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Original Research Article

MINERAL BONE DISORDERS IN NAÏVE CHRONIC KIDNEY DISEASE PATIENTS – A COHORT STUDY FROM A TERTIARY CENTRE IN SOUTH INDIA

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Abstract:

Background: Highest rates of morbidity and mortality in chronic kidney disease (CKD) are encountered with its cardiovascular complications and Mineral Bone Disorders (MBD). MBD is now being recognized as a systemic disorder with far-reaching consequences on the quality of life and is no longer merely restricted to the histomorphometric findings in the bone biopsy. Most of the classification systems of mineral bone disorders rely only on histological findings in the bone biopsy. However, the invasive nature of the procedure desires the need for reliable biochemical parameters with good predictive value to aid in the diagnosis of these disorders at the bedside and decide on the treatment protocol.

Objective: Few studies to date are available on the pattern of mineral bone disorders in Indian CKD population. Our primary aim was to study the varied patterns of CKD mineral bone disorders in our center based on biochemical parameters.

Patients & Methods: Cross-sectional study involving 75 newly diagnosed patients with CKD stages G3, G4 & G5D. Patients were categorized into two groups based on their KDIGO CKD staging- Group A – CKD stages G3a, G3b, G4; Group B – CKD stage G5D. The biochemical markers of CKD-MBD, namely, serum calcium, phosphorus, alkaline phosphatase, intact parathyroid hormone (PTH), and 25-hydroxyvitamin Vitamin D were measured.

Results: 24 patients were included in group A and 51 patients in group B. The most common underlying native kidney disease was chronic glomerulonephritis (41.3%), followed by diabetic nephropathy (37.3%) and chronic interstitial nephritis (21.3%). The mean age of our study population was 49.5 ± 22.9 years in group A and 54.1 ± 15.77 years in group B. The most prevalent type of MBD was Secondary hyperparathyroidism in group A (66.7%) and hyperphosphatemia in Group B (78.4%). There was a higher prevalence of hypocalcemia (Group A - 29.2%, Group B- 43.1%, p= 0.31) and hyperphosphatemia (Group A- 25%, Group B- 78.4%, p= <0.001) with increasing stage of CKD. Prevalence (Group A -28.6%, Group B - 53.5%, p=0.08) and magnitude (Group A -14.87 ± 11.55 ng/ml, Group B – 10.94 ± 12.37 ng/ml, p=0.19) of vitamin D deficiency was higher in End-stage renal disease compared to earlier stages of

CKD. Diabetic population had lower mean values of i PTH (280.2 ± 306.04 pg/ml in Diabetics vs. 378.8 ± 455.60 pg/ml in Non-Diabetics, p= 0.31) and Alkaline phosphatase (121.14 ± 82.20 IU/L in Diabetics vs. 150.0 ± 86.85 IU/L in Non-Diabetics, p=0.17) indicating a propensity for Adynamic Bone Disease. Calcium-phosphorus product was significantly higher in CKD Stage G5D (Group A – 37.16 ± 9.17 mg^2/dl^2, Group B- 49.64 ± 16.75 $mg^2/dl^{2,}$ ^{p}=<0.001).

Conclusions: A higher prevalence of hyperphosphatemia, hypocalcemia and vitamin D deficiency was observed in our CKD cohort. Early identification and treatment of these mineral bone disorders are of paramount importance to prevent complications, retard disease progression and improve quality of life.

Keywords: Chronic kidney disease, Mineral bone disorder, Noninvasive assessment

Introduction:

