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RESEARCH

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Study of serum calcium and phosphorus levels in chronic kidney disease patients with acute coronary syndrome

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Abstract

Background Cardiovascular (CVS) conditions remain the main etiology of death in individuals with chronic kidney disease (CKD) even after control of classic risk factors of cardiovascular disease (CVD).

Aim This study is to detect the sequalae of serum phosphorus and calcium level abnormalities in individuals with CKD and their relation to occurrence of acute coronary syndrome (ACS) in those cases.

Methods A cross-sectional work involved 100 individuals with CKD managed with or without dialysis. They were admitted to Internal Medicine Department, Coronary Care Unit of Sohag University Hospital. Each participant had been subjected to full history taking, clinical assessment, and investigations including serum calcium, phosphorus, creatinine, blood urea, parathyroid hormone level, lipid profile, troponin, CK-MB, electrocardiogram, and echocardiography.

Results A substantial elevation in serum calcium and phosphorus levels was existed in individuals with CKD with ACS group compared to patients with CKD without ACS group ($p=0.026$ and 0.001 respectively). The mean calcium/phosphorus ratio was 3.04 ± 2.14 in patients with CKD with ACS group, while it was 2.31 ± 1.17 in patients with CKD without ACS group. A substantial raise in calcium/phosphorus ratio was existed in CKD with ACS group as compared to patients with CKD without ACS group ($p=0.047$). ROC curve analysis shows that calcium/phosphorus ratio can predict acute coronary syndrome at cutoff 1.94 with area under the curve 0.652 with sensitivity and specificity that were 77.8% and 52.1% correspondingly ($p=0.007$).

Conclusion A substantial raise in calcium and phosphorus levels was existed in individuals with CKD with ACS group contrasted to individuals with CKD without ACS group. Calcium/phosphorus ratio can predict acute coronary syndrome at cutoff 1.94.

Clinical trial registration number NCT05134220.

Keywords Calcium, Phosphorus, Chronic kidney disease, Acute coronary syndrome

Introduction

Cardiovascular conditions remain the main etiology of death in those suffering from CKD even after control of the classic factors of risk of CVD like diabetes (DM), hypertension (HTN), hyperlipidemia, obesity, smoking, and hypervolemia. Also, the impact of addressing some nontraditional cardiac risk factors including anemia, microalbuminuria, inflammation, oxidative stress, and disorders of mineral and bone metabolism

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in decreasing cardiovascular complications among individuals with CKD is still unclear [1].

Hypocalcemia, hyperphosphatemia, and lack of vitamin D activation among individuals with CKD will lead to loss of negative feedback inhibition of parathyroid hormone synthesis which will lead to secondary hyperparathyroidism. Therefore, hyperparathyroidism is a strong indicator of minerals abnormalities in patients with CKD [2].

Individuals with CKD often experience irregularities of calcium (Ca) and phosphate (P) metabolism that leads to the development of vascular calcification. Increased levels of Ca and P directly impact vascular smooth muscle cells (VSMCs) by promoting vascular calcification. This includes stimulating the differentiation of cells into bone or cartilage cells, releasing vesicles, inducing apoptosis, reducing the presence of inhibitors, and breaking down the extracellular matrix. Hyperphosphatemia enhances the differentiation of VSMC into bone or cartilage cells, whereas hypercalcemia primarily induces the programmed cell death and release of vesicles in VSMC. Increased levels of calcium and phosphorus have a combined impact, which strongly promotes the calcification of blood vessels in CKD [3]. Coronary artery calcium (CAC) score assists in categorizing the risk of CVD in 10–20% of asymptomatic persons. The CAC score system has the ability to assess the risk stratification and forecast the prognostic outcomes in asymptomatic individuals with cardiovascular disease [4]. Asymptomatic individuals with a CAC score of zero are less likely to be prescribed unnecessary treatments, while also reducing their risk and predicting their probability of recovery. The use of CAC in statistical risk reclassification aids in distinguishing between high-risk and low-risk (asymptomatic) individuals with CVD [5]. The CAC score categorizes individuals into classes II, II-a, and I based on their varying levels of risk for CAD and CVD. Additionally, the CAC scores may be divided into four distinct categories: 0–1 (indicating minimum risk), 1–100 (suggesting moderate risk), 101–400 (indicating high risk), and 400 or beyond (signifying extremely high risk) [6]. This scan also provides information on lifestyle management strategies in the context of CVD, and the CAC scores ranging from 0 to 300 help determine the appropriate antiplatelet therapy for asymptomatic individuals with atherosclerotic CVD. A CAC score of 1000 or more provides guidance on the treatment methods for individuals with CVD [7].

