Analysis of the Prevalence and Severity of Dysregulated Bone Mineral Homeostasis in Nondialyzed Chronic Kidney Disease Patients

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Abstract

Background   Progressive loss of kidney function in chronic kidney disease (CKD) leads to altered mineral homeostasis, reflected by the imbalance in calcium and phosphorus, and has been associated with progression of renal failure.

Aims   The aim of this study was to investigate CKD-mineral bone disorder (CKD-MBD)-associated candidate variables and its relationship with parathyroid hormone (PTH), as well as to quantify the prevalence of CKD-associated mineral disturbances in non-dialyzed CKD patients.

Materials and Methods   This cross-sectional analytical study included 124 CKD patients and 157 control participants. Blood samples were analyzed for serum total calcium, phosphorus, PTH, electrolytes, and other hematological/hemodynamic parameters by standard methods. Suitable descriptive statistics was used for different variables.

Results   The 124 patients had a mean age of 50.2 ± 7.8 years with male to female ratio of 1.58; majority of patients had stage 3 CKD (40.32%), and the most common comorbid conditions were diabetes mellitus ($n = 78$ [62.9%]) and hypertension ($n = 63$ [50.8%]). A high prevalence of mineral metabolite abnormalities was observed in a patient cohort; overall prevalence of hyperparathyroidism was found in 57.25% patients, hypocalcemia in 61.29%, and hyperphosphatemia in 82.25% patients. Prevalence of abnormal homeostasis (with regard to total calcium, phosphate, and PTH) increased progressively with the severity of disease (analysis of variance; $p < 0.05$). Significant differences in the mean values of total calcium, phosphorus, alkaline phosphatase, and PTH were seen compared with healthy participants ($p < 0.0001$). Furthermore, there was a significant positive correlation between serum PTH with serum phosphorous (R^2: 0.33; $p < 0.0001$), serum creatinine (R^2: 0.084; $p < 0.0259$), serum potassium (R^2: 0.068; $p < 0.0467$), and a significant negative correlation with serum total calcium (R^2: 0.37; $p < 0.0001$).

Keywords
► chronic renal insufficiency
► calcium
► phosphorus
► PTH

Conclusions   CKD patients are at risk of or may already have developed secondary hyperparathyroidism apparent from PTH-linked derangements in mineral metabolism in predialysis CKD patients. These abnormalities start in early stages of CKD and worsen with disease progression. This accentuates the significance of early recognition of mineral bone disorder, understanding its pathophysiological consequences and scheduling necessary interventions/management strategies to protect the CKD patients from a plethora of complications.

Introduction

Chronic kidney disease (CKD) is characterized by slow progressive abrasion of nephron number or endogenous renal function by means of multifaceted etiologies and is associated with poor outcomes.[1,2] Outcomes of CKD include rapid progression to end-stage renal disease as well as increased rates of cardiovascular events, cognitive/sexual dysfunction, anemia, mineral, and bone disorders.[1–4]

CKD is stratified into five stages as per Kidney Disease Outcomes Quality Initiative Clinical Practice Guidelines for Chronic Kidney Disease (KDIGO-CKD)[1] staging and each of these stages is associated with significant perturbations in bone mineral homeostasis,[3] leading to altered serum concentrations of parathyroid hormone (PTH), phosphorus, calcium, and other markers of disordered bone-mineral metabolism,[3] with eventual progression to clinical syndrome termed as chronic kidney disease-mineral bone disorder (CKD-MBD).[3,4]

Early detection and management of CKD-associated mineral bone disorder are imperative as it is allied with abnormalities in bone remodeling, renal osteodystrophy, and extraskeletal calcification,[3] resulting in increased morbidity, augmented all-cause and cardiovascular-specific mortality owing to elevated soft tissue, and vascular and cardiac valvular calcification.[3,5,6]

Over the last two decades or so, numerous clinical and experimental studies have shown abnormal mineral homeostasis and higher mortality in hemodialysis patients.[5,6] Although these dysregulated bone mineral homeostasis develop early in the course of chronic renal insufficiency, that is, calcium–phosphorus homeostatic abnormalities are already there in patients who have CKD, even prior to commencement of dialysis,[1,2] their progression and spectrum in predialysis CKD patients are less well described, more so specifically in Gujarati population, in part owing to the lack of comprehensive clinical and biochemical analysis. Thus, this study is an attempt to investigate bone-associated candidate variables and its relationship with PTH as well as to quantify the prevalence of CKD associated mineral disturbances in non-dialyzed CKD patients.