Chronic kidney disease is being increasingly recognized as a global health threat affecting around 5 to 10 % of world population. The prevalence of CKD in India has been estimated to range between 0.78% and 0.87% [1, 2]. With the progressive deterioration of kidney function, CKD becomes an increasingly systemic disorder with several complications contributing to increased morbidity and mortality. One such dreaded complication of CKD is the disruption of BONE MINERAL HOMEOSTASIS manifesting as deranged levels of serum calcium, phosphorus and circulating hormones like PTH(Parathyroid hormone), Calcitriol, Fibroblast Growth Factor 23.Traditionally referred to as Renal Osteodystrophy – this terminology has now given way to the broader syndrome of CKD-Mineral Bone Disorder to throw light on its various systemic complications while Renal Osteodystrophy is confined to the bone histomorphometric changes in biopsy [3]. Alterations in the bone mineral homeostasis occur early in the course of CKD and are almost universal in ESRD. Identifying these abnormalities at the earliest is crucial in protecting bone health and preventing cardiovascular mortality from vascular complications [4]. Despite numerous studies on the association between bone mineral metabolism disorders and mortality in CKD, limited data are available on the spectrum of mineral bone disorders in South Asian Indian CKD population.

Objective:

To study the spectrum of mineral bone disorders in naïve chronic kidney disease patients- KDIGO stage G3, G4, G5D based on biochemical parameters.

Patients and methods:

A total of 75 patients attending the Department of Nephrology, Government Stanley Hospital Chennai, on both outpatient and inpatient basis were included.

Duration of Study: June 2016 to December 2016

Study Design: Cross-sectional study design

Inclusion Criteria:

1. Patients with GFR < 60 ml/ min/ 1.73 m2 based on MDRD formula.
2. Patients on maintenance hemodialysis or peritoneal dialysis for less than a month.

Exclusion Criteria:

1. Patients on treatment with bisphosphonates, calcimimetics, calcitriol and phosphate binders for more than a month
2. Patients with pre-existing bone disorders unrelated to CKD, Rheumatoid Arthritis, history of bone fractures in the last 6 months

Method of data collection:

A written informed consent was obtained from all our study participants in vernacular language. A blood sample was drawn for Hemoglobin, blood urea, Sr.

Creatinine, Sr. Calcium, Sr. Phosphorus, Sr. Albumin, Sr. PTH, Sr. Alkaline phosphatase, 25 hydroxyvitamin D.

Intact PTH and 25 OH Vitamin D were measured using Electro Chemiluminescence Assay run on a Cobas 6000auto analyzer (Roche Diagnostics, Mannheim, Germany; reference range 10–65 pg/ml)

GFR was calculated based on the MDRD formula [4]

GFR in mL/min per 1.73 m^2 = 175 x Serum $Cr^{-1.154}$ x $age^{-0.203}$ x 1.212 (if patient is black) x 0.742 (if female)

The normal range of parameters used in the assessment of mineral bone disorders are as follows [5]:

Parameters	**Normal Range**
Serum Calcium	8.5 to 10.5 mg/dl
Serum Phosphorus	2.5 to 4.5 mg/dl
Target Serum iPTH	
(CKD G3, G4)	10 to 65 pg/ml
(CKD G5D)	130 to 585 pg/ml
Serum 25 (OH) Vitamin D	>30 ng/ml
Serum ALP	Upto 112 IU/ L
Serum Albumin	4 to 6 g/dl

Based on the Sr. albumin, a corrected calcium level was obtained using the formula:

Corrected Ca = [0.8 x (normal albumin - patient's albumin)] + serum Ca

The normal albumin level defaulted to 4 mg/dL.

Statistical Methods

Descriptive statistical analysis has been carried out in our study. Results on continuous measurements are presented in Mean ± SD and results on categorical measurements are presented in percentage (%). Chi-square test has been used to find the significance of study parameters on a categorical scale between the two groups. Fischer exact t-test was used to find the significance of prevalence percentage of the various mineral bone disorders between the two study groups. Student't' test has been used to determine the significance between two group means. All analyses were two-tailed and p <0.05 was considered significant. SPSS version 16.0 was used for data analysis

Results:

Our study cohort was segregated into two groups based on their e GFR as

GROUP A: Patients with e-GFR between 15 to 59 ml/min/ 1.73 m2 (CKD stages G3a, G3b & G4)

GROUP B: Patients with e-GFR less than 15 ml/min/1.73 m2 (CKD stage G5)

Group A included 32% (n=24) and group B 68% (n=51) of the total study population. The demographic and clinical parameters of the study population are given in table 1. The prevalence of native kidney disease in our study population was Chronic glomerulonephritis in 41.3 %, diabetic nephropathy in 37.3 % and CIN in 21.3%. Laboratory parameters of the study population are given in table 2.

