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Calcium and Phosphorus Levels in Chronic Kidney Disease Patients with Acute Coronary Syndrome

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Abstract:

Background: Chronic kidney disease (CKD) is associated with significant alterations in mineral metabolism, particularly involving calcium and phosphorus. These changes can have profound effects on cardiovascular health, exacerbating conditions such as acute coronary syndrome (ACS). Understanding the levels of calcium and phosphorus in CKD patients presenting with ACS is crucial as these minerals can influence the severity of cardiovascular events, patient prognosis, and management strategies. Despite their potential impact, the precise role of calcium and phosphorus levels in the context of CKD and ACS remains underexplored.

Aim: To investigate the relationship between calcium and phosphorus levels and clinical outcomes in chronic kidney disease patients presenting with acute coronary syndrome.

Methods: This study was conducted on 150 CKD patients with and without dialysis who admitted to Zliten Medical Center, Zliten, Libya. Patients were divided into two groups: CKD without ACS group: 75 CKD patient with and without dialysis with no history of ACS and CKD with ACS group: 75 CKD patients with and without dialysis with chest pain consistent with Acute coronary syndrome (ACS). Calcium and Phosphorus were measured in all cases.

Results: There was significant elevation in calcium and phosphorus levels in CKD with ACS group compared to those without ACS group.

Conclusion: There are notable differences between CKD patients with and without ACS, and that calcium and phosphorus levels play a vital role in these patients.

Keywords: Calcium, Phosphorus, Chronic Kidney Disease, Acute Coronary Syndrome.

Introduction

A variety of distinct pathologic conditions linked are alludes to a gradual decline in the Glomerular Filtration Rate (GFR)to asChronic Kidney Disease (CKD). Because of the expensive and protracted/lifelong treatment, the patient will experience severe physical, social, and psychological effects. Chronic kidney disease (CKD) is a disease with five phases. Uremic syndrome is caused by an accumulation of toxins, fluid, and electrolytes that the kidneys should be able to eliminate. End stage renal disease is the term for this stage. If renal replacement therapy—such as dialysis or kidney transplantation—is unable to remove the toxins, this condition results in mortality **(*1*).**

The term "CKD-MBD (mineral and bone disorders)" refers to the anomalies in the parathyroid hormone (PTH)–vitamin D endocrine loop that are frequently seen in individuals with severe chronic kidney disease (CKD) include problems in bone turnover, mineralization, volume, and strength**(*2*).**

Evidence supporting the connection between CKD-MBD and many extra-skeletal consequences, including as arterial calcification, cardiovascular disease (CVD), and all-cause mortality, is growing. This is especially the case for typical indicators of mineral metabolism as phosphorus, calcium, and PTH. Nonetheless, the majority of research has been on the result of all-cause death in individuals requiring renal replacement therapy (RRT) due to end-stage renal disease (ESRD). The impact of serum calcium levels and phosphorus on mortality is less obvious and inconsistently revealed in these research, despite the significant link that has been regularly shown between elevated blood phosphorus levels and all-cause mortality. (***3, 4*).**

Adults with CKD whose GFR is less than 30 mL/min/1.73 m2 experience a vitamin D (1, 25(OH) 2D3) deficient condition. In this way, low vitamin D levels result in hypocalcemia, which then triggers secondary hyperparathyroidism. The release of calcium and phosphorus results from the demineralization of the bone caused by this secondary hyperparathyroidism. When CKD first starts, the kidneys eliminate extra phosphorus; however, as the disease progresses, phosphorus builds up and the serum phosphorus level rises to extremely high levels (***5*).**

The body then produces more PTH hormone as a result of the elevated serum phosphorus, which calcifies soft tissue and arteries. This rapid atherosclerosis, soft tissue calcification, and vascular calcification cause coronary blockages, which in turn cause coronary artery disease. Therefore, risk factor adjustment for patients with CKD should be at least as thorough as for those with clinically confirmed coronary heart disease, since their existence of CKD is regarded as coronary risk comparable (***6*).**

