https://doi.org/10.3329/cbmj.v15i2.91509

Comparative study of DEXA with biochemical bone markers in advanced CKD (stage 4 & 5) in diagnosis of osteoporosis

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Abstract

Metabolic bone disease (BMD) is a common complication of chronic kidney disease and is a part of a broad spectrum of disorder of mineral metabolism and result in both skeletal and extra skeletal consequences. To reduce osteoporotic bone fracture early diagnosis of BMD is essential. This study aimed to observe osteoporosis by biochemical bone markers and DEXA. This cross-sectional observational study was conducted in the outpatient Department of Nephrology, Bangabandhu Shekhi Mujib Medical University, Dhaka and inpatient Department of Mymensingh Medical college, Mymensingh, from July 2017 to September 2018. Fifty-eight CKD (stage 4-5) patient confirmed by KDOQI guideline were selected. Parathyroid hormone was measured with a Beckman coulter Uncial DX! 800 devices using an immunoradiometric method. Serum calcium and Inorganic phosphate levels were measured employing routine laboratory procedures. Statistical analysis was done by using SPSS version 22.0. A value of $p < 0.05$ was considered statistically significant for all tests. Mean age of the patients was 46.71±7.73 years with a range of 29 – 63 years and male to female ratio was 1: 1.1. Stage 4 was 51.7% and stage 5 was 48.3%. Mean serum calcium, serum inorganic phosphate and parathyroid hormone was 8.19 ± 0.62 mg/dl, 5.18 ± 0.64mg/dl and 397.38 ± 221.24 pg/ml respectively. Mean BMD of lumbar spine, right femoral neck and left femoral neck was -2.22 ± 0.62, -2.10 ± 0.74 and -2.12 ± 0.71 respectively. There were significant differences in serum calcium, serum inorganic phosphate and parathyroid hormone among osteoporosis, osteopenia and normal BMD. Osteoporosis was higher in stage 5 patients. Osteoporosis was present in LS (39.7), FN right (37.9%) and in FN left (36.2%) in this study. DEXA can be used for diagnosis of osteoporosis in absence of bone biopsy.

CBMJ 2026 July: Vol. 15 No. 02 P:267-275

Keywords: Chronic Kidney Disease (CKD), Metabolic Bone Disease (MBD), Osteoporosis, Dual-Energy X-ray Absorptiometry (DEXA), Parathyroid Hormone (PTH)

Introduction

Chronic kidney disease (CKD) is an irreversible deterioration in renal function which usually develops over a period of years. The symptoms of worsening kidney function are not specific and might felling generally unwell and experiencing a reduced appetite. Chronic kidney disease is emerging to be an important chronic disease globally. One reason is the rapidly increasing worldwide incidence of Diabetes and Hypertension.[1] chronic kidney disease is a growing problem that affects approximately 10% of the global population.[2] Metabolic bone disease (BMD) is a common complication of chronic kidney disease and is a part of a broad spectrum of disorder of mineral metabolism and result in both skeletal and extra skeletal consequences. Metabolic bone diseases are disorders of bone strength, usually caused by abnormalities of minerals (such as calcium or phosphate), vitamin D, bone mass or bone structure. The most common metabolic bone disorder is osteoporosis. In clinical terms, metabolic bone disease may results in bone pain and loss of height (due to compression of vertebrae) and they predispose patients to fracture. As kidney function declines, there is progressive deuteriation in mineral

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homeostasis, with a disruption of normal serum and tissue concentration of phosphorous and calcium and changes in circulating levels of hormones (parathyroid hormone). Impaired renal function is a well-established risk factor for increased loss of bone mineral density (BMD) and development of osteoporosis.[3] Osteoporosis is characterized by low bone mass. Metabolic changes, such as secondary hyperparathyroidism, increased phosphate levels, abnormal synthesis of 1.25-dihydroxyvitamin D, and chronic metabolic acidosis, alter bone turnover or mineralization and cause lower BMD in patients with chronic kidney disease (CKD).[4] The effects of the predialysis period on bone loss has not been well studied. Bone loss may vary between different stages of CKD.[5] According to some studies, osteoporosis begins to appear in the predialysis period.[6] Dual-energy X-ray absorptiometry (DEXA) is a precise, rapid and standard non-invasive method to determine BMD loss in patients with healthy kidney function. The result of measurement of bone density are usually expressed in terms of the patients bone density in relation to the mean peak bone density of people of the same sex and genetic background. The result is a measurement known as the T score. Osteopenia is defined as bone density that is more than one standard deviation below peak bone density (T score-1). Osteoporosis is defined as bone density that is 2 and half or more standard deviation below the mean peak bone density (T score-2.5). CKD is associated with higher serum concentrations of BTM.[7] Serum calcium, phosphate, parathyroid hormone (PTH), serum specific alkaline phosphates are widely used surrogate markers of high or low turnover bone disease in patients with CKD.[8] PTH is progressively increased as kidney function declines, and elevated PTH levels cause catabolic effects on cortical bone and an anabolic effect on trabecular bone—as a result of increased turnover, thickened and irregular bones occur.[7] This study was designed to investigate the usefulness of BMD obtained by DEXA and several biochemical markers of bone turnover, in the diagnosis of bone loss, and the relation of these factors with mild-severe CKD, which was determined by estimated glomerular filtration rate (eGFR).