The most prevalent mineral bone disorder in group A in decreasing order of frequency was hyperparathyroidism (66.7%), Vitamin D Insufficiency (61.9%), elevated serum ALP (58.3%), hypocalcemia (29.2%) and Vitamin D Deficiency (28.6%). The most prevalent mineral bone disorder in group B in decreasing order of frequency was hyperphosphatemia (78.4%), hyperparathyroidism (76.5%), elevated serum ALP (56.9%), Vitamin D Deficiency (53.5%), hypocalcemia (43.1%) (table 3).The prevalence of vitamin D deficiency (vitamin D < 10 ng/ml) was highest in group B (53.5%) compared to group A (28.6%) through the results were not statistically significant (P=0.08). Vitamin D insufficiency, on the other hand, was higher in group A - 61.9% in group A compared to 39.5 % in group B with a p-value of 0.08.

Majority of patients in group B had vitamin D levels less than 10 ng/ml and therefore did not fall under the Vitamin D insufficiency category. Serum alkaline phosphatase reflects the activity of bone-forming osteoblasts. Elevated serum level of Alkaline Phosphatase > 112 IU/L was prevalent in 58.3% patients in group A and 56.9 % patients in group B(P=0.98). Group B had the highest prevalence of Calcium phosphate product > 55 mg^2/dl^2 compared to group A (25.5% vs. 4.2%'p=0.02) with the results reaching statistical significance(P=0.02).

The entire study cohort was segregated into two groups based on their diabetic status irrespective of their eGFR and the various parameters of CKD MBD were compared. Of the total 75 patients in the study cohort, 28 were diabetics (37.3%) and the remaining 47 were nondiabetics (62.7 %). The results of the various CKD MBD parameters compared between the diabetic and nondiabetic group is shown in (table 4). The mean calcium-phosphorus product, serum alkaline phosphatase, i PTH, serum phosphorus and vitamin D were low in the diabetic population compared to nondiabetics. But there was no significant difference in comparing these parameters with the nondiabetic population.

Discussion: Mineral bone disorders are highly prevalent in patients with CKD. To date, only a few studies have been done to assess the spectrum of this disorder in Indian CKD patients based on noninvasive biochemical parameters. To the best of our knowledge, ours is the first study to look into the prevalence of the various mineral bone disorders in a south Indian cohort. The mean age of our study cohort was almost identical to that of previous studies. Males formed the predominant study population (58.7 % males vs. 41.3 % females) similar to numerous other studies that have also favored increased prevalence of CKD among males - The SEEK study from India (Screening and Early Evaluation of Kidney Disease) which included 5588 CKD patients from across the country showed a gender prevalence of 55.1% in males and 44.9% in females [6]. The Hisayama study from Japan points to a significantly high prevalence of CKD among males over the last three decades [7]. One reason that could be attributed to this gender difference in India is the fact that males seek medical attention much earlier and visit hospitals more often than females.

Serum Calcium, Phosphorus, Calcium Phosphorus product:

The mean value of corrected calcium in our study was within the normal range in both groups A and B - through the corrected calcium was lower in group B (8.91 ± 1.51) than in group A (9.37 ± 1.48), the results were not statistically significant (P=0.23). In the study by Ghosh et al, the mean value of serum corrected calcium was 8.44 ± 0.87 in CKD stage 4 and 8.24 ± 1.26 in CKD stage 5 [8]. Agarwal et al estimated a mean calcium of 8.8 and 8.1 mg/dl in CKD stage 4 and 5 respectively [9].