Higher serum phosphorus levels are linked to faster CKD progression toward ESRD and all-cause death in CKD patients who do not need dialysis, based on a new meta-analysis.However, the evidence is inconclusive, and the association may change with age (***7*).**After correcting for eGFR, serum phosphorus in patients with CKD stages 3 to 4 in the Modification of Diet in Renal Disease (MDRD) Study cohort were not significantly associated with all-cause or CVD mortality. Additionally, the Kidney Early Evaluation Program found no evidence of a connection between serum phosphorus and kidney disease (CKD) based on a study sample of 10,672 CKD patients and the faster course of CKD (***8*).**

There is mounting evidence in the general population that CVD and CV mortality are independently correlated with a little abnormal phosphorus level.This suggests that phosphorus has biological consequences beyond uremic toxicity (***9*).**

A higher risk of CVD was associated with higher serum phosphorus levels in Framingham Offspring study participants who did not have CVD or CKD at baseline. Participants in the prospective Coronary Artery Risk Development in Young Adults study used CT-based calcium scoring (CARDIA) research showed significantly more coronary calcification when their serum phosphorus level was higher, even when it was within the normal range (***10*).**

Replica tests have not been widely utilized to evaluate the effects of these long-term mineral abnormalities on mortality and the risk of CKD progression to dialysis, as well as to characterize the longitudinal trajectories of serum calcium and phosphorus during chronic kidney disease (CKD).A single study involving an ESRD population endeavored to correlate the all-cause death rate with the longitudinal variations of mineral properties, specifically PTH, Ca2+, PTH, and phosphorus(***2*).**

Subjects and Methods:

This study was a prospective observational research project at Zliten Medical Center, Zliten, libyaduring the period from 3/2022 to 3/2023 on patients with pre-existing chronic kidney disease (CKD) with and without regular hemodialysis stage 3 or higher—defined as an estimated glomerular filtration rate (eGFR) of less than 60 mL/min/1.73 m2 for at least three months—who were admitted to the coronary care unit and diagnosed with acute coronary syndrome (ACS) were included in the study. Consent in writing, fully informed, was acquired from all participants prior to enrollment.

Inclusion Criteria:

1. Individuals with chronic kidney disease (CKD) who were admitted to the coronary care unit with chest discomfort suggestive of ACS and any of the following characteristics:

a- Electrocardiogram (ECG) changes:

- T wave inversion.
- ST elevation.
- ST depression.
- The left bundle branch block recently.

b- Troponin T elevation.

2. The CKD patient without a history of ACS, either with or without dialysis.

Exclusion Criteria:

1. Individuals with a primary hyperparathyroidism diagnosis.
2. Any of the following conditions is referred to as acute kidney damage (AKI)**(11):**
    - Increase in S.Cr by ≥ 0.3 mg/dl (≥ 26.5 μmol/l) within 48hours; or
    - Increase in S.Cr to ≥ 1.5 times baseline, which is known or presumed to have occurred within the prior 7 days;or
    - Urine volume <0.5 ml/kg/h for 6 hours.
3. Hypercalcemia or hypocalcemia due to non-renal causes.

4. Patients on medications affecting calcium or phosphorus levels, such as phosphate. binders or calcimimetics, unless used as part of standard CKD management.
5. Recent (within 3 months) major surgical procedure or fracture.
6. Pregnancy or lactation.

Data Collection

All participants were subjected to the following: clinical features, medical history, and baseline demographic information were gathered from electronic medical records and patient interviews. Data on comorbidities, medications, and laboratory parameters, including serum calcium, phosphorus, PTH and creatininewererecorded.

Laboratory Measurements

Within a day of each participant's admission,venous blood samples were collected to be sent to the cardiac care unit. Serum phosphorus and calcium were determined using techniques based on ammonium molybdate and o-cresolphthaleincomplexone, respectively. Self-reports, previous prescription data, and medical records were used to gather the baseline population characteristics. Features of the echocardiography were checked at admission and reexamined as needed.