Methods

It was a cross-sectional observational study. Place of Study: Out Patient Department of Nephrology, Bangabandhu Sheikh Mujib Medical University, Dhaka and inpatient Department of Mymensingh Medical college, Mymensingh. Duration of study: This study was conducted from July 2017 to September 2018. Study population: Diagnosed CKD patients of out Patient Department of Nephrology, Bangabandhu Shekhi Mujib Medical University, Dhaka and inpatient Department of Mymensingh Medical College, Mymensingh. Sampling technique: Purposive sampling technique was used as per inclusion and exclusion criteria.

Inclusion criteria:

- Diagnosed CKD (Stage 4 & 5) patients.

Exclusion criteria:

- Patient with a history of malignancy,
- Patients who were currently taking medication (such as glucocorticoid, immunosuppressive agents, hormone replacement therapy, heparine or anticoagulant)
- Patients with any disease that could cause secondary osteoporosis

Data collection instrument: A semi-structured questionnaire has been developed in English. The questionnaire has been developed using the selected variables according to the specific

objectives. Data collection: Pre diagnosed CKD patients (stage 4 and 5) were selected from out Patient Department of Nephrology, Bangabandhu Shekhi Mujib Medical University, Dhaka and the inpatient Department of Nephrology in Mymensingh Medical College Hospital, Mymensingh. Informed written consent was taken. On the day of recruitment, they were evaluated clinically and blood samples were collected and DEXA scan was done in National Institute of Nuclear Medicine and Allied Science (NINMAS), BSMMU, Dhaka. Statistical analysis: Data was collected from all patients by face-to-face interview. Informed consent was obtained from all patients. Collected Data were compiled and appropriate analyses were done both manually and by using computer-based software, Statistical Package for Social Science (SPSS) version 21.0. Results were expressed as frequency, percentage, means ± SD. Quantitative variables was summarized by percentage. Qualitative variables was summarized by mean and Standard Deviation (SD). For statistical analysis chi square test, t test, ANOVA test were done. Level of significance was 5% and confidence limit was 95%. And all are presented by tables, diagrams and graphs based on data nature. Ethical Implication: No Physical/psychological risk is associated with the study. The study was approved by the institutional review board. All patients / guardian of patients was informed about the study. Informed consent was taken from each patient/ guardian of the patient.

Result

This cross-sectional observational study was conducted from July-2017 to September-2018. Fifty-eight CKD (stage 4-5) patients who visited Outpatient Department of Nephrology, BSMMU, Dhaka and inpatient Department of Nephrology Mymensingh Medical College, Mymensingh were included in this study to find out the bone mineral density and biochemical markers of bone metabolism. Results are as follows:

Table I: Distribution of patients according to age (n=58)

Variable	Frequency (n)	Percentage (%)
Age (years)		
≤40	17	29.3
41 - 50	20	34.5
>50	21	36.2
Mean±SD	46.71±7.73 (29 - 63)	
Gender		
Male	28	48.3
Female	30	51.7
Presenting complain		
Bone pain, arthralgia & muscle weakness	57	98.3
Bone deformity	1	1.7
Pruritus	34	58.6
Nausea, vomiting & bodyache	50	86.2
Primary diseases		
Hypertension	23	39.7
Diabetic Nephropathy	15	25.9
Chronic Glomerulonephritis	7	12.0
Polycystic Kidney Disease	2	3.4
Unknown	11	19.0
Smoking	23	39.7

Table I shows distribution of patients according to age. Most of the patients were more than 40 years old (70.7%). Mean age of the patients was 46.71±7.73 years with a range of 29 – 63. Male to female ratio was 1: 1.1. Most common presenting complain was bone

pain, arthralgia & muscle weakness followed by nausea, vomiting & bodyache (86.2%), Pruritus (58.6%) and bone deformity (1.7%). Most common etiology was hypertension (39.7%) followed by diabetic nephropathy (25.9%), chronic glomerulonephritis (12.0%), polycystic kidney disease (3.4%) and unkown etiology (19.0%). No history of taking drug was found. Smoker was 39.7% in this study. Table II shows general examination findings of the patients. Anaemia was present in 56 (96.6%) cases and Oedema was present in 23 (39.7%) cases. Table III shows distribution of patients according to CKD stages. Stage 4 was 51.7% and stage 5 was 48.3%. Mean eGFR was 22.19±3.51 in stage 4 and 12.72±1.42 in stage 5.

