Changing Spectrum of Mineral Bone Disorder in Chronic kidney disease stage 3 to 5 D and Its Associated Factors, A Prospective Cross-Sectional Study from Tertiary Care Hospital in Northern India

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Introduction. Mineral bone disease is an important complication of chronic kidney disease ends up in increased cardiovascular morbidity and mortality in these patients. The aim of present study was to determine the pattern, prevalence and the clinical, biochemical and radiological profile of mineral bone disease in predialysis and dialysis (stage 5D) patients of chronic kidney disease.
Methods. Patients of stage 3, 4, 5 and 5D of chronic kidney disease admitted to the department of nephrology were enrolled in this study.
Results. 200 patients of chronic kidney disease (19, 29, 43 and 109 cases of stage 3, 4, 5 and 5D respectively) with mean age of 52.4 ± 16.7 years and male to female ratio of 2.4:1 were enrolled. Diabetic nephropathy (45%), hypertensive nephropathy (33%), and chronic glomerulonephritis (14.5%) were the most common etiologies of chronic kidney disease. Proximal muscle weakness (91.5%) bone pain (59.5%) and pruritus (25.5%) were the common symptoms. Biochemical parameters showed hypercalcemia (19%), hypocalcaemia (55%), hyperphosphatemia (75.5%) and vitamin D deficiency in 84.5% of cases. High turnover bone disease was present in all predialysis and only 7% of dialysis patients. Adynamic bone disease was observed in 92.7% of dialysis patients. On univariate analysis i-PTH was significantly associated with sex, eGFR, serum calcium, and 25(OH) vit-D level and no association was found with age and FGF-23 levels.
Conclusion. Adynamic bone disease has emerged as the most common form of CKD-MBD in dialysis patients and secondary hyperparathyroidism being common in the predialysis patients of chronic kidney disease. Hyperphosphatemia and vitamin D deficiency were the most common reported biochemical abnormalities.

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INTRODUCTION

Chronic kidney disease related mineral bone disorder (CKD-MBD) is manifested by one or more abnormalities of calcium, phosphorus, parathyroid Hormone (PTH) or vitamin D metabolism; abnormalities in bone turnover, mineralization, volume, strength or linear growth; and vascular or other soft tissue calcification which affects 5 to 10% of the world population.[1,2]

Risk factors for vascular calcification are

hypocalcemia, hyperphosphatemia, and hyperparathyroidism that may lead to cardiovascular disease with an increased all cause and cardiovascular mortality and morbidity in CKD patients.[3,4]

However, despite high prevalence of mineral bone disorders in CKD patients, there is limited prospective data. We therefore, aimed to study the prevalence and the pattern of CKD-MBD in patients with stage 3, 4, 5, and 5D CKD.

MATERIALS AND METHODS

This crosssectional and prospective study was conducted in a tertiary care hospital during the study period of Oct 2018 to Nov 2019. Patients of stage 3, 4, 5, and 5D of chronic kidney disease admitted to the department of nephrology or attending nephrology clinic and dialysis unit were included in the study. Patients taking glucocorticoids, bisphosphonates, NSAID, phenytoin, or warfarin and patients having rheumatologic diseases such as rheumatoid arthritis and ankylosing spondylitis, or primary parathyroid hormone disorders, liver disease or a history of bone fracture in preceding 6 months and patients with failing allograft were excluded.

Chronic kidney disease was defined and classified as per Kidney Disease Outcome Quality Initiative (KDOQI) 2002.[2] Staging of chronic kidney disease was based on estimated Glomerular filtration rate (eGFR) using the CKD-EPI equation.[5]

After taking an informed written consent in each case, a detailed history included the etiology, duration of illness, mode of renal replacement therapy, treatment history and symptomatology pertaining to CKDMBD (bone pain, proximal muscle weakness, fragility fractures, pruritus), approximate daily sunlight exposure, medications and dietary history were recorded in each patient followed by a detailed physical examination.

Difficulty in getting up from a squatting position in the absence of hypokalemia, hypophosphatemia and steroid use for > 3 months was considered as proximal muscle weakness.

