



Association of serum phosphorus, calcium and parathyroid hormone with echocardiographic findings in regular hemodialysis patients

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Abstract

Introduction: Dialysis patients tend to have a greater prevalence of cardiovascular diseases.

Objectives: The aim of this study was to determine the prevalence of heart valves calcification, left ventricular hypertrophy, and left ventricular systolic and diastolic dysfunction. It also aimed to determining the relationship of the above mentioned parameters with serum calcium, phosphorus, parathormone and duration of dialysis.

Patients and Methods: This cross-sectional study was conducted on 100 hemodialysis patients who were referred to Hajar hospital in Shahrekord, Iran. Using echocardiography, patients were examined for the calcification of the heart valves, left ventricular hypertrophy, and left ventricular systolic and diastolic dysfunction. Serum calcium, phosphorus, and parathormone and duration of dialysis was also determined.

Results: The mean age of the patients was 58.10 ± 15.51 years. Around 24 patients suffered from calcification of the heart valves. Additionally, 85 patients suffered from left ventricular hypertrophy. The prevalence of left ventricular systolic and diastolic dysfunction was 26% and 86%, respectively. Common valvular abnormalities were mitral valve regurgitation (97%), followed by tricuspid regurgitation, aortic and pulmonary regurgitation, respectively. There was a significant relationship between serum phosphorus and calcification of cardiac valves, left ventricular hypertrophy, and left ventricular systolic dysfunction ($P < 0.05$). Duration of dialysis and calcium and serum parathyroid hormone levels had no significant relationship with left ventricular hypertrophy and dysfunction and calcification of cardiac valves ($P > 0.05$).

Conclusion: Cardiovascular diseases are common among hemodialysis patients. Hyperphosphatemia is a risk factor for the prevalence of left ventricular hypertrophy, left ventricular systolic dysfunction and calcification of the heart valves.

Keywords: Hyperphosphatemia, Hemodialysis patients, Valvular calcification, Left ventricular hypertrophy

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Introduction

Chronic renal failure (CRF) is an irreversible decline of renal function which finally leads to end-stage renal disease (ESRD). This condition is associated with renal replacement therapy including dialysis or transplantation (1). The annual rate of mortality from cardiovascular diseases in hemodialysis patients is around 9%, which is 30 times higher than that in general population (2). Ischemic heart diseases, atherosclerosis, myocardial dysfunction followed by heart failure, left ventricular hypertrophy and calcification of the heart valves are common diseases in hemodialysis patients (1,2). The high rates of cardiac complications in hemodialysis patients might be attributed to the higher prevalence of major risk factors among these patients, including high blood pressure, anemia, increased

blood volume, arteriovenous fistula, uremia, calcium and phosphorous imbalance and dyslipidemia. Other factors that are specifically related to hemodialysis patients and increase the rates of cardiovascular disease, included stress on myocardium caused by increased intravascular volume load, increase or decrease of trace elements that act as enzymatic factors and finally factors that inhibit myocardial ATPase (3,4). The progress of chronic kidney disease leads to the development of hyperphosphatemia, which increases the mortality. Hyperphosphatemia reduces serum levels of calcium via making a connection between calcium and phosphate and chronically inhibiting renal alpha-hydroxylase activity and reducing the synthesis of 1,25-dihydroxyvitamin D. The reduction of 1,25-dihydroxyvitamin D and calcium in the serum will

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■ Implication for health policy/practice/research/medical education

Hyperphosphatemia is a risk factor for the prevalence of left ventricular hypertrophy, left ventricular systolic dysfunction and calcification of the heart valves.

stimulate the parathyroid gland to secrete the parathyroid hormone (5). Acute or chronic hyperphosphatemia may cause metastatic calcification in people with normal or high levels of calcium (6).

Secondary hyperparathyroidism, which is characterized by elevated serum levels of parathyroid hormone, parathyroid gland hyperplasia, and imbalance of calcium and phosphorus metabolism, is common in hemodialysis patients. Parathyroid hormone is a uremic toxin causing renal osteodystrophy, calcification of the cardiovascular system and heart valves, changes in cardiovascular function and structure, immunodeficiency and anemia (7). Increased plasma levels of parathormone have been reported to increase the risk of hypertrophy and left ventricular failure in hemodialysis patients (1).

