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Original Research Article

Study of Chronic Kidney Disease-Mineral Bone Disorders in Advanced Renal Failure Patients: A Hospital-Based Cross-sectional Study

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Abstract

Background: Chronic kidney disease (CKD) is associated with significant disconcertion in bone and mineral metabolism, which leads to alteration in serum concentrations of calcium(Ca), phosphorus(P), parathyroid hormone (PTH), and Vitamin D and it also leads to abnormalities in bone remodeling, renal osteodystrophy (ROD) and extraskeletal calcification. So we aim to assess the alteration in mineral metabolism, abnormal changes in bone mineral density (BMD) and extra skeletal calcification in newly detected, untreated predialysis stage 4 and 5 chronic kidney disease (CKD) patients at a tertiary care hospital in North India. **Methods:** Hospital based cross sectional study was conducted in patients of CKD detected in Mahatma Gandhi Hospital Jaipur. Total 120 subjects of CKD measured for serum calcium (Ca), phosphorous (P), creatinine, 25-hydroxy Vitamin D [25(OH)D] and intact PTH (iPTH). Lateral lumbar X-ray performed in a standing position for abdominal aortic calcification (AAC) assessment using 24-point scale by Kauppila et al. **Results:** Kauppila scale(K scale) significantly ($p < 0.001$) increases with severity of CKD. K scale in stage 3 was 15.78 ± 3.27, in stage 4 it was 17.19 ± 3.20 and in stage 5 it was 19.62 ± 1.58. 'z' score for DEXA scan increases significantly ($p < 0.0001$) with severity of disease calcification. **Conclusion:** In our study we found newly detected Indian patients of CKD with high prevalence of disturbances in mineral metabolism which is shown by hyperparathyroidism, Vitamin D deficiency, BMD abnormality and valvular, vascular calcification.

Keywords: Chronic kidney disease, mineral and bone disorder, Abdominal aortic calcification, Kauppila scale

Introduction

CKD (Chronic kidney disease) arises from many heterogeneous pathways that irreversibly alters the structure and interferes the function of the kidney, over the years. Chronic kidney disease affect 5-10% of world population and it is a global public health problem.[1,2] The diagnosis of CKD depends upon establishing a chronic reduction in kidney function and structural kidney damage. The best available indicator of overall kidney function is glomerular filtration rate (GFR),[3] Current definition according to international guidelines CKD as decreased kidney function shown by GFR of less than 60 mL/min per 1·73 m² or markers of kidney damage or both for at least 3 months duration regardless of underlying cause.[4] When GFR is less than 15 mL/min per 1·73m² , shows end stage kidney disease (ESKD), at this point of time kidney function is so compromised so that a person is no longer able to sustain life over the long term.

There is progressive deterioration in mineral homeostasis as kidney function declines it manifest as change in serum and even tissue concentrations of phosphorus and calcium, as well as changes in circulating levels of hormones such as parathyroid hormone (PTH), 1,25-dihydroxyvitamin D [1, 25(OH)2D]. These levels of minerals, hormones, Vitamins functions are very important in the regulation of both initial bone formation during growth (bone modeling) and bone structure and function during adulthood (bone remodelling). This is the main reason that abnormalities in bones are found almost universally in patients with chronic kidney disease with chronic kidney disease stages 3–5.[5] However, despite high prevalence of mineral bone disorders (MBDs) in CKD patients, there are limited data on bone mineral disorder in Indian CKD patients. The aim of this work is to study the pattern of MBD in patients with chronic kidney disease.

Methodology:

Hospital based cross sectional study was conducted in patients of CKD detected in the OPD & IPD of general medicine or Casualty of Mahatma Gandhi Hospital from January 2018 to June 2019. Total 120 subjects of CKD were included in this study and each subject measured for serum calcium (Ca), phosphorous (P), creatinine,25-hydroxy Vitamin D [25(OH)D] and intact PTH (iPTH). Lumbar X-ray lateral view performed in standing position. Abdominal aortic calcification (AAC) was assessed using 24-point scale described by Kauppila et al. For the 24-point scoring calcified deposition along the anterior and posterior longitudinal walls of the abdominal aorta neighbouring to each lumbar vertebra from L1–L4 were assessed by using the midpoint of the intervertebral space above and below the vertebrae as the boundaries. Bone mineral density of hand (Anterior 1/3 of radius) assessed by DEXA scan. All cases of CKD irrespective of undergoing haemodialysis or not were included in this study while Age <20 years, pregnant females, patients with liver disease, thyroid illness, malignancy, hyperparathyroidism or malignancy were excluded from the study.