CKD–MBD was defined as one or a combination of abnormalities of calcium, phosphorus, PTH and vitamin D metabolism. Fibroblast growth factor (FGF-23) was measured where ever possible. Abnormalities in bone turnover, mineralization, volume, linear growth, strength; or vascular or other soft tissue calcifications were sought using X rays of skull, hands, spine and lateral abdominal X ray for abdominal aortic calcification and echocardiography for valvular calcification. Serum calcium was corrected by addition or subtraction of 0.8 mg/dl for each gram decrease or increase of serum albumin value of 4 g/dL. Definitions for corrected hypocalcaemia cCa < 8.5 mg/dL, hypercalcemia (cCa > 10.5 mg/dL), hyperphosphatemia (PO4 > 4.5 mg/dL), hypophosphatemia (PO4 < 2.5 mg/dL), elevated total alkaline phosphatase level (TA*P* > 112 IU/L), hyperparathyroidism (i-PTH > 69 pg/mL), hypoparathyroidism (i-PTH < 10 pg/mL), vitamin D deficiency (< 20 ng/mL), vitamin D insufficiency (20 to 30 ng/mL), and vitamin D sufficiency (> 30 ng/mL) were same for CKD stages 3, 4, 5, and 5D. However, the target range for i-PTH in CKD 3, 4, 5 was 10 to 69 pg/mL and 138 to 621 pg/mL (2 to 9 times upper limit of normal) for CKD stage 5D.[6]

Serum creatinine, serum albumin, serum calcium, serum phosphate (PO4), hemoglobin, uric acid, and urinary protein excretion were measured using standard laboratory techniques. Plasma intact parathormone (i-PTH) was measured using the electrochemiluminescence "ECLIA" assay (cobas e 411). Plasma 25OH vitamin D assay was done using the equilibrium electrochemiluminescence assay (cobas e 601). FGF-23 was measured using sandwich ELISA.

Written informed consent was taken from first degree relatives or others holding the power of attorney at enrolment. The study protocol was approved by the institutional ethics committee and it was complied with the Declaration of Helsinki 1975.

Information obtained from the patients was analysed using SPSS-21 software and statistical tests of quantitative variables (One-Way ANOVA and Chi-square test). Statistical significance of less than 0.05 was considered acceptable.

RESULTS

In this study 200 patients (predialysis 45.5% and dialysis 54.5%) of chronic kidney disease were enrolled. The mean age of participants was 52.4 ± 16.7 with age range of 9 to 95 years and male to female ratio of 2.4:1. There was male preponderance in all the groups. Diabetic nephropathy (45%), hypertensive nephropathy (33%), and chronic glomerulonephritis (14.5%)

were the most common etiologies of chronic kidney disease. Proximal muscle weakness (91.5%) followed by bone pains (59.5), and pruritus (25.5) were the common symptoms (Table 1).

Biochemical parameters showed hypocalcemia in 19%, hypercalcemia in 55%, hyperphosphatemia in 75.5%, vitamin D deficiency in 84.5% of the total cases. High turnover bone was present in all predialysis patients and only 7% of dialysis patients. Adynamic bone disease was observed in 92.7% of dialysis patients (Table 2).

On univariate analysis i-PTH was significantly associated with sex ($P < 0.004$), e GFR ($P < .02$), corrected serum calcium level ($P < .001$), serum phosphorus ($P < 0.001$), and 25(OH) vit-D ($P < 0.04$). On multivariate analysis a significant association of i-PTH was again seen with these variables except for Vitamin D. On univariate analysis no significant correlation was seen between FGF-23 and age of patient, sex, e-GFR, the diabetic status, serum calcium, serum phosphorus and serum 25 OH vitamin D levels. Radiological survey of skull, hands and lumbosacral spine and echocardiography showed changes of hyperparathyroidism, osteomalacia, and aortic and valvular calcification in stage 5 and 5D CKD patients (Table 3, 4, 5).

