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A Study of Mineral Metabolism Disorder of CKD Patients in A Tertiary Care Hospital In India.

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Abstract:
BACKGROUND: *Mineral bone disorder (MBD) is an important complication of chronic kidney disease (CKD). However, there are limited data on the pattern of MBD in Indian CKD population. The aim of this study was to describe spectrum of MBD in patients with CKD in our center.*
MATERIALS AND METHODS: *This was a hospital based cross-sectional observational study of CKD‐mineral and bone disorder (CKD‐MBD) over a period of 1 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 5D adult patients.*
RESULTS: *A total of 76 patients of CKD Stage 3–5D were studied. The frequency of various biochemical abnormalities was hypocalcemia (40.7%), hyperphosphatemia (53.9%), raised alkaline phosphatase (25%), secondary hyperparathyroidism (67.1%). 25OHD was done in all patients and 47.3% were found to have Vitamin D deficiency. Nondiabetic CKD as compared to diabetic CKD had a higher alkaline phosphatase a higher iPTH and higher uric acid level(p=0.012).*
CONCLUSION: *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, hyperparathyroidism, hyperphosphatemia, hypocalcemia, mineral bone disorder*

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I. Introduction:

Chronic kidney disease (CKD) is a global public health problem affecting 5-10% of world population. [1,2] As kidney function declines, there is progressive deterioration in mineral homeostasis manifesting as disruption of serum and tissue concentrations of phosphorus and calcium, as well as changes in circulating levels of hormones such as parathyroid hormone (PTH), 25-hydroxyvitamin D [25(OH)D], 1,25-dihydroxyvitamin D [1, 25(OH)2D], fibroblast growth factor-23 (FGF-23), and growth hormone. These mineral and endocrine functions are critically important in the regulation of both bone modelling and bone remodeling. As a result, bone abnormalities are found almost universally in patients with CKD requiring dialysis (stage 5D), and in the majority of patients with CKD stages 3-5.[3] Numerous cohort studies have shown associations between disorders of mineral metabolism and fractures, cardiovascular disease, and mortality in patients with CKD.[4-10] However, despite high prevalence of mineral bone disorders (MBDs) in CKD patients, there are limited data on MBD in Indian CKD patients. The aim of this work was to study the profile of mineral metabolism disorder in patients of CKD stage 3 to stage 5.

II. Materials and Methods:

This was a observational cross sectional study carried over period of 1 years (July 2020–June 2021). Study was conducted in the department of Nephrology GMCH, Guwahati. Study subjects were male and female, diagnosed as CKD .

Sample size : $N= 4*p*q/L^2$
(p=Prevalence; q=(100-p), L= Allowable error 5%; confidence interval=95%).here prevalence p=5%[1]
$N =(4x.5x95)/(5)^2 =76.$

Inclusion criteria:
The study population included newly diagnosed CKD Stage 3–5 and prevalent CKD Stage 5D adult patients of 18 years and above.

Exclusion criteria:
Patients with the following characteristics were excluded from the study:

1.CKD Stage 3–5 patients taking calcium supplement, phosphate binder, Vitamin D or its active metabolites and analogs, calcimimetic;
2.Patients on glucocorticoid,bisphosphonate, nonsteroidal antiinflammatory drugs, phenytoin, or warfarin;
3. patients having rheumatologic diseases such as rheumatoid arthritis and ankylosing spondylitis, or primary PTH disorders;
4. those having liver disease or history of bone fracture in preceding 6 months.

CKD was defined and classified as per kidney disease outcomes quality initiative (KDOQI) criteria.[3] The estimated glomerular filtration rates were calculated from serum creatinine level using the Cockcroft–Gault equation.[11]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 phosphatise level (>112 IU/L), hyperparathyroidism (iPTH >65 pg/ml), hypoparathyroidism (iPTH <10 pg/ml), and Vitamin D deficiency (25OHD level of <30 ng/ml) were used.

Different iPTH levels outside of the range established by the KDOQI guidelines were used.[11]For subgroup analysis of Vitamin D deficiency, common clinical cut- points were used with 25OHD levels of >30, 10-30, and <10 ng/ml classified as sufficient, insufficient, and deficient,respectively.[12]

Plasma iPTH was measured using the solid phase, two- site chemiluminescent enzyme- labeled immunometric assay (COBASE 411). Plasma Vitamin D (25OHD) assay was done using the equilibrium radioimmunometric assay.

