Original Article

Prevalence and severity of disordered mineral metabolism in patients with chronic kidney disease: A study from a tertiary care hospital in India

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ABSTRACT

Background: Disordered mineral metabolism is common complications of chronic kidney disease (CKD). However, there are limited data on the pattern of these disturbances in Indian CKD population. **Materials and Methods:** This was a prospective observational study of CKD-mineral and bone disorder (CKD-MBD) over a period of 3 years. The biochemical markers of CKD-MBD, namely, calcium, phosphorus, alkaline phosphatase, intact parathyroid hormone (iPTH), and 25-hydoxyvitamin Vitamin D3 (25OHD), were measured in newly diagnosed CKD Stage 3–5 and prevalent CKD Stage 5D adult patients. **Results:** A total of 462 patients of CKD Stage 3–5D were studied. The frequency of various biochemical abnormalities was hypocalcemia (23.8%), hypercalcemia (5.4%), hypophosphatemia (2.8%), hyperphosphatemia (55.4%), raised alkaline phosphatase (56.9%), secondary hyperparathyroidism (82.7%), and hypoparathyroidism (1.5%). 25OHD was done in 335 (72.5%) patients and 90.4% were found to have Vitamin D deficiency. About 70.6% of the patients had iPTH levels were above kidney disease outcomes quality initiative (KDOQI) target range. Nondiabetic CKD as compared to diabetic CKD had a higher alkaline phosphatase ($P = 0.016$), a higher iPTH ($P = 0.001$) a higher proportion of patients with iPTH above KDOQI target range ($P = 0.09$), and an elevated alkaline phosphatase ($P = 0.004$). The 25OHD levels were suggestive of severe Vitamin D deficiency in 33.7%, Vitamin D deficiency in 45.4%, and Vitamin D insufficiency in 11.3% patients. There was a significant positive correlation between iPTH with alkaline phosphatase ($r = 0.572$, $P = 0.001$), creatinine ($r = 0.424$, $P = 0.001$), and phosphorus ($r = 0.241$, $P = 0.001$) and a significant negative correlation with hemoglobin ($r = –0.325$, 0.001), age ($r = –0.169$, $P = 0.002$), and 25OHD ($r = –0.126$, $P = 0.021$). On multivariate logistic regression analysis, an elevated alkaline phosphatase was a significant predictor of hyperparathyroidism (odds ratio 9.7, 95% confidence interval 4.9–19.2, $P = 0.001$). **Conclusions:** There was a high prevalence of CKD-MBD in Indian CKD patients. CKD-MBD is more common and more severe and has an early onset as compared to the western populations.

Key words: Chronic kidney disease, chronic kidney disease-mineral and bone disorder, hyperparathyroidism, hyperphosphatemia, hypocalcemia, mineral metabolism disorder, Vitamin D

Introduction

Chronic kidney disease (CKD) constitutes a public health problem that is estimated to affect more than 10% of the global population, and the prevalence of which has increased in recent years.[1,2] The most important complication of CKD is cardiovascular disease, which is the primary cause of death in these patients. This increase in cardiovascular morbidity/mortality associated with CKD has been described even in patients with no evidence of ischemic heart disease[3] and is the explanation for the

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high mortality rate among patients in initial stages of CKD (20%, 24%, and 46% after 5 years for Stages 2, 3, and 4, respectively), which far surpasses the rate for patients who finally require dialysis.[4]

Bone mineral metabolism abnormalities, which the KDIGO guidelines[5] recently defined as CKD-mineral and bone disorder (CKD-MBD), have been clearly implicated not only in the development of secondary hyperparathyroidism (SHPT) and renal osteodystrophy but have also been associated with the progression of CKD and its complications, including cardiovascular complications[6] and they ultimately contribute significantly to an increase in morbidity and mortality rates among patients with CKD.[7,8]

CKD-MBD is a systemic disorder that is characterized by abnormal calcium, phosphorous, PTH, and Vitamin D metabolism, which, in addition to affecting the skeletal system, is related to the appearance of cardiovascular and soft tissue calcifications that in turn are associated with cardiovascular pathologies in patients with CKD.[9-12] The biochemical abnormalities are common in CKD and are the primary indicators by which the diagnosis and management of CKD-MBD is made.

The bone mineral metabolism abnormalities start during first stages of CKD as renal function decreases, long before the need for renal replacement therapy and can be positively or negatively influenced by the treatment strategy employed. As such, it is recommended that attending physicians monitor and control biochemical parameters early in the development of CKD,[3-5] before the need for dialysis.[13] However, despite high prevalence of MBDs in CKD patients, there are limited data on CKD-MBD from India.[14-17] Even the Indian CKD-MBD guidelines of 2011 were based on Western data and expert suggestions, due to paucity of data from the country and an urgent need for studies in this area was felt to fill the knowledge gap.[18] Therefore, a prospective study to investigate the prevalence and severity of MBD in CKD patients at our center was performed.

Materials and Methods

This was a prospective, observational study carried over a period of 3 years (July 2011–June 2014). The study population included newly diagnosed CKD Stage 3–5 and prevalent CKD Stage 5D adult patients of 18 years and above. Patients with the following characteristics were excluded from the study: (i) CKD Stage 3–5 patients taking calcium supplement, phosphate binder, Vitamin D or its active metabolites and analogs, calcimimetic; (ii) patients on glucocorticoid, bisphosphonate, nonsteroidal antiinflammatory drugs, phenytoin, or warfarin; (iii) patients having rheumatologic diseases such as rheumatoid arthritis and ankylosing spondylitis, or primary PTH disorders; and (iv) those having liver disease or history of bone fracture in preceding 6 months. Institute ethical committee approved this work. CKD was defined and classified as per kidney disease outcomes quality initiative (KDOQI) criteria.[19] The estimated glomerular filtration rates were calculated from serum creatinine level using the Cockcroft–Gault equation. The diagnosis of underlying basic kidney disease was made on clinical evidence.

