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Original Article

Profile of Mineral Bone Disease in Chronic Kidney Disease Patients in a Tertiary Care Center

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Abstract

Introduction: Chronic kidney disease related-mineral bone disorder (CKD-MBD) has been poorly studied in pre-dialysis Indian CKD patients.

Aim: The aim of the study is to study the clinical, mineral abnormalities in Stage 3-5 CKD patients.

Materials and Methods: A hospital-based cross-sectional survey including, demographic profile, history of CKD-MBD symptoms, measurement of serum calcium, intact parathyroid hormone (iPTH), magnesium, phosphorus, and Vitamin D bone alkaline phosphatase (BAP) in Stage 3-5 CKD patients.

Results: Of 83 patients, prevalence of Vitamin D deficiency in Stage 3-5 CKD is 9.64%. The overall prevalence of low BAP, normal BAP, and high BAP in Stage 3-5 CKD is 3.61%, 74.70%, and 21.69%, respectively, was not statistically significant.

Conclusion: Vitamin D deficiency is noted in earlier stages of CKD rather than late stages. BAP had statistically significant correlation with calcium, Vitamin D, and iPTH. Serum bone specific alkaline phosphatase assay should be included in CKD-MBD screening. The screening should begin in the early stage of CKD.

Key words: Chronic kidney disease related-mineral bone disorder, Valvular calcification, Vitamin D

INTRODUCTION

Chronic kidney disease (CKD) is now a public health problem affecting an estimated 10-13% of the world population.[1,2] As renal function declines, there is a progressive impairment in the regulation of mineral homeostasis leading to altered serum concentrations of calcium, phosphate, parathyroid hormone (PTH), and Vitamin D. The end result of these biochemical abnormalities is disordered bone growth and remodeling and extraskeletal calcification; collectively known as CKD related-mineral bone disorders (CKD-MBD). CKD is associated with significant perturbations in bone and mineral metabolism, leading to altered serum concentrations of calcium, phosphorus, PTH, and Vitamin D with abnormalities in bone remodeling, renal osteodystrophy, and extraskeletal calcification.[3] These changes can be detected as early as when the estimated glomerular filtration rate (eGFR) falls to ≤60 mL/min/1.73 m^2 body surface area. Early detection and management of CKD-MBD is important as it is associated with increased cardiovascular mortality due to associated increased risk of soft tissue, vascular, and cardiac valvular calcification.[4-6] Spectrum of CKD-MBD has been poorly studied in Indian CKD patients, especially in the pre-dialysis stage.

Aim

The aim of the study is to study the clinical, mineral abnormalities in Stage 3-5 CKD patients.

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MATERIALS AND METHODS

This cross-sectional survey was conducted at the Department of Nephrology, Government Kilpauk Medical College, Chennai, Tamil Nadu. Patients with newly

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diagnosed Stage 3-5 CKD (based on history, eGFR of <30 mL/min/1.73 m 2 by the abbreviated modification of diet in renal disease formula, biochemical, and ultrasonographic/histological evidence of CKD) who were not yet on dialysis or on hemodialysis/CAPD for <1 month at the time of enrolment in the study. Exclusion criteria include: Those who were already on dialysis, had pre-existing parathyroid abnormalities, already on non-steroidal anti-inflammatory drug, antiepileptics known liver diseases, rickets, osteomalacia patients, were excluded from the study. Renal transplant patient was also excluded from the study. Ethics committee approval from the institutional ethics committee was obtained before the study. Questionnaire regarding symptoms of CKD-MBD is given to all the patients in our study. Those who are having one or more of the symptoms are considered as symptomatic. Ophthalmic fundus examination is done. After obtaining consent from the patient, with aseptic precautions, about 8 ml of venous blood is obtained from the median cubital vein. Serum and plasma samples are stored at −20°C ice lined refrigerator. Plasma samples are analyzed for 25-hydroxy Vitamin D and intact PTH (iPTH). Serum samples are analyzed for all other biochemical parameters.

