

Spectrum of mineral bone disorder in patients with CKD stage 3-5 from eastern India

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ABSTRACT

Introduction: Chronic kidney disease mineral bone disorder (CKD-MBD) is a major determinant of CKD associated morbidity and mortality. We sought to find the spectrum of CKD-MBD in Eastern India.

Material and methods: This cross-sectional study was conducted at the Department of Nephrology Institute of Postgraduate Medical Sciences and Research Seth Sukhlal Karnani Memorial hospital Kolkata India from June 2014 and July. The patients with newly diagnosed stage 3-5 CKD were evaluated for bone mineral abnormalities. Patients already on some form of phosphate binders or vitamin D analogs were excluded.

Results: Total of 242 patients was included. Male to female ratio was 2.1:1. 52.1% had diabetic nephropathy. Mean eGFR was 26.51 ± 12.33 ml/min/1.73m². 36.8% had CKD stage 3, 46.7% CKD stage 4 and 16.5 % had CKD stage 5. 56% had hyperphosphatemia (Phosphate >4.0mg/dl). 30% had hypocalcaemia (corrected calcium <8.5mg/dl). 53.4% had Vit D deficiency (25-OH Vit D < 20ng/ml) and 64.9% had hyperparathyroidism (iPTH>65pg/ml). There was a significant negative correlation of eGFR with phosphate, iPTH and ALP. The distribution of phosphate, ALP and iPTH across CKD stage 3-5 was significantly different; $p < 0.001$. 21.3% of patients with iPTH more than twice the upper limit of normal had normal ALP. There was no significant difference in serum calcium and 25-OH Vit D levels across CKD stage 3-5.

Conclusions: CKD-MBD has a high prevalence. Secondary hyperparathyroidism is the most common type of CKD-MBD. 25-OH Vit D and serum calcium are determined predominantly by diet and exposure to sunlight. ALP can't serve as a surrogate marker for iPTH.

Keywords: Hypocalcemia, Hyperparathyroidism, Hyperphosphatemia, 25-OH Vit-D, Mineral bone disease.

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INTRODUCTION

Chronic kidney disease (CKD) is affecting 10-13% of the estimated world population^{1,2}.

CKD-MBD is a systemic disorder of mineral and bone metabolism due to CKD. It manifests by either one or a combination abnormality in mineral metabolism, bone physiology and/or extraskelatal calcification. These three processes make a major contribution to the morbidity and mortality of patients with CKD³⁻⁵. Diagnosis for CKD-MBD requires the invasive bone biopsy for bone turnover, mineralization, and volume which is not always possible in a resource-poor country. The biochemical abnormalities are

the primary indicators by which the diagnosis and management of CKD-MBD are made. However, despite the high prevalence of MBDs in CKD patients, there are limited data on CKD-MBD from India⁶⁻⁹. We sought to find the spectrum of bone mineral abnormalities in patients with CKD stage 3-5 from eastern India. To our knowledge, this is the first such study from eastern India.

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MATERIAL AND METHODS

This cross-sectional study was conducted at the Department of Nephrology, Institute of Postgraduate Medical Sciences and Research Seth Sukhlal Karnani Memorial hospital Kolkata India from June 2013 and July 2014. The patients with newly diagnosed stage 3-5 CKD presenting to nephrology outpatient clinics were evaluated for the spectrum of mineral abnormalities. Patients already on some form of phosphate binders, calcitriol or vitamin D analogs were excluded from the study. Serum iPTH was estimated using solid phase two-site chemiluminescent enzyme labeled immunometric assay¹⁰ and 25-OH Vit D was estimated using solid phase ELISA¹¹. Serum creatinine was measured using the modified Jaffe kinetic method.

Statistics: Descriptive statistics including means, standard deviation, and percentages are used to describe the demographic and clinical data. Group comparison is done by chi-square test for categorical data and by Kruskal wall for nonparametric continuous data. Pearson's correlation testing is used to look for associations between different parameters. Statistics is done using SPSS software version 20.

RESULTS

Total of 242 patients were included. Men and women were in a ratio of 2.1:1. Diabetic nephropathy was the most common cause of CKD accounting for 52.1%. The mean age was 53.55±13.99 years. Mean eGFR at presentation was 26.51±12.33 ml/min/1.73m² (Table 1). 36.8% of patients were found in CKD stage 3, 46.7% in CKD stage 4 and 16.5 % in CKD stage 5. Majority of our patients presented in the late stages of CKD.

