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Original Article

Relationship between Calcium-Phosphorus Product and Severity of Valvular Heart Insufficiency in Patients Undergoing Chronic Hemodialysis

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Abstract

Background: *Recent interests have mainly focused on the roles of serum calcium and phosphorus and their product (Ca-P product) in the development of valvular heart disease. The present study assessed the relationship between the Ca-P product and the severity of valvular heart disease in end-stage renal disease (ESRD) patients undergoing chronic hemodialysis.*

Methods: *This cross-sectional study reviewed the clinical course of 72 consecutive patients with the final diagnosis of ESRD candidated for chronic hemodialysis. The severity of valvular heart disease was determined using M-mode two-dimensional echocardiography. The serum calcium and phosphate values adopted were those values measured on the day between the two consecutive dialyses, and the Ca-P product was calculated.*

Results: *The most common causes of ESRD were diabetic nephropathy, malignant hypertension, and chronic glomerulonephritis. The mean Ca-P product level in the dialysis patients was 50.44 ± 17.78 mg2/dL2. The receiver-operator characteristic (ROC) curve illustrated that a Ca-P product level > 42 mg2/dL2 was the optimal value in terms of sensitivity and specificity for predicting the presence of valvular insufficiency. Aortic insufficiency was directly associated with a high Ca-P product value after adjustment for age, gender, serum albumin, diabetes, hypertension, hyperlipidemia, coronary artery disease, and serum creatinine (β = 0.412, SE = 158, p value= 0.011).*

Conclusion: *A positive relationship between the Ca-P product value and the severity of aortic insufficiency is expected. Achieving an appropriate control of the Ca-P product level may decrease aortic valve calcification and improve the survival of patients on chronic hemodialysis.*

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Keywords: *Heart valve disease • Renal dialysis • Kidney failure • Calcium • Phosphorus*

Introduction

Association between change in some serum chemical biomarkers such as serum phosphorous, calcium, and their product (Ca-P product) and increased cardiovascular morbidity and mortality in end-stage renal disease (ESRD) patients undergoing chronic dialysis has been described.[1] Recently, interest has mainly focused on the roles of serum calcium and phosphorus and their abnormalities in the development of valvular heart disease.[2] Meanwhile, valvular dysfunction related to abnormal calcium and phosphate

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metabolism, especially following chronic dialysis, is regarded as a strong and independent predictor of an adverse clinical outcome, including an increased risk of death and a need for valve replacement.[3] Calcium deposits in the cardiovascular system have been also suggested as a serious problem in patients on chronic dialysis in that they can lead to a high prevalence of aortic valve calcification.[4-6] Additionally, it has been indicated that phosphate elevation may aggravate the effects of coronary atherosclerosis through increased vascular calcification.[7, 8] However, usefulness of the Ca-P product index as a determinant of the valvular heart disease severity has been questioned. Some studies have managed to find higher levels of this product in patients with mitral annular calcium,[9] while some others have failed to obtain such findings.[10]

The present study assessed the relationship between the Ca-P product and the severity of valvular heart disease in ESRD patients undergoing chronic dialysis.

Methods

This cross-sectional study reviewed the clinical course of 72 consecutive patients with the final diagnosis of ESRD who underwent chronic hemodialysis in Shafa Hospital between June 1996 and June 2003. Chronic dialysis was defined as the receipt of dialysis for at least 90 days.[11] The study was reviewed and approved by the Review Board of Kerman University of Medical Sciences. All the studied patients were on maintenance hemodialysis for a mean time of 29.11 months (range: 1 to 120 months) on thrice-weekly 3 to 4 hours of standard bicarbonate hemodialysis, with a prescribed urea reduction > 65% in accordance with the standard protocol.[12]

The severity of valvular heart disease was determined using M-mode two-dimensional echocardiography. Valvular insufficiency was classified as normal (grade 0), trivial (grade 1), mild (grade 2), moderate (grade 3), and severe (grade 4).[13] Echocardiography was performed in keeping with the recommendations of the American Society of Echocardiography[14] and was analyzed by a single experienced cardiologist. Serum biomarkers were measured < 3 months after echocardiography using standard assays. Serum total calcium was measured with ortho-cresolphthalein complexone (o-CPC) and inorganic phosphate via the molybdenum blue method (Zist-Shimi Inc., Tehran, Iran) using an LKB spectrophotometer (Biochrom, Cambridge, UK). The serum calcium and phosphate values adopted were those values measured on the day between the two consecutive dialyses, and the Ca-P product was calculated. The other measured laboratory parameters were serum triglyceride and total cholesterol levels, serum creatinine, fasting blood sugar, and serum hemoglobin. The daily oral intakes of the drugs were also noted.

