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Research Article

Correlation of iPTH, Serum Calcium, and Serum Phosphorous with Different Stages of Chronic Kidney Disease

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Abstract:Background: CKD-mineral and bone disorders (CKD-MBD) include abnormalities in blood calcium (Ca), phosphate (P), and parathyroid hormone (PTH), as well as bony derangements and vascular calcification, which are increasingly more frequent in patients with chronic kidney disease (CKD) stages 4 and 5.

Objective: To assess the correlation of chronic kidney disease, mineral, and bone disorder (CK-MBD) with stages of CKD.

Materials and Methods: This is a cross-sectional, study conducted at the Tabba Kidney Institute, Serum levels of calcium, phosphate, and intact PTH (iPTH) were measured as part of the study at baseline. The statistical package of Social Sciences version 22 was used to enter, sort, and analyze data. To assess the risk of vascular calcification in different stages of CKD, odds ratio (OR) test was performed, keeping confidence interval as 95% and OR of 1 as positive risk of outcome after exposure.

Result: A total of 82 patients were enrolled in the study with a mean age of 59.6 ± 13.3 years. The results indicated positive odds of vascular calcification in CKD stage V with 1.418 and Confidence interval of 95% as a lower bound and upper bound of 1.121-10.817, indicating higher chances of vascular calcification in stage V patients. Similarly, CKD stage IV reported 0.042 OR with lower and upper bound of 0.352-4.162 confidence interval respectively.

Conclusion: This study concludes that CKD progression is directly associated with Bone mineral disorders and allied complications, including the risk of vascular calcification in patients which increases from stage III to V.

Keywords: iPTH, Bone minerals, CKD, Dialysis dependent, Vascular calcification, CKD 5-d, Calcium-phosphorus product.

INTRODUCTION

It is estimated that 5-10% of people worldwide suffer from chronic kidney disease (CKD) as a result of the high frequency of poorly managed chronic illnesses including diabetes mellitus and arterial hypertension [1-3]. Given that the kidney has a significant role in the metabolism of minerals and bone health; abnormalities in bone metabolism are seen as early as stages of chronic kidney disease (CKD) and gradually deteriorate bone health [4, 5].

Though the precise incidence of CKD in Pakistan is unknown, a study of the data that is currently available on the condition in Pakistan indicated that it was 17% in the neighboring nations. Based on an extrapolation of this figure to the current population of 207 million, the number of individuals living in Pakistan with compromised kidney functions would come to 35,326,000 (3.5 cores) [6]. Similar to the renal registry in other parts of Asia, the data on the prevalence of CKD in the present is rather limited and should be used to inform future estimates [7].

CKD-mineral and bone disorders (CKD-MBD) include abnormalities in blood calcium (Ca), phosphate (P), and parathyroid hormone (PTH), as well as bony derangements and vascular calcification, which are increasingly more frequent in patients with chronic kidney disease (CKD) stages 4 and 5 [8].

Epidemiological research links these disruptions to an increased risk of cardiovascular and all-cause death in CKD patients. As a result, the international Kidney Disease: Improving Global Outcomes (KDIGO) guidelines for CKD-MBD recommend keeping serum PTH, calcium, and phosphate within distinct target ranges for every stage of CKD. As such, monitoring and managing these biochemical parameters is a crucial part of the patient's routine care [9].

Most patients experience more severe disturbances in bone and mineral metabolism as their renal impairment worsens. These include Renal Osteodystrophy (ROD), which is characterized by bone pain, muscle-tendon rupture, pruritus, and an increased risk of fractures, increased risk of vascular calcification when Ca x PO4 product is > 55 and, a systemic disorder of mineral and bone metabolism brought on by CKD.

Studies have shown that individuals with CKD stages 3a–5D had poor bone mineral density (BMD) and 1.5-2 times the risk of fractures compared to the general population and BMD-matched patients without CKD. Studies show that in this patient population, CKD-MBD significantly increases the risk of death and morbidity as well as lowers quality of life [10].

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Poor clinical outcomes in pre-dialysis and dialysis patients have been linked to aberrant levels of CKD-MBD markers, according to observational study data. Numerous studies have shown that in patients with stages, 3-5 of CKD and HD, elevated levels of alkaline phosphatase were associated with an increased risk of hospitalization and mortality. In patients receiving maintenance hemodialysis, higher mortality was linked to the presence of elevated calcium and phosphate levels in conjunction with either low or high PTH levels. The pathophysiology of vascular calcification is significantly influenced by alkaline phosphatases, which may help to explain why elevated levels of these enzymes are linked to a higher death rate. Strong links have been shown in other research between low FGF23 levels and unfavorable renal outcomes [11].

