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# The Association of Calcium-Phosphorus Product With the Severity of Cardiac Valves Failure in Patients Under Chronic Hemodialysis

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## Abstract

**Background:** Recent studies have mainly focused on the roles of serum calcium and phosphorus product in the development of valvular heart failure. We determined the association of calcium-phosphorus product with the severity of heart valve failure in patients under chronic hemodialysis (being under hemodialysis for 6 months or more) in Boo-Ali Hospital in 2012 and 2013.

**Methods:** It was a cross-sectional, descriptive, comparative study. Thirty-three patients undergoing chronic hemodialysis were recruited to the study. All the patients were hospitalized at Boo-Ali Hospital. The study was done in a 2 years long time frame and the association of calcium-phosphorus product and severity of heart valve failure was evaluated among them.

**Results:** The results demonstrated that there was no significant association between age, gender, renal failure cause and hemodialysis duration ($P > 0.05$). Our results showed a negative correlation between the severity of cardiac valves failure and CA × P level. It was not a meaningful correlation though ($P > 0.05$).

**Conclusions:** Based on the obtained results, it is concluded that there is not any association between calcium-phosphorus product and the severity of heart valve failure in patients under chronic hemodialysis.

**Keywords:** Calcium; Phosphorus; Heart valve; Renal dialysis

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## Introduction

The prevalence of cardiac valve calcification (VC) is high in chronic renal failure (CRF) patients who are under hemodialysis. The prevalence of VC is eight times greater in patients under hemodialysis than the normal population [1]. This will eventually evolve into serious dysfunctions and will be life threatening [2]. Myocardial and coronary calcifications are also observed in CRF patients [3]. CRF is a compromising and dangerous problem which can be caused by many different causes. Diabetes mellitus (DM), chronic hypertension (HTN), obstructive uropathy, congenital and acquired cystic kidney disease (ACKD) complications, glomerulonephritis (GN) and urinary tract infection (UTI) are the main causes of CRF; however, 30% of the cases are idiopathic [4]. The only definite treatment for CRF is kidney transplantation but due to transplantation costs and also the small amounts of possible donors, other maintaining treatments need to be done. Peritoneal dialysis and hemodialysis are the treatments available. These have their own complications and side effects [5]. The adverse effects may be more than the benefits in some patients, especially the older ones [6]. The patients undergoing dialysis experience a poor life quality which is due to both the length of the treatment and the adverse effects [7]. One of the main disadvantages of the hemodialysis is its cardiovascular side effects. In 38.4% of the patients, this will show up as cardiac VC [8]. Several factors have been thought to cause this high rate of VC in hemodialysis patients. The mechanical stress and inflammation caused by the invasive process itself may be a factor in developing calcified valves [1]. High levels of CA × P products and dyslipidemia are also other candidates for the cause of calcified valves [8-10]. High phosphate levels have been observed in the end-stage renal failure patients and it is a prevalent problem. Forty percent of the patients under hemodialysis in US have phosphate level higher than normal range [10]. It is believed that high phosphate levels can start chain reactions leading to secondary hyperparathyroidism. It is the calcification of soft tissues and some other processes leading to cutaneous calciphylaxis. Studies show that high phosphate levels are independently associated with mortality rate in hemodialysis patients. It was also indicated that higher amount of CA × P may increase the mortality rate [10]. These findings started a new trend in the world with

this question: How does the elevated CA × P level contribute to higher mortality rates? Some answer the question by linking this to the speculation that elevated phosphate will cause smooth muscle proliferation and VC, so by constricting the coronary arteries, it will aid the atherosclerosis process [11]. Others think that phosphate will cause this high mortality rate by myocardial calcification [12]. The association of high CA × P product and calcification of heart valves is not a clear issue in current literature. This is a probable hypothesis but we did not find practical data supporting this.

We designed this study to see if there are any associations between high CA × P products level and the existence and intensity of cardiac VC in CRF patients under hemodialysis treatment. We tried to answer this question: Is there a relation between high levels of CA × P products with cardiac VC?