The biochemical markers of CKD-MBD, namely, calcium, phosphorus, alkaline phosphatase, intact parathyroid hormone (iPTH), and 25-hydoxyvitamin Vitamin D3 (25OHD), were measured.

When serum albumin concentrations are reduced, a corrected calcium (cCa) concentration is calculated by adding 0.8 mg/dl to the total calcium level for every decrement in serum albumin of 1.0 g/dl below the reference value of 4 g/dl for albumin. The definitions for hypocalcemia (cCa < 8.5 mg/dl), hypercalcemia (cCa >10.5 mg/dl), hyperphosphatemia (phosphorus >4.5 mg/dl), hypophosphatemia (phosphorus <2.5 mg/dl), elevated alkaline phosphatase level (>120 IU/L), hyperparathyroidism (iPTH >65 pg/ml), hypoparathyroidism (iPTH <10 pg/ml), and Vitamin D deficiency (25OHD level of <75 nmol/l) were used.

Different iPTH levels outside of the range established by the KDOQI guidelines were used.[20] For subgroup analysis of Vitamin D deficiency, common clinical cut-points were used with 25OHD levels of <75, <50, and <25 nmol/l classified as insufficient, deficient, and severely deficient, respectively.[21,22]

Plasma iPTH was measured using the solid phase, two-site chemiluminescent enzyme-labeled immunometric assay (immulite/immulite 1000). Plasma 25OH Vitamin D (25OHD) assay was done using the equilibrium radioimmunometric assay (DiaSorin I125 RIA Kit).

Statistical analysis

Descriptive statistics including means, standard deviation, and percentages were used to describe the demographic and clinical data. Comparison between groups was performed by Chi-square or Fisher's exact test for categorical data and Student's *t*-test, Mann–Whitney *U*-test, or analysis of variance (ANOVA) with *post hoc* Bonferroni test, and nonparametric Kruskal–Wallis H-test as appropriate for continuous data. Pearson's correlation testing was used to look for associations between different parameters. Multivariate binary logistic regression analysis was done

for factors predictive of an elevated iPTH. $P < 0.05$ was considered statistically significant. All statistics were carried out using SPSS, version 16 (SPSS, Chicago, IL, USA).

Results

Patient characteristics

A total of 462 patients were included in the study. Table 1 shows the demographic and clinical characteristics of the study patients. There were 99 (77.3%) males with diabetic nephropathy as compared to 29 (22.7%) females ($P = 0.001$). The sex distribution and proportion of diabetic patients in different CKD stages were not significantly different (P = NS).

Laboratory results

Laboratory parameters and frequency of various MBDs in the study patients are shown in Tables 2 and 3, respectively. 25OHD was done in 335 (72.5%) patients and 90.4% were found to have Vitamin D deficiency [Table 3]. Prevalence of hypocalcemia ranged from 14.2 to 25.1% in various CKD stages. Hypophosphatemia was seen in few patients (2.8%) varying from 0 to 4.9% in different CKD stage. There was a progressive increase in hyperphosphatemia with increasing stage of CKD varying from 32.8 to 83.6%. The elevated levels of alkaline phosphatase were seen in 41.5–72.4% in different CKD stages. Prevalence of SHPT was very common varying from 72.7 to 92.5% increasing with CKD stage, and maximum seen in CKD Stage 5. The prevalence of iPTH level outside the KDOQI/KDIGO target range varied from 53.1 to 78.8%, lowest seen in CKD Stage 5D. Treatment with calcium-based phosphate binders and Vitamin D or its active metabolites had decreased the prevalence of hypocalcemia and had increased that of hypercalcemia, reduced the prevalence of SHPT and iPTH levels outside the KDOQI/KDIGO target range in CKD Stage 5D as compared to that in CKD Stage 5. A few (0–2.7%) patients in different CKD stages had hypoparathyroidism [Table 3].

Table 1: Demographic and clinical characteristics (*n*=462)

Gender *n* (%)	
Male	263 (56.9)
Female	199 (43.1)
Age (years)	
Mean±SD	56.8±13.1
Range	18–90
Causes of CKD *n* (%)	
Diabetic nephropathy	128 (27.7)
Hypertension	115 (24.9)
Chronic glomerulonephritis	63 (13.6)
Chronic tubulointerstitial nephritis	134 (29)
Autosomal dominant polycystic kidney disease	22 (4.8)
Stage of CKD *n* (%)	
3	183 (39.6)
4	113 (24.5)
5	134 (29)
5D	32 (6.9)
Predialysis *n* (%)	430 (93.1)
Dialysis *n* (%)	32 (6.9)
Peritoneal dialysis *n* (%)	22 (4.8)
Hemodialysis *n* (%)	10 (2.1)

SD: Standard deviation, CKD: Chronic kidney disease

Table 2: Laboratory results of the study patients (*n*=462)

	Mean±SD	Range
Hemoglobin (g/dl)	10±2.2	4-17.3
Creatinine (mg/dl)	4.1±2.9	0.6-19.9
Albumin (g/dl)	3.8±0.5	1.6-5.4
Corrected calcium (mg/dl)	9±1.1	5-16
Phosphorous (mg/dl)	4.9±1.4	1.8-14
Alkaline phosphatase (U/L)	159±99	48-1165
iPTH (pg/ml)	309±322	23-2136
25OHD (nmol/l)*	39.9±33	2.5-375

*25OHD levels were done in 335 patients. SD: Standard deviation, iPTH: Intact parathyroid hormone, 25OHD: 25-hydoxyvitamin Vitamin D3

Vitamin D deficiency was the most common disorder of mineral metabolism seen in this study; 87–95.3% of patients had inadequate 25OHD levels in different CKD stages. Prevalence of 25OHD levels varied indicating Vitamin D deficiency (40.2–50.8%), severe deficiency (29–43.5%), and insufficiency (8–14%) in different CKD stages. A low proportion (4.7–13%) of patients in various CKD stages had an adequate Vitamin D levels. There was no significant difference in Vitamin D deficiency severity grades in various CKD stages (P = NS) [Table 3].

