

# Evaluation of Bone Mineral Density in Predialysis Osteoporotic Patients of Chronic Kidney Disease.

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## Abstract

**Background:** There are limited studies available especially of Indian Population about factors defining the pathophysiology of bone mineral density (BMD) in osteoporotic chronic kidney disease (CKD) patients, not on dialysis.

**Material:** This study included 100 adult patients. Patients were divided into two groups depending upon GFR. Serum creatinine, albumin, calcium, phosphate (PO<sub>4</sub>), alkaline phosphatase, iPTH and Vitamin D were measured at baseline. BMD was measured by dual energy X-ray absorptiometry.

**Results:** There were 76 male and 24 female patients. The mean serum phosphate, alkaline phosphatase and iPTH levels increased steadily as CKD progressed. On the other hand, mean corrected serum calcium and Vitamin D levels decreased progressively in group A to B. The mean serum PTH values in group A and B were 226.47±3.24 pg/ml and 245.66±13.61 pg/ml respectively. Significant increase was observed in mean PTH level from group A to group B (p<0.001). The mean level of vitamin D showed a trend of declination from group A to B (p<0.001). Bone densitometric parameters decreased significantly from patients in Group A to Group B. T score and Z score declined significantly Group A to B with progression of kidney disease from -2.60±0.08 to -3.17±0.24 and from -2.13±0.28 to -2.82±0.33 respectively (p<0.001). A positive correlation was seen between GFR, Vitamin D & serum calcium; while serum iPTH, phosphate and serum alkaline phosphatase correlated negatively with GFR.

**Conclusion:** Reduced bone density as estimated from reduced BMD levels was seen early in the course of CKD and it worsened with the progression of CKD.

**Key words:** Bone mineral density, Chronic Kidney Disease, dialysis.

## Introduction

Chronic kidney disease (CKD) is an emerging public health problem, that affects 5% to 10% of the world population, with increasing prevalence and adverse outcomes, including progressive loss of kidney function, cardiovascular disease and premature death [1]. Mineral and bone metabolism disorders associated with CKD form a multifactorial clinical entity. They are associated with considerable morbidity and mortality because of an increased frequency of bone fracture and also predispose to a greater risk for cardiovascular calcification [2]. Osteoporosis is a highly prevalent bone and mineral disorder in CKD patients along with the other determinants of the various aspects of renal osteodystrophy (ROD) such as secondary

hyperparathyroidism, osteomalacia or adynamic bone disease [3]. Osteoporosis is a condition characterized by low bone mass leading to reduced bone strength and increased risk of fractures. It is an important prevalent bone disorder in CKD patients because of their advanced age, post-menopausal status in women, sedentary life style, nutritional state and treatment including steroids. Early initiation of appropriate therapy may prevent or ameliorate the mineral and bone disorder that develops in late CKD so, it is important to define the underlying pathophysiologic process.

The World Health Organization (WHO) definition of osteoporosis is based on bone mineral density (BMD) measurements. Osteoporosis and renal osteodystrophy (ROD) may coexist in elderly patients with CKD, which makes the issue problematic to define. The failure of the skeleton to absorb positive phosphate balance in CKD is an important stimulus to heterotopic mineralization, and links the skeleton and osteoporosis in CKD to cardiovascular events and mortality. Therefore, its diagnosis and management in CKD cohort may differ from general population. Bone biopsy is the gold standard

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for diagnosing ROD, but it is rarely used because it is expensive and an invasive procedure that needs special equipment and the samples obtained require specialized processing that is not widely available. Consequently, in recent years, some biochemical markers of bone metabolism have been used and tested in the evaluation of bone remodelling in uremic patients [4]. Circulating PTH levels are used as a surrogate indicator of bone turnover, along with serum calcium, phosphorus and alkaline phosphatase levels to evaluate, diagnose and guide the treatment of renal osteodystrophy. Various other biochemical markers of bone formation and resorption have also been investigated, but their clinical applicability remains to be established [5]. Imaging has also been an important component of evaluating bone disease in the past, and remains the main tool in assessing extra skeletal calcification in CKD patients [6].