General demographic variables such as gender, age, cause of renal failure, time on hemodialysis, and serum creatinine level were used as confounders in subsequent analyses for the determination of the relationship between the Ca-P product and the severity of valvular disease. The results were expressed as mean ± SD for the quantitative variables and percentages for the categorical variables. The categorical variables were compared between the groups using the chi-square test. A cumulative logit model for determining the relationship between the severity of valvular heart disease and the Ca-P product and the presence of confounders was also employed. The optimal Ca-P product cut-off point, associated with the absence of valvular disease, was assessed using the receiver-operator characteristic (ROC) curve. The best discrimination limit for the Ca x P level was determined at the maximum of the Youden index: J = sensitivity + specificity – 1 (Rufino 2003). A multivariable linear regression analysis was utilized to evaluate the relationship between the Ca × P measurement and the aortic insufficiency severity. p values of 0.05 or less were considered statistically significant. All the statistical analyses were performed using SPSS version 13.0 (SPSS Inc., Chicago, IL, USA).

Results

The mean age of the studied patients was 52.17 ± 15.12 years (range: 22 to 90 years), and 58.3% of them were male. The most common causes of ESRD were diabetic nephropathy, malignant hypertension, and chronic glomerulonephritis (Figure 1).

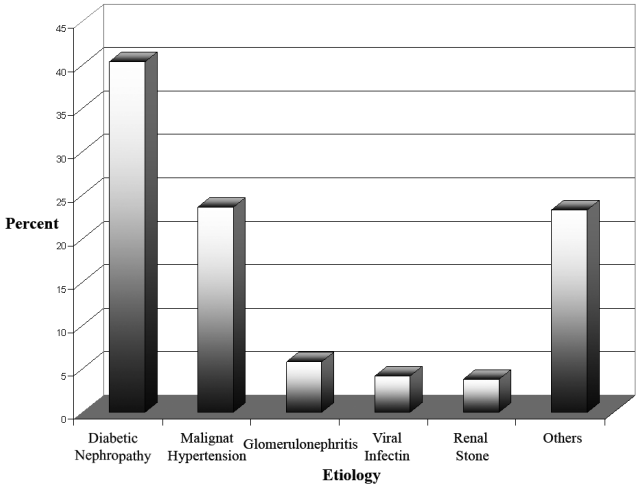

Figure1. Causes of end-stage renal disease in the studied patients

Etiology in 15.3% of the patients was also unknown. Regarding medical history, 58.3% of the patients were hypertensive and 40.3% of them had diabetes mellitus. Also, hyperlipidemia was observed in 13.9% of the subjects, and 23.6% of the studied cases suffered from

coronary artery disease, which was assessed on the basis of electrocardiography changes as well as the echocardiography report of wall motion abnormality. The biochemical data are presented in Table 1. More than two thirds of the patients had a serum calcium value lower than 9.5 mg/dl, and the serum PO_4 level in 52 patients was higher than 4.5 mg/dl, resulting in a calcium-phosphate product higher than 42 in 72.2% of the patients. With regard to oral medications within chronic hemodialysis (Table 2), common drugs administered were folic acid, calcium carbonate, beta-blockers, and angiotensin-converting enzyme (ACE) inhibitors. The echocardiographic data are summarized in Table 3. The mean left ventricular ejection fraction (LVEF) was 48.39 ± 11.43%, and the majority of the patients had an EF between 40 and 55%. Pericardial effusion was reported in 31.9% of the patients. Mild insufficiency was the most common finding among three types of valves. None of the patients had severe aortic insufficiency. Multiple valvular diseases were observed in 29.1% of the patients, and 6.9% of them suffered from triple valvular disease.