Objectives

It has been shown in various studies that calcium, phosphorus, and serum parathormone levels play a pivotal role in the progression of heart disease in hemodialysis patients. Therefore, the aim of this study was to investigate the prevalence of some cardiac diseases including calcification of the cardiac valves, left ventricular systolic and diastolic dysfunction, and left ventricular hypertrophy in hemodialysis patients. It was also aimed to determine their relationship with calcium, phosphorus, and serum parathormone levels and duration of hemodialysis.

Patients and Methods

Study population

This cross-sectional study was performed on patients with ESRD who were on regular hemodialysis 3 times a week for at least 6 months in Hajar hospital in Shahrekord, Iran. Exclusion criteria were: ages under 18 and over 80, past history of systolic heart failure and and coronary artery disease. First, general information such as name, age, weight, BMI, gender, duration of hemodialysis, frequency of hemodialysis per week, and history of cardiac risk factors were recorded using a questioner. Patients' blood samples were sent to the laboratory to determine the levels of calcium, phosphorus, intact parathormone (iPTH), and the ratio of blood urea nitrogen (BUN) to creatinine. The ratio of BUN to creatinine was measured pre- and post-dialysis. Echocardiography was conducted using an echocardiographic device (GE Vivid S6 ultrasound system). Echocardiographic findings including left ventricular systolic and diastolic function, left ventricular wall thickness and dimensions, and valvular heart disease

and calcification were recorded. It should be noted that patients were divided into three groups regarding of the duration of dialysis (6 months to 3 years, 3 to 5 years, and more than 5 years).

Ethical issues

This research was performed following the Declaration of Helsinki principles. The Ethics Committee of Shahrekord University of Medical Sciences approved the study (proposal # 1893). This article is extracted from general practitioner thesis of Parisa Irannejad. Informed consent was obtained and all information of patients was coded and kept confidential.

Statistical analysis

Laboratory and echocardiographic data including left ventricular systolic and diastolic function, left ventricular wall thickness and dimensions, and valvular heart disease and calcification were gathered. SPSS version 19 was used for data analysis. One-way analysis of variance (ANOVA) with post-hoc Tukey's test were used when appropriate. All results are expressed as mean and standard deviation (SD) and *P* value below 0.05 was considered significant.

Results

Of 100 studied patients, 64% were male. The mean age of the patients was 58.10 ± 15.51 years. Further details are presented in Table 1.

In this study we found, 71% of patients had mild left ventricular hypertrophy, 13% had moderate left ventricular hypertrophy, and 1% had severe left ventricular hypertrophy, while 15% of patients did not have left ventricular hypertrophy. We also found, no significant relationship of serum calcium and parathyroid hormone, with left ventricular hypertrophy; however, a significant relationship of serum phosphorus and left ventricular hypertrophy was detected (Table 2).

There was a significant difference in phosphorus levels

Table 1. Laboratory data and Echocardiographic findings of hemodialysis patients

Variable	Mean \pm SD
Pre-dialysis blood urea nitrogen (mg/dL)	68.10 \pm 18.64
Post-dialysis blood urea nitrogen (mg/dL)	21.94 \pm 7.21
Creatinine (mg/dL)	8.61 \pm 2.98
Calcium (mg/dL)	8.99 \pm 0.38
Phosphorus (mg/dL)	5.02 \pm 1.24
iPTH (pg/mL)	445.44 \pm 372.88
Late left ventricular filling velocity (A) (m/s)	0.86 \pm 0.29
Early left ventricular filling velocity (E) (m/s)	1.50 \pm 5.31
E/A ratio	0.94 \pm 0.49
Deceleration time (ms)	266.91 \pm 97.98
Deceleration slope (cm/s)	3.685 \pm 21.10

Table 2. Serum calcium, phosphorus, and parathormone levels in patients with and without left ventricular hypertrophy