Equations

The formula was used to adjust serum calcium level, which has been corrected for albumin (mmol/L) = measured serum calcium (mmol/L) – 0.025^{*} serum albumin (g/L) +1.0 (mmol/L) (***12).***

The estimated GFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) algorithm, accounting for factors such as age, sex, race, and serum creatinine levels.

ACS-Related Data

1. Type of ACS: STEMI, NSTEMI, or unstable angina.
2. Electrocardiogram (ECG) findings.
3. Coronary angiography results.

Outcome Measures

The mainoutcome measure is the link between Ca and P and severity of ACS as determined by type of ACS (ST-segment elevation myocardial infarction, non-ST-segment elevation myocardial infarction and unstable angina).

Statistical design

Where appropriate, averages and for continuous variables, the standard deviations, medians, and interquartile ranges were shown. The categorical variables were reported using percentages and frequencies. The association between serum calcium and phosphorus levels and the severity of ACS was investigated using logistic regression models, accounting for pertinent variables such age, sex, comorbidities, and medications.

Results

In the current study,therewas statistically significant increase in age in CKD with ACS group, than those without ACS. Regarding gender, 58.7% of cases were males and 41.3% were females in CKD withACS group while 53.3% of cases were males and 46.7% were

females in CKD without ACS group with no statistically significant difference. There was no statistically significant difference in relation to hypertension, DM, smoking status and family history of CAD between the two groups (Table 1).

Table 1: Demographic data among studied groups

		CKD without ACS (n=75)	**CKD with ACS (n=75)**	**P value**
Age (years)	**Mean ± SD**	51.34±8.30	60.50±9.57	**0.001**
	Range	35-66	38-79	
Sex	**Male**	40 (53.3%)	44 (58.7%)	0.514
	Female	35 (46.7%)	31 (41.3%)	
Hypertension	**Yes**	27 (36%)	35 (46.7%)	0.187
	No	48 (64%)	40 (53.3%)	
DM	**Yes**	34 (45.3%)	37 (49.3%)	
	No	41 (54.7%)	38 (50.7%)	0.626
Smoking	**Yes**	28 (37.3%)	31 (41.3%)	0.619
	No	47 (62.7%)	44 (58.7%)	
Family history of CAD	**Yes**	20 (26.7%)	17 (22.7%)	0.573
	No	55 (73.3%)	58 (77.3%)	

CKD: Chronic kidney disease, ACS: Acute coronary syndrome

In CKD with ACS group, 15 (20%) patients had anterior STEMI, 3 (4%) patient had extensive STEMI, 8 (10.7%) patients had inferior STEMI, 2 (2.7%) patient had MV replacement with UA, 27 (36%) patients had NSTEMI and 20 (26.7%) patients had unstable angina (Table 2).

Table 2: Site of Culprit vessel among studied groups

		CKD with ACS (n=75)
Site of Culprit vessel	**Anterior STEMI**	15 (20%)
	Extensive STEMI	3 (4%)
	Inferior STEMI	8 (10.7%)
	NSTEMI	27 (36%)
	MV replacement with UA	2 (2.7%)
	Unstable angina	20 (26.7%)

CKD: Chronic kidney disease, ACS: Acute coronary syndrome

In CKD with ACS, there was a notable increase in calcium and phosphorus levels compared to in CKD without ACS group (Table 3).

Table 3: Calcium and phosphorus among studied groups

		CKD without ACS (n=75)	**CKD with ACS (n=75)**	**P value**
Calcium (mg/dL)	**Mean ± SD**	2.12±0.11	2.16±0.09	**0.01**
	Range	1.9-2.3	2-2.3	
Phosphorus (mg/dL)	**Mean ± SD**	1.58±0.13	2.05±0.215	**0.001**
	Range	1.2-1.8	1.6-2.4	

CKD: Chronic kidney disease, ACS: Acute coronary syndrome

Serum cholesterol and LDL were notably greater in the CKD with ACS group than those without ACS. Meanwhile, CKD with ACS group had significant decline in HDL when compared to CKD without ACS group. Regarding triglycerides, there was no appreciable differences between the two studied groups (Table 4).

