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The Association Between Serum Phosphate Levels and Coronary Artery Disease

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Abstract

Objectives: To investigate the relationship between serum phosphate concentration and the severity of coronary artery obstruction.
Design: A cross-sectional study.
Setting(s): The data for all patients included in the study were extracted from patient files at a tertiary heart center.
Participants: A total of 184 patients with suspected coronary artery disease (CAD) were included. They were divided into two groups: a case group and a control group, with each group containing 92 patients.
Outcome Measures: Serum phosphate levels in CAD patients were evaluated.
Results: The mean age of the study population was 56.44 ± 11.19 years. The mean serum calcium concentrations for the case and control groups were 9.46 ± 0.48 mg/dL and 9.36 ± 0.35 mg/dL, respectively. No significant difference was found between those with obstructed coronary arteries and the control group ($P=0.12$). The mean serum phosphorus concentration for the case and control groups was $3.6\ 3 \pm 0.71$ mg/dL and 3.7 ± 0.63 mg/dL, respectively, with no statistical significance ($P=0.54$). The mean calcium-phosphorus product for the coronary artery obstructed and control groups was 33.4 ± 6.78 mg/dL and 34.7 ± 6.17 mg/dL, respectively, with no significant difference between the two groups ($P=0.14$).
Conclusions: Although previous studies have demonstrated a relationship between serum phosphorus concentration and CAD in patients with kidney disorders, this association was not confirmed in the general population in the present study.
Keywords: Coronary artery disease, Calcium, Phosphorus

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Introduction

Over the past decade, cardiovascular diseases have become the leading cause of mortality worldwide. As a chronic inflammatory disease, coronary artery disease (CAD) is characterized by the remodeling and narrowing of the coronary arteries, leading to a combination of clinical signs such as persistent chest pain (angina) and sudden death due to ischemic heart disease.[1,2] It is estimated that in 2015 alone, approximately 17.7 million deaths were attributed to CAD, accounting for roughly 31% of all deaths worldwide.[3,4] In the Middle East and North Africa, 42% of all deaths are caused by cardiovascular disease. Iran has a higher incidence of cardiovascular disease compared to countries such as Saudi Arabia and Jordan. The results of a randomized study composed of 3723 people in Iran revealed that 11.3% and 1.4 % of people showed signs of heart disease and myocardial infarction, respectively.[5] Likewise, the prevalence of cardiovascular

diseases among high-risk citizens of Tehran aged over 30 years could be as high as 21.8%. This underscores the importance of cardiovascular diseases as a major health concern in this area.[6]

Phosphorus plays an important role in various biological procedures, including metabolism, cell signaling, nucleic acid production, and cell membrane stability. Serum phosphorus concentration is regulated by renal uptake and secretion, which is rigorously controlled by vitamin D3 and parathyroid hormone (PTH).[7-10] Numerous studies have revealed that high phosphorus concentrations promote the proliferation of vascular smooth muscle cells (VSMCs), which enhances the expression of key markers of osteochondrogenic differentiation and extracellular calcification.[11-13] The calcification of coronary arteries is likely due to damage to the endothelium and VSMCs.[14] An extensive meta-analysis of 14 articles with 109 670 patients showed that patients with prior kidney disease

face an 18% increased risk of death for each 1 mg/dL increase in their serum phosphorus concentration.[15,16] Phosphorus can also negatively affect outcomes in normal people without kidney problems.[17]

Numerous studies have demonstrated that high serum phosphorus concentrations correlate with CAD and calcification in patients with chronic kidney disease (CKD). However, few studies have been carried out on the association between CAD and serum phosphorus concentration in the general population. The results of such studies may contribute to modifying people's behaviors and lifestyles, which could, in turn, help prevent and treat CAD. This study aimed to evaluate and compare individuals with evident CAD and those without CAD, in terms of their serum phosphorus concentration and the severity of the disease.

Methods

This research was an analytical, cross-sectional, case-control study. All patients with ischemic heart disease who underwent elective coronary angiography were included. The sample size, based on Rasouli and Mohseni Kiasari's[18] study, was estimated to be 92 patients in each group, resulting in a total of 184 participants. STATA 10 software was employed to determine the sample size, and the required data were extracted from patients' records.

Informed written consent was obtained from all patients. Blood samples were collected from patients before angiography, following 8 hours of fasting. Then, serum phosphorus and calcium concentrations were measured by the laboratory center. Patients then underwent angiography and were divided into two groups based on angiographic findings. The case group involved individuals with significant stenosis (50% or greater narrowing) in one or more of the three main coronary arteries: the right coronary artery (RCA), left circumflex artery (LCX), and left anterior descending (LAD). The control group encompassed individuals with normal or non-obstructive coronary arteries. Dara regarding the patients were collected from their medical records, and if any information was incomplete, the patient was re-interviewed.

