvular Calcification n=12	1 (4.76%)	2 (9.52%)	9 (42.86%)	

Severe mitral valve calcification seen in 12 cases out of 21 cases including cases of both mitral valve involvement and both valve calcification, out of 12 cases 9 cases were in stage 5. This association is statistically significant with p value of 0.046.

Table 7b : Association of Severity of Aortic Valve Calcification with Stage of CKD on Basis of Echocardiographic Finding

Aortic calcification n=18	Stage 3	Stage 4	Stage 5	P-value=0.014 X2 12.0300, HS
Mild n=5	4 (22.22%)	1 (5.55%)	0	
Moderate n=10	1 (5.55%)	3 (16.67%)	6 (33.33%)	
Severe n=3	0	0	3 (16.67)	

Aortic valve calcification was found in 18 patients including both categories of isolated aortic valve involvement and both aortic and mitral valve involvement. Mild aortic calcification was seen in 5 cases out of 18 and 4 patients were in stage 3, moderate calcification was seen in 10 cases 6 were in stage 5; only 3 patients had severe aortic calcification all were in stage 5. This association was significant with χ^2 12.0300 and p value of 0.014

Table 7b : Association of Severity of Aortic Valve Calcification with Stage of CKD on Basis of Echocardiographic Finding

Variable	Adjusted OR	95% C.I.	P-value
Age in years	1.16	1.04 1.29	0.004, HS
eGFR	0.88	0.82-0.95	0.002, HS
CaPO4	1.07	1.00 1.14	0.042, S

Age, eGFR (severity of chronic kidney disease) and calcium phosphorus product are independent predictors of Valvular calcification and found to be statistically significant.

Discussion :

Cardiac valves, particularly on the left side of the heart, are subject to cyclic mechanical stress from high pressure gradients and turbulent flow related to high peak velocities and rapid acceleration⁶. The mechanical stress on the valve with each cardiac cycle leads to endothelial microfractures that cause rearrangement of elastin and breakdown of the

collagen structure^{6,7}. Over time, the repetitive damage to the valve will result in fibrosis and calcification.

In most patients, MAC is initially isolated to the ventricular base under the posterior mitral leaflet, and can spread to involve the entire posterior annulus⁸. Advanced posterior MAC can cause mitral regurgitation (MR) due to restriction of the posterior

leaflet movement, while the anterior leaflet remains mobile. In patients with ESKD, MAC can progress further to involve the anterior annular ring. This circumferential calcific ring restricts the movement of both the anterior and posterior leaflets resulting in mitral stenosis⁸.

In the aortic valve, the increased calcium deposition often causes aortic stenosis (AS). Though symptoms of AS (angina, syncope, and dyspnea) are identical in patients regardless of baseline kidney function, the natural course of the disease is accelerated in patients with CKD and as a result these rapid progressors have severe, symptomatic AS at a younger age than the non-CKD population.

Changes in bone mineral metabolism and alterations in calcium and phosphate homeostasis occur early in the course of CKD and progress as kidney function declines. These changes are grouped under the umbrella term Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD) which includes renal osteodystrophy and extra skeletal (Vascular/Valvular) calcification related to abnormalities of bone mineral metabolism. The age group included in the present study was from 21 to 60 years and the mean was 42.5 with standard deviation 10.01 years. Ratio of male to female was 2:3 in this study which was comparable with another study **Murvet Yilmaz et al**⁹ with mean age of 42 ± 13 year.

In present study Echo was normal in 34 % cases and 68% control, Mitral Valvular calcification was seen in 26% as compared to 8% in controls, Aortic Valvular calcification seen in 20% of cases as compared to 4% in controls, both valves calcification in 16% cases as compared to 6% in controls.