Table 1: Baseline Characteristics

Age (years) ± SD	53.55±13.99
Serum Creatinine (mg/dl) ± SD	3.09±1.64
MDRD e GFR (ml/min/1.73m ²) ± SD	26.50±12.32
Corrected Calcium (mg/dl) ± SD	8.94±1.05
Serum Phosphate (mg/dl) ± SD	4.33±1.13
ALP (IU) ± SD	187.75±91.37
i PTH (pg/ml) ± SD	129.45±116.85
25-OH-Vit D (ng/ml) ± SD	22.5±15.71
Hb (g/dl) ± SD	10.83±1.98
Serum Albumin(g/l) ± SD	3.91±0.57

There was a statistically significant negative correlation between eGFR, phosphate, iPTH, and ALP; p-value <0.001 (Table 2). There was a positive correlation between eGFR, serum calcium and 25-OH-Vit D, however, it didn't reach clinical significance (Table 2).

Table 2: Correlation between Glomerular filtration rate, serum calcium, phosphate, intact parathyroid hormone and 25 hydroxy Vit D

eGFR	Calcium	Phosphate	iPTH	25-OH-Vit D	Hb
Pearsons Correlation	0.106	-0.413	-0.355	0.08	0.323
p-value	0.103	<0.001	<0.001	0.901	<0.001

eGFR-Estimated glomerular filtration rate, iPTH- intact parathyroid hormone, 25-OH-Vit D-25 hydroxy Vitamin D, Hb-Hemoglobin

There was a statistically significant difference in the distribution of serum phosphate, ALP, iPTH, and hemoglobin across CKD stage 3-5; p-value <0.001. The difference in serum calcium and 25-OH -Vit D across CKD stage 3-5 didn't reach statistical significance (Table 3)

Table 3: Comparison of mean serum calcium, serum phosphate, Alkaline phosphatase, intact parathyroid hormone, 25 hydroxy Vit D and hemoglobin across CKD Stage 3-5

	CKD Stage 3	CKD Stage 4	CKD stage 5	p-value
Cal (Mean ± SD mg/dl)	9.019 ± 1.003	8.968 ± 0.983	8.699 ± 1.306	0.621
Phosphate (Mean±SD) mg/dl	3.886 ± 0.825	4.344 ± 1.014	5.278 ± 1.438	<0.001
ALP (Mean±SD IU/L)	152.158±68.530 IU/L	198.342 ± 97.772	228.523 ± 78.624	<0.001
iPTH (Mean±SD pg/ml)	79.315 ± 64.864	138.323 ± 115.019	213.261 ± 153.306	<0.001
25-OH-VitD ng/ml	22.803±13.138	23.109±17.469	20.138±15.967	0.233
Hemoglobin g/dl	11.551±1.679	10.589±1.905	9.943±2.266	<0.001

ALP-Alkaline phosphatase, iPTH- intact parathyroid hormone, 25-OH-Vit D-25 hydroxy Vitamin D.

The prevalence of hypocalcaemia (corrected calcium <8.5mg/dl) in stage 3, 4 and 5 CKD was 28.2%, 30.6% and 31.7% respectively. The prevalence of normocalcemia (corrected calcium 8.5- 10mg/dl) in CKD stage 3, 4 and 5 was 61.2%, 55.9% and 61.0.% respectively. The prevalence of hypercalcemia (corrected calcium>10mg/dl) in CKD stage 3, 4 and 5 was 10.6%, 13.5% and 7.3% respectively. The overall prevalence of hypocalcemia, normocalcemia, and hypercalcemia in CKD stage 3-5 was 30%, 58.6% and 11.4 % respectively which was not statistically significant; p-value 0.826 (Table 4).

Table 4: Distribution of calcium, phosphate, iPTH,ALP, and 25 -OH Vit D across CKD stage 3-5 No of cases (%)

Serum Calcium(mg/dl)	CKD 3	CKD 4	CKD 5	Total
<8.5	24 (28.2)	34 (30.6)	13(31.7)	71 (30)
8.5 -10	52 (61.2)	62 (55.9)	25 (61)	139 (55.6)
>10	09 (10.6)	15 (13.5)	03 (7.3)	27 (11.4)
Phosphate (mg/dl)	CKD 3	CKD 4	CKD 5	TOTAL
<2.5	06 (2.5)	0	0	06 (2.5%)
2.5-4.0	46 (54.1)	44 (38.6)	10 (23.8)	100 (41.5)
>4.0	33 (38.8)	70 (61.4)	32 (76.2)	135 (56)
iPTH (pg/ml)	CKD 3	CKD 4	CKD 5	TOTAL
<16	05 (6.3)	02 (1.8)	02 (5)	09 (3.9)
16-65	37 (46.3)	29 (26.1)	06 (15)	72 (31.2)
>65	38 (47.5)	80 (72.1)	32 (80)	150 (64.9)
ALP (IU/L)	CKD 3	CKD 4	CKD 5	TOTAL
20-140	43 (53.1)	34 (31.5)	05 (13.5)	82 (36.3)
>140	38 (46.9)	74 (68.5)	32 (86.5)	144 (63.7)
25-OH Vit D (ng/ml)	CKD 3	CKD 4	CKD 5	TOTAL
< 20	40 (47.1)	61 (54.5)	26 (63.4)	127 (53.4)
20-50	41 (48.2)	41 (36.6)	13 (31.7)	95 (39.9)
> 50	04 (4.7)	10 (8.9)	02 (4.9)	16 (6.7)

Chi Square value for trend of hypocalcemia, normocalcemia and hypercalcemia across CKD Stage 3-5 is 1.505; p-value 0.826.

