Research Article

Heart Valve Disease And Disorders Related To Mineral Metabolism In Hemodialysis Patients At Dr. Soetomo Regional Hospital In Indonesia: The Mediator Function Of Valve Calcification

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Abstract

Malnutrition, chronic inflammation, and problems with mineral metabolism are frequently linked to calcification in patients with chronic kidney disease (CKD) receiving hemodialysis (HD). The purpose of this study is to examine the connection between heart valve problems and levels of calcium, phosphorus, albumin, and C-reactive protein (CRP) in patients with chronic kidney disease (CKD) receiving hemodialysis. This cross-sectional observational analytical study was carried out at Surabaya's Dr. Soetomo General Hospital. Laboratory testing provided information on calcium, phosphate, albumin, and CRP levels, and transthoracic echocardiography (TTE) was used to evaluate heart valve problems. The Spearman correlation test was used for the correlation analysis, with a significance level of $p < 0.05$. Most participants had normal albumin levels (98.3%), high CRP (65%), hyperphosphoremia (68.3%), and normal calcium levels (56.7%). The most prevalent valve condition (66.7%) with mild severity (60%) was mitral regurgitation. Heart valve calcification was substantially correlated with calcium, phosphorus, and CRP levels ($r = 0.430$; $p = 0.001$; $r = 0.296$; $p = 0.022$; $r = 0.262$; $p = 0.043$), but not with albumin levels ($p > 0.05$). The degree of heart valve damage was only substantially correlated with calcium levels ($r = 0.290$; $p = 0.025$). Furthermore, there was a significant correlation ($r = 0.365$; $p = 0.004$) between the degree of heart valve dysfunction and valve calcification. The degree of heart valve damage in CKD patients receiving hemodialysis was substantially correlated with calcium levels and valve calcification. One of the main mediators between clinical signs of heart valve deterioration and problems with mineral metabolism is valve calcification.

Keywords: Heart valve problems, hemodialysis, valve calcification, and chronic kidney disease.

1. Introduction

The prevalence of chronic kidney disease (CKD), a global health issue, is continuously rising. Over 10% of the world's population is known to have chronic kidney disease (CKD), which kills over 850,000 people each year. By 2030, the mortality rate is expected to be 14 per 100,000 (Kovesdy, 2022). The number of people with chronic kidney disease (CKD) in Indonesia is also on the rise, with the majority of patients in the later stages needing hemodialysis (HD), which accounts for around 60% of all patients in the country (Statista, 2017).

Patients with CKD are particularly vulnerable to cardiovascular problems after receiving HD. In patients with chronic kidney disease (CKD), the death rate from cardiovascular disease (CVD) is ten times greater than the mortality rate from CKD progression (Sarnak, 2003). Cardiovascular disease is the major cause of death in this population, with a considerably higher mortality risk than the general population. Left ventricular hypertrophy, coronary artery disease, heart failure, arrhythmias, and sudden death are examples of cardiovascular symptoms in CKD-HD patients (Zhang, 2023).

Heart valve disease (CHD) is one of the most prevalent but little-known cardiovascular problems. In individuals with chronic kidney disease (CKD), valve dysfunction is frequently asymptomatic in its early stages but can develop into serious hemodynamic problems. The main cause of stenosis and regurgitation in this

population is valve calcification, especially of the aortic and mitral valves (Cheung, 2021; Inker, 2014). Heart valve calcification in CKD-HD patients has a complex etiology that is intimately linked to problems with mineral metabolism. The conversion of valve interstitial cells into an osteoblastic phenotype, which subsequently results in calcium deposition in the valve tissue, is triggered by hyperphosphatemia, increased calcium-phosphorus production, and secondary hyperparathyroidism. Malnutrition and persistent inflammation are other factors that hasten the calcification process (Webster, 2017).

