Assessment of Bone Mineral Disorders by Biochemical Abnormalities and Bone Mineral Density by DEXA in Patients with Chronic Kidney Disease

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Abstract

Background: Chronic kidney disease (CKD) is a worldwide public health problem. Disturbances in mineral metabolism and bone disease are common, cause considerable morbidity, and decrease quality of life in patients with chronic kidney disease (CKD). Bone histology is the gold standard test for diagnosing Bone-mineral disturbance in CKD patients but it is invasive and expansive method. For these reason clinicians depend on some biochemical and imaging method to diagnosis and to differentiate bone disease in CKD.

Methods: In this cross sectional analytical study total 88 patients of CKD stage 4 and 5 ware evaluated serum biomarkers of bone turnover: Bone-specific alkaline phosphatase (BAP) along with parathyroid hormone, 25(OH) vitamin D, and bone mineral density (BMD) using dual absorption X-ray absorptiometry who met the inclusion and exclusion criteria for the enrollment.

Results: The study shows that observed T-score with high risk of fracture (>-3.5) was found in 16 (18.18%) of patients and Osteoporotic level (-2.5 to -3.5) consistent with high turnover bone disease was found in 28 patients (31.82%). Osteopenicstatus (-1 to -2.5) was seen in about 48.05% patients and in 31.82% patients BMD was normal(0 to -1). The BMD levels between CKD groups and found that osteoporosis in more frequent in stage 5 than stage 4(16 vs. 19; 35.55% vs. 44.20%). It was also observed that osteopenia is 40% (18) and 37.2% (16) in stage 5 CKD. It was also seen that high iPTH level is associated with low Vit-D level; BMD in more favour of osteoporotic range and higher BAP level.

Conclusion: Bone mineral disorders are common in CKD stage 4 and 5 patients when they are investigated by biochemical abnormalities and DEXA. Large number of patients should be studied for final recommendation.

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Introduction

Chronic kidney disease (CKD) is a worldwide public health problem. Disturbances in mineral metabolism and bone disease are common, cause considerable morbidity, and decrease quality of life in patients with chronic kidney disease (CKD).[1,2] By the time patients require renal replacement therapy, nearly all are affected of osteodystrophy. The onset of the which is detectable about the time 50% of kidney function is lost[3,4]. 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-hydroxyvitamin D (25(OH) D), 1,25-dihydroxyvitamin D (1,25 (OH)2D).

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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. The term CKD–MBD is used to describe the broader clinical syndrome encompassing mineral, bone, and calcific cardiovascular abnormalities that develop as a complication of CKD.The laboratory diagnosis of CKD–MBD includes the use of laboratory testing of serum PTH, calcium and phosphorus.

Bone biopsy is the gold standard for the diagnosis of bone disease in chronic kidney disease and is the only means of definitively differentiating them.[5]But it is an invasive and often expensive procedure. In the absence of direct pathologic studies, clinicians have relied on biochemical data to determine the probable presence of, or assess the risk for, bone abnormalities[2]. Low calcitriol (dihydroxyvitamin D_3) and calcium levels, and high phosphorus and PTH levels, are the classic abnormalities which develop with decreased GFR. The most common forms of renal osteodystrophy are attributable largely to variations in the plasma levels of parathyroid hormone (PTH). As such, circulating PTH levels have been used as a surrogate indicator of bone turnover, which are used together with measurements of serum calcium, phosphorus, and alkaline phosphatase levels to evaluate, diagnose, and guide the treatment of renal osteodystrophy. However, circulating PTH alone does not clearly distinguish adynamic or normal bone from hyperparathyroid bone disease[6] and is now regarded as a marker of parathyroid activity rather than bone turnover. It has been suggested that a combination of molecules that are synthesized during bone formation and protein fragments released as a result of matrix breakdown during bone resorption might serve as circulating biochemical markers of bone turnover.[7,8]

Of the various markers of bone formation such as osteocalcin, total alkaline phosphatase (TAP), bone-specific alkaline phosphatase (BAP), and procollagen type-1 carboxy and amino terminal peptides, BAP is accepted as the most sensitive and consistent in distinguishing the type of bone disease and estimating the bone formation rate.[9] High BAP levels have been associated with high bone turnover and low levels with adynamic bone disease in dialysis patients.