Materials and Methods

This was a cross-sectional study conducted on newly or previously diagnosed patients of CKD, reporting to the nephrology clinic/medicine outpatient department (OPD) or wards, and the emergency unit of the hospital over a period of 24 months. Inclusion criteria were patients who were $\geq$ 18 years of age and patients who have not been started on dialysis or hematinics. Exclusion criteria included patients of acute kidney injury; patients with a history of primary parathyroid disease, hematological neoplasm or solid organ malignancy; patients with chronic infections or patients using any prescription-based calcium supplements, vitamin D analogs, phosphate binders, steroids, anticonvulsants, anticoagulants, calcineurin inhibitors, calcimimetics, bisphosphonates, and other drugs that can affect bone mineral density, in the preceding 12 months; patients taking tobacco or alcohol or having a history of tobacco or alcohol intake (to exclude environmental/external factor for the deterioration of kidney function); pregnant and lactating females; and those patients refusing to sign the consent form.

A total of 281 participants (124 patients and 157 healthy controls) were recruited in the present study after explaining the study protocol and obtaining written informed consent form. Consecutive, convenient sampling technique was used for the enrollment of patient in this study, that is, all the patients who visited the nephrology clinic/medicine OPD or wards of hospital in the study period and fulfilled the criteria were included and it was ensured that 1:1 matching was done. So as per convenience, 124 patients and 157 healthy participants were recruited. Patients were categorized according to the Kidney Disease Outcomes Quality Initiative Clinical Practice Guidelines for Chronic Kidney Disease: Evaluation, Classification, and Stratification.[1] Healthy controls were selected at random from patients' relatives and participants on routine health checkup who did not have CKD or any significant medical illness. The study was approved by the Institutional Ethical Committee. Data regarding demographics (such as gender, age, education, economic status, residency), occupation, and history suggestive of any systemic illness were collected through a self-administered questionnaire. Blood pressure was measured in the seated position after 10 minutes of rest with a standard manual mercury sphygmomanometer and stethoscope by auscultatory method.[7] Age was defined as the age at the time of interview (though no documentary proof had been entertained). A sample of venous blood was drawn with an aseptic technique and subjected to estimation of serum total calcium,[8] serum phosphorus,[9] serum PTH,[10] serum alkaline

phosphatase,[11] serum creatinine,[12] serum urea,[13] plasma glucose,[14] serum sodium,[15] serum potassium,[15] and hemoglobin. All analysis was done on the same day of collection in a single laboratory using commercial kits.

The statistical analyses were performed using Med Cal statistical software and MS Excel. Data were expressed as mean $\pm$ standard deviation (continuous variables), or as percentages of total (categorical variables). Two-group comparisons were made using chi-squared test (x^2) for categorical variables and Students' t-tests or one-way analysis of variance (ANOVA) for continuous variables. For all analyses, the nominal level of statistical significance was < 0.05.

Results

Baseline characteristics are presented in ►Table 1 for the patient group and control participants. The mean patient age was 50.2 ± 7.8 years. There were 76 males and 48 females, giving a male to female ratio of 1.58:1. Diabetes mellitus was present in 62.9% of patients and 50.8% patients were hypertensive. Percentage of patients with a history of chronic glomerulonephritis, polycystic kidney disease, and obstructive uropathy was 18.5, 7.2, and 5.6%, respectively (►Table 1). Fifty-two patients had both diabetes and hypertension. Although there was a dominance of male individuals as compared with females in participants (►Table 1), male to female ratio ($p < 0.05$) was statistically similar in patient

group and control participants; also there was no statistically significant difference ($p = 0.1593$) in mean age between the studied groups, indicating that the two groups were well-matched for the analysis in question. ►Table 1 also describes the patients as per stratified stages of CKD. The majority of patients had stage 3 CKD (40.32%), distinctive as glomerular filtration rate between 30 and 60 mL/min/1.73m^2. In view of the fact that the study enrolled only predialysis CKD patients, it might be the reason for minimal patient in stage 4 (11.2%) and none in stage 5 of CKD (as no reported patient in our hospital setup were without the need of dialysis).