Several noninvasive methods are available for the assessment of BMD. Dual energy X-ray absorptiometry (DEXA), quantitative computed tomography and heel ultrasound are the widely used techniques. Quantitative computed tomography is the most precise and reliable method but its high radiation involvement and cost, limit its usefulness as a screening test in large populations.<sup>7</sup> Due to its lower cost, accuracy, short scan time and low radiation dose, DEXA is the most widely used method for BMD measurements. WHO definition for BMD are based on T-scores (T-score = measured BMD-young adult BMD/young adult standard deviation). Based on T-scores, patients may be divided into three groups: Normal (T > -1.0), osteopenic (T < -1.0 and > -2.5), and osteoporotic (T < -2.5). Ongoing developments in non-invasive imaging techniques almost certainly will lead to their improved and more widespread use in clinical diagnosis and decision-making in the near future.

There is a growing prevalence of lifestyle diseases like diabetes, hypertension and ageing in leading to CKD in the the current era. Therefore, there is a need to increase our knowledge about the nature, diagnosis and pathophysiology of reduced BMD in CKD patients. In spite of various studies have been carried out in the past regarding the risk factors and outcomes associated with renal osteodystrophy, there is insufficient knowledge about osteoporosis in predialysis patients. Various biochemical parameters like calcium, phosphate, serum alkaline phosphatase and hormone like PTH, vitamin D play an essential part in maintaining bone health. Therefore, there relation with bone mass needs to be studied in patients with CKD, thus leading to better treatment modalities and reduction of morbidity and mortality. There is a relative paucity of studies in Indian literature regarding bone mineral density and

biochemical markers of bone metabolism in predialysis osteoporotic patients of chronic kidney disease and hence the present study is undertaken.

## Material and Methods

The present study was conducted on hundred adult osteoporotic patients of chronic kidney disease either of stage 3 or 4 on regular follow up of kidney and dialysis clinic at Pt. B.D. Sharma PGIMS, Rohtak. The study included male patients between age 18-75 yrs and premenopausal non pregnant females greater than 18 yrs of age. All the patients were osteoporotic having T score < -2.5 on DEXA scan. Patients on haemodialysis, CKD stage 5 & 5 D, post renal transplants, with preexisting psychiatric illness and post-menopausal women were excluded. Patients having history of parathyroidectomy, hormone replacement therapy within previous 2 years, bone tumors, multiple myeloma and other causes of metabolic bone disease were also not included in the study.

After taking written informed consent and a thorough history, each participant went under detailed clinical, biochemical and radiological examination. The study was approved by ethical committee of Pt. B.D. Sharma University of Health Sciences. Patients were divided into two groups. Group A consisted of thirty four patients of CKD stage 3 (eGFR 45-30 ml/min/1.73m<sup>2</sup>) and Group B had sixty six patients of CKD stage 4 (eGFR 30-15 ml/min/1.73m<sup>2</sup>). Routine renal and other biochemical investigations including; blood urea, serum creatinine, serum corrected calcium levels, serum phosphorous levels, calcium phosphate product, serum protein, iPTH levels, serum sodium, serum potassium, blood sugar were carried out as per the standard methods used in Dept. of Biochemistry, PGIMS, Rohtak. GFR was measured by MDRD equation. Serum (iPTH) level was measured by chemiluminescent immune assay (CLIA) method. Serum 25 Hydroxy Vitamin D level was measured by enzyme linked immunosorbent assay (ELISA) method. Bone Mineral Density (BMD) was measured by dual energy x-ray absorptiometry at lumbar spine and neck of femur and lowest values were included (DEXA, Hologic Explorer QDR series 90797). The results were obtained in T score, Z score and bone mineral density (g/cm<sup>2</sup>). Z score is the number of standard deviations from the mean of a healthy age and gender matched normal population, which allows the comparison of BMD between patients of different age and gender. T score is the number of standard deviations from the mean of a healthy young adult population (20-40 years old); it is used for the definition of osteopenia (between -1.0 and -2.5 T score) and osteoporosis (< -2.5 T score).

## Statistical Analysis

At the end of the study, the data was expressed as mean±1SD or range. Probability values of <0.05 were considered to be significant in all the analysis. The Statistical analyses were performed using independent t-test. The correlations were tested using Pearson correlation coefficient analysis. All statistical calculations were carried out using SPSS 20.0 software.