Our primary areas of concentration were systematic reviews, meta-analyses, and randomized, controlled research and trials. A systemic disease of the metabolism of minerals and bone caused by chronic kidney disease (CKD) that presents as one or more of the following symptoms: Deviations in vitamin D, PTH, calcium, or phosphorus levels metabolism, Deviations from normal in terms of bone mineralization, volume, strength, or turnover and Vascular or other soft-tissue calcification [12].

This study aims to assess the correlation of chronic kidney disease, mineral, and bone disorder (CK-MBD) with stages of CKD. The secondary objectives of this study are to evaluate the association of Ca, PO4, and, iPTH with different stages of CKD and to estimate the risk of vascular calcification by calculating the Ca-P product.

MATERIALS AND METHODS

This is a cross-sectional, study conducted at the nephrology department, Tabba Kidney Institute, Karachi. Prior approval was obtained from the ethical review committee [TKI-HEC 32], data collection was started from 10th October 2023 till 10th January 2024, for the duration of three months. Adult patients, aged between 18 to 70 years old, with confirmed diagnosis of chronic kidney disease, CKD stages ranging from III to V-D, were included in the study. Patients with incomplete medical follow-up and/or requiring emergency medical interventions were excluded from the study. The sample size was calculated with the help of the WHO sample size calculator, keeping CKD prevalence in the Pakistani population at 16.7% [13]. The confidence interval was 95% the margin of error was 5%, and the minimum required sample size was 80. Informed consent in the language of understanding was signed by the primary investigator before enrollment, and a comprehensive clinical assessment and regular testing of laboratory markers were conducted at each appointment. During the clinical evaluation, demographic data was recorded.

Laboratory investigation includes Hemoglobin, platelet, serum creatinine, serum urea, albumin, iPTH, serum calcium, and serum phosphorous. Serum levels of calcium, phosphate, and intact PTH (iPTH) were measured as part of the study at baseline. To adjust the calcium levels, the following formula was used: KDIGO guidelines state that corrected calcium (mg/dL) is equal to measured total calcium (mg/dL) + 0.8 [4.0 − serum albumin (g/dL)]. Every laboratory assessment was carried out following the standard operating procedures of the laboratory department.

Age, sex, comorbidities, regular medication, and lab testing were additional study factors. Before participation, comorbidities that were recorded in our research forms were diabetes mellitus, smoking status, and a history of cardiovascular disease. Calcium supplements, Phosphate binding agents (PBAs), vitamin D compounds, erythropoiesis-stimulating agents (ESAs), oral or intravenous iron, and anti-hypertensive were among the current medications that were noted during each research visit.

Using the CKD-EPI formula, the estimated glomerular filtration rate (eGFR) was determined. Calcium–phosphorus product was calculated by multiplying both values, the result of the Ca-Phosphorus product maintained at < 55 mg2 /dL2 was considered as required. For the remaining laboratory parameters, the following scales were used.

STATISTICAL ANALYSIS

The statistical package of Social Sciences version 22 was used to enter, sort, and analyze data. To assess the normality of data, the Shapiro-Wilk test was used, and continuous variables were evaluated and represented in mean and standard deviation. The evaluation of two categorical variables was analyzed with the help of cross-tabulation, chi-square test was used to identify the significance of two mean values. The P-value of < 0.05 was considered as significant. To assess the risk of vascular calcification in different stages of CKD, odds ratio test was performed, keeping confidence interval as 95% and OR of 1 as positive risk of outcome after exposure.

RESULT

A total of 82 patients were enrolled in the study with a mean age of 59.6 ± 13.3 years. The gender distribution was 38 (45.2%) males and 46 (54.8%) females. The most frequently reported comorbidity was diabetes mellitus in a combination of hypertension in 36 (42.9%) followed by Hypertension in 27 (32.1%) of participants. The most frequently reported etiology of CKD was Diabetic Nephropathy in 42 (50%) of the participants followed by Bilateral Small Size Kidney in 25 (29.8%), while other were Obstructive uropathy, Amyloidosis and auto-immune glomerular nephritis. Chronic kidney disease stage distribution was identified as Stage III with 13 (15.5%) patients, stage IV with 17 (20.2%) patients, stage V with 29 (34.5%), and stage V-D with 25 (29.8%) patients respectively.

Upon division of CKD stages for laboratory investigations, results indicated p-value of 0.074 and 0.14 serum calcium and serum phosphate, respectively within stages III, IV, and V, remaining mean values were significant (Table **1**). However, the

mean values of CKD Stage V-D are reportedly different from stages IV and V with stable HB level as 9.9 ± 1.4 and other parameters as well (Tables **1**, **2**).