Exclusion criteria included chronic renal dysfunction, any history of myocardial infarction or revascularization (e.g., percutaneous coronary intervention and coronary artery bypass grafting), malignancy, heart failure, and active incontinence. After applying the exclusion criteria, 92 patients were selected for the case group, and 92 patients were included in the control group.

The data were collected and analyzed using SPSS 22 software. Descriptive statistics such as frequency, percentage, mean, and standard deviation (SD) were used to describe the data. The chi-square test or Fisher's exact test was applied to compare qualitative variables, while the independent t-test (Mann-Whitney test) and one-way ANOVA test were used to compare quantitative variables between two or more groups. The significance level of (type I error) was set at 5%. For better results, patients with missing data were excluded from the study. The research was conducted under code number IR.UMSU.REC.1397.306.

Results

The mean age of the patients' was 56.44 ± 11.19 years, with the oldest being 87 and the youngest being 30 years. The mean age for the case and the control groups was 60.41 ± 10.52 and 52.47 ± 10.45 years, respectively. The mean age for men and women was 55.41 ± 13.12 and 57.43 ± 8.92 years, respectively. Among the patients, 51.1% were female and 48.9% were male ($P = 0.001$). Furthermore, 55.4% of patients lived in urban areas, while 43.5% resided in rural areas ($P = 0.017$).

The results indicated that 11%, 21%, 51.1%, and 21% of patients had a history of dyslipidemia, diabetes, hypertension, and smoking, respectively. Additionally, 30.4% and 13% of patients in the case and control groups suffered from diabetes, respectively ($P = 0.007$). In terms of smoking history, 25% of patients in the case group and 17.4% in the control groups had a history of smoking ($P = 0.20$). Furthermore, 7.4% of women and 35.6% of men had a history of smoking ($P < 0.001$). A positive family history of ischemic heart disease was observed in 9.5% of patients in the case group and 13% of patients in the control group ($P = 0.001$).

The analyzed data revealed that the mean serum phosphate, serum calcium levels, and calcium-phosphorus product were not significantly different between the case and control groups ($P > 0.05$), as illustrated in Table 1. After adjusting for the effect of other variables through a logistic regression model, no significant relationship was observed between the case and control groups regarding their calcium, phosphorus, and calcium-phosphorus product levels.

Figure 1 shows the prevalence of coronary artery stenosis. In the female subgroup of the case group, 40%, 25.7%, and 34.3% had single-vessel disease (SVD), two-vessel disease (2VD), and three-vessel disease (3VD), respectively. Furthermore, in the male patients of the case group, 47.4%, 26.3%, and 26.3% had SVD, 2VD, and 3VD, respectively.

According to the results, the LAD coronary artery was most commonly affected, with 78 cases (84.8%), followed by the LCX with 55 cases (59.2%) and the RCA with 37 cases (40.2%), as depicted in Figure 2.

The results showed that regarding serum phosphorus and calcium concentrations, there was no significant relationship between individuals with SVD, 2VD, and 3VD (Table 2).

Discussion

CAD is a leading cause of death and disability throughout the world. Previous studies have demonstrated a significant association between CAD and CKD. The

Table 1. The Mean Serum Phosphorus Concentration, Serum Calcium Concentration, and Calcium Phosphorus Product in the Studied groups

|	Case Group	Control Group	P Value	Males	Females	P Value
Calcium	9.46±0.48	9.36±0.35	0.12	9.36±0.4	9.47±0.45	0.13
Phosphorus	3.63±0.71	3.7±0.63	0.54	3.61±0.61	3.72±0.66	0.25
Calcium-phosphorus multiplication	34.40±6.78	34.67±6.17	0.77	33.81±6.44	35.22±6.44	0.14
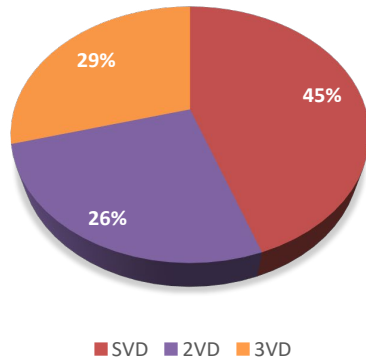
Figure 1. Prevalence of Coronary Artery Stenosis: SVD, 2VD, and 3VD. *Note.* SVD: Single-vessel disease; 2VD: Two-vessel disease; 3VD: Three-vessel disease

Figure 2. Prevalence of LAD, LCX, and RCA in the Studied Samples. *Note.* RCA: Right coronary artery; LCX: Left circumflex artery; LAD: Left anterior descending

incidence of ischemic heart disease increases significantly as kidney disease progresses, with elevated phosphate levels commonly observed in CKD patients. Previous studies have indicated that phosphate levels are increased in patients with ischemic heart disease,[17,19] and excessive phosphate is associated with endothelial dysfunction, left ventricular hypertrophy, and arterial calcification. Furthermore, phosphate levels within the normal range may adversely affect patients with a history of myocardial infarction.[20] Lipid metabolism could be affected by phosphate levels, and the effects of phosphate in different medical conditions need to be investigated separately.[21]