Tight control of the level of P and Ca in individuals with CKD will decrease the cardiovascular events and complications [8].

Materials and methods

A cross-sectional work was performed on 100 individuals with CKD managed with and without dialysis that was conducted during the period from October 2021 to April 2022. CKD is characterized by harm to the kidneys or a glomerular filtration rate (GFR) of < 60 mL/min/1.73 m^2 for a duration of 3 months or more, regardless of the underlying cause [9]. They were admitted to Internal Medicine Department, Coronary Care Unit, and Nephrology Unit of Sohag University Hospital.

Ethical approval

The Institutional Review Board, Faculty of Medicine, Sohag University, Sohag, Egypt, permitted this work [8/11/2021] (Approval no. NCT05134220), and all participants provided a well- informed consent to join the work.

They had been allocated into two groups.

Group I

Group I involved 45 patients with CKD who admitted in Coronary Care Unit with acute chest pain consistent with ACS.

Group II

Group II involved 55 patients with chronic kidney disease who were randomly selected among those admitted for follow-up their renal functions in Internal Medicine Department and patients on regular dialysis in nephrology unit with no past history of ACS.

Exclusion criteria

We excluded patients with primary hyperparathyroidism and acute kidney injury (AKI).

Methods

A comprehensive clinical history and examinations of all participants were done.

Laboratory assessment

Serum creatinine, blood urea nitrogen, lipogram, serum calcium phosphorus, parathyroid hormone level, troponin, and CK-MB.

Statistical analysis

Statistical package for social sciences (IBM-SPSS), version 25 was employed for statistical data analysis. Data displayed as mean, standard deviation (SD), numbers, and percentages. Mean and standard deviation had been utilized as descriptive value for quantitative data, while numbers and percentages were utilized to describe qualitative data.

Both groups were compared utilizing the chi-square test, the Mann–Whitney *U* test, and the Kruskal–Wallis test. *P* value ≤ 0.05 was considered statistically significant.

Results of the study

The current research involved 100 patients with CKD with and without dialysis. The mean age in individuals with CKD with ACS group and patients with CKD without ACS group were 57.56 ± 13.22 years and 49.13 ± 14.33 years correspondingly. The mean duration of CKD was 46.18 ± 30.36 months in patients with CKD with ACS group, while it was 35.91 ± 35.48 months in individuals with CKD without ACS group. A statistically significant rise in duration of CKD was existed in patients with CKD with ACS group ($p = 0.029$). Patients on dialysis in 66.7% of patients with CKD with ACS group and 40% in patients with CKD without ACS group. Dialysis was substantially greater among individuals with CKD with ACS group contrasted to individuals with CKD without ACS group ($p = 0.014$) (Table 1).

The mean calcium level in patients with CKD with ACS group and patients with CKD without ACS group was 9.12 ± 1.3 mg/dl and 8.31 ± 2.2 mg/dl respectively. The mean level of phosphorus in individuals with CKD with ACS group and patients with CKD without ACS group was 5.69 ± 2.35 mg/dl and 4.22 ± 1.61 mg/dl correspondingly. A substantial elevation in calcium and phosphorus levels was existed in individuals with CKD with ACS group contrasted to individuals with CKD without ACS group ($p = 0.026$ and 0.001 respectively). The mean calcium/phosphorus ratio was 3.04 ± 2.14 in patients with CKD with ACS group, while it was 2.31 ± 1.17 in patients with CKD without ACS group. A substantial rise in calcium/phosphorus ratio was existed in patients with CKD with ACS group compared to patients with CKD without ACS group ($p = 0.047$) (Tables 2 and 3).