Table 1. Biochemical data of patients undergoing chronic dialysis (n = 72)*

Calcium (mg/dl)	9.16±1.31
Calcium > 9.5 (mg/dl)	22 (30.6)
Phosphorus (mg/dl)	5.47±1.74
Phosphorus > 4.5 (mg/dl)	52 (72.2)
Calcium-Phosphorus product (mg^2/dL^2)	50.44±17.78
Urea (mg/dl)	138.82±50.15
Creatinine (mg/dl)	8.59±2.68
Triglyceride (mg/dl)	140.70±78.73
Cholesterol (mg/dl)	143.42±43.46
Hemoglobin (mg/dl)	10.05±2.08
Fasting blood sugar (mg/dl)	140.00±72.37

*Data are presented as mean ± SD
Numbers in the parentheses are the related percentages

Table 2. Oral medications in patients undergoing chronic dialysis (n = 72)

Folic acid	57 (79.2)
Calcium carbonate	46 (63.9)
Beta-blockers	36 (50.0)
ACE-inhibitors	33 (45.8)
Diuretics	19 (26.4)
Calcium-blockers	14 (19.4)
Glibenclamide	14 (19.4)
Insulin	10 (13.9)
Nitrates	10 (13.9)
Digoxin	4 (5.6)

Numbers in the parentheses are the related percentages
ACE, Angiotensin-converting enzyme

The mean Ca-P product level in the dialysis patients was 50.44 ± 17.78 mg^2/dL^2. The ROC curves illustrated that a Ca-P product > 42 mg^2/dL^2 was the optimal value in terms of sensitivity and specificity for predicting the presence of valvular insufficiency in our population.

Table 3. Echocardiographic findings in patients undergoing chronic dialysis (n = 72)

Pericardial effusion	23 (31.9)
Left ventricular hypertrophy	52 (72.2)
Left atrial hypertrophy	6 (8.3)
Wall motion abnormality	20 (27.8)
Valvular diseases	
Single valve	33 (45.8)
Two valves	16 (22.2)
Three valves	5 (6.9)
Mitral insufficiency	
Mild	22 (30.6)
Moderate	17 (23.6)
Severe	5 (6.9)
Aortic insufficiency	
Mild	14 (19.4)
Moderate	5 (6.9)
Severe	0 (0.0)
Tricuspid insufficiency	
Mild	8 (11.1)
Moderate	8 (11.1)
Severe	1 (1.4)

Numbers in the parentheses are the related percentages

Table 4. Relationship between calcium-phosphorus product and the severity of valvular defects in patients undergoing chronic dialysis (n = 72)

Insufficiency severity	Normal	Mild	Moderate	Severe	p value
Aorta					
Ca × P ≤ 42 mg^2/dl^2	40 (76.9)	11 (21.2)	1 (1.9)	0	0.025
Ca × P > 42 mg^2/dl^2	13 (65.0)	3 (15.0)	4 (20.0)	0	
Mitral					
Ca × P ≤ 42 mg^2/dl^2	8 (40.0)	5 (25.0)	6 (30.0)	1 (5.0)	0.821
Ca × P > 42 mg^2/dl^2	20 (38.5)	17 (32.7)	11 (21.2)	4 (7.7)	
Tricuspid					
Ca × P ≤ 42 mg^2/dl^2	14 (70.0)	4 (20.0)	2 (10.0)	0	0.469
Ca × P > 42 mg^2/dl^2	41 (78.8)	4 (7.7)	6 (11.5)	1 (1.9)	

Numbers in the parentheses are the related percentages
Ca, Calcium; P, Phosphorus

Table 5. Relationship between measurement of Calcium-Phosphorus (Ca-P) product and severity of aortic insufficiency with the presence of cofounders

Variable	β	Standard Error	p value
Ca-P product	0.412	0.158	0.011
Male gender	-0.177	0.147	0.232
Age	0.001	0.005	0.977
Serum albumin	-0.014	0.035	0.699
Diabetes	0.079	0.162	0.626
Hypertension	0.150	0.156	0.341
Hyperlipidemia	0.127	0.227	0.578
Coronary artery disease	0.146	0.188	0.440
Serum creatinine	0.031	0.028	0.279

R square: 0.179

Aortic insufficiency was directly associated with the severity of the Ca-P product value, so that insufficiency was more severe in Ca-P products > 42 mg^2/dL^2 than in those with lower values. Aortic insufficiency was also directly associated with a high Ca-P product value after adjustment for age, gender, diabetes, hypertension, hyperlipidemia, coronary artery disease, and serum creatinine ($\beta = 0.412$, SE = 0.158, p value = 0.011) (Tables 4 and 5). However, this product was not significantly associated with the severity of other valves insufficiency.