Results:

Total 120 patients were included in this study out of these patients 23 patients were in CKD stage III, 32 patients in CKD stage IV and 65 patients were in stage V. Mean age for stage 3 patients was 38.0± 11.52 years, for stage 4 38.8±8.2 years and for grade 5 it was 36.6±11.97 years. There was no statistically significant difference in mean age of all 3 stages (p=0630). Male patients in CKD stage III, IV, V were 16, 24, 54 respectively while females were 7, 8, 11 respectively. Mean eGFR in stage 3 was 44.15±6.92 mL/min per 1.73 m2, in stage 4 mean was 26.79±5.21 mL/min per 1.73 m2 and in stage 5 it was 7.7±2.3 mL/min per 1.73 m2.

Table 1: Comparison of different parameters of the study patients.

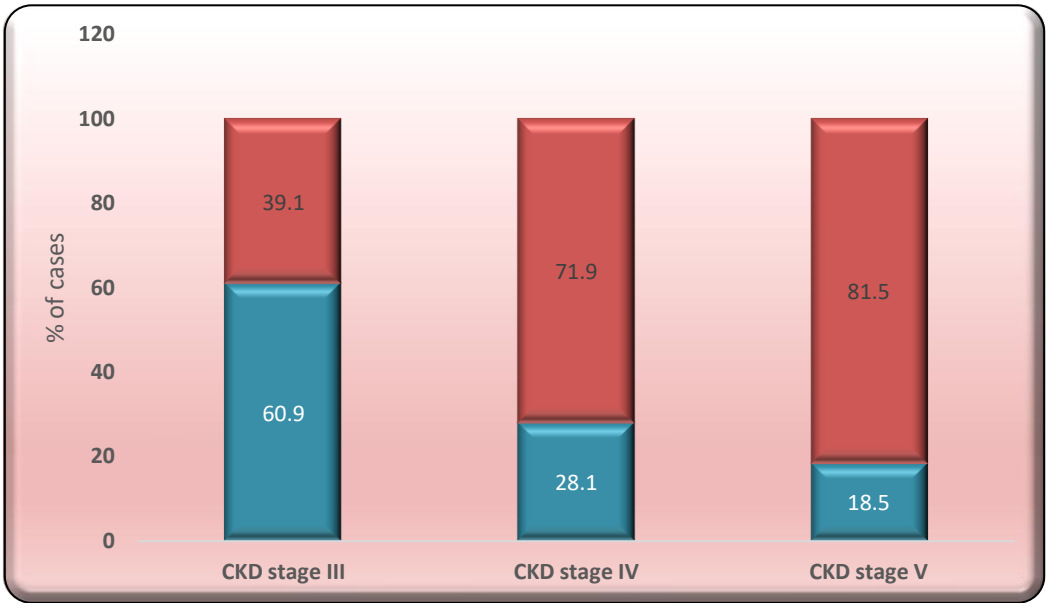
		CKD Stage III(23)	CKD Stage IV(32)	CKD Stage V(65)	P value
Age (years)		38.00 ±11.52	38.80±8.20	36.6±11.97	0.630 (NS)
Gender	Male	16 (69.6%)	24 (75%)	54 (83.1%)	
	Female	07 (30.14%)	08 (25%)	11 (16.9%)	
eGFR(ml/min/1.73m^2)		44.5 ± 6.92	26.79 ± 5.21	7.7 ± 2.30	<0.001
BUN (mg/dL)		49.0 ± 14.7	57.6 ± 20.2	65.6 ± 20.5	<0.001
Creat (mg/dL)		3.80 ± 0.81	4.34 ± 0.85	7.42 ± 1.81	<0.001
Vit D(ng/ml)		32.93 ± 6.80	25.90 ± 6.20	20.8 ± 8.20	<0.001
PTH (pg/ml)		82.08 ± 25.57	142.4 ± 86.6	290.2 ±202.4	<0.001
Calcium (mg/dl)		8.90 ± 0.50	8.32 ± 0.75	7.64 ± 0.74	<0.001
Phosphorus(mg/dl)		2.49±0.43	3.32±0.39	6.04±1.54	<0.001
K scale		15.78±3.27	17.19±3.20	19.62±1.58	<0.001