ROC curve analysis shows that calcium/phosphorus ratio can predict acute coronary syndrome at cutoff 1.94 with area under the curve 0.652 with sensitivity and specificity was 77.8% and 52.1% correspondingly ($p = 0.007$) (Fig. 1).

Discussion

Studies have shown a link between disorders in the regulation of calcium and phosphorus levels and increased risk of death from any cause and cardiovascular diseases among individuals who need long-term dialysis treatment [10].

Several research on individuals with ESRD have shown evidence supporting the idea that having high levels of phosphorus in the blood and greater levels of Ca × P enhance the chance of mortality from any cause. However, various studies have proposed different threshold values for these risk factors [11]. Nevertheless, the current recommendations lack specificity for the desired range of blood phosphorus levels and suggest

Table 1 Demographic and clinical characteristics among the both groups

		CKD with ACS group (No. = 45)	CKD without ACS group (No. = 55)	*P* value
		No (%)	No (%)	
Gender	**Male**	25 (55.6%)	32 (58.2%)	0.792
	Female	20 (44.4%)	23 (41.8%	
Age (years)	**Mean ± SD**	57.56 ± 13.22	49.13 ± 14.33	0.003
Duration of CKD (months)	**Mean ± SD**	46.18 ± 30.36	35.91 ± 35.48	0.029
Dialysis	**Not on dialysis**	15 (33.3%)	33 (60.0%)	0.014
	On dialysis	30 (66.7%)	22 (40.0%)	

$p \leq 0.05$ is considered statistically significant, $p \leq 0.01$ is considered high statistically significant, *SD* standard deviation, *Chi-Square test and Mann–Whitney *U* test.

Table 2 Comparison among both groups regarding serum Ca and phosphorus levels and calcium phosphorus ratio

	Group I CKD with ACS group (No. = 45)	Group II CKD without ACS group (No. = 55)	*P* value
	Mean ± SD	Mean ± SD	
Serum calcium (mg/dl)	9.12 ± 1.30	8.31 ± 2.20	0.026
Serum phosphorus (mg/dl)	5.69 ± 2.35	4.22 ± 1.61	0.001
Albumin (g/dL) *(3.5 to 5.5 g/dL)*	4.00 ± 0.39	3.88 ± 0.66	0.039
Calcium/phosphorus ratio	3.04 ± 2.14	2.31 ± 1.17	0.047

Table 3 Comparison among the studied groups as regard lipid profile, kidney function test, and PTH and its relation to dialysis

	Group I CKD with ACS group (No. = 45)		Group II CKD without ACS group (No. = 55)		*P* value
	Not on dialysis (*n* = 15)	On dialysis (*n* = 30)	Not on dialysis (*n* = 33)	On dialysis (*n* = 22)	
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	
TG (mg/dl)	139.95 ± 25.14	140.14 ± 22.04	135.61 ± 22.79	133.68 ± 19.54	0.650
Cholesterol (mg/dl)	174.34 ± 31.10	200.52 ± 47.78	153.50 ± 32.13	164.23 ± 23.80	0.043
HDL (mg/dl)	46.24 ± 8.58	41.67 ± 7.26	46.61 ± 8.05	49.27 ± 8.07	0.018
LDL (mg/dl)	102.45 ± 27.01	154.05 ± 28.16	56.75 ± 14.47	89.95 ± 20.57	0.048
Creatinine (mg/dl)	5.92 ± 1.75	14.60 ± 5.78	2.03 ± 2.21	10.84 ± 2.04	< 0.001
Urea (mg/dl)	87.00 ± 41.21	116.97 ± 21.28	103.71 ± 28.07	125.00 ± 22.30	< 0.001
PTH	404.53 ± 460.52	556.48 ± 484.35	131.73 ± 169.44	173.20 ± 682.0	< 0.001