	Left ventricular hypertrophy	Mean ± SD	P value
Calcium (mg/dL)	Normal	9.08 ± 0.38	0.21
	Mild left ventricular hypertrophy	8.95 ± 0.38	
	Moderate and severe left ventricular hypertrophy	9.10 ± 0.32	
iPTH (pg/mL)	Normal	498.60 ± 378.96	0.834
	Mild left ventricular hypertrophy	441.27 ± 376.47	
	Moderate and severe left ventricular hypertrophy	433.00 ± 336.87	
Phosphorus (mg/dL)	Normal	4.27 ± 0.67	0.028
	Mild left ventricular hypertrophy	5.13 ± 1.27	
	Moderate and severe left ventricular hypertrophy	5.30 ± 1.60	

between normal and mild left ventricular hypertrophy groups ($P=0.035$), however the difference between normal with moderate and severe left ventricular hypertrophy groups was slightly significant ($P=0.067$). Table 3 presents the data of left ventricular systolic and diastolic function in hemodialysis patients.

Accordingly, serum calcium and parathyroid hormone levels had no significant relationship with left ventricular

Table 3. Comparison of left ventricular systolic and diastolic function in patients undergoing hemodialysis

	No. (%)
Left ventricular systolic function	
Normal	58 (58)
Preserved function	16 (16)
Mild dysfunction	16 (16)
Moderate dysfunction	9 (9)
Severe dysfunction	1(1)
Left ventricular diastolic function	
Normal	13 (13)
Grade I dysfunction	81 (81)
Grade II dysfunction	4 (4)
Grade III dysfunction	2 (2)

Table 4. Serum calcium, phosphorus, and parathormone levels in patients with and without left ventricular systolic dysfunction

	Left ventricular systolic function	Mean ± SD	P value
Calcium (mg/dL)	Normal	8.96 ± 0.3552	0.35
	Preserved function	9.02 ± 0.3022	
	Mild dysfunction	9.13 ± 0.4801	
	Moderate to severe dysfunction	8.90 ± 0.4522	
iPTH (pg/mL)	Normal	463.07 ± 373.749	0.978
	Preserved function	472.50 ± 367.505	
	Mild dysfunction	359.45 ± 413.735	
	Moderate to severe dysfunction	434.00 ± 362.317	
Phosphorus (mg/dL)	Normal	4.84 ± 1.0005	0.01
	Preserved function	4.88 ± 1.1295	
	Mild dysfunction	5.63 ± 1.8304	
	Moderate to severe dysfunction	4.79 ± 1.2453	

systolic function. However, serum phosphorus levels had a significant relationship with left ventricular systolic function (Table 4). There was a significant difference in phosphate levels between normal and mild left ventricular systolic dysfunction groups ($P=0.014$) while no significant difference of mild systolic dysfunction and preserved left ventricular systolic function groups was observed ($P=0.097$) (Table 4). Moreover, serum calcium, phosphorus, and parathyroid hormone levels had no significant relationship with left ventricular diastolic dysfunction ($P>0.05$; Table 5).

Table 6 presents the data on the prevalence of aortic and mitral valves and their annulus calcification in hemodialysis patients. Common valvular abnormalities were mitral valve regurgitation (97%), followed by tricuspid, aortic and pulmonary regurgitation respectively.

Table 5. Serum calcium, phosphorus, and parathormone levels in patients with and without left ventricular diastolic dysfunction

	Left ventricular diastolic dysfunction	Mean ± SD	P value
Calcium (mg/dL)	Normal	8.98 ± 0.42	0.88
	Grade I	9.00 ± 0.38	
	Grade II	8.85 ± 0.26	
iPTH (pg/mL)	Grade III	8.95 ± 0.07	0.82
	Normal	413.23 ± 403.99	
	Grade I	461.26 ± 366.07	
Phosphorus (mg/dL)	Grade II	375.50 ± 459.81	0.71
	Grade III	654.00 ± 567.100	
	Normal	5.25 ± 1.21	
Phosphorus (mg/dL)	Grade I	4.97 ± 1.26	0.71
	Grade II	4.92 ± 0.89	
	Grade III	5.80 ± 1.69	

Table 6. Comparison of the heart valves calcification in hemodialysis patients

Calcification	Proportion (%)
Calcification of the aortic valve	20 (20)
Calcification of mitral valve	1 (1)
Calcification of mitral annulus	4 (4)
Mitral and aortic annulus calcification	6 (6)
Without calcification	69 (69)

