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Bone disorders in chronic kidney disease patients: A teaching hospital based study in central India

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Abstract
Background: Kidneys and bones are the major metabolic buffer systems in our body that help us to maintain the internal milieu. Disease in one naturally is going to affect the other in long term. The association between the two has long been known but not brought into the limelight till the recent decades. This increase in the importance being given to the mineral abnormalities is due to its high association with the cardiovascular disease and death due to CVD. Chronic kidney disease (CKD) is a progressive loss in renal function which involves in deterioration in mineral homeostasis with disruption of normal serum and tissue concentration of phosphorus and calcium. Also changes in circulating levels of hormones parathyroid hormone (PTH), calcitriol (1, 25(OH) 2 D), and fibroblast growth factor-23 (FGF-23). Here our aim is to study the prevalence of markers associated with MBD in CKD stage 3-5 patients. Patients with CKD stage 3-5 were included in this observational study with all necessary parameter. X-RAY abdomen and echocardiography was done to look for evidence of vascular and valvular calcification respectively.
Aims and Objectives: To evaluate the bone disorders in chronic kidney disease patients.
Material and Methods: This retrospective study was conducted in Department of Medicine, RKDF Medical College Hospital & Research Center, Bhopal, Madhya Pradesh, India. All CKD patients from stage 3-5 were included. Likewise Patients having pre-existing systemic diseases like SLE/RA, liver disease, patients on steroids or other drugs which have effect on bone metabolism like calcium, phosphate binders, vit D, bisphosphonates, patients with primary bone diseases, patients on maintenance hemodialysis and h/o fracture in last. Statistical analysis was done using SPSS software.
Results and Observations: A total of 175 patients (132 males, 43 females) (M:F = 3:1) were included in this study with a mean age of 50.54 years. Among CKD stages 3 to 5, the prevalence of hypocalcemia was 21.5%, 33.9% & 48.9%, hyperphosphatemia was 11.1%, 25.5% & 63%, hyperparathyroidism was 48.1%, 67.3% & 89.1%, high total alkaline phosphatase was 0%,
5.9% & 45.7%, low 25-OH-vit D was 59.2%, 70.6% & 79.4% respectively. Low 25 (OH) D levels, hyperparathyroidism, and hyperphosphatemia were the noticeable markers of CKD-MBD in our patients. Mineral bone disorder are common in CKD patients which start in early CKD stages & worsen with disease progression that causes morbidity and decreased quality of life.
Conclusion: Diabetic and Non-diabetic CKD-MBD are not different and hence need not be addressed separately. Serum bone marker assay should be included in CKD-MBD screening. The screening should begin in the early stage of CKD. In conclusion, we observed Low 25 (OH) D levels, hyperparathyroidism, and hyperphosphatemia were the noticeable markers of CKD-MBD in our patients. Mineral bone disorder are common in CKD patients which start in early CKD stages & worsen with disease progression that causes morbidity and decreased quality of life. Hence, this shows the importance of early recognition, understanding of their patho-physiological consequences & planning management strategies to prevent their progression, thereby reducing the cardiovascular morbidity & mortality.

Keywords: Metabolism, Bone disorder, CKD, MBD, hyperparathyroidism, hyperphosphatemia, hypocalcemia diabetic patients, non-diabetic patients

Introduction
In CKD, in bones there develops a resistance to the calcemic actions of PTH [1]. This resistance is due to decreased calcitriol levels, phosphate retention, N-terminal truncated PTH fragments which have antagonistic actions to PTH [2, 3]. Hence for mobilizing the bone calcium, parathyroid gland over secretes PTH. The abnormalities that occur within the parathyroid gland are gland hyperplasia, reduced calcium receptors & decreased expression of vitamin D receptors. Kidneys and bones are the major metabolic buffer systems in our body that help us to maintain the internal milieu.

Disease in one naturally is going to affect the other in long term. The association between the two has long been known but not brought into the limelight till the recent decades. This increase in the importance being given to the mineral abnormalities is due to its high association with the cardiovascular disease and death due to CVD. As the renal blood flow diminishes in CKD, so does the GFR. The minerals that need to be excreted normally get stagnated behind. Hence the parathyroids overwork to reduce some of the mineral load to the kidneys by depositing them on the tissues. They achieve it by mobilizing the calcium from the bones, form adducts with the excess phosphates and the products get deposited in the tissues. Chronic kidney disease (CKD) has a prevalence of 5-10% of the world population [4].

Patients with CKD have high rates of total and cardiovascular morbidity and mortality.