The results of CKD-Bone Mineral Disorder associated indices are summarized in ►Table 2. The mean values of serum phosphorus were 3.3 ± 0.8 and 6.4 ± 1.7 mg/dL in control and patients, respectively. The corresponding values for total calcium were 9.6 ± 1.4 and 6.7 ± 1.3 mg/dL, respectively. Mean estimated levels of serum PTH in healthy controls and CKD patients were 44.5 ± 10.2 and 364.4 ± 190.6 pg/dL, respectively, that is, the increase in serum PTH levels in patients is statistically significant ($p < 0.0001$). As expected, parameters reflecting renal efficiency (serum creatinine and serum urea) were also significantly elevated in patient cohort as compared with healthy individuals. The mean serum creatinine levels, in controls and CRI patients, were 0.81 ± 0.09 and 7.8 ± 2.4 mg/dL, respectively, while serum urea status in respective group were 23.8 ± 7.2 and 138.4 ± 35.8.

Table 1 Characteristics of cases and controls participants

Parameters	Controls (n = 157)	Cases (n = 124)	t-Value	p-Value	95% CI
	Mean $\pm$ SD	Mean $\pm$ SD			
Age (y)	48.8 ± 8.6	50.2 ± 7.8	1.41	0.15	–0.55 to 3.35
Sex, males; n (%)	88 (56.05%)	76 (61.29%)	0.582 (x^2)	0.44	–6.85 to 17.08
Systolic blood pressure (mm Hg)	124.8 ± 6.2	138.8 ± 18.4	8.91	< 0.0001	10.91 to 17.09
Diastolic blood pressure (mm Hg)	80.2 ± 2.8	86.2 ± 3.6	15.71	< 0.0001	5.25 to 6.75
Fasting plasma glucose (mg/dL)	80.7 ± 6.6	102.0 ± 21.4	11.78	< 0.0001	17.74 to 24.86
Hemoglobin (g/dL)	13.8 ± 2.8	7.9 ± 2.1	–19.52	< 0.0001	–6.49 to –5.31
Number (%) of patients in stratified CKD Stages					
Stage 1; n (%)		18 (14.5)			
Stage 2; n (%)		42 (33.87)			
Stage 3; n (%)		50 (40.32)			
Stage 4; n (%)		14 (11.2)			
Stage 5; n (%)		00 (00)			
Comorbid conditions					
Hypertension; n (%)		63 (50.8)			
Diabetes mellitus; n (%)		78 (62.9)			
Polycystic kidney Disease; n (%)		09 (7.2)			
Chronic glomerulonephritis; n (%)		23 (18.5)			
Obstructive uropathy; n (%)		07 (5.6)			

Abbreviations: CKD, chronic kidney disease; x^2, chi-squared test; CI, confidence interval; SD, standard deviation.

Table 2 CKD-bone mineral disorder indices of CKD patients and control groups

Parameters	Controls (n = 157)	Cases (n = 124)	t-Value	p-Value	95% CI
	Mean ± SD	Mean ± SD			
Creatinine (mg/dL)	0.81 ± 0.09	7.8 ± 2.4	36.4	< 0.0001	6.61 to 7.36
Urea (mg/dL)	23.8 ± 7.2	138.4 ± 35.8	39.13	< 0.0001	108.84 to 120.36
Alkaline phosphatase	73.6 ± 27.2	281.8 ± 117.6	21.47	< 0.0001	189.12 to 227.28
Serum PTH (pg/mL)	44.5 ± 10.2	364.4 ± 190.6	21.00	< 0.0001	289.92 to 349.88
Serum phosphorus (mg/dL)	3.3 ± 0.8	6.4 ± 1.7	20.19	< 0.0001	2.8 to 3.4
Serum total calcium (mg/dL)	9.6 ± 1.4	6.7 ± 1.3	−17.79	< 0.0001	−3.22 to −2.58
Serum sodium (mEq/L)	140.5 ± 4.2	138.8 ± 5.6	−2.90	0.0039	−2. 85 to −0.55
Serum potassium (mEq/L)	4.1 ± 0.6	4.8 ± 1.1	6.79	< 0.0001	0.5 to 0.9

Abbreviations: CI, confidence interval; CKD, chronic kidney disease; PTH, parathyroid hormone; SD, standard deviation.