Table 4: Lipid profile among studied groups

		CKD without ACS (n=75)	**CKD with ACS (n=75)**	**P value**
Cholesterol (mmol/l)	**Mean ± SD**	194.88 ±13.81	218.22±25.22	**0.001**
	Range	171-230	174-259	
Triglycerides (mmol/l)	**Mean ± SD**	125.97±12.58	128.97±14.12	0.172
	Range	94-146	102-173	
HDL(mmol/l)	**Mean ± SD**	55.73±5.64	41.626±6.21	**0.001**
	Range	41-66	31-59	
LDL (mmol/l)	**Mean ± SD**	114±14.86	150.84±26.05	**0.001**
	Range	87-153	101-202	

CKD: Chronic kidney disease, ACS: Acute coronary syndrome, HDL: High-density lipoprotein, LDL: low-density lipoprotein, SD: Standard deviation

PTH levels in the two groups differed statistically considerably, with PTH levels in the CKD with ACS group being considerably greater than in the CKD group that did not have ACS while there was no significant difference regarding creatinine (Table 5).

Table 5: creatinine and PTH among studied groups

		CKD without ACS (n=75)	**CKD with ACS (n=75)**	**P value**
creatinine(mg/dL)	**Mean ± SD**	2.11±0.37	2.20±0.39	0.151
	Range	1.5-2.9	1.5-2.9	
PTH (pg/mL)	**Mean ± SD**	260.17±23.83	601.013±69.20	**0.001**
	Range	203-341	500-790	

CKD: Chronic kidney disease, ACS: Acute coronary syndrome, PTH: Parathyroid hormone

In CKD with ACS group, calciumshowed positive correlation with serum phosphorus and negative correlation with HDL (Table 6).Also phosphorus showed positive correlation with age, cholesterol, LDL, creatinine and PTH and negative correlation with HDL (table 7).

Table (6): Correlation between calcium and different parameters among CKD with ACS.

	Calcium	
	r	P value
Age	0.021	0.802
Phosphorus	0.247**	**0.002**
Cholesterol	0.11	0.181
Triglycerides	0.049	0.553
HDL	-.213-**	**0.009**
LDL	0.156	0.057
Creatinine	0.012	0.88
PTH	0.148	0.07

Table (7): Correlation between Phosphorus and different parameters among CKD with ACS.

	Phosphorus	
	R	P value
Age	0.353**	**0.001**
Calcium	0.247**	**0.002**
Cholesterol	0.441**	**0.001**
Triglycerides	0.047	0.566
HDL	-0.650-**	**0.001**
LDL	0.576**	**0.001**
Creatinine	0.185*	**0.024**
PTH	0.728**	**0.001**

ROC curve analysis shows that calcium can predict acute coronary syndrome at cutoff 2.15 with area under the curve 0.611 with sensitivity and specificity was 59.1% and 57.1% respectively (p=0.019). Also ROC curve analysis shows that phosphorus can predict acute coronary syndrome at cutoff 1.75 with area under the curve 0.974 with sensitivity and specificity was 90.9% and 93.2% respectively (p=0.001) (Table 8).

Table (8): Receiver observing characteristic analysis of calcium and phosphorus for prediction of CKD with ACS.

	Cut-off	**AUC**	**Sensitivity**	**Specificity**	**PPV**	**NPV**	**P value**
Calcium	2.15	0.611	59.10%	57.10%	55%	64%	0.019
Phosphorus	1.75	0.974	90.90%	93.20%	93.30%	90.70%	0.001

Discussion

Our results showing elevated calcium and phosphorus levels in CKD patients with ACS and that are in line with earlier studies showing increased mortality and cardiovascular risk in end-stage renal disease (ESRD) populations associated with hyperphosphatemia and higher levels of calcium-phosphorus (Ca×P) products. The idea that hyperphosphatemia is associated with an increased risk of cardiovascular and all-cause mortality is supported by a large body of researches**(3, 13).**

Ting et al. (2)found that the increase in calcium and phosphorus were linked to considerably higher odds of developing acute coronary syndrome (ACS), end-stage renal disease (ESRD), and all-cause mortality when compared to those with ACS.