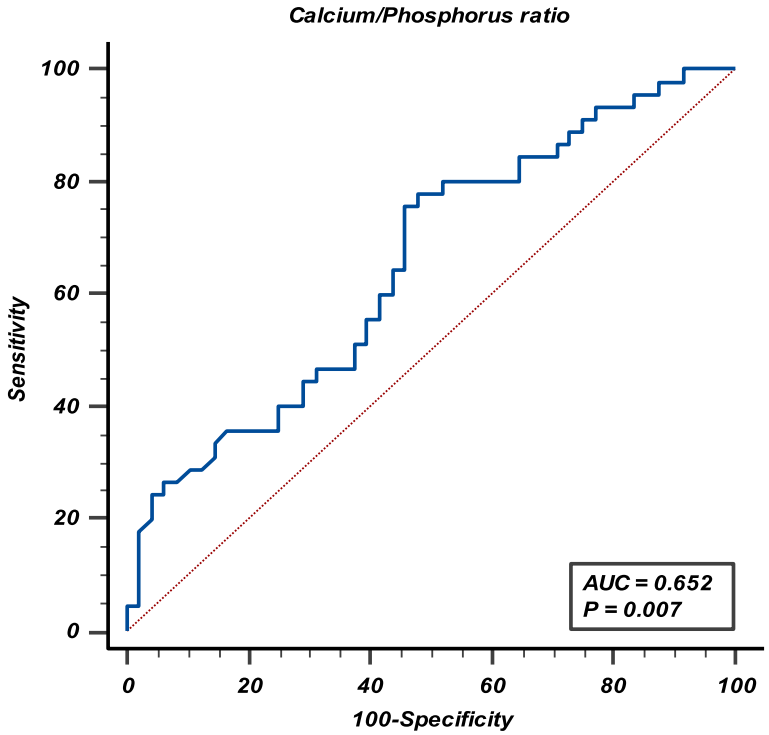

Fig. 1 ROC curve of diagnostic performance of calcium/phosphorus ratio

maintaining serum phosphorus within the "normal range" with little confidence in the quality of evidence [12]. Macro et al. demonstrated that individuals with levels of phosphorus in serum over 6.5 mg/dL or Ca × P values over 52 mg^2/dl^2 had a higher likelihood of experiencing cardiovascular mortality [13]. Ganesh et al. demonstrated a significant correlation between high levels of serum phosphorus (> 6.5 vs. 2.4–6.5 mg/dL) and Ca × P levels (RR 1.06 for every 10 mg^2/dL^2 rise in Ca × P) and CV mortality in HD recipients, particularly mortality resulting from CAD and sudden death [14].

Individuals with CKD have a poor prognosis after the first cardiovascular incident and a higher chance of acquiring CAD [15]. We investigate whether disorders of calcium and phosphate metabolism are associated with the progression of ACS in individuals with CKD.

In the current work, patients with CKD with ACS group (45 patients), 8 (17.8%) patients had Anterior STEMI, 1 (2.2%) patient had extensive STEMI, 3 (6.8%) patients had inferior STEMI, 1 (2.2%) patient had MV replacement with UA, 16 (35.6%) patients had NSTEMI, and 16 (35.6%) patients had UA.

In our present study, the mean calcium level in patients with CKD with ACS group and patients with CKD without ACS group was 9.12 ± 1.3 mg/dl and 8.31 ± 2.2 mg/dl correspondingly. The mean level of P in individuals with CKD with ACS group and patients with CKD without ACS group was 5.69 ± 2.35 mg/dl and 4.22 ± 1.61 mg/dl correspondingly. A substantial elevation in serum calcium and phosphorus levels in individuals with CKD in the ACS group was compared to patients with CKD without ACS group ($p = 0.026$ and 0.001) respectively.

Vascular calcification, particularly in the presence of high calcium-phosphorus product levels, has been suggested as a possible mechanism linking excessive phosphorus levels to negative cardiovascular consequences [16].

Vascular calcification is a multifaceted process that is not solely determined by an increased calcium-phosphorus product. It is controlled by various factors, which includes fibroblast growth factor-23 (FGF-23) and the inhibitors of crystallization such as inorganic pyrophosphate, uncarboxylated matrix Gla protein (ucMGP), and fetuin-A. [17]. Elevated levels of phosphorus encourage the development of non-atherosclerotic arterial calcification by prompting VSMCs to transition from a contractile state to an osteochondrogenic one. This transition stimulates the mineralization of the surrounding arterial tissues [16].