Despite considerable advances in understanding the pathophysiology, prevention, and treatment of osteodystrophy of CKD, an adequate substitute for bone biopsy in establishing the histological type of osteodystrophy has not been developed. Standard bone radiography can reliably detect bone erosions, but has a low sensitivity and a specificity for the identification of osteitisfibrosa using such erosions[15]. Sufficient data to assess the sensitivity and specificity of other imaging methods including computed tomography in the diagnosis of osteodystrophy of CKD do not exist. There are very few studies with sufficient detail about diagnostic protocols to assess the usefulness of dual energy X-ray absorptiometry (DEXA) in the diagnosis of osteodystrophy of CKD. Since BMD is helpful in the diagnosis of osteopenia and/or osteoporosis, and may assist in predicting risk for fractures, DEXA is a useful tool in assessing these abnormalities in CKD patients.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 field of management of renal osteodystrophy (ROD) in patients with chronic kidney disease (CKD).[10]

Use of these markers, either as such or in combination with bone mineral density (BMD) estimation, has the potential of

improving the diagnosis and the treatment of ROD. Such studies have been carried out in the Western population.[4,10] Because of differences body composition, and racial and genetic background, it is possible that our native people would exhibit a different pattern of abnormalities in CKD-MBD. In this study the intact PTH (iPTH), and 25(OH) vitamin D levels, bone-specific alkaline phosphatase (BAP) and BMD in CKD patients were measured to assess the bone mineral disorders in our community.

Method

It is a cross sectional study carried out in department of Nephrology, BSMMU from July 2014 to June 2015 in Purposive sampling technique. Patients attending Outpatient department Of Nephrology BSMMU with CKD stages 4 and 5(predialysis) meeting inclusion(age>18yrs and CKD stage 4 and 5) and exclusion(Having fracture, taking steroids, NSAIDS,endrogens,anti epileptic drugs or anti coagulant in recent past) criteria were included after proper explanation and taking informed written consent. e-GFR was calculated by MDRD and were grouped into stage 4 and5 of CKD according to K/DOQI 2002 guidelines. Then the patients were assessed with routine laboratory investigations CBC, renal function tests (serum creatinine, serum calcium, serum inorganic phosphate) with some other specific laboratory tests (serum albumin, serum iPTH, serum Vit-D) . Serum sample were collected after all aseptic preparation and were stored in -35º C freezer in Kidney Research Lab, Department of Nephrology, BSMMU, before the assay were done for BAP ELISA. DEXA scan of bone in femur neck of all patient was carried out.Data were analyzed using SPSS v 22.0 (IBM SPSS Statistics) software.

Results

In this study total 88 patients was included and among them 45 patients were from CKD stage 4 and 43 patients were from CKD stage 5. Their mean age was 50.9±15.25 years and male and female number was 42 and 46 respectively.

Table I: Comparison of measured parameters in chronic kidney disease stage 4 and stage 5 patients

Parameters	CKD stage-IV (n=45) Mean±SD	CKD stage-V (n=43) Mean±SD	P value
PO4 (mmol/L)	1.31±0.28	1.48±0.29	0.006*
Ca (mg/dl)	8.29±0.95	8.31±0.77	0.911
Alb (g/dl)	3.72±0.47	3.46±0.69	0.043*
PTH (pg/ml)	245.80±230.38	485.34±317.22	<0.001*
Vit-D (ng/ml)	19.40±7.60	16.20±5.11	0.024*
BAP (pg/ml)	2883.69±1104.23	3295.08±1135.86	0.089
BMD (T-score)	-2.43±1.11	-2.40±0.91	0.897

Unpaired student t-test were performed to calculate the p value

PO4 = phosphate ; Ca= calcium; Alb=albumin; PTH=parathyroid hormone; Vit-D =vitamin D; BAP=bone alkaline phosphatase; BMD=bone mineral density; SD=standard deviation; * = Significant

Table I shows the comparison of study parameters between groups of CKD in stage 4 and stage 5. CKD Stage 5 patients showed significantly higher levels of serum PO4 and serum PTH. CKD stage 5 patients also had significantly lower levels of serum albumin and serum Vit-D. No significant differences were noted among the CKD groups of serum calcium, BAP and BMD T-scores.