Statistical analysis: Statistical analyses were performed using the Statistical Package for the Social Science (SPSS). The categorical variables were shown as numbers of cases with percentage, and the continuous variables were shown as mean ± standard deviation (SD). For univariate analysis of differences between the two groups, continuous variables were assessed with the unpaired Student's *t* test, and categorical variables with the chi-square test. A *P* value of ≤0.05 was considered statistically significant.

III. Results:

A total of 76 patients (56 males,20 females) were included in the study. Mean age was 46.82±5.61yrs. Table 1shows the demographic and clinical characteristics of the study patients. There were 16 (72.7%) males with diabetic nephropathy as compared to 6 (27.3%) females. The sex distribution and proportion of diabetic patients in different CKD stages were not significantly different. The most common underlying native kidney disease in study subjects was diabetic nephropathy (DN 28.9%) followed by Hypertensive nephropathy (26.3%),chronic glomerulonephritis (CSGN 15.8%), chronic interstitial nephritis (CTID 23.6%) and polycystic kidney disease (APKD 5.26%). All patients of CKD stage 5 required dialysis at presentation and hence were essentially CKD stage 5D. Patients were divided into three groups: Group I included patients with CKD stage 3 and group II composed of patients with patients with CKD stage 4 and group III composed of CKD stage 5D.

Table 1: Demographic and clinical characteristics (*n*=76)

Male	56(73.5%)
Female	20(26.5%)
Age(yrs) (Mean ± S.D.)	46.82±5.61
Diabetic nephropathy	22(28.9%)
Hypertensive nephropathy	20(26.3%)
CSGN	12(15.8%)
CTID	18(23.6%)
ADPKD	4(5.26%)
Ckd stage 3	16(21.1%)
Ckd stage 4	20(26.3%)
Ckd stage 5/5D	40(52.6%)
Hemodialysis	30(75%)
Peritoneal dialysis	10(25%)

Laboratory parameters in the study patients were shown in Tables 2.

Table 2: Labaratory parameters of the study patients(n=76)

Parameters	Mean±SD
Haemoglobin(g/dl)	8.69±2.02
Creatinine(mg/dl)	5.35±2.90
Albumin(g/dl)	3.08±0.32

Corrected Calcium(mg/dl)	8.4±0.53
Phosphorous(mg/dl)	4.75±1.40
Alkaline phosphatase (U/L)	80.69±30.87
iPTH (pg/ml)	100.95±56.04
25OHD (nmol/l)	32.60±9.35
Uric acid(mg/dl)	7.02±0.96
Hypocalcemia	31(40.7%)
Hyperphosphatemia	41(53.9%)
Hyperparathyroidism	51(67.1%)
Vitamin D deficiency	36(47.3%)
Elevated ALP	19(25%)

Table 3: Comparison of Demographic, clinical and Labaratory parameters in patients with CKD stages (*n*=76)

Parameters mean±SD	Ckd 3(n=16)	Ckd 4(n=20)	Ckd5D n=40	P value
Age(yrs)	41.37±1.45	45.4±3.77	49.7±5.77	ns
Haemoglobin(g/dl)	10.16±2.12	9.83±2.01	7.53±1.09	ns
Creatinine(mg/dl)	1.79±0.27	2.79±0.09	8.03±0.69	ns
Albumin(g/dl)	3.33±0.22	3.15±0.19	2.94±0.33	ns
Calcium(mg/dl)	8.61±0.47	8.76±0.31	8.13±0.51	ns
Phosphorous(mg/dl)	3.42±0.41	4.44±0.68	5.45±1.49	ns
Alkaline phosphatase (U/L)	61±16.47	71±23.3	94.12±32.66	ns
iPTH (pg/ml)	68.47±19.9	88.38±29.88	122.2±66.41	ns
25OHD (nmol/l)	33.52±8.83	33.85±9.2	30.72±8.75	ns
Uric acid(mg/dl)	6.96±1.27	6.97±0.79	7.08±0.91	ns

Table 4: Comparison of demographic and laboratory results in diabetic and nondiabetic patients (*n*=76)