Intact parathyroid hormone and 25-hydoxyvitamin Vitamin D3 in different chronic kidney disease stages

In majority (82.7%) of the patients, iPTH was elevated (>65 pg/ml); 70.6% had iPTH level above KDOQI target range suggested for the CKD stages. The iPTH levels for CKD Stage 3, 4, 5, and 5D were 159 ± 205, 320 ± 307, 469 ± 324, and 458 ± 490 pg/ml, respectively. The prevalence of patients with iPTH levels >400 pg/ml was 6% in CKD Stage 3, 25.7% in CKD Stage 4, 54.5% in CKD Stage 5, and 40.6% in CKD Stage 5D. A percentage of 15 and 31.3, respectively, of CKD Stage 5 and 5D patients had iPTH levels of <150 pg/ml. In CKD Stage 5D, in 9 (31.3%) patients, levels of iPTH were <130 pg/ml (less than 2 times the upper limit of normal), in 9 (28.1%) patients, the iPTH levels were >585 pg/ml (more than 9 times the upper limit of normal), and in 3 (9.4%) patients, the iPTH levels were >1000 pg/ml. All the patients with PTH <130 pg/ml were on peritoneal dialysis (PD) ($P = 0.03$). Whereas 8 (80%) hemodialysis (HD) patients had iPTH levels above KDIGO stage target (>2 times the upper limit of normal) as compared to 9 (40.9%) PD patients (P = NS). PTH was above KDIGO stage target (>9 times the upper limit

Table 3: Frequency of various of mineral metabolism disorders (*n*=462)

		Stage of chronic kidney disease				*P*
		3	4	5	5D	
n	462	183	113	134	32	
Hypocalcemia (<8.5 mg/dl) *n* (%)	110 (23.8)	46 (25.1)	16 (14.2)	43 (32.1)	5 (15.6)	0.007
Hypercalcemia (>10.5 mg/dl) *n* (%)	25 (5.4)	10 (5.5)	4 (3.5)	6 (4.5)	5 (15.6)	0.057
Hypophosphatemia (2.5 mg/dl) *n* (%)	13 (2.8)	9 (4.9)	1 (0.9)	3 (2.2)	0 (0)	0.001
Hyperphosphatemia (>4.5 mg/dl)	256 (55.4)	60 (32.8)	59 (52.2)	112 (83.6)	25 (78.1)	0.001
Elevated alkaline phosphatase (>120 U/L) *n* (%)	263 (56.9)	76 (41.5)	68 (60.2)	97 (72.4)	22 (68.8)	0.001
Hypoparathyroidism (iPTH <10 pg/ml) *n* (%)	7 (1.5)	5 (2.7)	0 (0)	2 (1.5)	0 (0)	0.001
Hyperparathyroidism						
↑iPTH levels (>65 pg/ml) *n* (%)	382 (82.7)	133 (72.7)	97 (85.8)	124 (92.5)	28 (82.7)	0.001
↑iPTH levels>KDOQI target range *n* (%)	326 (70.6)	126 (68.9)	89 (78.8)	94 (70.1)	17 (53.1)	0.035
↑iPTH levels (>400 pg/ml) *n* (%)	126 (27.3)	11 (6)	29 (25.7)	73 (54.5)	13 (40.6)	0.001
iPTH levels (<150 pg/ml) *n* (%)	188 (40.8)	123 (67.2)	35 (31)	20 (15)	10 (31.3)	0.001
Vitamin D levels *n**	335	125	80	107	23	
Adequate (≥75 nmol/l) *n* (%)	32 (9.6)	16 (12.9)	8 (10.1)	5 (4.7)	3 (13)	0.165
Deficient (<75 nmol/l) *n* (%)	303 (90.4)	109 (87.2)	72 (90)	102 (95.3)	20 (87)	
Insufficiency (50-75 nmol/l) *n* (%)	38 (11.3)	10 (8)	10 (12.5)	15 (140)	3 (13)	
Deficiency (25-50 nmol/l) *n* (%)	152 (45.4)	63 (50.8)	39 (49.4)	43 (40.2)	7 (30.4)	
Severe deficiency (<25 nmol/l) *n* (%)	113 (33.7)	36 (29)	23 (29.1)	44 (41.1)	10 (43.5)	

*25 OHD levels were done in 335 patients. *P* value, asymptotic significant (two-sided). iPTH: Intact parathyroid hormone

of normal) in 5 (50%) of HD patients as compared to 4 (18.2%) PD patients (P = NS).