The study shows that observed T-score with high risk of fracture (>-3.5) was found in 16 (18.18%) of patients and Osteoporotic level (-2.5 to -3.5) consistent with high turnover bone disease was found in 28 patients (31.82%). Osteopenicstatus (-1 to -2.5) was seen in about 48.05% patients and in 31.82% patients BMD was normal(0 to -1)

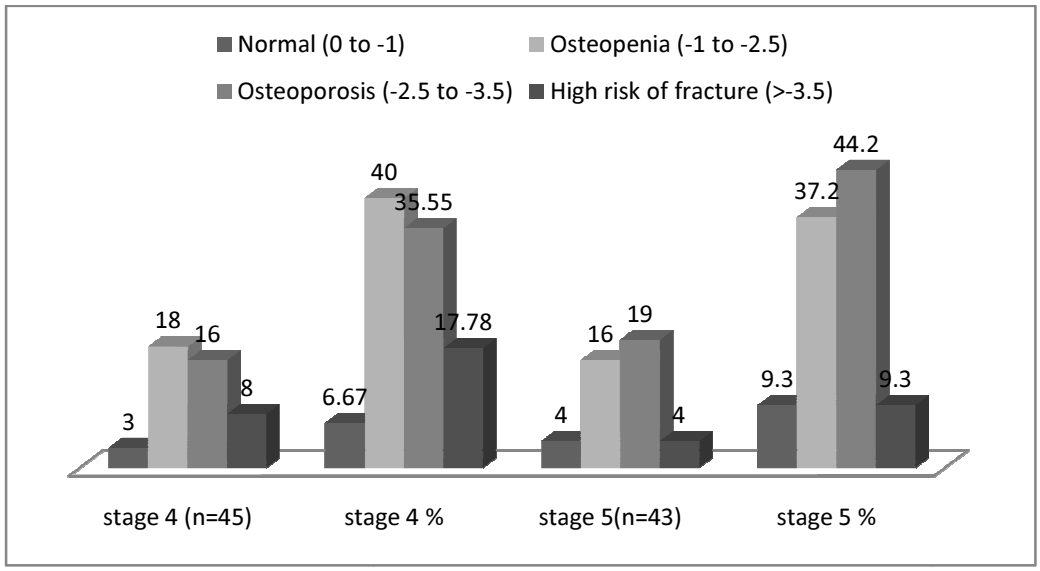

Figure 1. Comparison of BMD (T-score) in CKD stage 4 and stage 5 patients

Figure 1 compares the BMD levels between CKD groups and found that osteoporosis in more frequent in stage 5 than stage 4(16 vs. 19; 35.55% vs. 44.20%). It was also observed that osteopenia is 40% (18) and 37.2% (16) in stage 5 CKD.

Table II: Association between Vit-D, BMD and PTH in the study population (n=88) with PTH level 2

Vit-D <30 ng/ml+ iPTH>450 pg/ml	BMD	PTH		Total
		< 450 pg/ml (n=60)	> 450 pg/ml (n=28)	
28(100%)	< -2.5	28(46.7%)	12(42.9%)	44(50.0%)
	> -2.5	32(53.3%)	16(57.1%)	44(50.0%)
Total		60(100.0%)	28(100.0%)	88(100.0%)

Table II shows that high turnover PTH level (>450 pg/ml) was found in 28 (31.82%) patients and among them 16(57.1%) had BMD value in osteoporotic range (T-score >-2.5) and all of them 28(100%) had Vit-D <30 ng/ml that is in insufficient range.