## Results

In our study majority of patients were above 40 years of age. The mean age of the patients in Group A was 52.47±12.42 years and Group B had a mean age of 46.54±8.98 years. Out of total 100 patients, 74 were male and 26 were female, thus males comprising almost three fourth of the study group. The most common cause of CKD in Group A and Group B was diabetes mellitus followed by chronic glomerulonephritis and hypertension. Less frequent etiology included adult polycystic kidney disease, obstructive uropathy & renal amyloidosis. The important biochemical parameters of both the groups are depicted in Table 1.

The mean estimated Glomerular Filtration Rate (eGFR) ml/min/1.73 m<sup>2</sup> of Group A was 35.60±3.68 and 23.47±3.64 in Group B. The mean corrected serum

calcium in group A was 8.15±0.27 mg/dl and in group B was 7.50±0.16 mg/dl. The mean level of serum corrected calcium decreased from Group A to Group B. There was a statistically significant difference between the two groups (p<0.001). The mean phosphate levels increased from 6.32±0.32 mg/dl in Group A to 7.11±0.34 in Group B with a statistically significant difference (p<0.001). The mean serum alkaline phosphatase (SAP) values in Group A was 124±13.02 IU/L and in Group B 145.15±18.25 IU/L. Mean SAP values were higher in Group B as compared to Group A with a statistically significant difference (p<0.001).

The mean vitamin D level of Group A was 26.79±0.86 ng/ml, while Group B had a mean vitamin D level of 23.64±1.56 ng/ml. The mean vitamin D level decreased with progression of kidney disease from Group A to Group B with a statistically significant difference between the two groups (p<0.001). The mean serum intact Parathyroid Hormone (iPTH) values in Group A and B were 226.47±3.24 pg/ml and 245.66±13.61 pg/ml respectively. The mean serum iPTH level were higher in Group B as compared with Group A with a statistically significant difference (p<0.001).

There was significant decline in bone densitometric parameters from patients in Group A to Group B (Table 2). T score decreased from Group A to B with progression

**Table 1: Biochemical Parameters**

Biochemical Parameter	Group A	Group B	P value
Haemoglobin (g/dl)	8.15±0.85	7.76±0.67	>0.05
Blood Urea (mg/dl)	84.52±18.55	101.72±25.87	<0.05
Serum Creatinine (mg/dl)	2.08±0.16	2.83±0.32	<0.001
estimated Glomerular Filtration Rate (ml/min/1.73 m <sup>2</sup> )	35.60±3.68	23.47±3.64	<0.001
Corrected Serum Calcium (mg/dl)	8.15±0.27	7.50±0.16	<0.001
Serum Phosphate (mg/dl)	6.32±0.32	7.11±0.34	<0.001
Serum Alkaline Phosphatase (IU/L)	124.11±13.02	145.15±18.25	<0.001
25 Hydroxy Vitamin D (ng/ml)	26.79±0.86	23.64±1.56	<0.001
Intact Parathyroid Hormone (pg/ml)	226.47±3.24	245.66±13.61	<0.001

**Table 2: Comparison of Bone Densitometric Data in Group A and B**

Baseline bone densitometric data	Group A	Group B	P value
T score	-2.60±0.08	-3.17±0.24	<0.001
Z score	-2.13±0.28	-2.82±0.33	<0.001
Bone mineral density (g/cm <sup>2</sup> )	0.80±0.008	0.73±0.029	<0.001

of kidney disease from  $-2.60 \pm 0.08$  to  $-3.17 \pm 0.24$  with a statistically significant difference ( $p < 0.001$ ). Z score also decreased from Group A to B with progression of kidney disease from  $-2.13 \pm 0.28$  to  $-2.82 \pm 0.33$  with a statistically significant difference ( $p < 0.001$ ). Bone mineral density showed a similar pattern and decreased from  $0.80 \pm 0.008$  g/cm<sup>2</sup> to  $0.73 \pm 0.029$  g/cm<sup>2</sup> from Group A to Group B with a statistically significant difference ( $p < 0.001$ ).