Mean urea level in stage 3 was 49.0±14.7mg/dl, in stage 4 was 57.6±20.2 mg/dl and in stage 5 it was 65.6±20.5 mg/dl. This difference was statistically significant (p =002). Mean creatinine level in stage 3 was 3.80± 0.81 mg/dl, in stage 4 was 4.34±0.85 mg/dl and in stage 5 it was 7.42 ±1.81 mg/dl. This difference was statistically significant(p <0.0001). Mean Vit D level in stage 3 was 32.93± 6.80 ng/ml, in stage 4 was 25.90 ± 6.20 ng/ml and in stage 5 it was 20.8 ±8.20 ng/ml. This difference was statistically significant (p <0.0001). Mean PTH level in stage 3 was 82.08 ± 25.57 pg/ml, in stage 4 was 142.4 ± 86.6 pg/ml and in stage 5 was 290.2 ± 202.4 pg/ml. This difference was statistically significant (p <0.0001). Mean Calcium level in stage 3 was 8.90 ± 0.50 mg/dl, in stage 4 was 8.32 ± 0.75mg/dl and in stage 5 it was 7.64 ± 0.74mg/dl. This difference was statistically significant (p <0.0001). Mean Phosphorus level in stage 3 was 2.49 ± 0.43 mg/dl, in stage 4 was 3.32 ±0.39 mg/dl and in stage 5 was 6.04 ±1.54 mg/dl. This difference was statistically significant (p <0.0001).

Kauppila scale(K scale) in different stage of CKD. In stage 3 K scale was 15.78±3.27, in stage 4 it was 17.19±3.20 and in stage 5 it was 19.62±1.58. It shows increase K scale with severity of disease and this increase was statistically significant (p<0.0001).

Table 2: Distribution of cases on the basis of BMD DEXA z-score

z-score on DEXA	CKD Stage III (n = 23)	CKD Stage IV (n = 32)	CKD Stage V (n = 65)
< 2	14 (60.9)	09 (28.1)	12 (18.5)
>2	09 (39.1))	23 (71.9)	53 (81.5)



Graph 1: Distribution of cases on the basis of BMD DEXA z-score

Out of 23 patients of CKD stage III 14 patients (60.9%) had Z score < 2 while 9(39.1%) patients had score >2. Out of 32 patients of CKD stage IV 9 patients (28.1%) had score < 2 while 23(71.9%) patients had score >2. Out of 65 patients of CKD stage V 12 patients (18.5%) had score < 2 while 53(81.5%) patients had score >2. It shows with severity of disease calcification increases significantly (p<0.0001).

Table 3: Correlation of eGFR with various Bone- mineral metabolites

Parameters	Correlation coefficient	P-value
GFR vsVit D	0.500	0.0001
GFR vs PTH	-0.561	0.001
GFR vs Calcium	0.530	0.001
GFR vs Phosphorus	-0.755	0.001

P-value as obtained on applying Spearmann's correlation

Vit D and Calcium are positively and significantly correlates with GFR.(p 0.001) while PTH and Phosphorus correlates negatively and this correlation was statistically significant also(p 0.001).

Discussion:

Increasing affluence and sedentary lifestyle in conjunction with demographic changes led to raising tendency in non-communicable diseases worldwide, even in developing countries like India. Chronic kidney disease (CKD) is a silent epidemic. Glomerular filtration rate(GFR) is overall considered as a best indicator of kidney. "SEEK (screening and early evaluation of kidney disease) India cohort" estimated CKD prevalence 17.2% using community and hospital based screening camp approach, modification of diet in renal disease (MDRD- 3) equation eGFR <60 ml/min/1.73 m2 or urine protein ≥1+.[3] It is very difficult to estimate true incidence and prevalence of CKD with in a population, because early to moderate CKD were usually asymptomatic. End stage renal disease (ESRD) which is a consequence of CKD. ESRD is one of the most expensive diseases to treat

currently.[6] Only way is prevention rather than try to treat it.

Chronic kidney disease (CKD) is associated with significant perturbations in bone and mineral metabolism, which leads to alteration in serum calcium, phosphorus, parathyroid hormone (PTH), and Vitamin D levels with abnormalities in bone remodeling, renal osteodystrophy (ROD) and extra skeletal calcification.[7] Early detection and management of CKD-associated mineral bone disorder (CKD-MBD) is most important as it is linked with increase incidence of cardiovascular mortality due to associated increased risk of soft tissue, vascular and cardiac valvular calcification. Spectrum of CKD-associated mineral bone disorder has been poorly studied in Indian population with CKD, especially in the predialysis stage. Therefore, we decided to conduct a cross-sectional study for biochemical changes, skeletal abnormalities and extra skeletal calcification in newly detected, predialysis CKD stage 3, 4 and stage 5 patients at our tertiary care centre in North India.