25OHD was done in 335 (72.5%) patients and had levels of 39.9 ± 33 nmol/l. Thirty-two (9.6%) patients had adequate and 303 (90.4) patients had inadequate 25OHD levels. The 25OHD levels were suggestive of severe Vitamin D deficiency in 133 (33.7%), Vitamin D deficiency in 152 (45.4%), and Vitamin D insufficiency in 38 (11.3%) patients. There was no significant difference in the mean levels of 25OHD in the different CKD stages. 25OHD levels were significantly lower (36.8 ± 24.1 nmol/l) in patients with an elevated iPTH as compared to that (52.9 ± 55.9 nmol/l) in patients in whom the iPTH levels were normal (P = 0.021).

The linear regression analysis revealed significant positive correlation between iPTH levels with alkaline phosphatase (r = 0.572, P = 0.001), creatinine (r = 0.424, P = 0.001), and phosphorus (r = 0.241, P = 0.001) and a significant negative correlation with hemoglobin (r = −0.325, 0.001) age (r = −0.169, P = 0.002), and 25OHD (r = −0.126, P = 0.021). 25OHD had a significant positive correlation with calcium (r = 0.324, P = 0.001) and a significant negative correlation with alkaline phosphatase (r = −0.145, P = 0.008). On multivariate logistic regression analysis, taking age of the patient, stage of CKD, hypocalcemia, hyperphosphatemia, and elevated alkaline phosphatase, only elevated alkaline phosphatase was a significant predictor of hyperparathyroidism (odd ratio 9.7, 95% confidence interval [CI] 4.9–19.2, P = 0.001).

Comparison of laboratory parameters in different chronic kidney disease stages

The distribution of the laboratory parameters in different stages of CKD is shown through boxplots in Figure 1 (hemoglobin and creatinine), Figure 2 (calcium and phosphorus), Figure 3 (alkaline phosphatase and iPTH), and Figure 4 (25OHD). On ANOVA, a significant difference was found in the mean values of hemoglobin, creatinine, calcium, phosphorus, alkaline phosphatase, serum iPTH in the various CKD stages (P = 0.001); however, no significant difference was found in 25OHD levels in various CKD stages [Table 4]. The proportion of patients with hyperphosphatemia was higher (78.1%) in dialysis patients as compared to nondialysis patients (P = 0.009).

Comparison of demographic and laboratory parameters in diabetic and nondiabetic chronic kidney disease

The age of diabetic CKD patients was significantly higher as compared to patients with nondiabetic CKD (P = 0.001). Nondiabetic CKD as compared to diabetic CKD had a higher alkaline phosphatase (166 ± 107 IU/L vs. 141 ± 72 IU/L P = 0.016), a higher iPTH (341 ± 352 pg/ml vs. 227 ± 205 pg/ml P = 0.001) [Table 5 and Figure 5], a higher proportion of patients with iPTH above KDOQI target range (44 [73.3%] vs. 81 [63.3%] P = 0.09), alkaline phosphatase above 120 IU/L (205 [61.2%] vs. 58 [45.3%] P = 0.004). However, there was no significant difference between the two groups in the sex distribution and the mean levels of hemoglobin, serum creatinine, calcium, phosphorus, and 25OHD.

Table 4: Comparison of laboratory parameters in different stages of chronic kidney disease by one-way analysis of variance (*n*=462)*

	CKD stage				*P*
	3	4	5	5D	
n (%)	183 (39.6)	113 (24.5)	134 (29)	134 (29)	
Hemoglobin (g/dl)	10.7±2.1	10.1±2.1	8.9±1.9	9.6±2.1	0.001[a]
Creatinine (mg/dl)	2.1±0.9	3.2±0.8	6.7±2.9	7.5±2	0.001[a]
Calcium (mg/dl)	9.0±1.0	9.3±1.1	8.5±1.3	9.2±1.1	0.001[a]
Phosphorous (mg/dl)	4.1±1.1	4.6±1.1	5.5±1.6	5.8±1.4	0.001[a]
Alkaline phosphatase (U/L)	130±64	168±123	189±111	173±69	0.001[b]
iPTH (pg/ml)	159±205	320±307	469±324	458±490	0.001[b]
25OHD (nmol/l)*	41.5±30	44.2±46	35±22	40±33	0.425[b]

*25OHD levels were done in 335 patients. [a]Comparison of means by analysis of variance. One-way ANOVA, [b]Comparison of means by a nonparametric Kruskal-Wallis H-test. ANOVA: Analysis of variance, iPTH: Intact parathyroid hormone, 25OHD: 25-hydoxyvitamin Vitamin D3

Table 5: Comparison of demographic and laboratory results in diabetic and nondiabetic patients (*n*=462)

	Diabetic (*n*=128)	Nondiabetic (*n*=334)	*P*
Age (years)	61.5±9.1	55.1±13.9	0.001[a]
Sex, *n* (%)			
Male	26 (45.6)	2 (28.6)	0.454[c]
Female	31 (54.4)	5 (71.4)	
Hemoglobin (g/dl)	9.9±1.9	10±2.3	0.544[a]
Creatinine (mg/dl)	3.7±2.2	4.3±3.1	0.071[a]
Albumin (g/dl)	3.7±0.5	3.9±0.5	0.010[a]
Calcium (mg/dl)	9±0.9	9±1.2	0.878[a]
Phosphorous (mg/dl)	4.9±1.1	4.9±1.5	0.724[a]
Alkaline phosphatase (U/L)	141±72	166±107	0.016[b]
iPTH (pg/ml)	227±205	341±1352	0.001[b]
↑Alkaline phosphatase, *n* (%)	58 (45.3)	205 (61.6)	0.004[c]
↑iPTH, *n* (%)	81 (63.3)	244 (73.3)	0.09[c]

[a]Independent samples *t*-test, significant (two-tailed), [b]Mann-Whitney U-test, significant (two-tailed). Nonparametric independent samples test. [c]Chi-square with Fisher's exact test, significant (two-sided). iPTH: Intact parathyroid hormone

Discussion

Disordered mineral metabolism, SHPT, and deficiencies of Vitamin D are common complications of CKD.[23,24] A high prevalence of biochemical abnormalities of CKD-MBD was found in this observational study involving CKD Stage 3–5D patients. The Vitamin D deficiency (90.4%), SHPT (82.7%), elevated alkaline phosphatase (56.9%), hyperphosphatemia (55.4%), hypocalcemia (23.8%), and hypercalcemia (5.4%) were the major disorders seen in our patients. A high prevalence of disorders of mineral metabolism has been reported from the Western countries.[23-29] Our study is the largest study of 462 CKD patients from India, in which both the prevalence and severity of CKD-MBD was observed to be higher.