An elevated risk of cardiovascular and vascular calcification has been widely linked to high phosphorus levels. Additionally, calcium contributes to the calcification process, particularly when there is an imbalance with phosphorus. Additionally, it is known that the development of heart valve disease in CKD-HD patients is influenced by elevated levels of C-reactive protein (CRP), a marker of inflammation, and decreased albumin levels, a sign of malnutrition (Webster, 2017; Plytzanopoulou, 2020; Rapa, 2019). The noninvasive diagnostic technique of echocardiography is essential for the early identification of problems in the structure and function of the heart valves. Before clinical symptoms manifest, this examination enables the detection of valve calcification, leaflet thickening, and functional abnormalities such stenosis and regurgitation (USRDS, 2017).

The majority of research on CKD patients has concentrated on heart failure and coronary heart disease; however, there are still few studies that explicitly assess the connection between heart valve disorders and problems with mineral metabolism, inflammation, and malnutrition, especially in the population of CKD patients receiving hemodialysis in Indonesia. Thus, the purpose of this study is to examine how heart valve problems in CKD patients receiving hemodialysis relate to levels of calcium, phosphorus, albumin, and C-reactive protein.

2. Materials and Methods

This study used a cross-sectional design and was observational analytical in nature. Under the number 1374/KEPK/VII/2025, Dr. Soetomo Regional General Hospital in Surabaya granted ethical permission for the study, which was carried out there.

Population and sample

This study included all patients with CKD having hemodialysis. The Spearman correlation test formula was used to compute the sample size, and patients who met the study criteria were selected consecutively.

$$n = \left(\frac{Z_{\alpha/2} + Z_{\beta}}{0.5 \cdot \ln\left(\frac{1+r}{1-r}\right)} \right)^2 + 3$$

Description:
n: Sample size
α: Type 1 error rate. Limits the probability of the null hypothesis being rejected
β: Type 2 error rate. Probability of the null hypothesis being rejected
r: Correlation coefficient

There were 52 samples in this study, according to the findings of the computation using the Spearman correlation test formula. Patients with chronic kidney disease who received regular hemodialysis for at least three months, were at least eighteen years old, had complete laboratory data, including levels of calcium, phosphorus, albumin, and C-reactive protein (CRP), underwent transthoracic echocardiography (TTE), and were willing to participate in the study met the inclusion criteria. Acute infection or inflammation at the time of data collection, a history of primary heart valve disease or congenital anomalies, a history of heart valve surgery or intervention, and insufficient clinical or laboratory data were the exclusion criteria.

Data analysis

The statistical test used was the Spearman correlation test with a significance level of $p < 0.05$.

3. Results

In this investigation, laboratory and echocardiographic analyses were performed on sixty participants. Table 1 displays the findings of these analyses.

Table 1. Results of laboratory tests and echocardiography tests of research subjects

Variable	Category	N = 60	%
Calcium	Hypocalcemia	4	6.70
	Normal	34	56.70
	Hyperkalcemia	22	36.70
Phosphor	Hypophosphoremia	1	1.70
	Normal	18	30.00
	Hyperphosphoremia	41	68.30
Albumin	Hypoalbuminemia	1	1.70
	Normal	59	98.30
CRP	Normal	21	35.00
	Abnormal	39	65.00
Types of valve disorders	Mitral Stenosis	5	8.30
	Mitral Regurgitation	40	66.70
	Aortic Regurgitation	16	26.70
	Other valve disorders	24	40.00
Severity of valve disorders	Normal	11	18.30
	Mild	36	60.00
	Moderate	13	21.70
Degree of valve calcification	Tertile 1	23	38.30
	Tertile 2	23	38.30
	Tertile 3	14	23.30

Serum calcium levels were found to be within the normal range in 56.7% of study participants, hypercalcemia in 36.7%, and hypocalcemia in 6.7%. Only 1.7% of participants had hypophosphoremia, 30% were within the normal range, and 68.3% of subjects had hyperphosphoremia in the blood phosphorus level variable. Just 1.7% of patients exhibited hypoalbuminemia, whereas 98.3% of subjects had normal serum albumin levels. In the meantime, the C-Reactive Protein (CRP) test revealed that 35% of participants had CRP levels within the normal range and 65% had aberrant CRP levels.