Table 1. Patients Characteristics

Variables	Stage 3 n (%)	Stage 4 n (%)	Stage 5 n (%)	Stage 5D n (%)	Total	*P*
	19 (9.5)	29 (14.5)	43 (21.5)	109 (54.5)	200	
Age, y						
< 30	01 (5.3)	05 (17.2)	03 (7.0)	12 (11.0)	21 (10.5)	
30 to 50	08 (42.1)	08 (27.6)	12 (27.9)	28 (25.7)	56 (28.0)	> .05
50	10 (52.6)	16 (55,2)	28 (65.1)	68 (62.4)	122 (61.0)	
Sex						
Male	16 (84.2)	19 (65.5)	29 (67.4)	77 (70.6)	141 (70.5)	> .05
Female	03 (15.8)	10 (34.50	14 (32.6)	32 (29.4)	59 (29.5)	
Etiology						
Db Nephropathy	11 (57.9)	11 (37.9)	16 (37.2)	52 (47.7)	90 (45.0)	> .05
HT Nephropathy	02 (10.5)	08 (27.6)	19 (44.2)	37 (33.9)	66 (33.0)	< .001
CGN	06 (31.6)	08 (27.6)	03 (7.0)	12 (11.0)	29 (14.5)	< .001
CIN	0 (0)	02 (6.9)	01 (2.3)	01 (9.0)	04 (2.0)	> .05
ADPKD	0 (0)	0 (0)	03 (7.0)	0 (0)	03 (1.5)	
Obst Nephropathy	0 (0)	0 (0)	0 (0)	03 (2.8)	03 (1.5)	< .05
Others	0 (0)	0 (0)	01 (2.3)	04 (3.7)	04 (2.5)	
Dietary Habits						
Vegetarian	06 (31.6)	11 (37.9)	16 (37.2)	44 (40.4)	77 (38.5)	> .05
Non-vegetarian	13 (68.4)	18 (62.1)	27 (62.8)	65 (59.6)	123 (61.5)	
Milk Intake						
< 250	11 (57.9)	20 (69.0)	34 (79.1)	94 (86.2)	159 (79.5)	< .05
250 to 500	07 (36.8)	08 (27.6)	09 (20.9)	15 (13.8)	39 (19.5)	> .05
500	0 (0)	01 (3.4)	0 (0)	0 (0)	01 (0.5)	> .05
Sun Exposure, hour						
< 1	09 (47.4)	22 (75.9)	29 (67.4)	84 (77.1)	144 (72.0)	> .05
1 to 6	10 (52.6)	07 (24.1)	10 (23.3)	24 (22.0)	51 (25.5)	< .05
6	01 (5.3)	01 (3.4)	03 (7.0)	01 (0.9)	06 (3.0)	> .05
Related Medicines						
Calcium Acetate	15 (78.9)	20 (69.0)	41 (95.3)	100 (91.7)	176 (88.0)	< .05
Sevalamer	15 (78.9)	27 (93.1)	41 (95.3)	106 (97.2)	189 (94.5)	< .05
Vit D Analogues	12 (63.2)	18 (62.1)	35 (81.4)	79 (72.5)	144 (72.0)	> .05
Symptoms						
P M Weakness	18 (94.7)	27 (93.1)	38 (88.4)	100 (91.7)	183 (91.5)	> .05
Pruritis	01 (5.3)	02 (6.9)	12 (27.9)	36 (33.0)	51 (25.5)	< .05
Bone Pains	11 (57.9)	15 (51.7)	24 (55.8)	69 (63.3)	119 (59.5)	> .05

Abbreviations: Db, daibetes; HT, hypertension; CGN, chronic glomerulonephritis; CIN, chronic interstitial nephritis; ADPKD, autosomal dominant polycystic kidney disease; Obst, obstructive; PM, proximal muscle.

Table 2. Biochemical Parameters

Variable	Stage 3 n (%)	Stage 4 n (%)	Stage 5 n (%)	Stage 5D n (%)	Total	*P*
	19 (9.5)	29 (14.5)	43 (21.5)	109 (54)	200	
Corrected Calcium, mg/dL						
< 8.5	03 (15.8)	03 (10.3)	07 (16.3)	25 (22.9)	38 (19.0)	> .05
8.5 to 9.5	05 (26.3)	03 (10.3)	11 (25.6)	33 (30.3)	52 (26.0)	> .05
> 9.5	11 (57.9)	23 (79.3)	25 (58.1)	51 (46.8)	110 (55.0)	< .05
Serum Phosphorus, mg/dL						
< 2.5	0 (0)	0 (0)	02 (4.7)	01 (0.9)	03 (1.5)	
2.5 to 4.5	07 (36.8)	10 (34.5)	10 (23.3)	21 (19.3)	48 (24.0)	> .05
> 4.5	12 (63.2)	20 (69.0)	31 (72.1)	88 (80.7)	151 (75.5)	
Serum i-PTH, pg/dL						
< 150	12 (63.2)	10 (34.5)	10 (23.3)	40 (36.7)	72 (36.0)	< .05
to 300	02 (10.5)	13 (44.8)	18 (41.9)	34 (31.2)	67 (33.5)	> .05
300	05 (26.3)	06 (20.7)	15 (34.9)	35 (32.1)	61 (30.5)	> .05
S. 25 (OH) Vit. D, ng/mL						
< 20	17 (89.5)	22 (75.9)	38 (88.4)	92 (84.4)	169 (84.5)	
to 30	01 (5.3)	05 (17.2)	03 (7.0)	09 (8.3)	18 (9.0)	> .05
30	01 (5.3)	01 (3.4)	01 (2.3)	08 (7.3)	11 (5.5)	
S. ALP (mean ± SD)	319.42 ± 466.06	217.45 ± 85.44	245.49 ± 331.12	227 ± 179.78	238.43 ± 249.56	> .05
Type of MBD						
Above target range						
i-PTH > 69 / i-PTH > 621	19 (100.0)	29 (100.0)	43 (100.0)	8 (7.34)	99 (49.5)	< .001
Below target range						
i-PTH < 10 / i-PTH < 138	0 (0)	0 (0)	0 (0)	101 (92.66)	101 (50.5)	