Total 120 cases of CKD were included in this study. All cases had GFR ≤60 mL/min/1.73 m2. According to e GFR we divided these patients in 3 groups. Stage 3 patients had eGFR between 30 to 59 mL/min per 1.73 m2, Stage 4: eGFR between 15 to 29 mL/min per 1.73 m2, Stage 5: eGFR of < 15 mL/min per 1.73 m2 or end-stage renal disease. Out of these 120 cases 23 patients were in stage 3, 32 patients were in stage 4, 65 patients were in stage 5. Our study had age matched patients in all 3 stages. As there was no statistically significant difference in mean age of all 3 stages (p=0630). Male female ratio of this study was 48:13. Which signifies CKD effects male more than females. We found mean eGFR decrease as severity of disease increases and this decrease was statistically significant(p <0.0001). These results were according to definition of CKD which is defined on the basis of eGFR.

Mean urea, creatinine level shows significant (p <0.05) rise according to severity of disease. Serum creatinine is freely filtered from kidney but it is not reabsorbed or metabolized. A significant percentage of creatinine in the urine derives from proximal tubular secretion(PCT).[8] One of the requirements of utilizing estimating equations based on SCr is stable kidney function.

Mean Vit D level decreases with severity of CKD and this decrease was statistically significant(p <0.0001). We found significant positive correlation between Vit D and GFR(p 0.001) (r =0.500). A similar study conducted by César Augusto Restrepo Valencia et al[9] in 2016 showed that in a group of 331 patients with CKD glomerular filtration rate decreased from 90 mL/min to less than 15 mL/min, their levels of serum calcium, vitamin 25-(OH) D decreased proportionally. Another study conducted by A Levin et al[10] in 2007 found that as eGFR decreases with severity of CKD Vit D levels also decrease significantly(p value<0.001) . Low serum 1,25 OH2 D3 occurs for a variety of reasons, and has been recently described as being more prevalent than previously thought in western populations. Although decreased renal 1-a hydroxylase in CKD is largely responsible for reduced circulating levels of 1,25 OH2 D3, other potential factors may exist, which also suppress this hydroxylating enzyme.[11] In addition, low levels of the 25(OH)D3 substrate may contribute to decreased levels of 1,25 OH2 D3 production, particularly in CKD patients with nephrotic range proteinuria.[12]

In this study mean PTH level increase with severity of disease and this increase was statistically significant(p <0.0001). We found significant negative correlation between PTH and GFR(p 0.001) (r = -0.561). Similar study by A Levin et al[10] in 2007 found that PTH values start increasing likely with an eGFR <60 ml/min/1.73m^2 and that by the time the

GFR is less than 30 ml/min/1.73m^2 approximately 70% of patients will have an elevated PTH. Another study conducted by Slaiba W et al[13] 2009 found an increase in PTH levels typically develops when the glomerular filtration rate (GFR) drops below 60 mL/min/1.73 m^2. Abnormalities in serum levels of phosphorus and calcium tend to occur much later in the course of CKD (typically when the GFR drops below 40 mL/min/1.73 m^2). Probable mechanism for increasing PTH level may be Initially, the elevated PTH levels serve to increase renal phosphorus excretion. However, as the GFR declines further, serum phosphorus levels started to rise and induce hypocalcemia by binding bioavailable calcium as $CaHPO_4$, which indirectly leads to a further rise in PTH production. CKD also leads to decreased activity of 1-α-hydroxylase, thereby decreasing 1,25-OH vitamin D. A lack of 1,25-OH vitamin D inhibits gastrointestinal absorption of calcium and also directly stimulates the parathyroid glands.[13]

In this study mean Calcium level decreases with severity of disease and this was statistically significant ($p < 0.0001$). In this study we found significant positive correlation between PTH and GFR (p 0.001) ($r = 0.530$). A similar study conducted by César Augusto Restrepo Valencia et al[168] in 2016 determined that in a group of 331 patients with CKD, as their glomerular filtration rate decreased from 90 mL/min to less than 15 mL/min, their levels of serum calcium, vitamin 25-(OH) D decreased proportionally. Another similar Study by Cynthia J et al[14] 2017 found in their study that the (adjusted) change in the rate of decline in kidney function associated with one unit higher (i.e. mg/dl) of serum calcium. Lower baseline serum calcium is associated with a faster subsequent kidney function decline. A contrast study conducted by R. Freethi et al[15] in 2016 found no significant difference in calcium level between all 3 stages stage 3,4,5. (p value 0.06). Hypocalcemia in chronic renal failure is may be due to two primary causes - increased serum phosphorus and decreased renal production of 1,25 (OH)2 vitamin D. The former causes hypocalcemia by complexing with serum calcium and depositing it into bone and other tissues. The latter causes hypocalcemia by decreasing the GI absorption of calcium.