Abnormalities in levels of mineral metabolites and regulators, such as calcium, phosphate, parathyroid hormone, fibroblast growth factor-23 and vitamin D have been linked to the progression of cardiovascular disease and poor outcomes [5]. These mineral and endocrine capacities are basically significant in the guideline of both starting bone formation during development and bone structure & function all through adulthood (modeling and remodeling of bone) [6].

As kidney function declines, there is a progressive deterioration in mineral homeostasis with a disruption of normal serum and tissue concentrations of phosphorus and calcium and changes in circulating levels of hormones. These include parathyroid hormone (PTH), 25-hydroxy vitamin D, 1, 25-dihydroxyvitamin D and other vitamin D metabolites, fibroblast growth factor-23 (FGF-23), and growth hormone.

The ability of the kidneys to appropriately excrete a phosphate load is diminished when GFR falls below 60, leading to hyperphosphatemia, elevated PTH, decreased 1,25(OH)2D with associated elevations in the levels of FGF- 23. The conversion of 25(OH) D to 1, 25(OH) 2 D is impaired, reducing intestinal calcium absorption and increasing PTH. The kidneys fail to respond adequately to PTH, which normally promotes phosphaturia and calcium absorption, or to FGF-23, which also enhances phosphate excretion. In addition, there is evidence at the tissue level of a down regulation of vitamin D receptor and of resistance to the actions of PTH. Therapy is generally focused on correcting biochemical and hormonal abnormalities in an effort to limit their consequences. The mineral and endocrine functions disrupted in CKD are critically important in the regulation of both initial bone formations during growth (bone modeling). 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. More recently, there has been an increase concern of extra skeletal calcification that may result from the deranged mineral and bone metabolism of CKD and from the therapies used to correct these abnormalities [7].

Numerous cohort studies have shown associations between disorders of mineral metabolism and fractures,} cardiovascular disease and mortality. These observational studies have broadened the focus of CKD related mineral and bone disorders (MBDs) to include cardiovascular disease which is the leading cause of death in patients at all stages of CKD. All three of these processes (abnormal mineral metabolism, abnormal bone and extra skeletal calcification) are closely interrelated and together make a major contribution to the morbidity and mortality of patients with CKD. So we aim here to reveal the prevalence of markers of MBD in CKD stage 3-5 patients. Cardiovascular disease and mortality. These observational studies have broadened the focus of CKD related mineral and bone disorders (MBDs) to include cardiovascular disease which is the leading cause of death in patients at all stages of CKD. All three of these processes (abnormal mineral metabolism, abnormal bone and extra skeletal calcification) are closely interrelated and together make a major contribution to the morbidity and mortality of patients with CKD. So we aim here to reveal the prevalence of markers of MBD in CKD stage 3-5 patients.

Results

Materials and Methods

This retrospective study was conducted in Department of Medicine, RKDF Medical College Hospital & Research Center, Bhopal, Madhya Pradesh, India. All CKD patients from stage 3-5 were included. Likewise Patients having pre-existing systemic diseases like SLE/RA, liver disease, patients on steroids or other drugs which have effect on bone metabolism like calcium, phosphate binders, vit D, bisphosphonates, patients with primary bone diseases, patients on maintenance hemodialysis and h/o fracture in last 6 months are excluded from this study.

Glomerular filtration rate (eGFR) was estimated based on Cockroaft-Gault formula. Serum creatinine, albumin, calcium, phosphate (PO 4), TAP, hemoglobin, uric acid, and urinary protein excretion were measured using standard laboratory techniques. Plasma intact parathormone (iPTH) was measured using the solid phase, two-site chemiluminescent enzyme-labeled immunometric assay. Plasma 25-OH vitamin D (25-vitD) assay was done using the radio immunometric assay. Radiological survey like lateral X-ray of skull, abdomen and 2D echocardiography was carried out to detect vascular and valvular calcification respectively. Statistical analyses are performed using SPSS software. Various parameters of the whole group were analyzed as well as the parameters were compared between the groups. Parametric variables were compared using unpaired t-test and Mann-Whitney Rank Sum test. Non-parametric variables were compared using Chi-square test. At P value<0.05 was taken as significant.

Results and observations

Prevalence of various abnormalities in stages 3-5 of CKD observed are listed below.

The total 175 cases, out of which 132(75.43%) were males and 43(24.57%) were females were taken in this hospital-based cross-sectional observational study. Male: female ratio is 3:1. Majority of patients were middle aged, i.e, in 41-60 years age group with mean age of 50.54 years, Out of

all, 46% patients were diabetic and 86% patients were hypertensive.