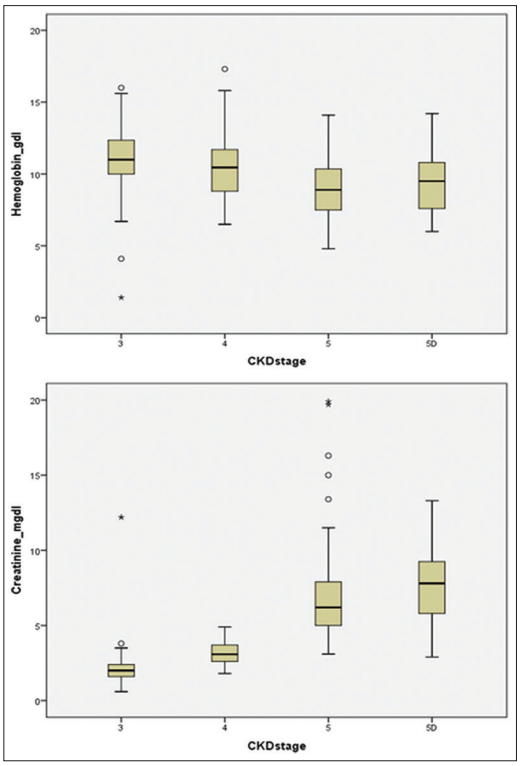

Figure 1: Box plots of hemoglobin and creatinine in different chronic kidney disease stages

Vitamin D deficiency was the most common biochemical abnormality of CKD-MBD seen in our patients. Vitamin D deficiency in patients with CKD Stages 3 and 4 is associated with increased PTH[27,28,30] and low bone mineral density (BMD).[30] In CKD 5D patients, Vitamin D deficiency is associated with mortality in incident dialysis patients[31] and increased cardiovascular events in PD patients.[32] These studies support the concern raised by the National Kidney Foundation KDOQI guidelines that low 25OHD levels in patients with CKD may contribute to the etiology of SHPT.[20]

Levels of 25OHD have been shown to be the best indicator of Vitamin D status and levels of 25OHD below 75 nmol/l are associated with increased PTH levels, low BMD, and increased risk of hip fractures.[21,22] In some studies, 25OHD showed inverse correlations with age, female gender, diabetes, and iPTH level.[33] In the current study, 25OHD had a significant positive correlation with calcium (r = 0.324, P = 0.001) and a significant negative correlation with alkaline phosphatase (r = −0.145, P = 0.008) and iPTH (r = −0.126, P = 0.021).

As in previous studies,[23,24,27-30] we did not observe differences in 25OHD levels between the different stages of CKD, regardless of treatment with Vitamin D. This

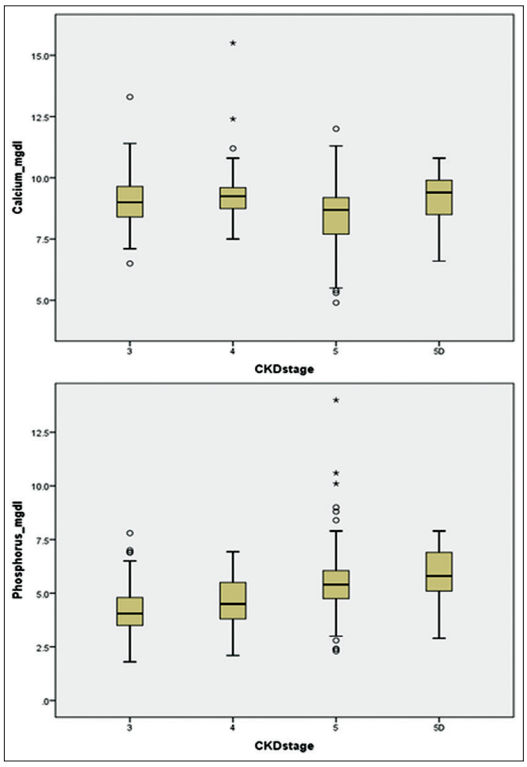

Figure 2: Box plots of calcium and phosphorus in different chronic kidney disease stages