Cao et al. (14)found that biomarkers of prognosis in those suffering from an acute myocardial infarction (AMI) were correlated with levels of both calcium and serum phosphorus. Specifically, higher levels of corrected calcium were found to be independently associated withincreased the risk of in-hospital HF, post-discharge HF, cardiac mortality, and all-cause death. These outcomes concur with the findings of our study.

Certain studies have found an independent association between higher serum phosphate levels and an increased risk of incident heart failure in patients who have had previous MI (**15, 16),** which was similar to our findings.

Higher blood calcium was previously found to be independently according to a community-based cohort research linked to an elevated risk of heart failure(**17**), and increased blood calcium levels in individuals with T2DM was a separate risk factor for HFpEF(**18**). The relationship might be attributed to a few possible mechanisms. First, because of the connection between high blood pressure and a number of metabolic disorders, including diabetes, obesity, and metabolic syndrome, high serum calcium may enhance left ventricular diastolic performance (**19**). Second, earlier researches has demonstrated a strong correlation between left ventricular hypertrophy and high serum calcium (**20**) and vascular stiffness (**19**).

Tsai et al. (21) revealed that, in comparison to individuals with a "normal" Ca x P trajectory, those with a "high" Ca x P trajectory had shorter dialysis-free survival, ACS-free survival, and overall survival. When juxtaposed with a "normal" Ca x P trajectory, the incidental ESRD adjusted hazard ratios (HRs) were 4.4 for a "moderate" Ca x P trajectory and 10.5 for a "high" Ca x P trajectory. The adjusted HRs for all-cause mortality were 1.71 for a "moderate" Ca x P trajectory and 2.47 for a "high" Ca x P trajectory, compared to a "normal" Ca x P trajectory. The association between Ca x P trajectories and the risks of ESRD, ACS, and mortality was consistent across different subgroups based on age, gender, diabetes and hypertension.

Moreover, **Jadhav and Oommen, (22)**revealed that individuals suffering from chronic kidney disease (CKD) receiving continuous dialysis, the calcium phosphorus product (CPP) was substantially linked to acute coronary syndrome (ACS). Significantly, higher CPP levels of more than 55 mg2/dl2 indicated an 18-fold increased risk of ACS.

Hyperphosphatemia was described by the Kidney Disease Outcomes Quality Initiative (KDOQI) 2002 criteria as serum phosphorus values >4.5 mg/dL (**23).** However, other studies have suggested higher cut-off points. For example, patients with baseline serum phosphorus levels >6.5 mg/dL had a 27% higher mortality risk compared to those with levels of 2.4–6.5 mg/dL. Patients with high Ca×P levels (>72 mg^2/dL^2) had a 34% higher mortality risk compared to those with levels of 42–52 mg^2/dL^2 (**24).**

A higher risk of death was associated with serum phosphorus levels in 40,538 hemodialysis patients >5.0 mg/dL. The relative risk (RR) of death for Ca×P levels of 50–55 mg^2/dl^2 was 1.14 (1.05–1.23), compared with when values were 40–45 mg^2/dL^2 (**25).**

Ganesh et al. (26)discovered that in patients receiving hemodialysis, elevated serum cholesterol, phosphorus (>6.5 mg/dL) and higher Ca×P values, especially in cases of

coronary artery disease (CAD) significantly increase the risk of cardiovascular death and sudden death.