Table 1: Distribution of calcium levels in different stage CKD patients

	Calcium			Total
	<8.5	8.5-10.5	>10.5	
CKD 3 count	6	22	0	28
%within CKD 3	21.5%	78.5%	0%	100%
CKD 4 count	18	33	2	53
% within CKD4	33.9%	62.3%	3.8%	100%
CKD 5 count	46	48	0	94
%within CKD5	48.9%	51.1%	0%	100%
Total count	70	103	2	175
% within CKD	40.0%	58.8%	1.2%	100%

In stage 3 CKD patients (n=28), majority (78.5%) had calcium levels in the normal range, only 21.5% had calcium below normal range. In stage 4 patients (n=53), calcium levels were in the normal range in 62.3% of patients, 33.9% had calcium below normal range and 3.8% had higher calcium levels than normal. In stage 5 CKD patients (94), calcium levels were in the normal range in 51.1% of patients, while a significant number of patients (48.9%) had low levels of calcium (Table 1). The results were found statistically significant with p value <0.05. Elevated phosphorus levels (>4.5mg/dl) in 13.8% patients of CKD stage 3, 26.4% patients of CKD stage 4 and 63.4% patients of CKD stage 5 were found which is also statistically significant. [Table 2].

Table 2: Elevated phosphorus levels in 3 different stage CKD patients

	Phosphorus		
	2.5-4.5	4.5	Total
CKD 3 count	25	4	29
%within CKD3	86.2%	13.8%	100%
CKD 4	39	14	53
%within CKD 4	73.6%	26.4%	100%
CKD 5	34	59	93
%within CKD5	36.6%	63.4%	100%
Total count	98	77	175
%within CKD	56%	44%	100%

[Table 3] shows the results, which are found statistically significant with p value <0.05. The serum iPTH levels in CKD stage 3 patients, 51.9% patients had normal iPTH levels whereas in significant number (48.1%) of patients, iPTH was elevated above normal range. In CKD stage 4 patients, 66% patients had iPTH above normal range and in only 34% patients, iPTH was normal. In CKD stage 5 patients, iPTH was normal in only 7.4% patients, 89.4% had high levels of iPTH and in 3.2% patients, it was below normal range.

Table 3: The serum iPTH level in CDK 3, 4 and CDK5

	Intact parathyroid hormone			Total
	Below Normal	Normal	Above Normal	
CKD 3 count	0	14	13	27
% within CKD 3	0%	51.9%	48.1%	100%
CKD 4 count	0	18	35	53
%within CKD 4	0%	34%	66%	100%
CKD 5 count	3	7	85	95
% within CKD 5	3.2%	7.4%	89.4%	100%
Total count	3	39	133	175
% within CKD	1.7%	22.3%	76%	100%

Total alkaline phosphatase levels were within normal range in all patients of CKD stage 3. In stage 4 CKD patients, total ALP was within normal range in 94.3% patients and remaining 5.7% had high levels. In stage 5 CKD patients, ALP was above normal in 45.3% patients and normal in 54.7% patients (Table 4). The results are statistically significant.

Table 4: Alkaline phosphatase levels in 3 different stages in CDK

	<310	>310	Total
CKD 3 count	27	0	27
% within CKD 3	100%	0%	100%
CKD 4 count	50	3	53
% within CKD4	94.3%	5.7%	100%
CKD 5 count	52	43	95
% within CKD 5	54.7%	45.3%	100%
Total count	129	46	175
%within CKD	73.7%	26.3%	100%

Similarly (Table 5) shows 25 OH vitamin-D levels were below normal in 59.2% CKD stage 3 patients. Majority (70.3%) patients in CKD stage 4 had low levels of 25 OH vitamin-D and rest had normal levels. In CKD stage 5, 25 OH vitamin-D was low in 79.8% patients and in rest, it was normal.

Table 5: 25 Hydroxy vitamin D in CDK 3, 4 and CDK5

	25 Hydroxy Vitamin D			Total
	<20	20 -30	>30	
CKD 3 count	8	8	11	27
% within CKD	29.6%	29.6%	40.8%	100%
CKD 4 count	20	18	16	54
% within CKD	37%	33.9%	29.7%	100%
CKD 5 count	45	30	19	94
% within CKD	47.9%	31.9%	20.2%	100%
Total count	73	56	46	175
% within CKD	41.7%	32%	26.3%	100%

[Table 6] and [Figure 1] shows 8 patients of CKD stage 3, who have calcification. Among 21 patients of CKD stage 4, only 1(4.8%) had evidence of vascular calcification and 10(29.4%) had evidence of vascular calcification out of 34 patients of CKD stage 5 patients. The results were found statistically significant with p value <0.05.