►**Table 3** reveals the prevalence of abnormal mineral homeostasis in patients as per Kidney Disease Outcomes Quality Initiative Clinical Practice Guidelines for Chronic Kidney Disease (KDIGO-CKD) staging.[1] Of the 124 patients, there were 76 with state of hypocalcemia. One-hundred two of the 124 patients (82.25%) were hyperphosphatemic, and hyperparathyroidism was reported in 71 patients. Prevalence of abnormal homeostasis (with regard to total calcium, phosphate and PTH) increased progressively with severity of disease (ANOVA; $p < 0.05$). Serum levels of clinicobiochemical variables in stratified stages of disease are presented in ►**Table 4**. Result suggests that severity of abnormality associated with each of these parameters increased with advanced CKD stage. Serum levels of calcium, phosphorus, potassium, alkaline phosphatase, and creatinine were all strongly associated with the PTH (►**Table 5**). However, no correlation could be established between the PTH and serum sodium or urea levels.

Discussion

Animal models[16,17] have convincingly demonstrated bone-associated abnormal mineral homeostasis in uremia; few clinical and experimental studies in humans also have explored this.[18–20] Even though these disturbances commence in earlier stages of CKD, their progression in predialysis CKD patients, particularly to stratified stages of CKD, has been contrasting. Therefore, in this study, it is considered worthwhile to assess markers of disordered bone and mineral metabolism as well as to evaluate the prevalence of CKD associated mineral disturbances and found significant derangements of bone mineral homeostasis in the nondialyzed CKD patients. Our findings support the work of other researchers.[18–22] Among the inducted patient cohort, most commonly stated symptoms (related to CKD-MBD) were bone pains and myalgias, observed in 41.93% (n: 52) of patients and most common comorbid conditions were diabetes mellitus (n = 78 [62.9%]) and hypertension [n = 63 [50.8%]).

We observed an overall prevalence of hyperparathyroidism in 57.25% patients, hypocalcemia in 61.29%, and hyperphosphatemia in 82.25% of patients. Similar biochemical abnormalities were reported by few studies. For example, in 2016, Vikrant and Parashar[23] reported hypocalcemia in 23.8%, hyperphosphatemia in 55.4%, and secondary hyperparathyroidism in 82.7% patients; and Agarwal[21] illustrated hypocalcemia, hyperphosphatemia, and hyperparathyroidism in 29.9, 45, and 57.8% of CKD stage 4 patients, respectively. Progressive loss of kidney function in CKD leads to altered mineral homeostasis, that is reflected by an increasing prevalence of mineral disturbance with the advancing stages of CKD (►**Table 3**). Moreover, prevalence of aforementioned variables disturbances at each stage was significantly higher from its preceding stage (►**Table 3**; ANOVA, $p < 0.05$), substantiated by the observation that hypocalcemia (78.57%), hyperparathyroidism (85.71%), and hyperphosphatemia (92.85%) were more prevalent in CKD stage 4 patients than any of the preceding stages of CKD (►**Table 3**). Similar

Table 3 Prevalence of total calcium, phosphorus, and PTH disturbance in stratified stages of CKD (n = 124)

Stages of CKD	Hypocalcemia, n (%)	Hyperphosphatemia, n (%)	Hyperparathyroidism, n (%)
1	7 (38.88%)	10 (55.55%)	6 (33.33%)
2	23 (54.76%)	35 (83.33%)	21 (50.00%)
3	35 (70.00%)	44 (88.00%)	32 (64.00%)
4	11 (78.57%)	13 (92.85%)	12 (85.71%)
Total	76 (61.29%)	102 (82.25%)	71 (57.25%)

Abbreviations: CKD, chronic kidney disease; PTH, parathyroid hormone.

Table 4 CKD-bone mineral disorder indices of patients in stratified stages of CKD

Parameters	Stage 1	Stage 2	Stage 4	Stage 4	ANOVA
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	p-Value
Creatinine (mg/dL)	3.3 ± 1.1	6.8 ± 3.1	8.6 ± 2.9	9.1 ± 1.8	< 0.001
Urea (mg/dL)	78.5 ± 27.1	127.3 ± 33.6	145.8 ± 57.2	157.1 ± 66.5	< 0.001
Alkaline phosphatase	202 ± 111.2	243.2 ± 107.7	298.3 ± 131.9	327.2 ± 133.1	< 0.01
Serum PTH (pg/mL)	141.4 ± 47.2	233.3 ± 128.6	414.8 ± 187.5	451.1 ± 203.3	< 0.001
Serum phosphorus (mg/dL)	3.9 ± 0.6	4.6 ± 1.2	6.9 ± 1.4	7.7 ± 1.8	< 0.001
Serum total calcium (mg/dL)	7.4 ± 1.6	6.9 ± 1.3	6.3 ± 1.0	6.0 ± 0.8	< 0.01
Serum sodium (mEq/L)	141.3 ± 4.2	137.1 ± 5.2	133.5 ± 6.1	124.6 ± 4.1	< 0.05
Serum potassium (mEq/L)	4.3 ± 0.7	4.6 ± 1.4	4.9 ± 1.3	5.0 ± 0.7	< 0.05