Fukagawa et al. conducted comprehensive case-cohort research in Japan, focusing on individuals suffering from CKD Stage 5D and secondary hyperparathyroidism who were undergoing hemodialysis. The study revealed that the blood calcium level served as a reliable indicator for predicting death in these individuals [18].

In a study carried out in the United States, a group of 35,114 individuals who were receiving hemodialysis were followed for a median period of 1.3 years. The study found that among those individuals who had greater residual renal urea clearance, an increased risk of death was exited among those with greater amounts of serum phosphorus [19].

Nevertheless, in a group of 10,672 individuals with CKD who were observed for a median period of 2.3 years, the researchers discovered no noteworthy connection between initial blood phosphorus levels and the risk of death from any cause or the progression to ESKD [20].

Individuals with CKD who have a high calcium-phosphorus product (Ca-P product) are at risk for developing CAC and CAD [21].

The mean calcium/phosphorus ratio was 3.04 ± 2.14 in patients with CKD with ACS group, while it was 2.31 ± 1.17 in patients with CKD without ACS group. A substantial rise was existed in calcium/phosphorus ratio in patients with CKD with the ACS group compared to patients with CKD without the ACS group ($p = 0.047$).

Our results showed that the calcium/phosphorus ratio can predict acute coronary syndrome at cutoff 1.94 with the area under the curve 0.652 with sensitivity, and specificity was 77.8% and 52.1% correspondingly ($p = 0.007$).

A statistically substantial variance was existed among both groups as regards PTH level ($p < 0.001$) as it was substantially greater in individuals with CKD with ACS group contrasted to individuals with CKD without ACS group.

Even in healthy individuals, elevated serum phosphorus concentrations raise PTH levels. It is recognized that raised PTH levels induce the production of pro-inflammatory IL6 and promote bone resorption. It is recognized that elevated levels of IL6 and hs-CRP increase the risk of cardiovascular disease. Increased levels of serum phosphorus may be indicative of subclinical renal dysfunction, with cardiovascular complications [22].

Conclusion

In the current study, our aim is to detect the sequalae of serum calcium and phosphorus level abnormalities in individuals with CKD and their relation to the occurrence of acute coronary syndrome (ACS) in those cases. We found a significant elevation in serum calcium and phosphorus levels among individuals with CKD with the ACS group compared to patients with CKD without the ACS group. In the current study, calcium/phosphorus ratio can predict acute coronary syndrome at cutoff 1.94 with the area under the curve 0.652 with sensitivity, and specificity was 77.8% and 52.1% respectively. Further prospective randomized multicenter studies with larger sample size is needed. Tight control of serum phosphorus and calcium levels in CKD patients will decrease cardiovascular events and complications.

Limitation

- Our study has some limitations, small sample size also differences in participants characteristics may have influenced the results.
- CAC scanning-guided risk stratification and prognostication were not assessed in our study.
- Further prospective randomized multicenter studies with larger sample size is needed.

Abbreviations

ACS	Acute coronary syndrome
Ca	Calcium
CAC scoring	Coronary artery calcium scoring
CK-MB	Creatine kinase-MB
CKD	Chronic kidney disease
CVD	Cardiovascular disease

EF	Ejection fraction
GFR	Glomerular filtration rate
eGFR	Estimated glomerular filtration rate
hs-CRP	High-sensitive C-reactive protein
HDL	High-density lipoprotein
HTN	Hypertension
LDL	Low-density lipoprotein
NSTEMI	Non-ST-elevation myocardial infarction
MV	Mitral valve
PTH	Parathormone hormone
ROC curve	Receiver operating characteristic curve
SPSS	Statistical Package for the Social Sciences
SD	Standard deviation
STEMI	ST-elevation myocardial infarction
TG	Triglycerides
UA	Unstable angina
TnT	Troponin-T
VSMCs	Vascular smooth muscles

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Author contributions
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Availability of data and materials
The data that support the findings of this study are available from corresponding author upon reasonable request.

Declarations

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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