Table 1. Mean and Standard Deviation of Laboratory Investigations in CKD Stages III to V.

Variables	CKD Stage III	CKD Stage IV	CKD Stage V	P-Value
Hemoglobin	10.8 ± 1.5	9.8 ± 1.3	8.9 ± 1.3	0.005
Serum Urea	56.6 ± 24.6	87.5 ± 45.8	160.2 ± 80.9	0.0007
Serum Creatinine	1.7 ± 0.2	3.0 ± 0.4	7.3 ± 4.6	0.0001
Serum Calcium	9.0 ± 0.8	8.5 ± 0.8	7.7 ± 0.7	0.074
Serum Albumin	3.4 ± 0.8	3.5 ± 0.5	3.4 ± 0.7	0.0005
Serum Phosphorus	3.9 ± 0.8	5.5 ± 0.6	7.0 ± 2.0	0.14
Serum iPTH	87.2 ± 73.6	144.4 ± 161.9	280 ± 192.5	0.0001
Serum Alkaline Phosphate	135.2 ± 55.8	174.3 ± 89.7	179.5 ± 156.7	0.0001

Table 2. Mean and Standard Deviation of Laboratory Investigations in CKD stage V-D.

Variables	V-D
Hemoglobin	9.9 ± 1.4
Serum Calcium	8.4 ± 0.96
Serum Albumin	3.9 ± 0.4
Serum Phosphorus	5.8 ± 1.6
Serum iPTH	392.7 ± 396.9
Serum Alkaline Phosphate	277.3 ± 154.4

The calcium-phosphorus product was calculated and 58 (69.9%) of patients had < 55 of Ca + Phosp. product result while remaining 25 (30.1%) reported > 55 respectively. While categorizing Ca + Phosp. Product according to CKD stages, the results indicated < 55 result product in CKD stage III and IV while > 55 result product was highest in CKD stage V. CKD stage III had 10 (12.1%), and 0, Stage IV had 15 (18.2%) and 2 (2.4%), stage V had 10 (12.1%) and 18 (21.9%) and Stage VD had 18 (21.9%) and 5 (6%) of <55 and >55 result product respectively. The overall p-value was significant (0.00005) (Table **3**).

Table 3. Distribution of CKD Stage in Association with Calcium and Phosphorus Products.

Ca + Phosphorus Product	CKD Stages				P-Value
	III	IV	V	VD	
≤ 55	10 (12.1%)	15 (18.2%)	10 (12.1%)	18 (21.9%)	0.0005
> 55	0	2 (2.4%)	18 (21.9%)	5 (6%)	

A regression test was applied to assess the risk of vascular calcification in study participants with calcium-phosphorus product results, the results indicated positive odds of vascular calcification in CKD stage V with 1.418 and Confidence interval of 95% as a lower bound and upper bound of 1.121 - 10.817, indicating higher chances of vascular calcification in stage V patients. Similarly, CKD stage IV reported 0.042 OR with lower and upper bound of 0.352-4.162 confidence interval respectively (Table **4**).

Table 4. Estimation of Odds Ratio for Vascular Calcification within Different Stages of CKD.

Variables	Ca + Phosphorus Product		Odds Ratio	CI 95%
	≤ 55	>55		
CKD Stage III	10 (12.1%)	0	0.011	0.003-0.726
CKD Stage IV	15 (18.2%)	2 (2.4%)	0.042	0.352-4.162
CKD Stage V	10 (12.1%)	18 (21.9%)	1.418	1.121-10.817
CKD Stage V-D	18 (21.9%)	5 (6%)	0.004	0.044-0.542

All study participants were asked about dietary supplement intake, patients on maintenance dialysis were the highest frequency group taking dietary supplements regularly hence their results were seemingly better. The p-value was significant for all variables (Table **5**).

Table 5. Frequency of Dietary Supplement Use in Study Participants Categorized according to Stages.

