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 candidate 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 mg\textsuperscript{2}/dL\textsuperscript{2}. The receiver-operator characteristic (ROC) curve illustrated that a Ca-P product level > 42 mg\textsuperscript{2}/dL\textsuperscript{2} 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.

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.\textsuperscript{1} Recently, interest has mainly focused on the roles of serum calcium and phosphorus and their abnormalities in the development of valvular heart disease.\textsuperscript{2} Meanwhile, valvular dysfunction related to abnormal calcium and phosphate...
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: \(J = \text{sensitivity} + \text{specificity} – 1\) (Rufino 2003). A multivariable linear regression analysis was utilized to evaluate the relationship between the Ca x 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).

![Figure 1. Causes of end-stage renal disease in the studied patients](image-url)

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)*

| Parameter                  | Value          |
|----------------------------|----------------|
| 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)

| Medication          | Value (n)       |
|---------------------|----------------|
| 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)

| Condition                      | Value (n) | Percentage |
|--------------------------------|-----------|------------|
| 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)

| Variable | Insufficiency | 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 | 0.025 |
| 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) | 0.821 |
| Tricuspid| Ca × P ≤ 42 mg^2/dL^2 | 14 (70.6) | 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) | 0.469 |

Numbers in the parentheses are the related percentages

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 mg²/dL² 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 (β = 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 mg²/dL² 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. It was also shown that the ESRD patients with Ca-P products > 72 mg²/dL² had a relative mortality risk of 1.34 relative to those with products of 42 to 52 mg²/dL² and, therefore, higher levels of the Ca-P product could beget substantial morbidity and mortality seen in ESRD patients. Elsewhere, it was demonstrated that for every 10 higher units of the Ca-P product, the relative risk of sudden death increased by 7%. 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. 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. 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. 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. Huting et al. observed that valve calcification was simultaneously associated with the severity of predialysis hypertension and high levels of the Ca-P product. A causal link between hypertension and aortic valve disease has also been shown in animal studies. 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 mg²/dL². This discrimination level was different in other studies. Movilli et al. obtained a break point of 55 mg²/dL² for an optimal Ca-P product discrimination value. Rufino et al. illustrated that a Ca-P product level > 43 mg²/dL² was the optimal value in terms of sensitivity and specificity for predicting the presence of valvular calcification in their patient population. 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 mg²/dL². Other related studies have found different means of Ca-P product levels such as 57 ± 19 in one study and 34.7 ± 6.3 mg²/dL² in another one. In the Qunibi et al. study, this parameter was 59 ± 6 mg²/dL². 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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References

1. Egbuna OL, Taylor JG, Bushinsky DA, Zand MS. Elevated calcium phosphate product after renal transplantation is a risk factor for graft failure. Clin Transplant 2007;21:558-566.

2. Rasoul M, Kiasari AM. Serum calcium and phosphorus associate with the occurrence and severity of angiographically documented coronary heart disease, possibly through correlation with arterogenic (apo)lipoproteins. Clin Chem Lab Med 2006;44:43-50.

3. Rosenhek R, Binder T, Porena G. Predictors of outcome in severe, asymptomatic aortic stenosis. N Engl J Med 2000;343:611-617.

4. Ohara T, Hashimoto Y, Matsumura A, Suzuki M, Isobe M. Accelerated progression and morbidity in patients with aortic stenosis on chronic dialysis. Circ J 2005;69:1535-1539.

5. Mills WR, Einstadter D, Finkelhor RS. Relation of calcium-phosphorus product to the severity of aortic stenosis in patients with normal renal function. Am J Cardiol 2004;94:1196-1198.

6. McFalls EO, Archer SL. Rapid progression of aortic stenosis and secondary hyperparathyroidism. Am Heart J 1990;120:206-208.

7. Schwarz U, Buzello M, Ritz E, Stein G, Raabe G, Wiest G, Mall G, Amann K. Morphology of coronary atherosclerotic lesions in patients with end-stage renal failure. Nephrol Dial Transplant 2000;15:218-233.

8. Amann K, Ritz E. Microvascular disease: the Cinderella of uremic heart disease. Nephrol Dial Transplant 2000;15:1493-1503.