Abbreviations: n, number of cases; i-PTH, intact parathyroid hormone; S, serum; MBD, mineral bone disease; S. ALP, serum alkaline phosphatase.

Table 3. Factors Affecting FGF-23, Univariate Analysis

Independent Variable	Beta Coefficients	*P*	95% Interval Lower Bound	Confidence For B Upper Bound
Age	0.27	> .05	-22.29	80.79
Sex	-0.32	> .05	-3835.98	727.23
eGFR	-0.39	> .05	-348.82	34.25
Diabetes Mellitus	-0.14	> .05	-1690.78	1526.69
Calcium	-0.21	> .05	-751.67	296.32
Phosphorus	-0.33	> .05	-1204.95	205.51
25 OH Vit D	0.11	> .05	-123.98	198.88

DISCUSSION

Chronic diseases have become a major cause of morbidity and mortality globally and become major health problem in developed countries. Nowadays it becomes a major cause of death in developed countries. In India the expected death due to chronic kidney disease estimated to be 66.7% of total death in 2020.[7]

In North India the prevalence of CKD stage 3 was found in 0.79% subjects out of 4972.[8] There was a male preponderance in our study with a male to female ratio of 2.2:1. This pattern was observed in all groups of patients in various stages of CKD. Similar findings have been reported by others.[9,10] The mean age of our study population was similar to other studies.[11-13]

In many geographic areas diabetic nephropathy is the commonest cause of CKD. Moreover registry confirms diabetic nephropathy as the prominent cause of CKD in India.[6] Currently, however, diabetic kidney disease is recognized as the most frequent cause of CKD across the country and nowadays increase urbanisation in the country leads to increased diabetic patient in country that may

Table 4. Radiological and Echocardiographic Characteristics of Patients

Variable	Stage 3 n (%)	Stage 4 n (%)	Stage 5 n (%)	Stage 5D n (%)	Total	*P*
	19 (09.5)	29 (14.5)	43 (21.5)	109 (54.5)	200	
X-ray Skull						
Focal Radiolucency	0 (0.0)	0 (0.0)	0 (0.0)	03 (2.8)	03 (1.5)	> .05
Pepper Pot Skull	0 (0.0)	0 (0.0)	0 (0.0)	01 (0.9)	01 (0.5)	> .05
Subperiostal Resorption	0 (0.0)	0 (0.0)	0 (0.0)	09 (8.3)	09 (4.5)	< .05*
X-ray Hand						
Subperiostal Erosions	0 (0.0)	0 (0.0)	06 (14.0)	28 (25.7)	34 (17.0)	< .05*
Others	02 (10.5)	03 (10.3)	06 (14.0)	19 (17.4)	30 (15.0)	> .05
X-ray LS Spine						
Osteosclerosis/Osteoporosis	10 (52.6)	17 (58.6)	28 (65.1)	67 (61.5)	122 (61,0)	> .05
Abdominal Aorta Calcification (AAC)	10 (52.6)	18 (62.1)	26 (60.5)	74 (67.9)	128 (64.0)	> .05
Echocardiography						
Mitral Annular calcification (VC)	11 (57.9)	15 (51.7)	11 (25.6)	37 (33.9)	74 (37.0)	< .05*
AAC + VC	04 (21.1)	07 (24.1)	06 (14.0)	27 (24.8)	44 (22.0)	> .05

Abbreviations: VC, valvular calcification.
*Statistically Significant

be one of the reason of increased CKD in India.[14]

There is a change in the etiology of CKD with emergence of diabetic nephropathy followed by hypertensive nephropathy as the leading causes. In India diabetes and hypertension account for 40 to 60% cases of CKD.[15,16] CKD was due to diabetic nephropathy (45%) and hypertensive nephropathy (33%) in ¾ of cases in our study.