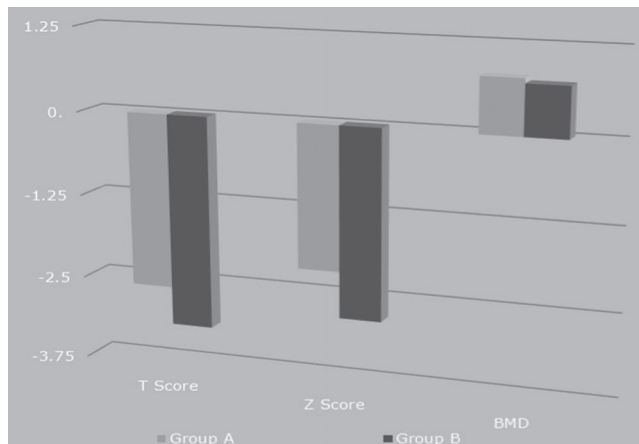


Figure 1: Comparison of Bone Densitometric Data in Group A and B

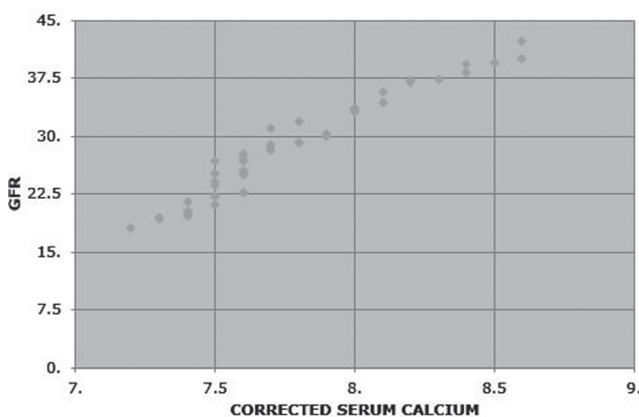


Figure 2: Correlation between Glomerular Filtration Rate (GFR) and Corrected Serum Calcium

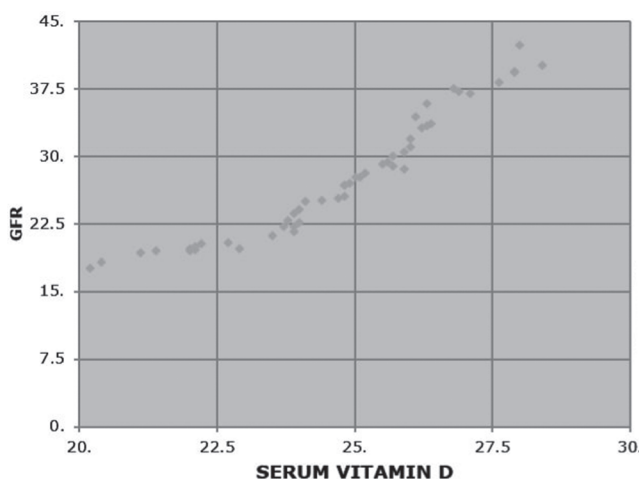


Figure 3: Correlation between Glomerular Filtration Rate (GFR) and Vitamin D

On correlation analysis, there was statistically significant association between GFR and Corrected serum calcium, serum phosphate level, SAP, Vitamin D and iPTH levels. The corrected serum calcium and vitamin D were positively correlated with the GFR. On the other hand, serum phosphate, SAP & iPTH correlated negatively with eGFR. T-score, Z-score and BMD correlated (g/cm<sup>2</sup>) positively correlated with GFR.

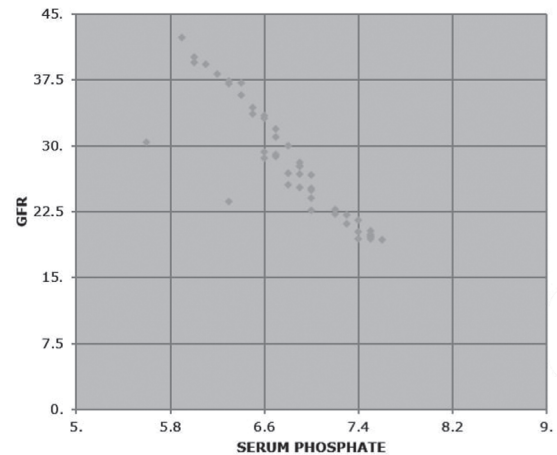


Figure 4: Correlation between Glomerular Filtration Rate (GFR) and Serum Phosphate