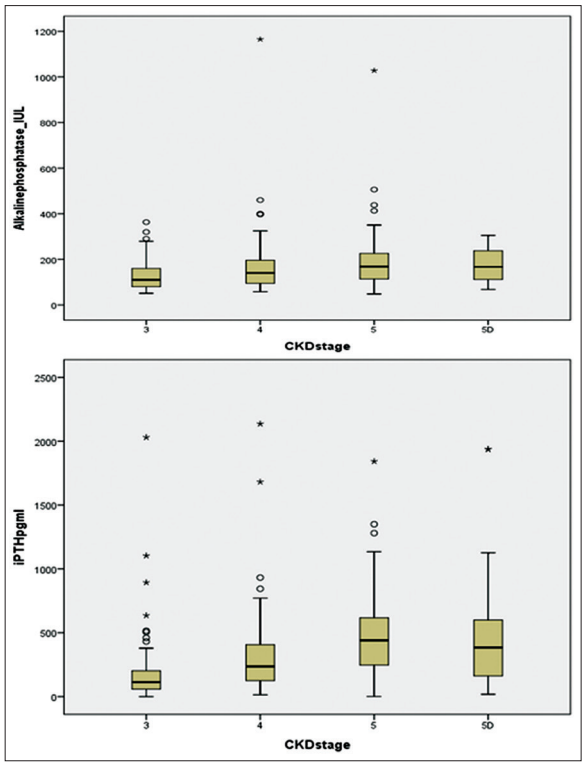

Figure 3: Box plots of alkaline phosphatase and intact parathyroid hormone in different chronic kidney disease stages

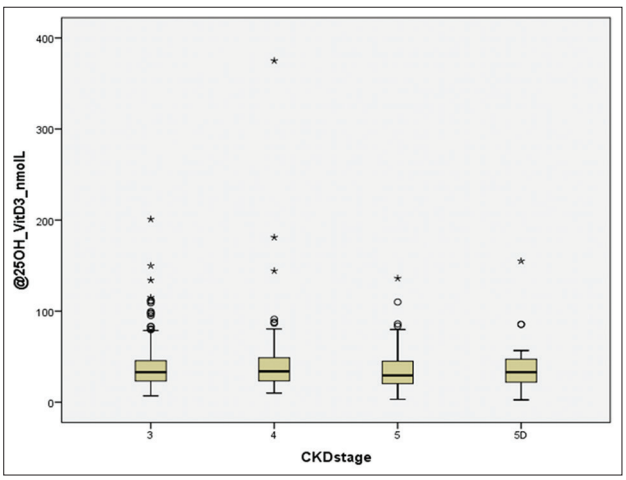

Figure 4: Boxplots of 25-hydoxyvitamin Vitamin D3 in different chronic kidney disease stages

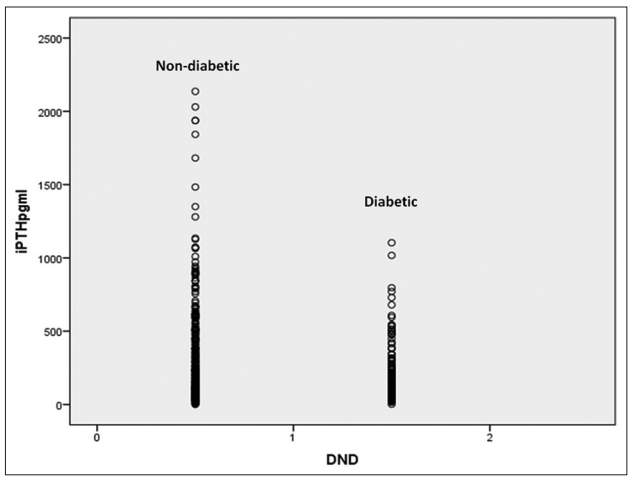

Figure 5: Scatter plot intact parathyroid hormone levels versus diabetic and nondiabetic patients ($P = 0.001$)

appears to indicate that 25OHD levels are fundamentally determined by nutritional intake and exposure to sunlight, rather than by renal function, although recent studies have described direct effects of uremia on photoconversion of Vitamin D[34] and/or hepatic hydroxylation.[35]

Hyperphosphatemia is important in the development and progression of SHPT. Serum phosphorous and alkaline phosphatase levels were a strong and significant predictor of the serum iPTH level. In addition, the serum PTH level showed a strong, incremental, and linear association with increased risk of hyperphosphatemia and an elevated alkaline phosphatase. Moreover, there was a U-shaped association between the serum PTH level and risk of hypercalcemia, in that very low levels and high levels of PTH, both are associated with hypercalcemia.[36] In our study, 56.9% of the subjects had an elevated alkaline phosphate. A significantly positive correlation between the levels of iPTH levels and alkaline phosphatase ($r = 0.572$, $P = 0.001$) was observed. On multivariate logistic regression analysis, an elevated alkaline

phosphatase was a significant predictor of SHPT (odds ratio 9.7, 95% CI: 4.9–19.2, $P = 0.001$).

PTH plays an essential role in the pathophysiology of CKD-MBD due to its effect on phosphorus regulation and bone remodeling. Alkaline phosphatase is an indicator that reflects osteoblastic activity if there is no liver alteration. Abnormal serum levels of these two indicators are related, albeit weakly, to the degree of bone turnover, fracture risk, and other clinical events, including mortality[37] Although bone biopsy remains the gold standard for the diagnosis of the type of renal osteodystrophy, it is not readily accessible for most patients; the determination of bone or total alkaline phosphatase and iPTH can be used to estimate bone turnover.[38]

A high (82.7%) prevalence of SHPT was found in our study subjects. Further, a high proportion (70.6%) had an iPTH above target range is of concern. The majority (58%) of CKD Stage 5 and 5D and a quarter of CKD Stage 4 had iPTH >400 pg/ml, representing high risk for high turnover bone disease. They need aggressive treatment to suppress PTH. Further, study results indicate that even in early stage Indian CKD patients, there is high prevalence of high turnover bone disease. It is speculated that in them, the biochemical abnormalities of CKD-MBD begin before CKD Stage 3 and coupled with widespread Vitamin D deficiency contributed to high prevalence of high turnover bone disease. It is suggested that in Indian CKD patients, monitoring for CKD-MBD should begin in CKD Stage 2 earlier than recommended by the guidelines.

