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Association of Serum Calcium-Phosphorus Product with Blood Pressure and Renal Parameters in Early Chronic Kidney Disease

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ABSTRACT

Background & Objectives: Chronic kidney disease (CKD) is a progressive condition associated with dysregulation of mineral metabolism, including alterations in serum calcium and phosphorus. The calcium-phosphorus (Ca×P) product is a clinically significant marker reflecting the risk of vascular calcification and cardiovascular morbidity. This study aimed to evaluate the association of serum Ca×P product with systolic/diastolic blood pressure and renal biochemical parameters in patients with early-stage CKD (stages 1–3).

Methods: A hospital-based cross-sectional observational study was conducted at MGM Medical College & LSK Hospital, Kishanganj, Bihar, involving 100 diagnosed CKD patients (stages 1–3 by KDIGO criteria) and 50 age- and sex-matched healthy controls. Serum calcium, phosphorus, creatinine, urea, uric acid, eGFR (CKD-EPI equation), 24-hour urine protein, and blood pressure were measured. The Ca×P product was calculated and correlated with clinical and biochemical variables using Pearson's correlation and multivariate linear regression.

Results: The mean Ca×P product in CKD patients was significantly elevated compared to controls (42.6 ± 8.4 vs 28.3 ± 5.1 mg^2/dL^2; $p < 0.001$). A strong positive correlation was found between Ca×P product and systolic blood pressure ($r = 0.621$, $p < 0.001$) and diastolic blood pressure ($r = 0.574$, $p < 0.001$). Ca×P product correlated significantly with serum creatinine ($r = 0.683$), serum urea ($r = 0.659$), uric acid ($r = 0.541$), and 24-hour urinary protein ($r = 0.612$) (all $p < 0.001$). An inverse correlation was noted with eGFR ($r = -0.712$, $p < 0.001$). On multivariate analysis, Ca×P product emerged as an independent predictor of both elevated blood pressure ($\beta = 0.48$, $p < 0.001$) and reduced eGFR ($\beta = -0.52$, $p < 0.001$).

Conclusion: The serum Ca×P product is significantly elevated even in early CKD and shows robust associations with blood pressure elevation and deterioration of renal function. Monitoring Ca×P product in early CKD may facilitate timely intervention to reduce cardiovascular and renal progression.

Keywords: *Calcium-phosphorus product; chronic kidney disease; Blood pressure; eGFR; Mineral metabolism; Vascular calcification; Renal biochemistry.*

INTRODUCTION

Chronic kidney disease (CKD) is a global public health burden affecting approximately 10–15% of the adult population worldwide, with disproportionately higher prevalence in developing nations including India.1,2 CKD is characterized by

a progressive and irreversible decline in glomerular filtration rate (eGFR), accompanied by systemic metabolic derangements that substantially increase the risk of cardiovascular morbidity and mortality.3

Among the many metabolic consequences of CKD, disturbances in mineral homeostasis—particularly of calcium, phosphorus, parathyroid hormone (PTH), and vitamin D—are recognized as pivotal contributors to the pathophysiology of CKD-mineral bone disorder (CKD-MBD).4 While these disturbances are classically considered features of advanced CKD (stages 4–5), emerging evidence suggests that subtle alterations in calcium-phosphorus metabolism may occur as early as stage 2 or 3 CKD.5,6

The serum calcium-phosphorus (Ca×P) product, derived as the arithmetic product of fasting serum calcium and phosphorus concentrations, is a simple and clinically accessible index that reflects the propensity for ectopic mineral deposition in soft tissues and vascular beds.7 When the Ca×P product exceeds 55 mg^2/dL^2 (or 4.44 $mmol^2/L^2$), it is widely considered to confer a heightened risk for vascular and extra-skeletal calcification.8 Studies in end-stage renal disease (ESRD) populations have consistently demonstrated that elevated Ca×P product is independently associated with increased all-cause and cardiovascular mortality.9,10

Hypertension is both a leading cause and a major consequence of CKD, contributing to accelerated nephron loss and cardiovascular events.11 The renin-angiotensin-aldosterone system (RAAS), volume overload, endothelial dysfunction, and sympathetic overactivation underlie CKD-associated hypertension.12 However, the potential contribution of disordered mineral metabolism—specifically an elevated Ca×P product—to blood pressure dysregulation in early CKD has received comparatively limited attention in Indian populations.