Chi Square value for trend of hypophosphatemia, normal serum phosphate and hyperphosphatemia across CKD Stage 3-5 is 25.8; p-value<0.001.

Chi Square value for trend of low serum iPTH, normal serum iPTH and high serum iPTH across CKD stage 3-5 is 18.63; p-value<0.001.

Chi Square value for trend of normal serum ALP and high serum ALP across CKD stage 3-5.

is 20.068; p-value<0.001.

Chi Square value for trend of low serum 25-OH Vit D, normal serum 25-OH Vit D and high serum 25-OH Vit D across CKD stage 3-5 is 5.611; p-value 0.230.

The prevalence of low phosphate levels (<2.5mg/dl) in CKD stage 3, 4 and 5 was 7.1%, 0% and 0% respectively. The prevalence of normal phosphate levels (2.5-4.0mg/dl) in CKD stage 3, 4 and 5 was 54.1%, 38.6% and 23.8% respectively. The prevalence of hyperphosphatemia (>4.0mg/dl) in CKD stage 3, 4 and 5 was 38.8%, 61.4% and 76.2% respectively. The overall prevalence of hypophosphatemia, normal phosphate levels and hyperphosphatemia in CKD stage 3-5 was 2.5%, 41.5% and 56% respectively which was statistically significant; p-value<0.001 (Table 4).

The prevalence of hypoparathyroidism(iPTH<16pg/ml) in CKD stage 3,4 and 5 was 6.3%,1.8% and 5.0% respectively. The prevalence of normal parathyroid levels (iPTH 16-65pg/ml) in CKD stage 3, 4 and 5 was 46.3%, 26.1% and

15% respectively. The prevalence of hyperparathyroidism (iPTH>65pg/ml) in CKD stage 3, 4 and 5 was 47.5%, 72.1% and 80% respectively. The overall prevalence of hypoparathyroidism, normal parathyroid levels and hyperparathyroidism in CKD stage 3-5 was 3.9%, 31.2% and 64.9% respectively which was statistically significant; p-value 0.001 (Table 4).

The prevalence of normal ALP (20-140) in CKD stage 3, 4 and 5 was 53.1%, 31.5%, and 13.5%respectively. The prevalence of high ALP (>140) in CKD stage 3, 4 and 5 was 46.9%, 68.5%, and 86.5% respectively. The overall prevalence of low ALP, normal ALP and high ALP in CKD stage 3-5 was 0%, 36.3% and 63.7% respectively which was statistically significant; p-value<0.001 (Table 4).

ALP and iPTH showed a significantly positive correlation with each other; p-value<0.001. However, 21.3% patients with iPTH more than twice the upper limit of normal had ALP in normal range signifying that ALP can't be used as a surrogate marker for iPTH to predict the bone turn over in CKD.

The prevalence of low 25-OH Vit D levels (<20ng/ml) in CKD stage 3, 4 and 5 was 47.1%, 54.5%, and 63.4% respectively. The prevalence of normal 25-OH Vit D levels(20-50ng/ml) in CKD stage 3, 4 and 5 was 48.2%, 36.6%, and 31.7% respectively. The prevalence of high 25-OH Vit D levels(>50ng/ml) in CKD stage 3, 4 and 5 was 4.7%, 8.9%, and 4.9% respectively. The overall prevalence of low 25-OH Vit D levels, normal 25-OH Vit D levels and high 25-OH Vit D levels in CKD stage 3-5 was 53.4%, 39.9% and 6.7% respectively which was not statistically significant; p-value 0.245 (Table 4).

In addition to bone mineral abnormalities, hemoglobin (Hb) and serum albumin were seen to correlate positively and significantly with eGFR. The mean± SD Hb in CKD stage 3, 4 and 5 was 11.55±1.68g/dl, 10.59± 1.90g/dl, and 9.94± 2.27g/dl respectively. The difference was statistically significant; p-value<0. 001. The mean± SD albumin in CKD stage 3, 4 and 5 was 4.03±0.48g/dl, 3.83±0.56g/dl and 3.68±0.62g/dl respectively. The difference was statistically significant; p-value 0.003.