The mean value of serum phosphorus in our study was significantly higher in group B (5.67 ± 1.63) compared to group A (4.02 ± 0.8) with a p-value <0. 001.In addition, patients in Group B also had a significant elevation in mean calcium-phosphorus product compared to group A, indicating an increased predilection for vascular calcification in End Stage Renal Disease. Elevated serum phosphate has emerged as a non-traditional risk factor for cardiovascular events in CKD [10,11], as well as in the general community [12]. Hyperphosphatemia in CKD drives vascular calcification by promoting estrogenic chondrogenic differentiation of vascular smooth muscle cells and apoptosis [13]. Though a higher calcium-phosphorus product has been linked with coronary

calcification [14], from a treatment perspective, KDIGO 2017 guidelines suggest that individual values of serum calcium and phosphate evaluated together to be used to guide clinical practice rather than the mathematical construct of the calcium-phosphate product [15]

Serum intact PTH:

The mean iPTH in group B was 400.4pg/ml, significantly higher than that in group A (217.4 pg/ml). The mean iPTH measure of both groups in our study was higher than that obtained with previous studies. The phenomenon, of secondary hyperparathyroidism (SHPT), begins early in the course of CKD and increases in prevalence and severity as the GFR falls. Bricker proposed that a temporary rise in plasma phosphate with progressive CKD and decreasing nephron number reduces serum calcium through the formation of complexes; parathyroid cells sense this reduction and raise PTH in response; increased PTH restores normal serum calcium through actions on target organs and simultaneously corrects serum phosphorus by reducing tubular phosphate reabsorption. A "tradeoff" thus occurs in which SHPT is the price paid for normal calcium and phosphorus. This trade-off hypothesis explains the hyperparathyroidism in our patients belonging to group A (CKD Stages G3 & G4) with normal average calcium and phosphorus levels [16]

In later stages of CKD, hyperphosphatemia develops in the majority of patients and serum 25(OH) vitamin D decreases. Hyperphosphatemia can directly stimulate PTH secretion through stabilization of PTH mRNA [17]. Vitamin D which normally inhibits PTH secretion cannot exert its inhibitory effect on parathyroid gland as Vitamin D receptors are downregulated [18] and the levels of vitamin D decreases with worsening renal function as mentioned earlier. The hyperparathyroidism in Group B is thus explained by the increasing prevalence of hyperphosphatemia, hypocalcemia and 25 (OH) Vitamin D deficiency in ESRD. Along with a high total alkaline phosphatase level, the spectrum in Group B is consistent with that of a high turnover bone disease.

Prevalence of Various mineral bone disorders:

We observed a prevalence of hypocalcemia of 29.2% and 43.1% and hyperphosphatemia of 25% and 78.4% in CKD stages G3, G4 (combined) and stage G5 respectively. In a western study by LaClair et al, hypocalcemia (calcium < 8.5 mg/dl) was prevalent in 8% and 28 % while hyperphosphatemia was noted in 20% and 50% of patients with stage G4 and stage G5 CKD respectively [19]. This striking difference in results with western data, emphasizes the more rampant prevalence of hypocalcemia and hyperphosphatemia in Indian CKD population. Compared to the Indian studies by Agarwal et al [9] and Ghosh et al [8] where hyperphosphatemia was prevalent in 50% & 70.27% of patients in CKD stage G5 respectively, we observed a much higher prevalence of hyperphosphatemia (78.4%) in our ESRD cohort.

Agarwal et al in their study used a cut off value of i PTH> 11O pg/ml in stage G4 CKD and i PTH> 300 pg/ml in CKD G5 to define hyperparathyroidism which led to a prevalence of 57.8% in stage 4 CKD and 39.4% in CKD stage 5 [9]. However, in our study using the KDIGO 2012 guidelines i PTH in group A > 65 pg/ml and > 585 pg/ml in group B was used to define hyperparathyroidism [5]. Using this cutoff, the prevalence of hyperparathyroidism in our study was 66.7% in stage 4 and 21.6% in stage G5 CKD. The different iPTH values used to define hyperparathyroidism in stage G5 CKD could explain the marked

difference in prevalence rates between our results and that of previous studies.