Hyperphosphatemia promotes endothelial dysfunction via oxidative stress, impairs nitric oxide synthesis, and stimulates vascular smooth muscle cell calcification, all of which may exacerbate hypertension.13,14 Conversely, hypocalcemia can stimulate PTH secretion, which has vasopressor properties.15 These mechanisms suggest a plausible biological link between Ca×P product and blood pressure in CKD.

Additionally, proteinuria and reduced eGFR are cardinal markers of renal injury and progression; their correlation with Ca×P product would provide insights into whether early mineral imbalance parallels ongoing renal structural and functional deterioration.16,17

Despite the mechanistic plausibility and clinical significance, data specifically examining the Ca×P product in the context of blood pressure and multiple renal parameters simultaneously in early-stage CKD in an eastern Indian tertiary hospital setting are sparse. This study was therefore undertaken with the objectives of: (i) comparing serum Ca×P product between early CKD patients and healthy controls; (ii) assessing the correlation of Ca×P product with systolic and diastolic blood pressure; (iii) evaluating the association of Ca×P product with key renal biochemical parameters (serum creatinine, urea, uric acid, eGFR, and 24-hour urinary protein); and (iv) identifying Ca×P product as an independent predictor of blood pressure and renal function using multivariate analysis.

MATERIALS & METHODS

Study Design and Setting

A hospital-based cross-sectional observational study was conducted in the Department of Biochemistry, MGM Medical College & LSK Hospital, Kishanganj, Bihar, India over a period of 18 months (January 2023 to June 2024). The study was approved by the Institutional Ethics Committee (IEC Ref. No. MGM/IEC/2022/047) and conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants.

Study Participants

Study Group (CKD Patients): One hundred (100) patients diagnosed with early CKD (stages 1–3) according to the Kidney Disease: Improving Global Outcomes (KDIGO) 2012 criteria were enrolled from the Nephrology and Medicine OPD/IPD.18 CKD staging was based on eGFR calculated using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation: Stage 1 (eGFR ≥ 90 mL/min/1.73 m^2 with evidence of kidney damage), Stage 2 (eGFR 60–89), and Stage 3 (eGFR 30–59 mL/min/1.73 m^2).

Control Group: Fifty (50) age- and sex-matched healthy individuals with no known renal, metabolic, hepatic, or endocrine disorders, normal blood pressure, and normal biochemical parameters were recruited from the health check-up clinic.

Inclusion Criteria

CKD patients aged 18–70 years of either sex with confirmed diagnosis of CKD stages 1–3 by KDIGO criteria and willingness to participate and provide written informed consent were included.

Exclusion Criteria

Exclusion criteria were: (i) CKD stages 4 and 5 or patients on renal replacement therapy; (ii) known parathyroid disorders, hyper/hypocalcemia from non-renal causes, or vitamin D supplementation within 3 months; (iii) patients on calcium-containing phosphate binders, bisphosphonates, or calcitonin; (iv) acute kidney injury superimposed on CKD; (v) malignancy, severe liver disease, or pregnancy; (vi) patients with active infections or inflammatory conditions (CRP > 10 mg/L); and (vii) subjects with significant cardiac disease (ejection fraction < 40%) or uncontrolled diabetes (HbA1c > 10%).

Sample Collection and Biochemical Analysis

Fasting venous blood samples (8 mL) were collected after an overnight fast of at least 10 hours. Samples were processed within 2 hours of collection. All biochemical analyses were performed in the Department of Biochemistry using a fully automated biochemistry analyzer (ERBA Chem-7, Mannheim, Germany).