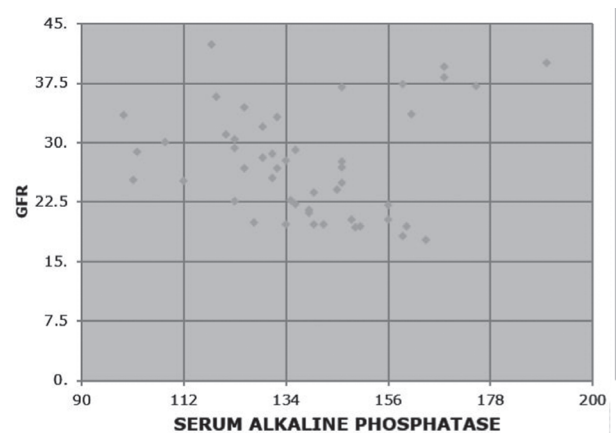


Figure 5: Correlation between Glomerular Filtration Rate (GFR) and Serum Alkaline Phosphatase (SAP)

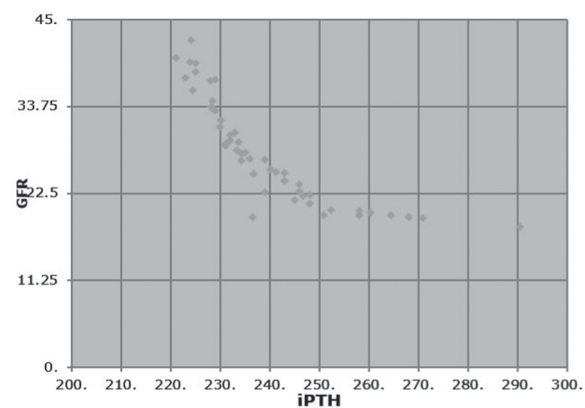


Figure 6: Correlation between Glomerular Filtration Rate (GFR) and intact Parathyroid Hormone (iPTH)

## Discussion

CKD-mineral and bone disorder (CKD-MBD) is a systemic disorder that is associated with increased risk of fracture and cardiovascular disease thus leading to increased morbidity and mortality. Abnormal regulation of calcium, phosphorous, vitamin D and parathyroid hormone (PTH) is associated with disturbed bone and mineral metabolism. Bone Mineral Density (BMD) being an important component of bone strength is a good predictor of future fracture risk, particularly when coupled with age, prior fracture. Therefore its measurement has to be an important part of investigative workup. Osteoporosis is a complex multi-factorial disease that remains asymptomatic until a fracture occurs, and therefore strategies need to be developed to accurately identify "high risk" subjects who may benefit from preventive treatments for fracture. In osteoporosis, once a fracture occurs, the risk of a subsequent fracture is high. The risk of fracture increases 1.5-3 times for each standard deviation decrease in the BMD [8]. Therefore, the diagnosis of osteoporosis should be made before the first fracture occurs, so that the patient can undertake lifestyle changes and undergo treatment to prevent fractures. The early initiation of appropriate treatment may prevent or ameliorate the mineral and bone disorder that develops in late CKD, therefore the pathophysiologic process underlying abnormality needs to be defined.

Osteoporosis and renal osteodystrophy may coexist in elderly patients with CKD, which makes the issue problematic to define. In a patient with renal osteodystrophy, there is the potential for low BMD to coexist with an enormous range of functional abnormalities. These range from high turnover bone lesions in patients with uncontrolled hyperparathyroidism to severely reduced bone remodelling activity in patients with adynamic bone disease. This is in contrast to the non CKD patients with osteoporosis where bone remodelling is not severely affected. Osteoporosis in CKD is a part of the constellation of metabolic bone problem and therefore, its diagnosis and management may differ from general population.

In present study the mean level of serum calcium was found to decline with GFR from group A to group B. There was a statistically significant difference between the two groups ( $p < 0.001$ ). Increased levels of FGF-23 promote renal phosphate excretion and decreases renal synthesis of 1-alpha-hydroxylase, resulting in calcitriol deficiency and hypocalcaemia [9]. The mean phosphate levels were observed to increase from group A to group B with a statistically significant difference between the two groups. Phosphate retention begins early in CKD and

progresses with the advancement of renal dysfunction. Hyperphosphatemia is associated with high rates of mortality observed in CKD patients. The mechanism underlying this association is unclear but may be related to increased nephrocalcinosis, hyperparathyroidism, alterations in cellular energy metabolism, or altered renal hemodynamics.