Table III: Association between BAP and PTH (n=88)

BAP range	PTH		Total
	< 100 pg/ml (n=25)	>100 pg/ml (n=63)	
Lower than mean	6(24.0%)	27(42.9%)	33(37.5%)
More than mean	19(76.0%)	36(57.1%)	55(62.5%)
Total	25(100.0%)	63(100.0%)	88(100.0%)

Table III shows that the PTH level more than 2 times the upper limit was found in 63(71.6%) patients and among them 36 (57.1%) patients had BAP values more than the mean value.

Discussion

This is a study to evaluate comprehensively the various indicators of bone disease in patients with CKD stage 4 and stage 5 attending to the Department of Nephrology, BSMMU. My study involved diagnosed or newly diagnosed stable CKD patients who met the inclusion and exclusion criteria.

Total of 88 patients were ultimately included for the study. Where the mean age of population was 50.9±15.25. It was observed that number of male patients was less than female (42 male and 46female)

In the comparative study of measured parameters in chronic kidney disease stage 4 and stage 5 patients in table-1 it was observed that CKD Stage 5 patients showed significantly higher levels of serum PO4 and serum PTH. CKD stage 5 patients also had significantly lower levels of serum albumin and serum Vit-D. No significant differences were noted among the CKD groups of serum calcium, BAP and BMD T-scores.In the comparison of Vit-D levels in CKD stages it was found that in stage 5 the level of Vit-D decreases significantly. The uremic state presents multiple stimuli to parathyroid glands, leading to secondary hyperparathyroidism. In this study it was observed that vit-D level has a significant negative correlation with iPTH level (table-2) in CKD. A study from UK suggested that low plasma 25 (OH) vitamin D is a major risk factor for hyperparathyroidism and Looser's zones in chronic dialysis patients.[11]

PTH Levels consistent with the high bone turnover that is the iPTH was found significantly higher in stage 5 patients than stage 4 (Table I).

In the study of BMD T-score among the study subjects level with high risk of fracture by WHO criteria (>-3.5) was found in 16 (18.18%) of patients and the level consistent with the high turnover bone disease (-2.5 to -3.5) was found in 28 (31.82%) patients (Figure 1). Osteoporosis was more frequent in stage 5 than in stage 4 (19 vs. 16; 44.2% vs. 35.55%, respectively) (Figure-1)

In this study it was found the marker combinations to be consistent with high turnover bone disease as suggested by elevated iPTH (>450 pg/ml) and BMD T-score >-2.5 in 57.1% of the subjects when iPTH level was 8 times higher than the normal upper limit of 65 pg/ml and all the patients (100%) had shown to have Vit-D level below 30 ng/ml that is insufficient level (Table II).

My findings suggest that iPTH, and markers of bone formation or resorption that is BAP moved in the same direction. However, as noted by Kidney Disease: Improving Global Outcomes (KDIGO) workgroup, there have

been no studies with sufficient power to assess whether iPTH in combination with other bone-derived biomarkers would be more predictive than individual markers.[12]

The higher levels of iPTH as well as the markers of bone formation and resorption among osteoporotic subjects suggest a contribution of high turnover in the reduction of bone mass. Previous studies have shown an inverse relationship between BMD and PTH and some other markers[13,14,15] In my study I also found higher iPTH is associated with BMD in osteoporotic range (T-score >-2.5) (Table II). This is similar to the study carried out by Hamdy NA et al.[16]

Conclusions

The study assessed the bone and mineral disorders by laboratory investigations among 88 CKD stage 4 and stage 5 patients where over 57.10 % of the stage 4 and stage 5 CKD patients showed significant elevation of IPTH and Phosphate and all of them have insufficient Vitamin D level which is consistent with high turnover bone disease. High turnover could contribute to the development of osteoporosis. Vitamin D deficiency is widespread and seems to have a role in the genesis of hyperparathyroidism and high turnover renal bone disease.

Limitations

The most important is the absence of bone histology. Therefore, although the nature of ROD can be suggested on the basis of the markers studied room for doubt remains, especially in those with low values.

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