In this study mean Phosphorus level increases with severity of disease and this increase was statistically significant($p < 0.0001$). We also found significant negative correlation between PTH and GFR(p 0.001)($r = -0.755$). A similar study conducted by R. Freethi et al[15] in 2016 found significant difference in Phosphorus level between all 3 stages stage 3,4,5. (p value =0.004). This is commensurate with the studies of Scialla JJ et al[16], who have reported that, Parathormone, and phosphate levels rose over time in patients with renal disease and that participants with faster rates of decline in measured GFR had the greatest increases in these parameters. Probable mechanism for increases level of phosphorus. With the progression of kidney disease there is diminished filtration and excretion of phosphate which leads to hyperphosphatemia, this finding observed in our study and many more studies. Initially, this is compensated by an elevation in the serum level of PTH, which leads to decrease reabsorption of phospahte. However, eventually with time there is hyperplasia and hypertrophy of the parathyroid gland occur as a result of this physiological compensation, setting the stage for secondary hyperparathyroidism, and the enormous range of metabolic, vascular, rheumatologic, and cardiac complications that are associated with its onset.[17]

In this study we did the lateral lumbar x ray for calcification in vascular system(CVC) for this purpose we used Kauppila scale(K scale) in different stage

of CKD. We found calcification in all patients. We found increase K scale with severity of disease and this increase was statistically significant($p<0.0001$). Pressman et al, describes semi-quantitative echocardiographic scoring of CVC but this scoring has not been validated in CKD patients.[18] In a study by Valson et al[19], CVC was identified in 96% of predialysis patients with CKD stages-4 and -5.[19] In another study on Caucasian patients of CKD in predialysis stage, CVC was detected in 31% of patients.[20] Among all patients 10.5% patients noted with AAC on lateral abdominal X-ray. But there is inconsistent results in the literature regarding this relationship. Some observational studies have reported a positive correlation between phosphate, PTH, calcium, and vascular calcification;[21-23] However, some other studies have not reported this association[24] and reasons for these inconsistent results are unclear. There was no association between AAC and VC in our study.

In this study we studied the bone density of distal 1/3 of radius and it denotes by Z scoring. Out of 23 patients of CKD stage III 14 patients (60.9%) had score < 2 while 9(39.1%) patients had score >2. Out of 32 patients of CKD stage IV 9 patients (28.1%) had score < 2 while 23(71.9%) patients had score >2. Out of 65 patients of CKD stage V 12 patients (18.5%) had score < 2 while 53(81.5%) patients had score >2. It shows with severity of disease calcification increases significantly ($p<0.0001$)

There is inconsistency to predict fractures or other clinical outcomes in patients with CKD stages 3, 4, 5 with BMD. The reason for the poor performance of DXA is because the measurements of BMD may be cause of overestimation in arthritic conditions, scoliosis, and aortic calcifications. In patients of CKD, high serum PTH increases the cancellous bone volume but decreases cortical thickness. Quantitative computed tomography (CT) scan, which separately measures cortical and trabecular bone as it is a three-dimensional technique, can be a better tool instead of DXA as DXA cannot differentiate between cortical and trabecular bone. In our study we found high prevalence of abnormal BMD at the forearm, Several other studies have also shown that BMD on DXA predicted status of fracture in patients with CKD.[25] A number of randomized controlled trials of antiresorptive therapy have described the fracture risk in the subset of patients with CKD stages 3–4 is predicted by BMD.[26-29] We observed in 20.8% of our patients high prevalence of low bone mass (Z-score $\leq$-2). They were more prone to develop hyperparathyroidism, 25(OH) D deficiency and less likely to be obesity. Based on WHO criteria, T-scoring of BMD, osteoporosis and osteopenia were more commonly found on the forearm, probably due to the effect of secondary hyperparathyroidism.

Conclusion

In conclusion we can say that mineral and bone disorders are complex abnormalities those leads to morbidity and decrease quality of life in patients with CKD. In this study we found high prevalence of disturbances in mineral metabolism in CKD patients it includes hyperparathyroidism, Vitamin D deficiency, abnormal BMD and valvular and vascular calcification even before initiating dialysis. Prevalence of fractures was low in our study. These two disorders caused by CKD is expected to greatly enhance communication, facilitate clinical decision making, and promote the evolution of evidence based clinical-practice guidelines worldwide.

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