Table 7. Serum calcium, phosphorus, and parathormone levels in patients with and without heart valve calcification

	Calcification	Mean \pm SD	P value
Calcium (mg/dL)	Aortic valve	9.07 \pm 0.41	0.084
	Mitral annulus	9.05 \pm 0.31	
	Mitral valve	8.50 \pm 0.17	
	Without calcification	9.01 \pm 0.36	
	Mitral and aortic annuluses calcification	8.60 \pm 0.33	
iPTH (pg/mL)	Aortic valve	413.30 \pm 325.25	0.501
	Mitral annulus	608.75 \pm 371.50	
	Mitral valve	173.00 \pm 0.00	
	Without calcification	452.97 \pm 391.77	
	Mitral and aortic annuluses calcification	556.17 \pm 351.300	
Phosphorus (mg/dL)	Aortic valve	5.00 \pm 1.35	0.784
	Mitral annulus	5.65 \pm 1.06	
	Mitral valve	6.00 \pm 0.00	
	Without calcification	4.99 \pm 1.261	
	Mitral and aortic annuluses calcification	4.86 \pm 0.88	

Table 8. Left ventricular wall thickness (mm) in hemodialysis patients

	<1 year	1-3 years	3-5 years	>5 years	P
IVSd(cm) ^a	1.1 \pm 0.28	1.15 \pm 0.181	1.16 \pm 0.17	1.1 \pm 0.011	0.49
LVPWd (cm) ^a	1 \pm 0.11	1.07 \pm 0.15	1.13 \pm 0.19	1.07 \pm 0.14	0.65

^a Values are presented as mean \pm SD.

We found, no significant relationship of serum calcium, phosphorus and parathyroid hormone with calcification of the valves (Table 7).

Table 8 shows the data of the end diastolic interventricular septum (IVSd) and left ventricular posterior wall thickness (LVPWd). We detected that diastolic interventricular septum (IVSd) and posterior wall thickness (LVPWd) had not significant relationship with the duration of dialysis ($P > 0.05$).

Discussion

Cardiovascular diseases account for 40%-50% of mortality rate among hemodialysis patients, which is approximately 3 to 10 times more than that among healthy counterparts of the same age (8,9).

In this study, we investigated the prevalence of echocardiographic findings in hemodialysis patients including calcification of cardiac valves, valvular disease, left ventricular systolic and diastolic dysfunction, and left ventricular hypertrophy in hemodialysis patients admitted to our hospital in Shahrekord. We also studied the relationship between above mentioned parameters with

serum calcium, phosphorus, and parathyroid hormone, and also with duration of hemodialysis.

In this study, aortic valve calcification, mitral valve calcification, and mitral annulus calcification were observed in 20%, 1%, and 4% of hemodialysis patients, respectively. In the study conducted by Jalali et al, mitral valve calcification and aortic valve calcification were observed in 3.9% and 1.9% respectively in hemodialysis patients, which were significantly lower than the values observed in our study (3). In another study by Avila-Diaz et al, the prevalence of mitral valve calcification, aortic valve calcification and calcification of both valves in hemodialysis patients were 26.3% 57.8%, and 15.8% respectively (10). The prevalence of aortic valve calcification in the study by Avila-Diaz et al was somewhat similar to our study, however, the prevalence of mitral valve calcification was significantly higher. This disparity, especially the difference in the prevalence of aortic valve calcification can be due to the disparities in the age of the studied patients. Moreover, in the present study, the calcification of the mitral valve and mitral annulus were described separately, while they are reported collectively in other studies.

In the present study, serum calcium and parathyroid hormone levels were not significantly associated with the calcification of the heart valves, but serum phosphorous levels had a significant positive relationship with the calcification of the heart valves. In addition, the duration of dialysis did not have a significant relationship with the heart valves calcification. According to some studies, the calcification of heart valves has a significant relationship with calcium, phosphorus, and parathormone levels while other studies have not reported such a relationship. In the study of Raggi et al in 2002, the severity of calcification of the heart valves had a relationship with the duration of dialysis and serum phosphorus and calcium levels (6). Moreover, Avila-Diaz et al concluded that serum parathyroid hormone level was a major risk factor for the calcification of heart valves and had a direct relationship with valve calcification (10). In the study of Mousavi-Movahed et al, no significant relationship between serum calcium and phosphorus levels with calcification of the heart valves was detected. However, the prevalence of hyperparathyroidism among hemodialysis patients was 77%, which it had a significant relationship with calcification of the heart valves (11). These differences can be due to the therapeutic effects of medications administered to the dialysis patients in various study groups.