Mitral regurgitation was the most prevalent form of heart valve condition discovered in the study patients, accounting for 66.7%, followed by other valve abnormalities (40%), aortic regurgitation (26.7%), and mitral stenosis (8.3%). Mild disorders accounted for 60% of individuals and were the most prevalent category based on the severity of valve diseases. In contrast, 21.7% of participants had mild abnormalities, while 18.3% of subjects had normal valve function. When the Global Cardiac Calcium Score (GCCS) was used to review the degree of valve calcification, tertiles 1 and 2 were the most prevalent categories, each with a proportion of 38.3%, while tertile 3 was identified in 23.3% of participants. The results of the test of agreement and intraobserver variability can be seen in Table 2.

Table 2. The results of the test of agreement and intraobserver variability

Variable	Kappa Value (K)	p-value
GCCS Agreement	0.933	<0.001
Intraobserver Variability	0.933	<0.001

Table 5.4 indicates that the interobserver variability was 0.933, or 93.3%, based on the Kappa test results. The GCCS evaluation is regarded as reliable and can be used for additional analysis because this value shows that the

interobserver agreement is considerable (p < 0.001) and extremely strong. The average of the two assessors is the GCCS value utilized in the analysis. The same assessor's Kappa test findings revealed a very strong and statistically significant degree of agreement with a Kappa value of 0.933 and a p value of less than 0.001. These results show that the GCCS assessment procedure is consistent when used by the same assessor at different periods in addition to being accurate among assessors. The results of the correlation test of variables with heart valve calcification can be seen in Table 3.

Table 3. The results of the correlation test of variables with heart valve calcification

Variable	Correlation Coefficient (r)	p-value
Calcium	0.430	0.001*
Phosphor	0.296	0.022*
Albumin	0.149	0.257
CRP	0.262	0.043*

*Statistically significant

The association between heart valve calcification morphology based on tertile division (Tertile 1, Tertile 2, and Tertile 3) and calcium levels (hypocalcemia, normal, and hypercalcemia) was evaluated using the Spearman correlation test. A substantial, unidirectional link with a moderate correlation strength (r = 0.430; p = 0.001) was revealed by the analytical results. This result suggests that the degree of heart valve calcification increases with serum calcium levels.

The degree of heart valve calcification and phosphorus levels (hypophosphoremia, normal, and hyperphosphoremia) exhibited a significant, unidirectional link with a modest correlation strength (r = 0.296; p = 0.022) according to Spearman's correlation test. This suggests that there is a modest correlation between the degree of heart valve calcification and elevated phosphorus levels. There was no significant correlation (r = 0.149; p = 0.257) between the degree of valve calcification and albumin levels (hypoalbuminemia and normal), despite the relationship's unidirectional direction and weak strength. These findings show that the degree of heart valve calcification in the research participants is not substantially correlated with albumin levels.

Meanwhile, a Spearman correlation test between CRP levels (normal and abnormal) and the degree of valve calcification revealed a significant, unidirectional link with a low correlation strength (r = 0.262; p = 0.043). This result implies that, although the correlation is not very strong, greater CRP levels are linked to a higher degree of valve calcification.