Furthermore**, Abe *et al*. (27)**demonstrated that there was a higher risk of cardiovascular death in patients with serum phosphorus levels >6.5 mg/dL or Ca×P values >52 mg2/dl2. Serum phosphorus, calcium, and magnesium levels were measured in 14,829 HD patients utilizing the United States Renal Data System (USRDS) and Ca×P were linked to both fatal and nonfatal cardiovascular events (**28).**

The "precipitation–calcification hypothesis" or hyperphosphatemia may contribute to the underlying pathophysiology that explains why aberrant Ca-P trajectories are linked to the advancement of CKD: Chronic renal failure is defined by a gradual loss of function brought on by calcium phosphorus microcrystals that precipitate and accumulate in the interstitium, capillaries, and renal tubular lumenas a result of excess phosphorus in the kidney (**29).**

The results of the study by are consistent with the higher blood cholesterol and lower HDL values seen in CKD patients with ACS **Mencarelli et al. (30),**which demonstrated that one of the main risk factors for cardiovascular disease is dyslipidemia, which is prevalent in CKD patients.

In accordance, **Liang et al. (31**) concluded that there was a higher chance of low-density lipoprotein, high total cholesterol, and elevated triglycerides, as well as the onset of acute chronic kidney disease and a reduction in estimated glomerular filtration rate (eGFR).

Keane et al. (32) demonstrated that the high prevalence of hypercholesterolemia in patients with apparent proteinuria and CKD. Reduced high-density lipoproteins (HDL) and elevated triglyceride levels are associated with impaired renal function. The lipid profile of CKD patients shows elevated levels of triglycerides and very low-density lipoproteins (VLDL). Anomalies of the lipid metabolism-related enzymes will lead to an increase in the triglyceride content.

The elevated PTH levels in the CKD with ACS group are in line with findings from the research by **Xu et al. (33**), which discovered that individuals with chronic kidney disease frequently had secondary hyperparathyroidism, which is linked to poor cardiovascular outcomes. Increased arterial stiffness and vascular calcification brought on by elevated PTH may exacerbate ACS.

Rostand et al. (34) found that Ca and P were found to be strongly positively correlated with cardiac calcification in patients with end-stage renal disease.

Shanahan et al., (35) established that the VSMCs that cause vascular calcification are directly impacted by calcium and phosphorus. Elevated phosphorus levels impact many signaling pathways, such as apoptosis, vesicle release, extracellular matrix (ECM) disintegration, reduced calcification inhibitors, and osteo/chondrogenic differentiation, that increase the vulnerability of VSMCs to calcification. Moreover, increased levels of phosphorus and calcium have synergistic effects that serve as a primary trigger for vascular calcification in chronic kidney disease (CKD).

Our study's noteworthy connections with the calcium and phosphorus suggest that it may be used as a sign of advanced chronic renal disease (ACS) in individuals. This new discovery implies that further investigation is necessary to completely comprehend the clinical value of the calcium and phosphorus levels. Our findings offer a fresh viewpoint on mineral metabolism in CKD patients with cardiovascular problems because prior research has mostly concentrated on individual mineral levels rather than their ratios.

ROC curve analysis shows that calcium can predict acute coronary syndrome at cutoff 2.15 with area under the curve 0.611 with sensitivity and specificity was 59.1% and 57.1% respectively (p=0.019). Also ROC curve analysis shows that phosphorus can predict acute coronary syndrome at cutoff 1.75 with area under the curve 0.974 with sensitivity and specificity was 90.9% and 93.2% respectively (p=0.001).

Based on ROC curve interpretation, **Jadhav and Oommen, (22)**obtained a result indicating that if the calcium and phosphorus levels exceeds the normal levels, there is a significant increase in the study population's risk for ACS.

It's critical to acknowledge the study's limitations, such as its small sample size, possible confounding variables, and cross-sectional design, which makes it impossible to prove causal links.

Conclusion:

We concluded that there are notable differences between CKD patients with and without ACS, and that calcium and phosphorus levels play a vital role in these patients. These results open the door for more investigations and enhanced clinical management approaches while also adding to the increasing body of information regarding the significance of mineral metabolism in cardiovascular health among individuals with chronic kidney disease.

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