Abbreviations: ANOVA, analysis of variance; CKD, chronic kidney disease; PTH, parathyroid hormone; SD, standard deviation.

findings were reported by earlier researchers[22,23] that mineral disturbances were higher in patients with CKD stage 5 than CKD stage 4. Among the studied indices, most prevalent abnormality was hyperphosphatemia, accounting for 82.25% of the patients.

The mean value of serum phosphors in CKD patients was significantly higher than in healthy controls ($p < 0.0001$; ►**Table 2**). This finding complements earlier studies[20,22,23] that demonstrated levels of phosphorus concentration in newly detected advanced renal failure patients to be high. On contrary to serum phosphorus levels, ►**Table 2** reveals a significant decrease in the average values of serum total calcium in patient group in contrast to controls. Levels of total calcium concentration in CKD patients have been found to be low in studies conducted in varied geographical areas.[19–23] Furthermore, it was observed that serum PTH has linear negative correlation with serum total calcium (R^2: 0.37; $p < 0.0001$; ►**Table 5**) and linear positive correlation with serum phosphorous (R^2: 0.33; $p < 0.0001$; ►**Table 5**). In the study, it was also found that the serum PTH (331.68 ± 204.99 pg/mL) was significantly higher in patient group as compared with controls (►**Table 2**; $p < 0.0001$) and there was a significant progressive increase in levels of PTH with an advancing stage of CKD (►**Table 4**; ANOVA, $p < 0.0001$), which substantiates the relationship between severity of hyperparathyroidism and the degree of renal impairment. These findings are in accordance with Levin et al[19] in 2007, Vikrant and Parashar[23] in 2016, and Arora et al (2018).[24]

The pathophysiology behind the observed effect seems to be secondary hyperparathyroidism resultant to CKD. With declining kidney function, the first event that usually occurs is the declined filtration and excretion of phosphate ensuing in hyperphosphatemia.[24,25] In the beginning, it is overcome by increase in serum PTH levels, which reduces reabsorption of phosphate from proximal tubules.[25] However, in due course there is hyperplasia and hypertrophy of the parathyroid gland, setting the stage for secondary hyperparathyroidism.[25] Concurrently, with progressive decline in kidney function, paucity of activated vitamin D occurs due to decrease of renal 1-hydroxylase activity.[26] Under normal physiological conditions, calcitriol decreases PTH secretion primarily by stimulating the VDR (expressed in the parathyroid glands) and by down regulating the synthesis of PTH as a result of an effect at the level of transcription of the PTH gene.[25,26] Both of these changes, that is, diminished filtration/excretion of phosphate and scarcity of activated vitamin D, stimulate an increase in PTH synthesis and secretion. In addition, fibroblast growth factor-23 (FGF-23), micro-RNAs, Wnt-b-catenin molecular signaling pathway, epidermal growth factor receptor (EGFR), and transforming growth factor-α (TGF-α) are suggestive conceivable molecular reasons for the connotation of hyperparathyroidism in CKD. FGF-23 elevates in CKD to regulate phosphate level, but increased FGF-23 leads to decreased production of calcitriol in kidney, which in turn causes initiation/progression of secondary hyperparathyroidism.[27] Wnt binds with receptor complex of frizzled-LRP5/6, which stimulates bone development and differentiation. Inhibitors of Wnt-b-catenin signaling pathway (namely, Dickkopf-1 and Sclerostin) were found to be associated with dysregulated mineral metabolism with subsequent hyperparathyroidism in patients of CKD.[28] With repute to EGFR and TGF-α, increased expression of EGFR and TGF-α in parathyroid gland of patients with CKD is reported, which in turn results in polyclonal hyperplasia and hyperparathyroidism.[28,29] Upregulation of miR-21, miR-148, miR-29, miR-30, and miR-141 and downregulation of miR-10, miR-25, and miR-125 have