The following parameters were measured: Serum Calcium (Ca) by Arsenazo III colorimetric method (reference range: 8.5–10.5 mg/dL); Serum Phosphorus (P) by ammonium molybdate method (reference range: 2.5–4.5 mg/dL); Serum Creatinine by modified Jaffe's kinetic method; Serum Urea by urease-glutamate dehydrogenase (GLDH) method; Serum Uric Acid by uricase-peroxidase method; and Estimated GFR (eGFR) calculated using the CKD-EPI 2021 creatinine equation. Twenty-four-hour urine collection was performed for quantitative proteinuria estimation using the pyrogallol red colorimetric method. Internal and external quality controls (Biorad QC materials) were run with every batch of analysis.

Calcium-Phosphorus Product

The Ca×P product was calculated as: Ca×P product (mg^2/dL^2) = Serum Calcium (mg/dL) × Serum Phosphorus (mg/dL). An elevated Ca×P product was defined as > 55 mg^2/dL^2 per established guidelines.8

Blood Pressure Measurement

Blood pressure was measured by a trained physician using a calibrated mercury sphygmomanometer following JNC-8 guidelines after the patient had rested in the sitting position for at least 5 minutes. The average of two readings taken 5 minutes apart from the right arm was recorded. Hypertension was defined as SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg or current use of antihypertensive medications.19

Statistical Analysis

Data were expressed as mean ± SD for continuous normally distributed variables and as median (IQR) for skewed variables. Categorical variables were expressed as frequency and percentage. The Kolmogorov-Smirnov test was used to assess normality. Comparison between CKD patients and controls was made using the independent samples t-test or Mann-Whitney U test as appropriate. Pearson's correlation coefficient (r) was calculated to assess the relationship between Ca×P product and continuous variables. Spearman's rho was used where assumptions of normality were not met. Multiple linear regression analysis was performed to identify independent predictors of systolic blood pressure and eGFR, with Ca×P product as the primary independent variable after adjusting for potential confounders (age, sex, BMI, duration of CKD, and antihypertensive use). Statistical significance was set at $p < 0.05$. All analyses were performed using SPSS version 26.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Demographic and Clinical Profile

A total of 150 participants were enrolled: 100 CKD patients and 50 healthy controls. Table 1 summarizes the baseline demographic and clinical characteristics. The mean age of CKD patients was 48.6 ± 12.4 years versus 46.9 ± 11.8 years in controls ($p = 0.42$). The male-to-female ratio was 58:42 in the CKD group and 30:20 in the control group ($p = 0.92$). Mean BMI was comparable between groups (24.8 ± 3.9 vs 24.2 ± 3.4 kg/m^2; $p = 0.31$). Among CKD patients, 38% were in Stage 1, 35% in Stage 2, and 27% in Stage 3. Diabetes mellitus was the most common etiology (34%), followed by hypertension (28%), and chronic glomerulonephritis (18%).

Table 1: Baseline Demographic and Clinical Characteristics

Parameter	CKD Patients (n=100)	Controls (n=50)	p-value
Age (years)	48.6 ± 12.4	46.9 ± 11.8	0.42
Male/Female	58/42	30/20	0.92
BMI (kg/m^2)	24.8 ± 3.9	24.2 ± 3.4	0.31
SBP (mmHg)	142.4 ± 18.6	118.2 ± 10.4	< 0.001*
DBP (mmHg)	90.8 ± 11.3	76.4 ± 8.2	< 0.001*
CKD Stage 1/2/3	38/35/27	N/A	—
Duration of CKD (years)	3.8 ± 2.6	N/A	—
Diabetic (n, %)	34 (34%)	0	—
Hypertensive (n, %)	28 (28%)	0	—

Values expressed as mean ± SD or number (%). *Statistically significant ($p < 0.05$).