RESULTS

Of the total 83 patients, slight female predominance with 42 (56%), the M:F ratio is 0.9:1. The average age of the CKD patients in our study is 54.3 years. 34% of patients in CKD Stage 4 followed by Stage 3 and 5. 59.03% of are asymptomatic. The serum total calcium observed is corrected for serum albumin. The prevalence of calcium abnormalities is shown in Table 1.

In our study, we had 25, 34, and 24 Stage 3, 4, and 5 CKD patients. The normal value of serum calcium is 8.6-10 mg/dl. The prevalence of hypocalcaemia in Stage 3, 4, and 5 are 12%, 11.6%, and 37.5%, respectively. The prevalence of normocalcemia in Stage 3, 4, and 5 CKD are 76%, 79.41%, and 58.33%, respectively. The prevalence of hypercalcemia in Stage 3, 4, and 5 CKD are 12%, 8.82%, and 4.17%, respectively. The overall prevalence of hypocalcaemia, normocalcemia, and hypercalcemia in Stage 3-5 CKD is 19.28%, 72.29%, and 8.43%, respectively, which is not statistically significant.

The prevalence of hypoparathyroidism in Stage 3, 4, and 5 are 12%, 2.94%, and 4.17%, respectively, normoparathyroidism in Stage 3, 4, and 5 CKD are 36%, 38.24%, and 8.33%, respectively, hyperparathyroidism in Stage 3, 4 and, 5 CKD are 52%, 58.82%, and 87.5%, respectively. The overall prevalence of hypoparathyroidism, normoparathyroidism, and hyperparathyroidism in Stage 3-5 CKD is 6.02%, 28.92%, and 65.06%, respectively, which is statistically significant (Table 2).

The prevalence of Vitamin D deficiency in Stage 3, 4, and 5 are 4%, 20.59%, and 0%, respectively. The prevalence of no deficiency of Vitamin D in Stage 3, 4, and 5 CKD are 96%, 79.41%, and 100%, respectively. The overall prevalence of Vitamin D deficiency and no deficiency in Stage 3-5 CKD is 9.64% and 90.36%, respectively, which is statistically significant (Table 3).

The prevalence of hypermagnesemia in Stage 3, 4, and 5 are 16%, 28 %, and 56%, respectively, normomagnesemia in Stage 3, 4, and 5 CKD are 17.65%, 47.06%, and 35.29%, respectively, hypermagnesemia in Stage 3, 4, and 5 CKD are 20.83%, 41.67%, and 37.50%, respectively. The overall prevalence of hypomagnesaemia, normoagnesemia, and hypermagnesemia in Stage 3-5 CKD is 18.07%, 39.76%, and 42.17%, respectively, had no significance (Table 4).

Table 1: Distribution of calcium abnormalities in study patients

Calcium	eGFR			
	Number of cases (%)			
	Stage 3	Stage 4	Stage 5	Total
BN	3 (12)	4 (11.76)	9 (37.5)	16 (19.28)
N	19 (76)	27 (79.41)	14 (58.33)	60 (72.29)
AN	3 (12)	3 (8.82)	1 (4.17)	7 (8.43)
Total	25 (100)	34 (100)	24 (100)	83 (100)

eGFR: Estimated glomerular filtration rate, BN: Below normal, N: Normal, AN: Above normal

Table 2: Distribution of iPTH abnormalities in study patients

iPTH	eGFR			
	Number of cases (%)			
	Stage 3	Stage 4	Stage 5	Total
BN	3 (12)	1 (2.94)	1 (4.17)	5 (6.02)
N	9 (36)	13 (38.24)	2 (8.33)	24 (28.92)
AN	13 (52)	20 (58.82)	21 (87.5)	54 (65.06)
Total	25 (100)	34 (100)	24 (100)	83 (100)

eGFR: Estimated glomerular filtration rate, iPTH: Intact parathyroid hormone, BN: Below normal, N: Normal, AN: Above normal