Table 3. Correlation of Variables with Heart Valve Calcification

Variable	Koefisien Korelasi (r)	p-value
Calcium	0.430	0.001*
Phosphor	0.296	0.022*
Albumin	0.149	0.257
CRP	0.262	0.043*

4. Discussion

The majority of participants in this study had calcium levels within the normal range (56.7%), with a comparatively high percentage of hyperphosphoremia (68.3%) and increased CRP levels in 65%. These results are in line with severe chronic kidney disease (CKD), where patients receiving hemodialysis frequently have problems with mineral metabolism and persistent inflammation (Webster, 2017; Rapa, 2019; Stenvinkel, 2005). The prevalence of mitral regurgitation (66.7%) at mild degrees (60%) suggests that valve abnormalities in CKD-HD patients are still in the early or subclinical stages. This is consistent with research showing that structural alterations in heart valves in chronic kidney disease (CKD) frequently start with modest calcification before developing into serious hemodynamic problems (USRDS, 2017; Baumgartner et al., 2017).

Although the connection strength varied, the results demonstrated a substantial relationship between heart valve calcification and levels of calcium, phosphorus, and CRP. Phosphorus and CRP had a small but

significant correlation, whereas calcium had a moderate correlation (r = 0.430; p = 0.001). These results provide credence to the theory of CKD-Mineral and Bone Disorder (CKD-MBD), which holds that the calcification of vascular tissue and heart valves is largely caused by an imbalance in calcium and phosphorus metabolism (Webster, 2017; Moe, 2008; dan KDIGO, 2017). It is known that hyperphosphatemia causes valve interstitial cells to differentiate into an osteoblastic phenotype by activating molecular pathways including Runx2 and bone morphogenetic protein (BMP), which causes calcium to accumulate in the valve tissue (Demer, 2008; Johnson, 2023)

Furthermore, by increasing oxidative stress and activating proinflammatory cytokines like TNF-α and IL-6, chronic inflammation marked by elevated CRP also aids in the calcification process. In individuals with CKD-HD, the combination of inflammation and poor mineral metabolism speeds up the development of valve calcification. The minimal variance in albumin levels across patients, with the majority having albumin levels within the normal range, may be the reason for the lack of a meaningful correlation between albumin levels and valve calcification in this study. This result is consistent with other research demonstrating that albumin is more of a nutritional status indicator than a direct contributor to the pathophysiology of calcification (Plytzanopoulou P et al., 2020; Kalantar-Zadeh K et al., 2003).

In the study of the degree of heart valve disease, only calcium levels exhibited a significant connection (r = 0.290; p = 0.025), whereas phosphorus, albumin, and CRP did not. These results imply that while phosphorus and CRP are involved in the first phases of pathogenesis (calcification), calcium has a greater impact on the clinical signs of valve disease. Changes in the structure and function of heart valves are more significantly influenced by calcium because it directly contributes to the process of mineral deposition in valve tissue (Webster, 2017; Ketteler M et al., 2018). These findings support the idea that heart valve problems in CKD-HD patients develop gradually, beginning with problems with mineral metabolism, progressing to valve calcification, and ultimately leading to serious hemodynamic problems (Webster AC et al., 2017; London GM, 2011).

The degree of cardiac valve disease and valve calcification have a substantial connection (r = 0.365; p = 0.004), indicating that valve calcification plays a crucial role in bridging the gap between metabolic problems and clinical symptoms. This suggests that the pathophysiological pathway of valve illness in CKD-HD patients may be significantly influenced by valve calcification (Urena-Torres P et al., 2011; London GM et al., 2003). Therefore, treatments targeted at reducing calcification, such as lowering calcium and phosphorus levels, may be able to stop heart valve disease from getting worse (KDIGO, 2017). The results of this study highlight the need of keeping an eye on the levels of inflammatory markers, calcium, and phosphorus in CKD-HD patients. Additionally, the use of echocardiography as an early detection method is essential for detecting structural abnormalities in the valves before clinical symptoms manifest, enabling earlier intervention.

5. Conclusion

The findings of this study show that mineral metabolism abnormalities, notably calcium levels, play a substantial role in valve calcification and cardiac valve diseases in CKD-HD patients. Valve calcification is a possible target in attempts to minimize cardiovascular problems in individuals with chronic kidney disease (CKD) because it serves as a crucial mediator connecting metabolic variables to clinical symptoms.

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