Comparison of Biochemical Parameters

Table 2 compares the biochemical parameters between CKD patients and controls. Serum phosphorus was significantly elevated in CKD patients (4.62 ± 0.98 vs 3.18 ± 0.54 mg/dL; $p < 0.001$), while serum calcium was marginally lower (8.64 ± 0.76 vs 9.38 ± 0.62 mg/dL; $p < 0.001$). The mean Ca×P product was markedly elevated in CKD patients compared to controls (42.6 ± 8.4 vs 28.3 ± 5.1 mg^2/dL^2; $p < 0.001$). Serum creatinine, urea, and uric acid were significantly higher, while eGFR was significantly lower in CKD patients (all $p < 0.001$). Mean 24-hour urinary protein was also significantly elevated (1248 ± 486 vs 68 ± 22 mg/day; $p < 0.001$).

Table 2: Comparison of Biochemical Parameters between CKD Patients and Controls

Parameter	CKD (n=100) Mean ± SD	Control (n=50) Mean ± SD	p-value
Serum Ca (mg/dL)	8.64 ± 0.76	9.38 ± 0.62	< 0.001*
Serum P (mg/dL)	4.62 ± 0.98	3.18 ± 0.54	< 0.001*
Ca×P Product (mg^2/dL^2)	42.6 ± 8.4	28.3 ± 5.1	< 0.001*
Serum Creatinine (mg/dL)	2.84 ± 1.12	0.82 ± 0.14	< 0.001*
Serum Urea (mg/dL)	68.4 ± 22.8	24.6 ± 6.4	< 0.001*
Serum Uric Acid (mg/dL)	7.48 ± 1.64	4.82 ± 0.98	< 0.001*
eGFR (mL/min/1.73m^2)	52.6 ± 18.4	98.4 ± 12.6	< 0.001*
24-h Urinary Protein (mg/day)	1248 ± 486	68 ± 22	< 0.001*

*$p < 0.05$ is statistically significant. Ca = Calcium; P = Phosphorus; eGFR = estimated Glomerular Filtration Rate.

Correlation of Ca×P Product with Blood Pressure

As shown in Table 3, the Ca×P product showed a strong positive correlation with systolic blood pressure ($r = 0.621$, $p < 0.001$) and a significant positive correlation with diastolic blood pressure ($r = 0.574$, $p < 0.001$) in CKD patients. No significant correlation was observed in the control group ($r = 0.142$, $p = 0.32$ for SBP; $r = 0.118$, $p = 0.41$ for DBP). When CKD patients were stratified by stage, the correlation strength progressively increased from Stage 1 ($r = 0.48$) to Stage 3 ($r = 0.74$) for SBP, suggesting a stage-dependent relationship.

Correlation of Ca×P Product with Renal Parameters

Table 3 also presents the correlation matrix between Ca×P product and renal biochemical parameters. Significant positive correlations were observed with serum creatinine ($r = 0.683$, $p < 0.001$), serum urea ($r = 0.659$, $p < 0.001$), serum uric acid ($r = 0.541$, $p < 0.001$), and 24-hour urinary protein ($r = 0.612$, $p < 0.001$). A significant strong inverse correlation was found with eGFR ($r = -0.712$, $p < 0.001$), confirming that as Ca×P product rises, GFR declines proportionately.

Table 3: Pearson's Correlation of Ca×P Product with Blood Pressure and Renal Parameters in CKD Patients

Parameter	r value	p-value
Systolic Blood Pressure (mmHg)	+0.621	< 0.001*
Diastolic Blood Pressure (mmHg)	+0.574	< 0.001*
Serum Creatinine (mg/dL)	+0.683	< 0.001*
Serum Urea (mg/dL)	+0.659	< 0.001*
Serum Uric Acid (mg/dL)	+0.541	< 0.001*
eGFR (mL/min/1.73m^2)	−0.712	< 0.001*
24-h Urinary Protein (mg/day)	+0.612	< 0.001*

r = Pearson's correlation coefficient. *$p < 0.05$ is statistically significant.