Supplements Intake		CKD Stages				P-Value
		III	IV	V	V-D	
Calcium supplements	Yes	0	1 (1.2%)	1 (1.2%)	16 (19.5%)	0.0005
	No	13 (15.8%)	16 (19.5%)	28 (34.1%)	7 (8.5%)	
Vitamin-D supplements	Yes	1 (1.2%)	3 (3.6%)	1 (1.2%)	16 (19.5%)	0.0005
	No	12 (14.6%)	14 (17%)	28 (34.1%)	7 (8.5%)	

Continue

Continue

Ca, Phosp Binder supplements	Yes	0	0	0	10 (12.1%)	0.0005
	No	13 (15.8%)	17 (20.7%)	29 (35.2%)	13 (15.8%)	
Non Calcium Binder supplements	Yes	0	0	0	5 (6%)	0.003
	No	13 (15.8%)	17 (20.7%)	29 (35.2%)	18 (21.9%)	

DISCUSSION

The results of this study indicated that bone minerals including iPTH, Phosphorus, and alkaline phosphate values increase while calcium values decreases parallel to CKD prognosis, representing the decline in overall renal function [14-16]. Bone mineral disorder pathophysiology identifies that after CKD stage 3 primary changes in vitamin D (calcidiol and calcitriol) and calcium, phosphate and PTH occur, resulting in significant changes in bone and vascular metabolism with very negative clinical consequences, including increased vascular and valvular calcification, decreased bone mass, and increased fragility fractures [17-21]. The results of this study indicate a higher risk of mortality and associated morbidity in CKD patients, as mentioned in a study conducted in California in 2013, disrupted values of Calcium, iPTH, Phosphorus, and Vitamin D are highly associated with increased risk of mortality and morbidity in maintenance dialysis-dependent patients [22]. Because of the complex relationships between the biologic variables of PTH, calcium, and phosphate, modifications to one of these variables-whether de novo or as a result of treatment-inevitably impact the others. Consequently, there is a high likelihood that these variables will share elements on the causal pathway leading to unfavorable outcomes [23]. Abnormal PTH, calcium, and phosphate come in a variety of phenotypes, each associated with a unique risk of cardiovascular hospitalization and mortality. It is crucial to take into account both the number of patients exposed to the danger and the risk associated with each phenotype to enhance the quality of dialysis therapy. Available literature, indicate that 20% of patients have good control on their iPTH, Calcium and phosphorus values with dietary supplementation [24]. It is noteworthy that increased iPTH and phosphate are present in CKD stage IV and V [25]. The economics of CKD-MBD treatment will significantly change if oral phosphate binders and calcimimetics are affordable [26]. The identification of high-risk patterns of iPTH, calcium, and phosphate can aid in identifying groups at higher risk of unfavorable outcomes and their total contribution to mortality in dialysis patients [27]. A variety of problems related to hormones and biochemistry, poor bone architecture, development and fragility, and extra skeletal calcification are all associated with CKD-MBD. To reduce morbidity and mortality in CKD patients, it is crucial to manage CKD-MBD [28].

Because all three are interconnected and changing one usually impacts the others, this calls for an integrated strategy and a working knowledge of physiology. The challenge of the future will be studies that concentrate on combination treatment to concurrently address all features of CKD-MBD [29]. In summary, the fundamental processes behind bone loss and fractures in individuals with chronic kidney disease are intricate and not fully comprehended [30]. The current non-invasive investigative methods to identify both bone quantity and quality losses are clinically inadequate as screening or diagnostic methods, in contrast to bone biopsy. It has been demonstrated that bone-targeted medication only slightly reduces the frequency of fractures, and in this particular demographic, it may have unanticipated negative consequences [31]. These individuals may benefit differently from traditional but customized therapy, such as vitamin D supplements, phosphate management using phosphate binders, anti-resorptive medications, dialysis, and medical and surgical PTX. Researchers should continue delving into the specific processes of pathophysiology and explore tailored treatments for the quantity- and quality-related bone loss associated with chronic kidney disease (CKD) [32].

This study has some limitations, such as cross-sectional study design and lack of follow-up, counseling of patients regarding nutritional management and re-assessment after a few weeks is recommended. However, this study is one of a kind in the Pakistani population as to the best of our knowledge the overall association has not been assessed before in our population with CKD diagnosis.

CONCLUSION

The results of this study indicate that the advancement of chronic kidney disease (CKD) is directly linked to bone mineral abnormalities and related consequences, such as an increased risk of vascular calcification in patients from stage III to stage V. However, because they are receiving the right care, monitoring, and nutritional supplements, patients on maintenance dialysis are exhibiting a somewhat decreased risk of related problems.

AUTHORS' CONTRIBUTION

- **Muhammad Talha Jawaid**: Objective, Write-up.
- **Bilal Jamil**: Final approval, Subject specialist.
- **Ameen Zubair Syed**: Ethical consideration.
- **Kulsoom**: Data collection, Consultation, Analysis.
- **Asif Mehdi**: Writing supervision
- **Erum Alam**: Writing manuscript, Data entry.

CONFLICT OF INTEREST

Declared none.

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