Discussion

This study shows that the dialysis patients with a Ca-P product measurement > 42 mg^2/dL^2 had more severe aortic insufficiency than did the other patients. Most of the similar studies hitherto published have underscored the value of the Ca-P product in predicting cardiac events and even sudden cardiac death. One study found that the relative risk of sudden death was strongly associated with an elevated level of the Ca-P product.[15] It was also shown that the ESRD patients with Ca-P products > 72 mg^2/dL^2 had a relative mortality risk of 1.34 relative to those with products of 42 to 52 mg^2/dL^2 and, therefore, higher levels of the Ca-P product could beget substantial morbidity and mortality seen in ESRD patients.[16] Elsewhere, it was demonstrated that for every 10 higher units of the Ca-P product, the relative risk of sudden death increased by 7%.[15]

Calcification of the aortic valve has been clearly described and is regarded as the potential mechanism through which elevated serum PO4 may contribute to these causes of death.[17] It seems that high morbidity due to the severity of aortic insufficiency can be related to Ca-P product elevation and valvular calcification. Previous findings were mainly focused on the association between aortic stenosis and this product, whereas our study obtained this positive relationship between the aortic valve insufficiency and the Ca-P product measurement. As is shown in the Mills et al. study, the Ca-P product is associated with the severity of aortic stenosis in dialysis patients as measured by the aortic valve area and transvalvular gradients.[18] Potential effects of elevated Ca-P products on the aortic valve insufficiency can be explained by two mechanisms. Firstly, accelerated calcium deposition on the aortic valve, which is commonly observed following chronic dialysis, can be the responsible factor for the induction of aortic valve insufficiency.[19] Secondly, the role of protruding calcium deposits in the augmentation of the rest flow velocity across the aortic valve is thought to give rise to aortic valve calcification, especially in hypertensive patients.[20] Huting et al. observed that valve calcification was simultaneously associated with the severity of predialysis hypertension and high levels of the Ca-P product.[21] A causal link between hypertension and aortic valve disease has also been shown in animal studies.[22] Given that most of our studied patients suffered from primary hypertension or diabetes-related hypertension, aortic insufficiency following aortic valve calcification may be due to the progression of the complications of hypertension.

Our findings also showed that the optimal cut-off point for the Ca-P product measurement for predicting the severity of aortic insufficiency was 42 mg^2/dL^2. This discrimination level was different in other studies. Movilli et al. obtained a break point of 55 mg^2/dL^2 for an optimal Ca-P product discrimination value.[23] Rufino et al. illustrated that a Ca-P product level > 43 mg^2/dL^2 was the optimal value in terms of sensitivity and specificity for predicting the presence of valvular calcification in their patient population. [12] Obtaining a lower cut-off point highlights the importance of this product for discriminating valvular disease, and our study is a case in point for this significance. Be that as it may, this lower threshold may be related to the exclusion of those with severe aortic insufficiency in the current study.

In our study, the mean Ca-P product level in the dialysis patients was 50.44 ± 17.78 mg^2/dL^2. Other related studies have found different means of Ca-P product levels such as 57 ± 19 in one study[15] and 34.7 ± 6.3 mg^2/dL^2 in another one.[24] In the Qunibi et al. study, this parameter was 59 ± 6 mg^2/dL^2.[25]

Our findings, in comparison with those reported by other studies, showed a better control of serum calcium and phosphorus levels and, therefore, Ca-P product measurements in our patients. Therefore, this marker can facilitate the prediction of appropriate outcome and low cardiac events, especially aortic insufficiency-related morbidity, in patients on maintenance hemodialysis.

Conclusion

Based on the present study, we found a positive relationship between the Ca-P product value and the severity of aortic insufficiency. Consequently, to prevent aortic insufficiency progression and its co-morbidities, a measurement of the serum Ca-P product level in ESRD patients undergoing chronic dialysis can be valuable. Thus, achieving an appropriate control level of the Ca-P product may decrease aortic valve calcification and improve the survival of patients on chronic hemodialysis.

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