In our cross-sectional study, we multiplied calcium by phosphorus in hemodialysis patients and the result was 44.95 mg²/dL². According to the study of Block et al, for every 10 units of Ca \times PO₄ product increase, the mortality rate of hemodialysis patients increased by 7% (12). In a study by Mills et al, Ca \times PO₄ product levels had a significant

positive relationship with the stenosis of the heart valves (13). In fact, increasing the level of $\text{Ca} \times \text{PO}_4$ product in plasma leads to calcium deposition in the heart valves and increases blood pressure, which in turn may increase the risk of narrowing and insufficiency of the heart valves (14). Therefore, it is recommended to maintain serum calcium-phosphorus levels of hemodialysis patients within the normal range of less than $42 \text{ mg}^2/\text{dL}^2$ to $55 \text{ mg}^2/\text{dL}^2$, to prevent the development and progression of cardiovascular diseases.

Of 100 hemodialysis patients, 71% had mild hypertrophy, 13% had moderate hypertrophy, and 1% had severe left ventricular hypertrophy. In the study of Yildiz et al, left ventricular hypertrophy in 69% of hemodialysis patients was observed. The reported prevalence is slightly lower than the prevalence observed in our study (15). Concerning the relationship between serum calcium, phosphorus, and parathyroid hormone with left ventricular hypertrophy, we found, left ventricular hypertrophy had no significant relationship with serum calcium and parathyroid hormone, though a significant positive relationship between serum phosphorus and left ventricular hypertrophy was detected. The risk factors associated with the prevalence of left ventricular hypertrophy are investigated by several studies (16-18). Some factors such as the duration of dialysis, age of patients, proportion of dialysis per week, and medical care after dialysis may affect the incidence of these disorders (3). In addition, the significant progress made in echocardiographic devices can be a cause of discrepancy between the results of various studies.

In the present study, pulmonary artery systolic pressure in a range of less than 35 mm Hg was observed in 59% of hemodialysis patients and pulmonary artery systolic pressure in a range of more than 35 mm Hg was observed in 41% of hemodialysis patients. In a study by Sedighi et al, the prevalence of pulmonary hypertension in hemodialysis patients was 44%, which is similar to the results of the present study (19).

In our study, 81% of hemodialysis patients were suffering from grade I, 4% from grade II, and 2% from grade III of left ventricular diastolic dysfunction. We also found, 26 persons (26%) had left ventricular systolic dysfunction. Jalali et al detected the prevalence of left ventricular dysfunction was estimated to be 18.4%, which is somewhat similar to our study (3). Concerning the relationship between serum calcium, phosphorus and parathyroid hormone levels and left ventricular systolic and diastolic dysfunction, we found serum calcium, phosphorus and parathyroid hormone levels had no significant relationship with left ventricular diastolic dysfunction. Serum calcium and parathyroid hormone levels had no significant positive relationship with left ventricular systolic dysfunction, but serum phosphorus level had a significant relationship with left ventricular systolic dysfunction. Duration of dialysis had no significant relationship with left ventricular

systolic and diastolic dysfunction.

Conclusion

Hyperphosphatemia was a risk factor for the prevalence of left ventricular hypertrophy, left ventricular systolic dysfunction, and calcification of the heart valves.

Limitations of the study

This study was a single center investigation, with a limited proportion of hemodialysis patients. We suggest larger multi-centric studies on this aspect of hemodialysis patients.

Authors' contribution

SM, MF and PI contributed to the study design and gathered the patients and their data. AN conducted all echocardiography of patients. MB conducted the analysis of data. SM, PI, MRT and MF prepared the primary draft. SM and MB prepared final revision. All authors read and approved the paper.

Conflicts of interest

The authors declare that they do not have any conflicts of interest.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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