## Materials and Methods

It was a descriptive cross-sectional study in Boo-Ali Hospital in Tehran, Iran from 2011 to 2013. After the confirmation of local health authorities and obtaining a permit from the local ethical committees, 33 consecutive patients with end-stage renal disease (ESRD) were recruited to the study. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki. At the baseline, they were interviewed, the study was explained to them completely and signed consents were obtained from the patients. Inclusion criterion was defined as if the patient was responsive and oriented while diagnosed with ESRD. All patients were on thrice-weekly 3.5 - 4.5 h of standard bicarbonate hemodialysis, with a prescribed urea reduction of 65% [8]. Patients under hemodialysis for less than 6 months were excluded. Blood samples were obtained from the patients and were sent for laboratory tests the day between two consecutive dialyses. P and CA levels were evaluated and recorded for each patient. The presence and intensity of heart VC was evaluated using 2D echocardiography performed by a qualified cardiologist. Valvular insufficiency was classified as normal (grade 0), trivial (grade 1), mild (grade 2), moderate (grade 3), and severe (grade 4) [13]. Serum total calcium was measured with ortho-cresolphthalein complexone (oCPC) and inorganic phosphate via the molybdenum blue method (Zist-Shimi Inc., Tehran, Iran) using an LKB spectrophotometer (Biochrom, Cambridge, UK). All of the costs were on the authors and the patients did not pay anything during the study. The sample was divided into two groups; NL group had normal CA × P levels and ANL group had abnormal CA × P levels. Then the acquired data were sent to a biostatistician for analyses. Abundance and percentage were calculated for qualitative variables. For quantitative variables, mean and standard deviation were calculated. Fisher test and Chi-square tests were used for analyses and P value lower than 0.05 was defined as significantly meaningful.

**Table 1.** Gender Frequency

| | Sex | | Total |
|---|---|---|---|
| | M | F | |
| CA × P | | | |
| NL | 13 | 13 | 26 |
| ANL | 4 | 3 | 7 |
| Total | 17 | 16 | 33 |

NL: normal; ANL: abnormal.

## Results

Thirty-three people were recruited into this study. Of these 33, 17 (51.5%) were males and 16 (48.5%) were females. Of these 33 patients, seven (21.21%) had abnormal CA × P levels (ANL group) and 26 (78.79%) had normal CA × P levels (NL group). Complete data regarding sexual distribution can be found at Table 1.

Regarding the cause of renal failure, DM had the highest portion with 30.3%. Other causes and their abundance can be found at Table 2.

There were not any significant differences regarding age, hemodialysis duration and CA between the groups ($P > 0.05$).

The intensity of cardiac valve failure was not significantly different between the groups ($P > 0.05$). Five patients had calcifications. The complete set of data regarding severity of cardiac valves failure can be found at Table 3.

Patients' gender did not have any meaningful relation with the severity of cardiac heart valves failure ($P > 0.05$). Renal failure cause, age, CA and P were not related to the severity of cardiac valves failure ($P > 0.05$) (Table 4).

CA × P was 38.68 $mg^2/dL^2$ for NL group and 66.32 $mg^2/dL^2$ for abnormal group.

Mean hemodialysis duration, mean CA level and mean P level were higher in patients with cardiac valves failure but the

**Table 2.** Renal Failure Causes in the Patients

| | Renal failure causes | | | | | | Total |
|---|---|---|---|---|---|---|---|
| | PCKD | DM | HTN | > 1 | Others | Unknown | |
| CA × P | | | | | | | |
| NL | 1 | 8 | 4 | 8 | 3 | 2 | 26 |
| ANL | 1 | 2 | 3 | 0 | 1 | 0 | 7 |
| Total | 2 | 10 | 7 | 8 | 4 | 2 | 33 |

NL: normal; ANL: abnormal; PCKD: polycystic kidney disease; DM: diabetes mellitus; HTN: hypertension; > 1: more than one cause.