There was a statistically significant difference for SAP between the two groups ( $p < 0.001$ ). SAP values increase with decreasing eGFR due to the altered bone dynamics and increase in bone turnover. SAP inactivates pyrophosphate, an endogenous inhibitor of hydroxyapatite formation, resulting in medial arterial vascular calcification, thereby contributing to cardiovascular disease and mortality in CKD. We observed hyperparathyroidism commencing early in CKD and as GFR decreased further, the level of PTH increased. The mean serum iPTH values in group A and B were  $226.47 \pm 3.24$  and  $245.66 \pm 13.61$  pg/ml respectively. The mean serum iPTH levels were observed to increase from group A to group B with a statistically significant difference ( $p < 0.001$ ). Secondary hyperparathyroidism (SHPT) is associated with several complications. Patients with SHPT have abnormalities in bone histology and increased bone resorption. The classical skeletal abnormality observed in patients with CKD stages 3, 4 and 5 is osteitis fibrosa cystica, although adynamic bone disease can also be observed it is less frequently seen [10].

The mean vitamin D level decreased from group A to group B with a statistically significant difference ( $p < 0.001$ ). Patients with kidney disease are at risk for vitamin D deficiency due to increased levels of FGF-23 resulting in calcitriol deficiency, reduced sun exposure, decreased intake of foods containing Vitamin D and decreased endogenous synthesis of Vitamin D in skin [11]. The reduction in calcitriol occurs despite a progressive rise in serum PTH concentrations, which stimulates 1-alpha hydroxylase activity. Reduced functional renal mass, phosphate retention, and other metabolites that accumulate in kidney failure also contribute to 1-alpha hydroxylase inhibition thus lowering circulating calcitriol concentrations in CKD.

The various parameters of bone metabolisms affect each other. It has been well known that hyperparathyroidism in chronic renal failure results from hypocalcemia, occurring, in part, from phosphate retention and/or deficient 1, 25-dihydroxyvitamin D<sub>3</sub> (1, 25(OH)<sub>2</sub> D) synthesis. The presence of hyperparathyroidism and 1, 25(OH)<sub>2</sub> D deficiency were consistent with the observations done by Pitts et al [12]. They measured creatinine clearance (CCr), fractional excretion of phosphorus (FEP), serum phosphorus, ionized calcium,

PTH and  $1, 25(\text{OH})_2 \text{D}$  concentrations in 21 normal subjects and 51 patients with renal failure. Patients with mild renal failure ( $\text{GFR} > 40 \text{ ml/min}$ ) had normal mean serum phosphorus and ionized calcium and decreased mean  $1, 25(\text{OH})_2 \text{D}$  levels compared with those in normal subjects. In patients with moderate renal failure ( $\text{GFR} 20\text{-}40 \text{ ml/min}$ ), the mean ionized calcium level was normal, plasma PTH levels and FEP were elevated, and the decrement in  $1, 25(\text{OH})_2 \text{D}$  was more pronounced. They noticed that mean ionized calcium level was decreased only in the group of patients with severe renal failure ( $\text{GFR} < 20 \text{ ml/min}$ ) while in our study we demonstrated hypocalcaemia beginning in patients with moderate renal dysfunction.

In a cross sectional study, Ghosh et al evaluated biochemical parameters of bone metabolism in 150 predialysis patients [13]. Serum creatinine, albumin, calcium, phosphate, alkaline phosphatase, hemoglobin, uric acid and urinary protein excretion were measured. They concluded that hyperphosphatemia, hypocalcemia, increased alkaline phosphatase, 25 vitamin D deficiency and insufficiency and hyperparathyroidism were quite common in CKD 4 and 5 patients.

Our results were in concordance with a cross sectional analysis done by Stavroulopoulos et al in 112 predialysis patients, 67 men and 45 women, of which seventy patients had CKD stage 3 and 42 patients, had CKD stage 4 [14]. The mean calcium levels were  $2.46 \pm 0.08 \text{ mmol/L}$ , the mean phosphate serum levels were  $1.17 \pm 0.22 \text{ mmol/L}$ . Mean vitamin D levels of the total participants were  $52.13 \text{ nmol/L}$  (median:  $47 \text{ nmol/L}$ ) with 90 patients (80%) having vitamin D levels below  $75 \text{ nmol/L}$ . Forty-nine patients (44%) had vitamin D insufficiency, 34 (30%) had vitamin D deficiency and seven (6%) had severe deficiency. Median PTH was 76 (9–283)  $\text{ng/L}$  and was above the target in 25 of the 60 patients with CKD stage 3 ( $> 70 \text{ ng/L}$ ). They concluded that vitamin D levels were correlated with the GFR and advancement of renal failure. On subgroup analysis, the prevalence of hyperparathyroidism was seen maximum in the vitamin D deficient group highlighting the role of vitamin D deficiency in the pathogenesis of Secondary Hyperparathyroidism.