In **present study** of 50 cases, 32 were on maintenance hemodialysis. As mitral valve involvement seen in 13 cases, 10 cases were on HD. out of total 10 cases in which aortic valve was calcified 9 (90%) cases were on HD and out of 8 cases in which both valves were calcified 7 cases were on HD

In present study out of 13 cases in which mitral valve was calcified 19.35% cases were in stage 4, out of 10 cases of aortic valve calcification 19.35% of cases were in stage 5 and in 8 cases in which both valves were involved 22.59% cases were in stage 5. This finding suggests that frequency of Valvular calcification increases with severity of CKD.

Caroline S. Fox et al⁵ did Framingham study in which eGFR (ml/min per 1.73 m²) was 78 ± 25 in patients with Valvular calcification which is comparable with present study.

In the present study, out of total population including cases and control 40% had Valvular calcification and 47.5% had CaPO₄ product of > 60 which was comparable with study done by **S. Hariprasad et al**¹⁰ and **Masoumeh Kahnooji et al**¹¹.

MARGARITA RUFINO et al¹² and **Hariprasad S. et al**¹⁰ found that maximum patients had mitral valve calcification which is similar to present study while **Ribeiro s et al**¹³ found that frequency of aortic valve calcification was more than mitral valve / annular calcification.

Hayriye Sayarlioglu et al¹⁴ found that out of 129 hemodialysis patients; 30 patients (23.3%) had MVC, 28 (21.7%) had AVC, and 15 (11.6%) had both MVC and AVC which is comparable with present study.

In present study, severe mitral valve calcification was seen in 12 out of 21 cases including cases of isolated mitral valve calcification and both valve calcification, out of 12 cases 9 cases were in stage 5. In present study aortic valve calcification was found in 18 patients including both categories of isolated aortic valve involvement and both aortic and mitral valve involvement. Mild aortic calcification was seen in 5 cases out of 18 and 4 patients were in stage 3, moderate calcification was seen in 10 cases 6 were in stage 5, Only 3 patients had severe aortic calcification, all were in stage 5. **YrjöLeskinen et al**¹⁵ found that in contrast to the mitral valve, calcification of the aortic valve in CKD was more distinct in the valve cusps (20-33% prevalence) than the annulus (10-17%) and the prevalence increases by severity of CKD.

Conclusion :

The mean age of cases was 42.58 years. Majority of the patients were in the age group of 41-50 years, which included 18 patients (36%). Male to female ratio being 2:3.

Out of total population including cases and control 40% had Valvular Calcification (31 cases and 9 controls).

Total prevalence of Valvular calcification in cases was 62% as compared to 18% in controls. In cases out of 62%, 26% had mitral valve calcification, 20% had aortic valve calcification and 16% had both Valvular calcification. Isolated mitral Valvular calcification was seen in more number of cases as compared to isolated aortic and both valve calcification.

In present study out of 50 cases 32 were on maintenance hemodialysis, of which 26 cases had Valvular calcification.

Mitral valve calcification was seen in 13 cases, of which 10 cases were on HD. Of the total 10 cases in which aortic valve was calcified, 9 cases were on HD and out of 8 cases in which both valves were calcified 7 cases were on HD.

In present study out of 13 (26%) cases in which mitral valve was calcified, 6 cases were in stage 4, while in 10 (20%) cases of aortic valve calcification, 6 cases were in stage 5 and in 8 (16%) cases were both valves were involved 7 cases were in stage 5.

Prevalence of Valvular calcification increased with severity of chronic kidney disease. along with calcium phosphorus product. Aortic Valvular calcification was found to be more prevalent in early stages of chronic kidney disease. While both valve calcification was predominantly seen in stage 5.

Age, eGFR (severity of chronic kidney disease) and calcium phosphorus product are independent predictors of Valvular calcification

Limitation :

1. Relatively small sample size.
2. Echocardiography, does not differentiate between valvular sclerosis or calcification effectively.

Clinical implication :

- Use of a simple and noninvasive, echocardiography is useful for risk stratification of CKD patients.
- Effectively management of calcium phosphorus metabolism reduces occurrence of Valvular calcification.
- Yearly Echocardiography is recommended.

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