Table 5 Correlation coefficients for PTH with various biochemical measurements

Parameters	R^2	p-Value
Serum total calcium	0.37	< 0.0001
Serum phosphorus	0.33	< 0.0001
Serum sodium	0.074	0.1207
Serum potassium	0.068	0.0467
Serum alkaline phosphatase	0.59	< 0.001
Serum urea	0.061	0.3556
Serum creatinine	0.084	0.0259

Abbreviations: PTH, parathyroid hormone; R, correlation coefficient.

been associated with hyperparathyroidism in experimental model, providing an indication of their role in CKD induced hyperparathyroidism.[29]

Hypocalcemia (a finding in current study; ►Tables 2 and 3) is a powerful stimulus for PTH secretion and for parathyroid growth.[25,30] Calcium exerts negative feedback on PTH secretion through the calcium sensing receptors on the parathyroid.[25,30] Decrease in serum calcium during the course of CKD caused by phosphate retention and decreased 1,25 dihydroxy cholecalciferol attenuate this feedback and lead to increased PTH mRNA levels and proliferation of parathyroid cells.[30] The number of calcium sensing receptors also may decrease in hypertrophied parathyroid tissue and lead to inadequate suppression of PTH secretion even in the setting of normal or high calcium levels.[30] This explains for the increase in phosphorus level and corresponding decrease in the calcium levels in present study.

The mean value of serum sodium and serum potassium in this study was 138.8 ± 5.6 mEq/L and 4.8 ± 1.1 mEq/L, respectively, in CKD patients. Also, it was found that these values were significantly different (►Table 2) from the observed values in healthy control population. There was no statistical significant difference noticed among healthy controls and CKD patients with reference to diet, physical activity, and any other lifestyle variation. However, patients had higher plasma glucose ($p < 0.0001$), systolic blood pressure readings ($p < 0.0001$), and diastolic pressure ($p < 0.0001$) as compared with healthy counterparts, in spite of being under medication, probably because diabetes mellitus and hypertension were found to contribute maximally to the patients as a comorbid disease (►Table 1).

The observed findings of altered levels of calcium, phosphorus, and PTH not only result to bone mineral defects/disease but also may lead to extraskeletal calcification and potentially calciphylaxis,[31] causing other harmful repercussion. In the serum, as the level of one or both ions elevates, there is an amplified risk for an ionic bond to form, generating an insoluble complex, which actually aggravates the effects of coronary atherosclerosis through increased vascular calcification and smooth muscle proliferation.[31,32] Elevated phosphorus may alter microcirculatory hemodynamics through increased extravascular resistance and further compromise myocardial perfusion. Vascular calcification, manifested as reduced vessel wall elasticity, increased intima-media layer thickness, or enhanced pulse-wave velocity, individually or collectively leads to left ventricular hypertrophy.[31,32] Thus, biochemical indices such as PTH, calcium, phosphate, and other associated parameters must be sustained within target ranges to prevent bone disease, extraskeletal calcification, and to maintain homeostasis of other body systems.

To summarize and conclude, our study reveals a PTH-linked derangements in mineral metabolism apparent from hyperphosphatemia and hypocalcemia in predialysis CKD patients. These abnormalities start in early stages of CKD and worsen with disease progression. This accentuates the significance of early recognition of mineral bone disorder, understanding its pathophysiological consequences and

scheduling necessary interventions/management strategies to protect the CKD patients from a plethora of complications.

Nonetheless, a few limitations of our study have to be acknowledged. First, it was a hospital-based study in a referral center, with a stringent selection criteria and voluntary recruitment; thus, sampling may not be a true reflection of the patient community. Hence, data need to be cautiously generalized to the entire population of patients with CKD. Second, the study was cross-sectional in nature and hence, we are not able to infer cause effect relationship between PTH levels and CKD, but confirm the need to monitor PTH and mineral levels from the early stages of CKD. Another limitation is that single measures of calcium, phosphate, and PTH were done. Moreover, few studies suggest prospective changes in bone mineral metabolic parameters; therefore, use of a single value has not been validated.

In summary, results of the study have shown CKD patients are at risk of or may already have developed secondary hyperparathyroidism; hence, findings of this study have implications for the care of CKD patients. Patients and care providers should give the highest priority for early identification and treatment of secondary hyperparathyroidism. It is crucial to preventing or controlling the consequences of this complication. If this can be achieved, the number of patients, in whom plethora of complications develops, should decline. However, additional prospective studies and clinical trials are warranted to clarify the role of secondary hyperparathyroidism in progression of CKD.

Conflict of Interest
None.

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