9. Nair CK, Sudhakaran C, Aronow WS, Thomson W, Woodruff MP, Sketch MH. Clinical characteristics of patients younger than 60 years with mitral annular calcium: comparison with age- and sex-matched control subjects. Am Heart J 1984;54:1286-1287.

10. Aronow WS, Ahn C, Kronzon I. Association of mitral annular calcium with symptomatic peripheral arterial disease in older persons. Am J Cardiol 2001;88:333-334.

11. Wald R, Quinn RR, Luo J, Li P, Scales DC, Marmadani MM, Ray JG; University of Toronto Acute Kidney Injury Research Group. Chronic dialysis and death among survivors of acute kidney injury requiring dialysis. JAMA 2009;302:1179-1185.

12. Rufino M, García S, Jiménez A, Alvarez A, Miquel R, Delgado P, Marrero D, Torres A, Hernández D, Lorenzo V. Heart valve calcification and calcium x phosphorus product in hemodialysis patients: analysis of optimum values for its prevention. Kidney Int Suppl 2003;85:115-118.

13. Lange R, Cleuziou J, Hörer J, Holper K, Vogt M, Tassani-Prell P, Schreiber C. Risk factors for aortic insufficiency and aortic valve replacement after the arterial switch operation. Eur J Cardiothorac Surg 2008;34:711-717.

14. Tarrass F, Benjelloun M, Zamd M, Medkouri G, Hachim K, Benghanem MG, Ritz E. Heart valve calcifications in patients with end-stage renal disease: analysis for risk factors. Nephrology (Carlton) 2006;11:494-496.

15. Ganesh SK, Stack AG, Levin NW, Hulbert-Shearon T, Port FK. Association of elevated serum PO(4), Ca x PO(4) product, and parathyroid hormone with cardiac mortality risk in chronic hemodialysis patients. J Am Soc Nephrol 2001;12:2131-2138.

16. Block GA, Hulbert-Shearon TE, Levin NW, Port FK. Association of serum phosphorus and calcium x phosphate product with mortality risk in chronic hemodialysis patients: a national study. Am J Kidney Dis 1998;31:607-617.

17. London GM, Pannier P, Marchais SJ, Guerin AP. Calcification of the aortic valve in the dialyzed patient. J Am Soc Nephrol 2000;11:778-783.

18. Mills WR, Einstadter D, Finkelhor RS. Relation of calcium-phosphorus product to the severity of aortic stenosis in patients with normal renal function. Am J Cardiol 2004;94:1196-1198.

19. Fujise K, Amerling R, Sherman W. Rapid progression of mitral and aortic stenosis in a patient with secondary hyperparathyroidism. Br Heart J 1993;70:282-284.

20. Tenenbaum A, Fisman EZ, Schwammenthal E, Adler Y, Shemesh J, Sherer Y, Motro M. Aortic valve calcification in hypertensive patients: prevalence, risk factors and association with transvalvular flow velocity. Int J Cardiol 2004;94:7-13.

21. Hütting J. Mitral valve calcification as an index of left ventricular dysfunction in patients with end-stage renal disease on peritoneal dialysis. Chest 1994;105:383-388.

22. Cuniberti LA, Stutzbach PG, Guevara E, Yannarelly GG, Laguens RP, Favaloro RR. Development of mild aortic valve stenosis in a rabbit model of hypertension. J Am Coll Cardiol 2006;47:2303-2309.

23. Movilli E, Feliciani A, Camerini C, Brunori G, Zubani R, Scolari F, Parrinello G, Cancarini GC. A high calcium-phosphate product is associated with high C-reactive protein concentrations in hemodialysis patients. Nephron Clin Pract 2005;10:161-167.

24. Menon V, Greene T, Pereira AA, Wang X, Beck GJ, Kusek JW, Collins AJ, Levey AS, Sarnak MJ. Relationship of phosphorus and calcium-phosphorus product with mortality in CKD. Am J Kidney Dis 2005;46:455-463.

25. Qunibi WY, Nolan CA, Ayus JC. Cardiovascular calcification in patients with end-stage renal disease: a century-old phenomenon. Kidney Int Suppl 2002;82:73-80.