Using 112 IU/L as the cut off for abnormal serum ALKALINE PHOSPHATASE, our study showed a near equal prevalence of raised alkaline phosphatase in both the groups (58.9 % in group A compared to 56. % in group B). A 60 % prevalence of elevated alkaline phosphatase was found in both CKD stage 4 and stage 5 in the work by Jabbar et al using a lesser cut off for elevated alkaline phosphatase (> 45 IU/L) [20]

The spectrum of Mineral bone disorders in Diabetics & Non-Diabetics:

Among 21 patients with iPTH below target (<130 pg/ml) in patients with CKD stage G5, 42.86% of patients had diabetes (n=9) while diabetes was seen in only 27.27% of patients in CKD 5 with iPTH above target (> 585 pg/ml). Besides, the diabetic population in our study demonstrated lower levels of mean phosphorus, alkaline phosphatase, and iPTH compared to nondiabetics though the difference was not of statistical significance which could be due to the small sample size. The above described biochemical parameters noted in diabetic CKD patients favors an increased prevalence of Adynamic Bone Disease in this population. However, this cannot be emphasized too strongly due to lack of corroboratory evidence of bone biopsy findings of adynamic bone disease. A similar trend was noted by Ghosh et al, where patients with diabetes had significantly lower serum phosphorus, i PTH and total alkaline phosphatase than nondiabetic population. Risk groups for the adynamic bone disease include Diabetes, peritoneal dialysis and advancing age [8].

Disorders of Vitamin D Metabolism:

Vitamin D levels less than 30 ng/ ml was prevalent in 92.2% of our study similar to the study by Jabbar et al where greater than 90% of the study population had vitamin D levels less than 30 ng/ml [20]. In a study on Asian CKD population by Bancha et al, the mean 25 (OH) vitamin D level was 24.09 ± 11.65 and 20.82 ± 9.86 ng/mL in CKD stages G4 and G5 [21]. We noted a much higher prevalence and greater magnitude of vitamin D deficiency (14.86 ± 11.5 in group A and 10.93 ± 12.37 in group B, p=0.19) in both early and late stages of CKD. The ubiquitous presence of 25(OH) Vitamin D deficiency in the Indian subcontinent has a deep-rooted nutritional, genetic and socio-economic basis. This includes, low dietary intake of vitamin D, lack of a national vitamin D food fortification program [22], increased activity of the Vitamin D degrading enzyme 24 hydroxylase in skin fibroblasts of Indians [23] and dark skin pigmentation requiring longer exposure to ultraviolet (UV) rays to achieve adequate 25(OH) Vitamin D levels [24]. Most importantly, serum levels of active Vitamin D are inversely related to the rate of decline in renal function and mortality [25].

Another interesting finding in our study was the low mean vitamin D levels in patients with diabetes compared to nondiabetics (10.03 ± 8.75 ng/ml in Diabetics vs. 13.48 ± 13.74 ng/ml in nondiabetics, p= 0.23) through the difference was not statistically significant. 96.43 % of CKD patients with diabetes mellitus had vitamin D levels less than 30 ng/ml. Rozita et al observed that diabetes mellitus was an independent predictor of low serum vitamin D level [26]. Other studies have also shown a very high prevalence of suboptimal vitamin D levels in CKD patients with diabetes and albuminuria [27]. Podocyte damage has emerged as an important precipitant in CKD through parenchymal inflammation, tubular injury and interstitial fibrosis. The Wnt-beta-catenin signaling pathway has been shown to play an important role in podocyte injury

leading to proteinuria and fibrosis in CKD [28]. Paricalcitol (a vitamin D analog) has been shown to inhibit Wnt Beta-catenin pathway and reduce proteinuria in animal models [29]. The antiproteinuric effect of paricalcitol has also been confirmed in human studies [30]. Hence monitoring and treating Vitamin D deficiency might help in retarding the progression of CKD.

Conclusion:

The two most prevalent mineral bone disorders in our study cohort were hyperphosphatemia and secondary hyperparathyroidism. A significant proportion of our study population belonging to both early and late stages of CKD had vitamin D deficiency. Diabetic CKD population demonstrated lower levels of serum phosphorus, parathormone and total alkaline phosphatase –a pattern consistent with the Adynamic bone disease. Vitamin D levels were relatively lower in our diabetic CKD population supporting the role of diabetes as an independent predictor of Vitamin D deficiency.