Table 6: CKD Stage and vascular calcification

	Vascular Calcification		Total
	Positive	Negative	
CKD 3	0, 0%	8, 100%	8, 100%
CKD 4	1, 4.8%	20, 95.2%	21, 100%
CKD 5	10, 29.4%	24, 70.6%	34, 100%
Total	11, 19%	52, 81%	63, 100%

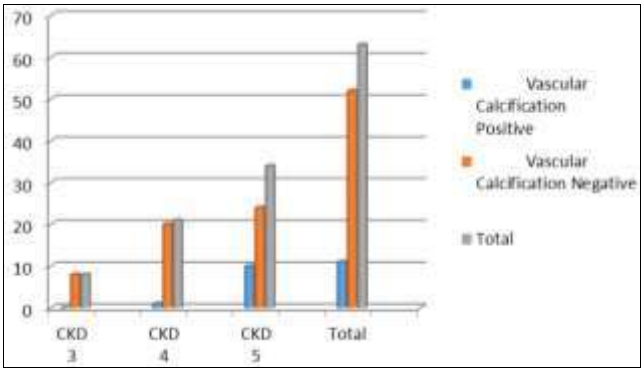

Fig 1: CKD stages and vascular calcification

Table 7 and Figure 2 shows 8 patients of CKD stage 3 who have undergone echocardiography, none had evidence of valvular calcification. Among 21 patients of CKD stage 4, all had evidence of valvular calcification and out of 34 patients of CKD stage 5 patients, 29(85.3%) had evidence of valvular calcification.

Table 7: CKD stage and valvular calcification

	Valvular Calcification		Total
	Positive	Negative	
CKD 3	0, 0%	8, 100%	8, 100%
CKD 4	0, 0%	21, 100%	21, 100%
CKD 5	5, 14.7%	29, 85.3%	34, 100%
Total	5, 7.9%	58, 92.1%	63, 100%

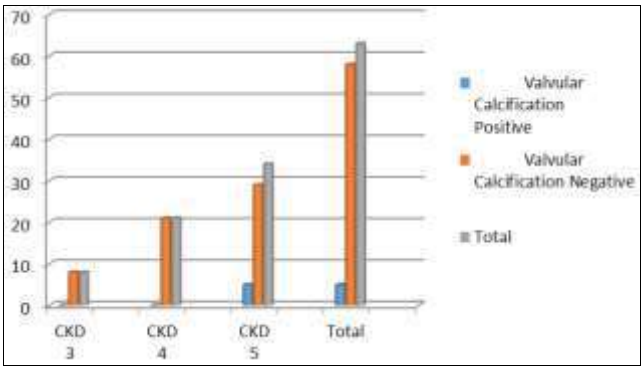

Fig 2: CKD stages and valvular calcification

Discussion

The prevalence of CKD in our Indian population is estimated to be between 0.78% and 0.87%. The main purpose of our study is to describe the profile of CKD-MBD patients in our hospital. We studied 83 CKD stage 3-5 patients. The average age of the CKD patients in our study is 54.3 +/- 12.67 years. The symptomatic CKD-MBD individuals according to our study comprised 40.96%. Remaining 59.03% didn't have any symptoms related to CKD-MBD. This further reveals how disguising the clinical picture of MBD is in our setup.

The mean age of our study population was higher (50.5 years) to other studies by Agarwal SK *et al.* (44 years), Sakuja V *et al.* (46.2 years) and B. Ghosh *et al* (45.7 years) [8, 9, 10]. We observed that males outnumbered females (M: F = 3:1). 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 twofold ratio was maintained at all levels of serum creatinine [11]. Among Indian studies, Agarwal *et al.* [12] 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 One of the main reasons for these differences in may be that, in India, more males and younger persons attend hospitals than females and the elderly. MBDs are well described in patients with CKD.

Agarwal *et al* described hypocalcemia in 29.9% and 49.6% in CKD stage 4 and 5, respectively, and hyperphosphatemia in 45% and 41.8%, respectively. LaClair, *et al.* [13] found hypocalcemia in 8% and 28%, and hyperphosphatemia in 20% and 50% of patients of CKD stages 4 and 5, respectively. In our study, hypocalcemia was found in 21.5%, 33.9% and 48.9% cases of CKD stages 3, 4 and 5 respectively. Hyperphosphatemia was found in 13.8%, 26.4% and 63.4% cases of CKD stages 3, 4 and 5 respectively.