Table 3: Distribution of Vitamin D abnormalities in study patients

Vitamin D	eGFR			
	Number of cases (%)			
	Stage 3	Stage 4	Stage 5	Total
Non deficient	24 (96)	27 (79.41)	24 (100)	75 (90.36)
Deficient	1 (4)	7 (20.59)	0 (0)	8 (9.64)
Total	25 (100)	34 (100)	24 (100)	83 (100)

eGFR: Estimated glomerular filtration rate

The prevalence of hypophosphatemia in Stage 3, 4, and 5 are 20%, 8.82%, and 0%, respectively, normophosphatemia in Stage 3, 4, and 5 CKD are 76%, 73.53%, and 50%, respectively, hyperphosphatemia in Stage 3, 4, and 5 CKD are 4%, 17.65%, and 50%, respectively. The overall prevalence of hypophosphatemia, normophosphatemia, and hyperphosphatemia in stage 3-5 CKD is 9.64%, 67.47%, and 22.89%, respectively, has significance (Table 5).

The prevalence of low bone alkaline phosphatase (BAP) in Stage 3, 4, and 5 are 8%, 0% and 4.17%, respectively, normal BAP in Stage 3, 4, and 5 CKD are 84%, 70.59%, and 70.83%, respectively, high BAP in Stage 3, 4, and 5 CKD are 8%, 29.41%, and 25%, respectively. The overall prevalence of low BAP, normal BAP, and high BAP in Stage 3-5 CKD is 3.61%, 74.70%, and 21.69%, respectively, which has statistically no significance (Table 6).

The prevalence of abnormal bone turnover marker BAP in symptomatic and asymptomatic CKD-MBD patients is as follows.

The difference in bone turnover marker in Stage 3-5 CKD in asymptomatic and symptomatic MBD patients is statistically not significant (Table 7).

A positive correlation is seen between BAP and Vitamin D and it is statistically significant. There is a positive correlation between BAP and iPTH with a Pearson correlation of 0.34 which is statistically significant. The iPTH and Vitamin D are inversely correlated but this correlation is not statistically significant. iPTH and calcium are found to be negatively correlated, i.e., when calcium falls iPTH rises and the reverse occurs in hypercalcemia. The parathormone is a minute-to-minute compensatory response of the body to the fall in serum ionized calcium levels. Hence, this correlation is strong.

Table 4: Distribution of magnesium abnormalities in study patients

Magnesium	eGFR			
	Number of cases (%)			
	Stage 3	Stage 4	Stage 5	Total
BN	4 (16)	6 (17.65)	5 (20.83)	15 (18.07)
N	7 (28)	16 (47.0)	10 (41.67)	33 (39.76)
AN	14 (56)	12 (35.29)	9 (30.75)	35 (42.17)
Total	25 (100)	34 (100)	24 (100)	83 (100)

eGFR: Estimated glomerular filtration rate, BN: Below normal, N: Normal, AN: Above normal

Table 5: Distribution of phosphorus abnormalities in study patients

Phosphorus	eGFR			
	Number of cases (%)			
	Stage 3	Stage 4	Stage 5	Total
BN	5 (20)	3 (8.82)	0 (0)	6 (9.64)
N	19 (76)	25 (73.53)	12 (50)	56 (67.47)
AN	1 (4)	6 (17.65)	12 (50)	19 (22.89)
Total	25 (100)	34 (100)	24 (100)	83 (100)

eGFR: Estimated glomerular filtration rate, BN: Below normal, N: Normal, AN: Above normal

Table 6: Distribution of abnormal BAP in study patients

BAP	eGFR			
	Number of cases (%)			
	Stage 3	Stage 4	Stage 5	Total
BN	2 (8)	0 (0)	1 (4.17)	3 (3.61)
N	21 (84)	24 (70.59)	17 (70.83)	62 (74.7)
AN	2 (8)	10 (29.41)	6 (25)	18 (21.69)
Total	25 (100)	34 (100)	24 (100)	83 (100)

eGFR: Estimated glomerular filtration rate, BAP: Bone alkaline phosphatase, BN: Below normal, N: Normal, AN: Above normal