Limitations:

1. Small sample size
2. Interpreting the type of mineral bone disorder with biochemical parameters in the absence of bone biopsy remains presumptive as biochemical and hormonal assay interpretations are limited by interassay variability, lack of standardization, diurnal and seasonal variations.

However, there are studies in recent times which demonstrate the good predictive value of biochemical parameters in classifying the various mineral bone disorders and our study is a synopsis of the results that we could expect in our everyday practice.

Table 1: Demographic and clinical parameters of the study population

PARAMETERS Mean ± SD	**GROUP A (N=24)**	**GROUP B (N=51)**	**P-VALUE**
Age in years	49.50 ± 22.87	54.05 ± 15.85	0.35
Male: female	11:33	13:18	0.12
Hemoglobin (g/dl)	9.18 ± 1.45	8.35 ± 1.86	0.046
UREA (mg/dl)	66.68 ± 35.86	145.02 ± 57.0	<0.01
Creatinine(mg/dl)	2.71 ± 8.64	8.64 ± 3.29	<0.01
e Gfr (ml/min/1.73 m^2)	26.83 ± 12.15	7.20 ± 2.54	<0.01

Table:2 MBD- Biochemical parameters of the study population

	Group	**Mean**	**Std. Deviation**	**P-value**
Calcium mg/dl	A	9.008	1.46	0.23
	B	8.554	1.57	
c_Calcium mg/dl	A	9.375	1.48	0.22
	B	8.916	1.51	
Phosphorous mg/dl	A	4.021	.81	**<0.001**
	B	5.676	1.63	
Ca*P mg^2/dl^2	A	37.167	9.17	**<0.001**
	B	49.647	16.75	
Sr. albumin	A	3.588	.56	0.59

g/dl	B	3.657	.51	
Intact pth pg/ml	A	217.4	283.22	0.06
	B	400.4	443.99	
Vitamin D ng/ml	A	14.87	11.55	0.19
	B	10.94	12.37	
SAP IU/L	A	152.33	101.39	0.34
	B	132.24	77.48	

Table 3: Mineral and bone disorders in the study population

S NO	TYPE OF MBD	GROUP A N= 24 % prevalence	GROUP B N=51 % prevalence	P-VALUE
1	Hypocalcemia	29.2	43.1	0.31
2	Hypercalcemia	8.3	3.9	0.58
3	Hyperphophatemia	25	78.4	**<0.001**
4	Secondary Hyperparathyroidism I PTH >65 pg/ml	66.7	76.5	0.40
5	Elevated ALP	58.3	56.9	0.98
6	i PTH ABOVE TARGET (> 65 pg/ml in Group A, >585 pg/ml in Group B)	66.7	21.6	**<0.001**
7	i PTH BELOW TARGET (<10 pg/ml in Group A <130 pg/ml in Group B)	0	41.2	-
8	Calcium Phosphorus Product >55 mg^2/dl^2	4.2	25.5	**O. O2**
9	Vitamin D Insufficiency	61.9	39.5	0.08
10	Vitamin D Deficiency	28.6	53.5	0.08

P <0.05 Statistically Significant

Table 4: laboratory parameters of the diabetic and nondiabetic study population

MBD Type	Mean ± SD		P Value
	Diabetic N=28	Non-Diabetic N=47	
C Calcium (mg/dl)	9.04 ± 1.55	9.07±1.49	0.93
Phosphorus(mg/dl)	5.0 ±1.57	5.2 ± 1.64	0.56
i PTH (pg/ml)	280.2 ± 306.04	378.8 ± 455.60	0.31
ALP (IU/L)	121.14 ±82.20	150.0 ± 86.85	0.17
Calcium Phosphorus product	44.0±13.76	46.6±16.97	0.49
25 OH Vitamin D (ng/ml)	10.03 ± 8.75	13.48 ± 13.74	0.23

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