Parameters mean±SD	Diabetic(n=22)	Nondiabetic(n=54	P value
Age(yrs)	49.22±5.66	45.85±5.34	0.0165
Male	16(72.7%)	40(74%)	0.9078
Female	6(27.3%)	14(26%)	0.9078
Haemoglobin(g/dl)	8.57±1.94	8.73±2.06	0.7558
Creatinine(mg/dl)	6.31±2.85	4.96±2.85	0.0650
Albumin(g/dl)	2.95±0.47	3.13±0.21	0.0232
Calcium(mg/dl)	8.29±0.62	8.44±0.49	0.2669
Phosphorous(mg/dl)	4.4±1.01	4.9±1.52	0.1689
Alkaline phosphatase (U/L)	74.18±24.95	83.35±32.97	0.2445
iPTH (pg/ml)	83.25±34.19	108.16±61.63	0.0787
25OHD (nmol/l)	33.04±9.38	32.44±9.42	0.8016
ipth<138 pg/ml	22(100%)	41(75.9%)	0.012
Uric acid(mg/dl)	7.54±0.67	6.81±0.98	0.0020

Table 5: Frequency of Mineral and bone disorders in patients with in patients with CKD stages (*n*=76)

Parameters	Ckd 3(n=16)	Ckd 4(n=20)	Ckd5D n=40
Hypocalcemia	3(18.7%)	3(15%)	25(62.5%)
Hyperphosphatemia	1(6.25%)	9(45%)	31(77.5%)
Hyperparathyroidism	8(50%)	14(70%)	29(72.5%)
Vitamin D deficiency	7(43.7%)	8(40%)	21(52.5%)
Elevated ALP	1(6.25%)	3(15%)	15(37.5%)

Prevalence of hypocalcemia ranged from 15 to 62.5% in various CKD stages. Hypophosphatemia was seen in varying from 6.25 to 77.5% in different CKD stage. The elevated levels of alkaline phosphatase were seen in 6.25–37.5% in different CKD stages.(Table.5)

IV. Discussion:

The mean age of our study population was similar to other studies.[13-17]However, higher mean age was reported in an Western and an Indian study.[18,19] We observed that males outnumbered females in the study group. There is male predominance among CKD population in most studies. In Nissenson's prevalence study from the United States, males had an overall prevalence of 1.6% and females 0.8%, this two‑ fold ratio was maintained at all levels of serum creatinine.[20] Among Indian studies, Agarwal *et al*.[19] (community based) showed a male prevalence of 48% among patients with serum creatinine more than 1.8 mg/dL, while other hospital‑ based studies found males constituting 60–78% of CKD population[13-17]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 (47.3%), elevated alkaline phosphatase (25%), hyperphosphatemia (53.9%),

hypocalcemia (40.7%), and Hyperparathyroidism (67.1%) were the major disorders seen in our patients. A high prevalence of disorders of mineral metabolism has been reported from the Western countries.[21-25]

The age of diabetic CKD patients was not significantly higher as compared to patients with nondiabetic CKD (P = 0.0165). Nondiabetic CKD as compared to diabetic CKD had a higher alkaline phosphatase (83.35 ± 32.97 IU/L vs. 74.18 ± 24.95 IU/L P = 0.2445), a higher iPTH (108.16±61.63pg/ml vs. 83.25±34.19pg/ml P = 0.0787). Diabetic CKD has higher uric acid level as compared to non diabetic CKD, which was satistically significant(7.54±0.67mg/dl vs. 6.81±0.98mg/dl,p=0.002). 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.

Suppression of PTH to normal values is also not desirable (below 138 pg/ml) since it is associated with a higher prevalence of adynamic bone disease, in which bone turnover is low. Adynamic bone disease is a significant concern in patients on PD compared to those on HD and patient with 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. A higher proportion 25patients (62.5%) of subjects in CKD Stage 5D had iPTH level below 138 pg/ml, all were on PD.

V. Conclusion:

In summary, MBDs such as secondary hyperparathyroidism, hyperphosphatemia, hypocalcemia, and vitamin D deficiency were quite prevalent in all stages of CKD and in dialysis patients.

Limitations of the study: Bone biopsy not done to assess the abnormalities in bone turnover, mineralization, volume, linear growth, or strength. The categorization of bone disease in the absence of bone biopsy remains presumptive at the best. Nonetheless, studies have shown biochemical parameters to correlate well with the bone histology and this study gives an overview of what we could expect in our day to day clinical practice.

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