The present study demonstrated that in osteoporotic patients T-score, Z-score and Bone Mineral Density (BMD) significantly decreased as the CKD progressed from stage 3 to stage 4. The findings of our study corroborated with the previous studies. Bianchi et al evaluated BMD in 69 patients with CKD and in healthy controls matched for age and sex [15]. BMD was found to be decreasing with the worsening of renal failure and is an important component of bone strength. A low BMD, therefore is a good predictor

of future fracture risk, particularly when coupled with age, prior fracture, and other risk factors emphasizing the importance of this investigation.

These findings indicate that alteration in BMD although begin early in CKD, is related to the severity of kidney function and majority of patient with advanced CKD have reduced bone density and therefore predisposed to increased risk of fractures [16]. With the progression of CKD as glomerular filtration rate (GFR) declines, the filtered load of phosphate decreases and phosphate retention ensues. Hyperparathyroidism, calcitriol deficiency and hyperphosphatemia contribute to skeletal resistance [17]. They adversely affect the bone remodelling thus to accelerating the deterioration of bone microstructure that accompanies normal ageing, trabecular thinning and perforation, dropout of trabeculae, cortical thinning, and porosity and therefore may prematurely decrease bone quality and strength and increase susceptibility to fragility fracture [18-19]. With progression of disease in CKD patients, health related quality of life shows a declining trend and thus associated with increased morbidity and mortality [20]. Thus therapies directed towards improving BMD can lead to a improved quality and healthier life thus decreasing the morbidity.

In order to determine the factors contributing to the reduced bone mineral density, we did a correlation analysis. The mean GFR negatively correlated with serum phosphate, SAP and iPTH which was statistically significant ( $p < 0.001$ ). Serum calcium and vitamin D positively correlated with GFR ( $p < 0.001$ ). These are the main factors which lead to decrease in BMD as the stage of CKD progresses. As elevated PTH levels increase bone turnover, these biochemical alterations could cause deterioration in cortical architecture, leading to reduced cortical density and increased cortical porosity much earlier in the course of CKD [21]. Cortical bone has an important contribution in maintaining bone mechanical competence, therefore these architectural changes could account for the increased fracture susceptibility seen in patients with CKD [22]. Several other investigators have also found a similar negative correlation between PTH levels using a variety of measurement of BMD [16,23]. Labao et al. did a histomorphometric analysis and observed a significant association between Adynamic bone disease and iPTH level less than  $150 \text{ pg/mL}$ , whereas higher values of iPTH were associated with osteomalacia [24]. Vitamin D was positively associated with GFR. There was a strong, positive correlation which emphasizing the need for achieving adequate Vitamin D levels to maintain bone density and hence in prevention of fracture. In a study, it was observed that  $1, 25(\text{OH})_2 \text{D}$  values correlated

positively with GFR and negatively with the log of plasma PTH and serum phosphorus concentrations. Log of plasma PTH correlated negatively with CCr. The ionized calcium concentration correlated very weakly with CCr and the log of the plasma PTH level [25].

## Conclusion

To conclude, patients of CKD have reduced bone density seen early in the course of disease and it worsens with the progression of CKD. This leads to increased prevalence of osteoporosis and therefore an increased fracture risk contributing to morbidity and mortality. Osteoporosis is a complex multi factorial disease that remains asymptomatic until a fracture occurs and therefore there is an unmet need to understand its pathophysiology and its association with various metabolic parameters. In developing country like India due to financial barriers, simple & inexpensive, outpatient based non invasive methods, such as BMD measurements and biochemical parameters of bone metabolism can provide a vital opportunity in early diagnosis of osteoporotic disorders. Considering low BMD osteoporosis an increasing problem affecting quality of life in CKD patients, there is need to develop affective treatment modalities based on the related biochemical parameters, to improve BMD in these patients.

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<b>Funding:</b>	No external funding
<b>Guarantor:</b>	Dr Deepak Jain will act as guarantor of this article on behalf of all co-authors.

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