**Table 3.** Severity of Cardiac Valves Failure

| | Severity of cardiac valves failure | | | | Total |
|---|---|---|---|---|---|
| | NL | Trivial | Mild | Moderate | |
| CA × P | | | | | |
| NL | 8 | 2 | 12 | 4 | 26 |
| ANL | 3 | 1 | 2 | 1 | 7 |
| Total | 11 | 3 | 14 | 5 | 33 |

NL: normal; ANL: abnormal.

differences were not meaningful (P > 0.05).

## Discussion

Based on what mentioned before, in patients under hemodialysis, cardiovascular diseases are one of the inevitable adverse effects. Calcification of the cardiac valves is one of the many cardiovascular complications that can happen alongside hemodialysis. As we hypothesized, it can be due to fluctuation and elevation in CA × P products level in the serum. This study tried to evaluate this hypothesis and found that there is no significant relation between these. People in normal group had a higher mean of age but it was not significant. It shows that the myth which says elders are more prone to valve complications is relatively wrong. In our results, we found that patients with more CA × P had less cardiac valve problems and complications; however, this was not a significant thing. In a paper by Block, it is suggested that there is a meaningful negative correlation between CA × P products level and the prognosis of the hemodialysis patient. Block also suggested that patients with CA × P lower than 55 $mg^2/dL^2$ may face a better prognosis. It is also recommended that with a better CA intake, we can force this elevation and as a consequence lower the mortality rate [14].

A study done by Qunibi et al published in 2002, they concluded that controlling CA × P level will result in less calcification of the cardiac valves .They suggest that people with lower CA × P levels have better prognosis compared to the ESRD patients with higher CA × P products level [15]. We did not find a meaningful correlation in our study regarding this issue.

In a study by Raggi et al, it was indicated that the severity of VC has a positive correlation with CA × P levels in patients under hemodialysis [16]. Our results lack enough evidence to support Raggi's conclusion. Compared to us, they had a bigger sample size and this lack of evidence can be attributed to this. As we emphasized on the patients referring to one hospital, we could not recruit more patients because of unavailability. Maybe it is better to perform another study in multiple hospitals or in a national wide scale.

In a cross-sectional study done by Kahnooj et al in Turkey, they recruited 72 ESRD patients to the study. It was demonstrated that the severity of VC in hemodialysis patients is significantly related to CA × P level. They found that in the patients with CA × P more than 42 $mg^2/dL^2$, the severity of VC is relatively higher, so the prognosis is poor [17]. Once again our results cannot confirm this, because we observed a non-meaningful negative correlation.

In another study by Ribeiro et al done in Portugal, 92 hemodialysis patients were compared to 92 healthy people regarding cardiac VC and CA × P levels. They found that aortic and mitral VC is more prevalent among hemodialysis patients. They also found a meaningful positive correlation between aortic and mitral VC and CA × P levels. They suggest that it is necessary to monitor CA metabolites level in renal failure patients [18].

Based on our results, we cannot confirm a positive correlation between CA × P products level and the severity of cardiac VC. As some studies suggest that the mentioned correlation is present, more studies with a bigger sample size are suggested.

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**Table 4.** Age, Hemodialysis Duration, CA and P in Both Groups

| | Group | Mean | Standard deviation |
|---|---|---|---|
| Age (year) | NL | 67.27 | 12.60 |
| | ANL | 56.57 | 12.34 |
| Hemodialysis duration (years) | NL | 2.19 | 1.29 |
| | ANL | 2.64 | 1.43 |
| Ca (mg/dL) | NL | 8.23 | 0.60 |
| | ANL | 8.82 | 0.97 |
| P (mg/dL) | NL | 4.70 | 0.96 |
| | ANL | 7.52 | 1.74 |

eration.

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## Conflicts of Interest

There were no conflicts of interest.

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