Suppression of PTH to normal values is also not desirable (below 150 pg/ml) since it is associated with a higher prevalence of adynamic bone disease, in which bone turnover is low.[13] In our study, 18% of CKD Stage 5 and 5D subjects had low iPTH levels. A higher proportion (31.3%) of subjects in CKD Stage 5D had low iPTH; all were on PD. Multiple risk factors for adynamic bone disease have been identified, including increased age and diabetes. The principal factor underlying adynamic bone disease appears to be oversuppression of PTH release, which may be induced by the relatively high doses of Vitamin D analogs and possibly of calcium-based phosphate binders.[39] Adynamic bone disease is a significant concern in patients on PD compared to those on HD. One of the factors for this increased occurrence is the iatrogenic factor of giving a high or normal calcium dialysate in the PD.[18]

Strength of this study lies in large sample size, single center study, relevance to clinical practice on a disorder on which data are relatively limited. Nevertheless, this study had several limitations.

First, most important is the cross-sectional nature of the study which permits examination of association but not causal or temporal relationship. Information on dietary intake of calcium and phosphorus was not collected. A bone biopsy was not carried out. Nonetheless, studies have shown biochemical parameters to correlate well with the bone histology and this study gives a clinically relevant overview of what we could expect in our day to day clinical practice. Finally, although study reports a high prevalence of disordered mineral metabolism, only randomized trials could definitively determine whether early screening and treatment of these abnormalities may have a salutary effect on CKD, bone, or cardiovascular endpoints.

Conclusion

To conclude, this study found a spectrum of CKD-MBD in CKD Stage 3–5D. It showed that SHPT, hyperphosphatemia, hypocalcemia, increased alkaline phosphatase, and Vitamin D deficiency were quite common in Indian CKD subjects. The most common type of MBD was SHPT. The disorders of mineral metabolism, particularly SHPT and 25D deficiency, are more common, more severe, and develop earlier in the course of CKD in Indian CKD patients as compared to that in western populations. Monitoring for CKD-MBD should begin at early CKD stage. However, to know the impact of early screening and treatment of the abnormalities on CKD and its complications, more studies are required.

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Conflicts of interest
There are no conflicts of interest.

References

1. Coresh J, Astor BC, Greene T, Eknoyan G, Levey AS. Prevalence of chronic kidney disease and decreased kidney function in the adult US population: Third National Health and Nutrition Examination Survey. Am J Kidney Dis 2003;41:1-12.
2. Coresh J, Selvin E, Stevens LA, Manzi J, Kusek JW, Eggers P, *et al.* Prevalence of chronic kidney disease in the United States. JAMA 2007;298:2038-47.
3. Furuhashi T, Moroi M, Joki N, Hase H, Masai H, Kunimasa T, *et al.* The impact of chronic kidney disease as a predictor of major cardiac events in patients with no evidence of coronary artery disease. J Cardiol 2010;55:328-36.
4. Keith DS, Nichols GA, Gullion CM, Brown JB, Smith DH. Longitudinal follow-up and outcomes among a population with chronic kidney disease in a large managed care organization. Arch Intern Med 2004;164:659-63.
5. Moe S, Drüeke T, Cunningham J, Goodman W, Martin K, Olgaard K, *et al.* Definition, evaluation, and classification of renal osteodystrophy: A position statement from kidney disease: Improving global outcomes (KDIGO). Kidney Int 2006;69:1945-53.