DISCUSSION

The biochemical abnormalities are common in CKD and are the primary indicators by which the diagnosis and management of CKD-MBD are made. CKD-MBD is a

contributory factor for the increase in cardiovascular morbidity/mortality associated with CKD even in patients with no evidence of underlying ischemic heart disease¹². This explains high mortality rate among patients 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 dialysis¹³. With a decline in eGFR, there is a gradual accumulation of phosphate which serves as a stimulant for phosphaturic hormones predominantly iPTH and FGF23. Further with worsening renal dysfunction, there is a decrease in renal 1 α -hydroxylase which leads to decrease in the conversion of 25-OH Vit D to 1, 25-OH Vit D. This in addition to Vit D resistance at the receptor level leads to a decrease in the gut and renal absorption of calcium giving rise to hypocalcemia in advanced stages of CKD. However, it is now believed that serum calcium and Vit D homeostasis is determined primarily by diet and sun exposure rather than by the degree of renal function as was supported by our study. A study by Julius U et al from South-East Nigeria also showed comparable serum calcium between patients with CKD stage 3-5 and age-matched controls¹⁴.

The mean age in our study group was 53.55 $\pm$ 13.99 years. This is very close to the mean age of 54.3 years reported by Shanker P et al in a study from south India¹⁵. Most of the patients in our study presented in stage 4 CKD (46.7%). This finding is similar to a study by Julius U et al who showed most patients presenting in CKD stage 4¹⁴. Our study showed hyperparathyroidism, defined as iPTH>65pg/ml in 72.1% of patients in CKD stage 4 and 80% in CKD stage 5 with an overall prevalence of 64.9%. These results are very similar to data from other Indian studies which show hyperparathyroidism to be 73% in Stage 4 and 89.5% in Stage 5 CKD¹⁶. Secondary hyperparathyroidism was the most common manifestation of CKD-MBD. A study was done by Vikrant S et al which also showed secondary hyperparathyroidism as the most common type of CKD-MBD⁽¹⁷⁾. 33.9% of patients in our study showed iPTH more than two times the upper limits of normal. 21.3% of patients with iPTH more than twice the upper limit of normal had ALP in normal range meaning that ALP can't be used as a surrogate marker for iPTH to predict bone turnover. Similar results were shown in a study from south India by Shanker P et al¹⁵.

Hyperphosphatemia was seen in 38.8%, 61.4% and 76.2% of patients in CKD stage 3, 4 and 5 respectively with increasing prevalence as eGFR declines. This is more than seen in other Indian studies probably due to high phosphate diet in people from eastern India.

The prevalence of low 25-OH Vit D levels in CKD stage 3, 4 and 5 was 47.1%, 54.5%, and 63.4% respectively. Normal 25-OH Vit D levels were defined as a level between 20-50 ng/ml as per recommendation from the food and nutrition Board of the US Institute of Medicine (IOM). There was no significant difference in Vit D levels across CKD stage 3-5; p-value-0.233. The prevalence of hypocalcemia in stage 3, 4 and 5 CKD were 28.2%, 30.6%, and 31.7% respectively. There was no significant difference in serum calcium levels across CKD stage 3-5; p-value 0.621. This suggests that 25-OH Vit D levels and serum calcium is determined primarily by sun exposure and diet rather than by the stage of CKD.

The mean $\pm$ SD Hb in CKD stage 3, 4 and 5 was 11.55 $\pm$ 1.68 g/dl, 10.59 $\pm$ 1.90g/dl, and 9.94 $\pm$ 2.27g/dl respectively. The difference was statistically significant; p-value<0.001. This highlights the influence of eGFR on erythropoiesis. The mean $\pm$ SD albumin in CKD stage 3, 4 and 5 was 4.03 $\pm$ 0.48g/dl, 3.83 $\pm$ 0.56g/dl and 3.68 $\pm$ 0.62g/dl respectively. The difference was statistically significant; p-value 0.003. This might reflect the worsening malnutrition and inflammation in patients with worsening eGFR beyond CKD stage 3 to 5.

Limitations of the study: Being a cross-sectional study patient were assessed only at presentation. There is a chance of change in CKD stage on patient follow up. The patients assessed were on variable calcium, and phosphate containing diet. Information on the timing of blood samples and the relationship with meals was not collected. Bone-specific ALP and FGF-23 could not be measured in the study. Finally, although the study reports a high prevalence of disordered mineral metabolism, randomized trials are needed to determine whether treatment of these abnormalities will have any beneficial effects on CKD progression, bone, and cardiovascular endpoints.

CONCLUSIONS

CKD-MBD has a high prevalence. Secondary hyperparathyroidism is the most common type of CKD-MBD. ALP correlates highly significantly with iPTH

however it can't serve as a surrogate marker for iPTH. 25-OH Vit D and serum calcium are determined predominantly by diet and exposure to sunlight rather than by the stage of CKD.

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