Valson *et al.*[12] in their study reported the prevalence of proximal muscle weakness and bone pain as 26.2 and 33.5%, respectively; in chronic kidney disease stage 4 and 5, the incidence of these were 91 and 59% in our study. Three patients had fragility fractures (fracture in neck of femur in 2, and vertebral fracture in one case).

CKD-MBD is characterized by abnormal calcium, phosphorous, PTH, and Vitamin D leading to changes in the bone morphology and the cardiovascular and soft tissue calcifications. The term of renal osteodystrophy should exclusively be used to describe disorders of bone histology associated with CKD.[15] However, in clinical practice, bone biopsy is less frequently utilised as it is invasive and cumbersome procedure and requires highly skilled personnel to interpret the tissue samples that is not available at most centres. For these reasons, clinicians largely depend on trends in the levels of parathyroid hormone in conjunction with levels of serum phosphate, calcium and alkaline phosphatase as markers of bone turnover to guide the treatment of mineral bone disorder.[6]

Serum markers of CKD-MBD in our study showed hypocalcaemia in 22%, hypercalcemia in 8%, hyperphosphatemia in 74%, elevated serum alkaline phosphatase (mean value of 238.43 ± 249.56 units and serum 25 (OH) Vitamin D deficiency in 84.5% of cases. Similar observations have been made by others.[11-13,17] Although not considered as an essential component of CKDMBD assessment in KDIGO guideline, 25 (OH) vitamin D deficiency plays an important role in modifying and potentiating CKDMBD.

Vitamin D deficiency is a common problem in end-stage renal disease patients under hemodialysis.[18] In Present study biochemical parameters showed hypocalcemia in 19%, hypercalcemia in 55%, hyperphosphatemia in 75.5%, vitamin D deficiency in 84.5% of the cases.

In Present study i-PTH was significantly associated with sex ($P < .004$), eGFR ($P < .02$), corrected serum calcium level ($P < .001$), serum phosphorus ($P < 0.001$), and 25(OH) vit-D ($P < 0.04$). On multivariate analysis a significant association of i-PTH was again seen with these variables except for Vitamin D. Previously, Parathyroid hormone and serum calcium, phosphate, creatinine, and urea showed prominently higher levels in the patients receiving haemodialysis compared with control individuals.[19]

Based on the intact parathyroid hormone levels (KDIGO guideline),[6] all of our patients in stage 3, 4, and 5 CKD had high turnover bone disease; and none had low turnover bone disease.

However only 7% of our patients of CKD stage 5D had high turnover bone disease meanwhile 91% had low turnover bone disease. The high prevalence of adynamic bone disease (ABD) in dialysis patients was likely to be due to the old age, high prevalence of diabetic CKD and injudicious use of active vitamin D analogues and calcium containing phosphate binders in our study population.

ABD is increasingly important in CKD-MBD because of the high percentage of affected individuals (> 40% in CKD stage 5) and its association with cardiovascular calcification and mortality. Furthermore, fracture incidence is estimated to be twice as high in individuals with low bone turnover as compared with high bone turnover cases. The ABD prevalence is markedly increasing in bone biopsy registries of dialysis patients.[17,20]

A large cohort and prospective evaluation are the strong points of the study. However, the cross-sectional design and the absence of bone biopsy are the limitations. Nevertheless, studies have shown biochemical parameters to correlate with the bone histology.

In conclusion, our results show that in non-dialysis CKD patients high turnover bone disease is common and the trend reverses in dialysis patients where low turnover bone disease is present in around 90% of patients. The high incidence of adynamic bone disease in dialysis patients seems to be due to injudicious use of phosphate binders (especially calcium containing) and vitamin D analogues. Thus, a careful approach is advocated to diagnose, prevent and treat various bone mineral abnormalities in CKD patients. Daily consumption of 6 g/d of flaxseed oil may reduce bone resorption in hemodialysis patients.[21] Moreover, haemoglobin and nutritional and bone metabolism factors, should be considered for optimal dialysis outcomes.[22] This will help in preventing significant morbidity and mortality in these patients.

CONFLICT OF INTEREST

We declared that we do not have conflict of interest in this manuscript.

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