Our study results corroborated with previous studies

Total ALP also signifies high turnover bone disease when elevated and interpreted in appropriate circumstances.

In this study, elevated ALP was present in 5.7% and 45.3% of patients of CKD stage 4 and 5, respectively. Indeed, KDIGO recommended that the treatment of MBD be based on trend in changes of biochemical parameters rather than on abnormalities at a single point of time. B. ghosh *et al.* found raised ALP in 43.59% and 76.66% of patients of CKD stage 4 and 5D, respectively. Jabbar, *et al.* found raised bone alkaline phosphatase in 60% of their stage 4 and 5 CKD patients. Vitamin D abnormalities were common in all CKD stages. 60-80% patients had low levels of 25 hydroxy vitamin D. 1, 25-dihydroxyvitamin D deficiency is known to occur during the progression of CKD, because the final hydroxylation step of 25-hydroxyvitamin D to 25(OH)2D to 1, 25 (OH)2D is mediated by kidney 1α-hydroxylase. Severity of deficiency did not correlate with CKD stage or other mineral abnormalities. In our study, the prevalence of deficiency of 25(OH) D3 increased as CKD progressed. Low 25(OH)D3 levels were found in 73.6% of patients. Jabber *et al.* [14] reported Vitamin D deficiency in 80%, and insufficiency in 13% of the patients. B. Ghosh *et al.* reported 83.13% of patients with CKD stage 4 and 5D had vitamin D level less than 30 ng/mL. Our study results corroborated with these studies.

Literature shows that, hyperparathyroidism presents early in CKD & worsens with progression of CKD stages. There is an increase in the prevalence of hyperparathyroidism from CKD stage 4.

Hyperparathyroidism was present in 66% patients in CKD stage 4 & 89.4% patients in CKD stage 5 which was similar to Levin A *et al.* [15] study in which 56% patients in CKD with e GFR < 60ml/min had hyperparathyroidism. Agarwal *et al.* found hyperparathyroidism in 57.8% of patients with CKD stage 4 and in 39.4% of patients with CKD stage 5.

Jabbar, *et al*. Observed prevalence of hyperparathyroidism in 60% of their patients of CKD stage 4 and 5. In our study, hyperparathyroidism was higher than other studies.

Adynamic bone disease as evident by low iPTH levels was uncommon and found in 3.2% patients of stage 5 CKD. Vascular (Abdominal aortic) calcification was seen in 4.8% and 29.4% in CKD stage 4 and 5 patients respectively. Shantha *et al*. [16] using a lateral abdominal X-ray for screening, found a prevalence of 76.9% in 26 Indian pre-dialysis Stage 5 CKD patients who had a mean age of 56.6 years, 65% of whom were receiving calcium containing phosphate binders. A.T. Valson *et al*. [17] reported 6.8% of cases having vascular calcification. Valvular calcification was present in 14.7% of stage 5 CKD patients in our study, which is much lower than that reported in Caucasian pre-dialysis CKD subjects (31%) by Leskinen *et al*. [18] Ghosh *et al*., reported VC in 25% and 46% of Indian CKD Stage 4 and 5D patients respectively. A.T. Valson *et al*. reported 96% of cases having valvular calcification. Among those having vascular or valvular calcification, most of the patients were older than 50 years and had evidence of hyperphosphatemia, hyperparathyroidism in comparison with those not having evidence of calcification. Studies comparing bone formation in bone biopsy vs serum bio-markers of bone formation show that there is some correlation between Bone specific Alkaline Phosphatase and bone formation rate than PTH which was once thought to reflect bone turnover. PTH is a marker of parathyroid activity rather than bone turnover [19] and also BAP might predict high or low bone turnover [20, 21, 22]. Other markers like deoxypyridinoline, Tumor necrosis factoralpha, osteocalcin, osteoprotegrin have insufficient evidence to be used as markers.

Conclusion

This study concluded that Vitamin D deficiency pattern has changed in CKD. Diabetic and Non-diabetic CKD-MBD are not different and hence need not be addressed separately. Serum bone marker assay should be included in CKD-MBD screening. The screening should begin in the early stage of CKD. In conclusion, we observed Low 25 (OH) D levels, hyperparathyroidism, and hyperphosphatemia were the noticeable markers of CKD-MBD in our patients. Mineral bone disorder are common in CKD patients which start in early CKD stages & worsen with disease progression that causes morbidity and decreased quality of life. Hence, this shows the importance of early recognition, understanding of their patho-physiological consequences & planning management strategies to prevent their progression, thereby reducing the cardiovascular morbidity & mortality.

Conflict of Interest

Not available

Financial Support

Not available

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