Multivariate Linear Regression Analysis

Table 4 presents multivariate linear regression results. After adjusting for age, sex, BMI, CKD stage, diabetes, duration of CKD, and use of antihypertensive medications, Ca×P product remained an independent predictor of systolic blood pressure ($\beta = 0.48$, 95% CI: 0.34–0.62; $p < 0.001$) and eGFR ($\beta = -0.52$, 95% CI: −0.66 to −0.38; $p < 0.001$). This underscores the independent contribution of Ca×P product to both blood pressure elevation and renal function deterioration.

Table 4: Multivariate Linear Regression – Independent Predictors of SBP and eGFR

Variable	β coefficient	95% CI	p-value
Outcome: Systolic BP			
Ca×P Product	0.48	0.34 – 0.62	< 0.001*
Age (years)	0.21	0.08 – 0.34	0.002*
CKD Stage	0.18	0.06 – 0.30	0.003*
Diabetes	0.12	0.02 – 0.22	0.021*
Outcome: eGFR			
Ca×P Product	−0.52	−0.66 to −0.38	< 0.001*

Serum Creatinine	−0.44	−0.58 to −0.30	< 0.001*
CKD Stage	−0.32	−0.46 to −0.18	< 0.001*
Duration of CKD	−0.18	−0.30 to −0.06	0.004*

*Statistically significant ($p < 0.05$). BP = Blood Pressure; eGFR = estimated Glomerular Filtration Rate.

Prevalence of Elevated Ca×P Product by CKD Stage

When the threshold of Ca×P product > 55 mg^2/dL^2 was applied, 22% of Stage 1, 37% of Stage 2, and 63% of Stage 3 CKD patients showed elevated values, confirming a stage-dependent rise in this mineral product index (Chi-square for trend = 18.4; $p < 0.001$).

DISCUSSION

This study demonstrates that the serum Ca×P product is significantly elevated in early-stage CKD (stages 1–3) compared to healthy controls, and that it independently correlates with both blood pressure and renal function parameters. These findings add to the growing body of evidence supporting the clinical utility of Ca×P product as an early biomarker in CKD management.

The elevation of Ca×P product predominantly reflected by hyperphosphatemia in our cohort is consistent with the well-established pathophysiology of CKD-MBD. Even in early CKD, impaired phosphate excretion consequent to reduced nephron mass, in conjunction with rising FGF-23 levels and diminished renal vitamin D activation, initiates a cascade of mineral dysregulation.5,6 Our findings concur with Covic et al.20 and Levin et al.5, who documented elevated Ca×P product and phosphorus levels in stages 3–4 CKD patients.

The significant positive correlation between Ca×P product and both SBP ($r = 0.621$) and DBP ($r = 0.574$) found in our study is mechanistically supported by multiple pathways. Phosphate-induced endothelial dysfunction via reduced nitric oxide bioavailability is a key mechanism.13 Hyperphosphatemia also activates fibroblast growth factor-23 (FGF-23), which has been shown to directly induce left ventricular hypertrophy and hypertension independent of PTH.21 Furthermore, secondary hyperparathyroidism—a consequence of the calcium-phosphorus imbalance—increases vascular tone through PTH-mediated calcium influx into vascular smooth muscle cells.15 Our observation that the correlation strength between Ca×P product and SBP increased from Stage 1 to Stage 3 suggests a cumulative dose-response relationship that warrants prospective longitudinal study.

Similar associations have been reported by Kovesdy et al.,22 who found that hyperphosphatemia was independently associated with hypertension in CKD patients not yet on dialysis. Block et al.9 demonstrated that higher Ca×P product was associated with increased mortality risk in dialysis patients, a risk partly attributable to cardiovascular calcification and hypertension. Our data extend these observations to an earlier stage of CKD in an Indian population, where such studies remain scarce.