Table 7: Distribution of abnormal bone turnover marker BAP in symptomatic and asymptomatic CKD-MBD patients

BAP	eGFR		
	Number of cases (%)		
	Asymptomatic	Symptomatic	Total
BN	2 (4.08)	1 (2.94)	3 (3.61)
N	36 (73.47)	26 (76.47)	62 (74.7)
AN	11 (22.45)	7 (20.57)	18 (21.69)
Total	49 (100)	34 (100)	83 (100)

eGFR: Estimated glomerular filtration rate, CKD-MBD: Chronic kidney disease related-mineral bone disorder, BAP: Bone alkaline phosphatase, BN: Below normal, N: Normal, AN: Above normal

DISCUSSION

The prevalence of CKD in our Indian population is estimated around 0.78% and 0.87%.[7] We studied 83 CKD stage 3-5 patients. The average age of the CKD patients in our study is 54.3 ±12.67 years. Of them, 42 were females and 41 males leading to a slight female predominance, the M:F ratio is 0.9:1. The symptomatic CKD-MBD individuals comprised 40.96%. Remaining 59.03% did not have any symptoms related to CKD-MBD. The prevalence of hypoparathyroidism is 6.02% indicating the possible load of low turnover bone disease, whereas hyperparathyroidism, with a cutoff of iPTH >65 pg/ml, is noted in 58.82% in Stage 4 and 87.5% in Stage 5, with overall 65.06% indicating high turnover bone disease. Other Indian studies show hyperparathyroidism to be 73%,[8] 57.3% in Stage 4 CKD and 89.5% in Stage 5 CKD and 84.62% in Stage 4 and 88.29% in Stage 5. High turnover state assessed by Jabbar *et al.* is 60%[8]

with a cutoff of iPTH as >300 pg/ml. In our study, 39.7% of patients have a iPTH value of more than two to nine times the normal upper limit out of which 57.6% have high BAP indicating the truly high turnover state exists in less than what is actually estimated by iPTH. The prevalence of hypocalcaemia in our study is noted to be 12%, 11.76%, and 37.5% in Stages 3, 4, and 5, respectively. Study by Agarwal showed that 29.9% and 49.6% of hypocalcemia is prevalent in Stages 4 and 5.[9] Hyperphosphatemia is found in 4%, 17.65%, and 50% in Stages 3, 4, and 5 of CKD with an overall of 22.89% in our study. It is in concordance with other Indian studies - Valson *et al.* 59%[7] of Vitamin D deficiency is found only in Stages 3 and 4 of CKD, 4% and 20%, namely, in our study. Surprisingly in Stage 5 CKD, none of them are deficient. Previous studies showed up to 80% of Vitamin D deficiency.[8] Prevalence of an abnormal BAP, is not found in a statistically significant percentage with any of the following, i.e., symptomatic individuals/ patients with abnormal fundus examination. Thus, none of the above features in a CKD-MBD patient can predict an abnormal bone turnover. Only bone turnover markers next to bone biopsy can predict bone turnover diseases in CKD. The prevalence of hypomagnesaemia in Stage 3-5 CKD, in our study, shows that magnesium is not associated with bone turnover abnormalities. In our study, statistically significant correlation, as analyzed by Pearson coefficient, is seen between iPTH and calcium ($r = -0.30$; $P = 0.01$); iPTH and BAP ($r = 0.34$; $P = 0.001$); BAP and Vitamin D ($r = 0.28$; $P = 0.01$). Various studies showed that biological variation was half less than that PTH, BAP is emerging as alternative marker for CKD-MBD.[10-12]

CONCLUSION

Vitamin D deficiency is noted in earlier stages of CKD rather than late stages. BAP had statistically significant correlation with calcium, Vitamin D, and iPTH. Serum bone specific alkaline phosphatase assay should be included in CKD-MBD screening. The screening should begin in the early stage of CKD.

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