6. Danese MD, Belozeroff V, Smirnakis K, Rothman KJ. Consistent control of mineral and bone disorder in incident hemodialysis patients. Clin J Am Soc Nephrol 2008;3:1423-9.
7. Block GA, Klassen PS, Lazarus JM, Ofsthun N, Lowrie EG, Chertow GM. Mineral metabolism, mortality, and morbidity in maintenance hemodialysis. J Am Soc Nephrol 2004;15:2208-18.
8. Russo D, Corrao S, Battaglia Y, Andreucci M, Caiazza A, Carlomagno A, *et al.* Progression of coronary artery calcification and cardiac events in patients with chronic renal disease not receiving dialysis. Kidney Int 2011;80:112-8.
9. Mizobuchi M, Towler D, Slatopolsky E. Vascular calcification: The killer of patients with chronic kidney disease. J Am Soc Nephrol 2009;20:1453-64.
10. Kalantar-Zadeh K, Kuwae N, Regidor DL, Kovesdy CP, Kilpatrick RD, Shinaberger CS, *et al.* Survival predictability of time-varying indicators of bone disease in maintenance hemodialysis patients. Kidney Int 2006;70:771-80.
11. Young EW, Albert JM, Satayathum S, Goodkin DA, Pisoni RL, Akiba T, *et al.* Predictors and consequences of altered mineral metabolism: The dialysis outcomes and practice patterns study. Kidney Int 2005;67:1179-87.
12. Wald R, Tentori F, Tighiouart H, Zager PG, Miskulin DC. Impact of the kidney disease outcomes quality initiative (KDOQI) clinical practice guidelines for bone metabolism and disease in a large dialysis network. Am J Kidney Dis 2007;49:257-66.
13. Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Work Group. KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease-mineral and bone disorder (CKD-MBD). Kidney Int Suppl 2009;76(Suppl 113):S1-130.
14. Sankarasubbaiyan S, Abraham G, Soundararajan P, Chandrasekaran V, Padma G. Parathyroid hormone and biochemical profile in chronic kidney disease patients in South India. Hemodial Int 2005;9:63-7.
15. Jabbar Z, Aggarwal PK, Chandel N, Kohli HS, Gupta KL, Sakhuja V, *et al.* High prevalence of Vitamin D deficiency in north Indian adults is exacerbated in those with chronic kidney disease. Nephrology (Carlton) 2009;14:345-9.
16. Ghosh B, Brojen T, Banerjee S, Singh N, Singh S, Sharma OP, *et al.* The high prevalence of chronic kidney disease-mineral bone disorders: A hospital-based cross-sectional study. Indian J Nephrol 2012;22:285-91.
17. Bansal B, Bansal S, Mithal A, Kher V, Marwaha R. Vitamin D deficiency in hemodialysis patients. Indian J Endocrinol Metab 2012;16:270-3.
18. Jha V, Kher V, Pisharody R, Sharma RK, Abraham G, Gokulnath, *et al.* Indian commentary on the 2009 KDIGO clinical practice guideline for the diagnosis, evaluation, and treatment of chronic kidney disease-mineral and bone disorders. Indian J Nephrol 2011;21:143-51.
19. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: Evaluation, classification, and stratification. Kidney disease outcome quality initiative. Am J Kidney Dis 2002;39 2 Suppl 1:S1-266.
20. National Kidney Foundation. K/DOQI clinical practice guidelines for bone metabolism and disease in chronic kidney disease. Am J Kidney Dis 2003;42:1-201.
21. Holick MF. Vitamin D deficiency. N Engl J Med 2007;357:266-81.
22. Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, *et al.* Evaluation, treatment, and prevention of Vitamin D deficiency: An endocrine society clinical practice guideline. J Clin Endocrinol Metab 2011;96:1911-30.
23. Levin A, Bakris GL, Molitch M, Smulders M, Tian J, Williams LA, *et al.* Prevalence of abnormal serum Vitamin D, PTH, calcium, and phosphorus in patients with chronic kidney disease: Results of the study to evaluate early kidney disease. Kidney Int 2007;71:31-8.
24. Gutiérrez OM, Isakova T, Andress DL, Levin A, Wolf M. Prevalence and severity of disordered mineral metabolism in blacks with chronic kidney disease. Kidney Int 2008;73:956-62.
25. Samokhvalova NA, Romanchishen AF, Gerasimchuk RP, Grinev KM, Zemchenkov AI. Secondary hyperparathyroidism: Incidence, clinical presentations, treatment. Vestn Khir Im I I Grek 2007;166:78-81.
26. Owda A, Elhwairis H, Narra S, Towery H, Osama S. Secondary hyperparathyroidism in chronic hemodialysis patients: Prevalence and race. Ren Fail 2003;25:595-602.
27. LaClair RE, Hellman RN, Karp SL, Kraus M, Ofner S, Li Q, *et al.* Prevalence of calcidiol deficiency in CKD: A cross-sectional study across latitudes in the United States. Am J Kidney Dis 2005;45:1026-33.
28. Elder GJ, Mackun K. 25-Hydroxyvitamin D deficiency and diabetes predict reduced BMD in patients with chronic kidney disease. J Bone Miner Res 2006;21:1778-84.
29. González EA, Sachdeva A, Oliver DA, Martin KJ. Vitamin D insufficiency and deficiency in chronic kidney disease. A single center observational study. Am J Nephrol 2004;24:503-10.
30. Tomida K, Hamano T, Mikami S, Fujii N, Okada N, Matsui I, *et al.* Serum 25-hydroxyvitamin D as an independent determinant of 1-84 PTH and bone mineral density in non-diabetic predialysis CKD patients. Bone 2009;44:678-83.
31. Wolf M, Shah A, Gutierrez O, Ankers E, Monroy M, Tamez H, *et al.* Vitamin D levels and early mortality among incident hemodialysis patients. Kidney Int 2007;72:1004-13.
32. Wang AY, Lam CW, Sanderson JE, Wang M, Chan IH, Lui SF, *et al.* Serum 25-hydroxyvitamin D status and cardiovascular outcomes in chronic peritoneal dialysis patients: A 3-y prospective cohort study. Am J Clin Nutr 2008;87:1631-8.
33. Lagunova Z, Porojnicu AC, Lindberg F, Hexeberg S, Moan J. The dependency of Vitamin D status on body mass index, gender, age and season. Anticancer Res 2009;29:3713-20.
34. Rojas-Rivera J, De La Piedra C, Ramos A, Ortiz A, Egido J. The expanding spectrum of biological actions of Vitamin D. Nephrol Dial Transplant 2010;25:2850-65.
35. Michaud J, Naud J, Ouimet D, Demers C, Petit JL, Leblond FA, *et al.* Reduced hepatic synthesis of calcidiol in uremia. J Am Soc Nephrol 2010;21:1488-97.
36. Li J, Molnar MZ, Zaritsky JJ, Sim JJ, Streja E, Kovesdy CP, *et al.* Correlates of parathyroid hormone concentration in hemodialysis patients. Nephrol Dial Transplant 2013;28:1516-25.
37. Coen G, Ballanti P, Bonucci E, Calabria S, Costantini S, Ferrannini M, *et al.* Renal osteodystrophy in predialysis and hemodialysis patients: Comparison of histologic patterns and diagnostic predictivity of intact PTH. Nephron 2002;91:103-11.
38. Lehmann G, Ott U, Kaemmerer D, Schuetze J, Wolf G. Bone histomorphometry and biochemical markers of bone turnover in patients with chronic kidney disease stages 3-5. Clin Nephrol 2008;70:296-305.
39. Brandenburg VM, Floege J. Adynamic bone disease-bone and beyond. NDT Plus 2008;1:135-47.