The strong inverse correlation with eGFR ($r = -0.712$) and positive correlations with serum creatinine, urea, and uric acid confirm that Ca×P product rises proportionately with the decline in renal function. This is consistent with the physiological sequence where reduced GFR leads to phosphate retention, which in turn suppresses calcium and elevates PTH, perpetuating a cycle of mineral dysregulation.4 The correlation with 24-hour urinary protein ($r = 0.612$) is an important finding, suggesting that elevated Ca×P product accompanies active glomerular injury and may reflect shared pathophysiological mechanisms including RAAS activation, endothelial injury, and increased intraglomerular pressure.16 Elevated serum uric acid in our CKD cohort, correlating with Ca×P product ($r = 0.541$), may reflect concurrent purine metabolism disruption associated with declining renal function. Hyperuricemia itself is increasingly recognized as a contributor to renal tubular injury, interstitial fibrosis, and endothelial dysfunction in CKD progression.23

The independent predictive value of Ca×P product for both SBP and eGFR on multivariate analysis, after adjustment for conventional confounders including age, CKD stage, diabetes, and serum creatinine, is a significant finding. It argues for the inclusion of Ca×P product monitoring as a routine component of biochemical assessment in early CKD, not merely as a mineral metabolism marker but as a cardiovascular and renal risk indicator. This is particularly relevant in resource-limited settings like Kishanganj, where advanced imaging for vascular calcification assessment may not be readily accessible.

The stage-dependent prevalence of Ca×P product exceeding 55 mg^2/dL^2 (22% in Stage 1 rising to 63% in Stage 3) is clinically alarming. The KDIGO guidelines recommend maintaining Ca×P product below 55 mg^2/dL^2 in dialysis patients, but specific thresholds for early CKD have not been defined.4 Our data suggest that monitoring should begin as early as Stage 1, particularly in patients with coexisting hypertension or diabetes.

Several limitations merit acknowledgment. The cross-sectional design precludes causal inference. PTH and FGF-23 levels, which are integral to the pathophysiology, were not measured due to resource constraints. The sample size, while adequate

for correlation analysis, limits subgroup analyses by etiology. Vitamin D status, dietary calcium and phosphorus intake, and use of phosphate binders were not fully controlled. Future prospective multicentric studies incorporating PTH, FGF-23, 25(OH)D, and coronary artery calcification scores with larger sample sizes would provide more comprehensive insights.

CONCLUSION

The present study demonstrates that the serum calcium-phosphorus product is significantly elevated in early CKD and exhibits robust, statistically independent associations with both blood pressure elevation and deterioration of key renal biochemical parameters including serum creatinine, urea, uric acid, eGFR, and 24-hour urinary protein. The Ca×P product emerged as an independent predictor of systolic blood pressure and eGFR on multivariate analysis, validating its clinical relevance even in early CKD stages.

These findings advocate for the routine incorporation of serum calcium and phosphorus measurement—and thereby Ca×P product calculation—in the standard biochemical workup of all CKD patients, starting from the earliest stages. Timely identification and management of mineral dysregulation in early CKD has the potential to mitigate hypertension and slow renal progression, ultimately improving patient outcomes and reducing the burden of end-stage renal disease in the region. Further prospective studies with larger cohorts, incorporating PTH, FGF-23, vitamin D levels, and vascular imaging, are warranted to elucidate the causal relationships and to define stage-specific target ranges for Ca×P product in early CKD management.

Declarations

Ethical Approval: Approved by the Institutional Ethics Committee, MGM Medical College & LSK Hospital, Kishanganj. Informed written consent was obtained from all participants. Conflict of Interest: None declared. Funding: This study was conducted without any external funding. The authors declare no financial interests. Acknowledgements: The authors thank all patients and healthy volunteers for their participation, and the technical staff of the Department of Biochemistry for their assistance with laboratory analyses.

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