The results of this study indicated that the patients in the case group were older than those in the control group, suggesting that age is a strong risk factor for CAD. In a study by Cancela et al, it was found that people with coronary artery calcification tended to be older.[22] Similarly, the study by Park et al demonstrated similar findings to our study.[23]

The results also indicated a statistically significant difference between the control and case groups in terms of residence. Patients in the case group were mostly urban residents, whereas those in the control group were mainly rural residents. Moreover, a study was conducted by Kulshreshtha et al to investigate the difference in CAD mortality between urban and rural residents, suggesting that the prevalence of CAD was significantly higher among urban residents compared to their rural counterparts.[24]

The results also revealed a significant difference in gender between the case and control groups, with males being higher in the case group than in the control group. This suggests that males were at a higher risk for heart disease than females. Likewise, Cancela et al found that males were more prone to coronary artery calcification.[22]
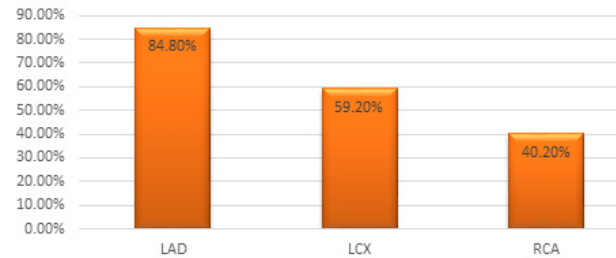
Additionally, Park et al reported similar results.[23]

Furthermore, the results displayed no significant difference between the case and control groups in terms of smoking history. This finding contrasts with a study by Rasouli and Mohseni Kiasari, in which the rate of smoking in the case group was higher than in the control group.[18] The lack of a significant relationship between case and control groups in our study can be due to the selection of elective patients for angiography.

However, our study revealed a significant difference between the case and control groups regarding the history of diabetes. The prevalence of diabetes in the case group was notably higher than in the control group.

Additionally, our study did not find any significant differences in the mean serum phosphorus and calcium concentrations, or the calcium/phosphorus product between the case and control groups ($P > 0.05$). Conversely, a study by Foley et al showed a strong association between serum phosphorus concentration and coronary artery calcification and stenosis in patients with suspected CAD.[25] They reported that the mean serum phosphorus and calcium concentrations were 3.6 mg/dL and 9.5 mg/dL, respectively, and found that serum phosphorus concentrations above 3.9 mg/dL were associated with increased calcium concentrations in the coronary arteries.[25]

Earlier studies have primarily focused on the relationship between phosphorus and CAD in patients with underlying renal problems. However, the present study was conducted on a general population undergoing selective angiography. Furthermore, while earlier studies often used coronary artery calcification, trying to compare individuals via CT angiography to obtain scores, the present study used CAD as the primary yardstick for comparison. Notably, in our study, the mean serum phosphorus concentration was highest in patients with 3VD. In addition, studies such as the one by Grønhøj et al, which examined the connection between calcium

Table 2. Serum Phosphorus Concentration, Serum Calcium Concentration, and Mean Calcium-Phosphorus Product in SVD, 2VD, and 3VD Patients

	Phosphate	Calcium	Ca*Phos
SVD	3.61 ± 0.62	9.41 ± 0.39	34.07 ± 6.0
2VD	3.40 ± 0.53	9.61 ± 0.66	32.78 ± 5.6
3VD	3.88 ± 0.9	9.38 ± 0.4	36.43 ± 8.1
P value	0.083	0.174	0.263

Note. SVD: Single-vessel disease; 2VD: Two-vessel disease; 3VD: Three-vessel disease.

and phosphorus concentrations and coronary artery calcification cases, reported no association between serum phosphorus concentrations and coronary artery calcification,[26] which is in line with our study.

Limitations of the Study
The main limitation of this study is its sample size. A larger study population and subgroup analysis would allow for a better understanding of the relationship between phosphorus levels and CAD. We suggest that future studies investigate the association between serum phosphorus levels and oxidative stress.

Conclusions
Our investigation suggests no significant association between the mean serum concentrations of phosphorus, calcium, and the product of calcium/phosphorus multiplication and CAD. Although earlier studies have documented the association between serum phosphorus concentration and CAD in patients with renal impairment, the current study did not confirm such an association in the general population.

Author contributions
Conceptualization: Naser Khalili.
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Resources: Majid Hajibabaei.
Supervision: Roghayeh Afsargharebagh.
Validation: Naser Khalili.
Visualization: Roghayeh Afsargharebagh.
Writing–original draft: Naser Khalili, Majid Hajibabaei.
Writing–review & editing: Reza Hajizadeh.

Data availability statement
Data gathered for the study are available from the corresponding author upon reasonable request.

Ethical approval
Ethical approval was obtained from the Ethics Committee of Urmia University of Medical Sciences (IR.UMSU.REC.1397.306).

Consent for publication
None.

Conflict of interests
The authors declare that they have no conflict of interests.

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