Table II: Distribution of patients according to general examination (n=58)

General examination	Frequency (n)/ (Mean ± SD)	Percentage (%)/ (Min - max)
Anaemia	56	96.6
Oedema	23	39.7
Pulse (bpm)	86.77 ± 9.81	64 - 100
Systolic BP (mm of Hg)	137.81 ± 12.75	105 – 170
Diastolic BP (mm of Hg)	86.93 ± 6.67	60 – 95
BMI (kg/m^2)	24.30 ± 2.38	17.79 - 33.64

Table III: Distribution of patients according to CKD stages (n=58)

CKD stages	n (%)	eGFR (mean±SD)
Stage 4	30 (51.7)	22.19±3.51
Stage 5	28 (48.3)	12.72±1.42

Table IV shows Biochemical parameters level of the patients. Mean Hb, ESR, serum Bilirubin, SGPT and serum creatinine was 9.60 ± 1.22 g/dl, 56.68 ± 20.34 mm in 1st hour, 0.84 ± 0.18 mg/dl, 26.39 ± 9.92 mg/dl and 3.79 ± 1.04 mg/dl respectively. Table V shows biochemical markers level of the patients. Mean serum calcium, serum inorganic phosphate and parathyroid hormone was 8.19 ± 0.62 mg/dl, 5.18 ± 0.64mg/dl and 397.38 ± 221.24 pg/ml respectively. Table VI shows T-score level of the patients. Mean T-score of lumbar vertebrae, right femoral neck and left femoral neck was -2.22 ± 0.62, -2.10 ± 0.74 and -2.12 ± 0.71 respectively. Table VI shows T-score level of the patients. Mean T-score of lumbar vertebrae, right femoral neck and left femoral neck was -2.22 ± 0.62, -2.10 ± 0.74 and -2.12 ± 0.71 respectively.

Table IV: Biochemical findings of the patients (n=58)

Variable	Mean ± SD	Min - max
Hb (g/dl)	9.60 ± 1.22	7.40 – 13.40
ESR (mm in 1st hour)	56.68 ± 20.34	5.00 - 110.00
Serum bilirubin (mg/dl)	0.84 ± 0.18	0.40 - 1.40
SGPT (mg/dl)	26.39 ± 9.92	8.00 - 47.00
Serum creatinine (mg/dl)	3.79 ± 1.04	2.10 - 6.10

Table V: Biochemical markers level of the patients (n=58)

Biomarkers	Mean ± SD	Min - max
Serum calcium (mg/dl)	8.19 ± 0.62	5.70 - 9.90
Serum Inorganic Phosphate (mg/dl)	5.18 ± 0.64	3.90 - 6.30
Parathyroid Hormone (pg/ml)	397.38 ± 221.24	60.00 - 871.90

Table VI: T-score level at different sites of the patients (n=58)

Site	Mean ± SD	Min - max
Lumbar spine	-2.22 ± 0.62	-3.40 to -0.80
Right femoral neck	-2.10 ± 0.74	-3.30 to -0.30
Left femoral neck	-2.12 ± 0.71	-3.20 to -0.20

Table VII shows level of biochemical marker in osteoporosis patients, osteopenia patients and healthy control. There were significant differences in serum calcium, serum inorganic phosphate and parathyroid hormone among osteoporosis, osteopenia and healthy controls. Table VIII shows level of biochemical marker in CKD stage 4 and stage 5. There were no significant differences in serum calcium, serum inorganic phosphate and parathyroid hormone between stage 4 and stage 5. Table IX shows osteoporosis at different CKD stages. Osteoporosis was higher in stage 5 patients.

Table VII: Level of biochemical marker at different T score (n=58)

Biochemical marker	T-score			p-value
	Osteo-porosis (≤-2.5) (n=30)	Osteo-penia (-2.5 to -1) (n=21)	Normal (≥-1) (n=7)	
Serum calcium (mg/dl)	8.01± 0.72	8.28 ±0.26	8.67±0.64	0.023
Serum Inorganic Phosphate (mg/dl)	5.34± 0.64	5.12±0.63	4.67± 0.29	0.035
Parathyroid Hormone (pg/ml)	473.2±221.8	357.6±203.9	192.0±71.4	0.004

ANOVA test was done to measure the level of significance. Data were presented as mean±SD.

Table VIII: Level of biochemical marker at different CKD stages (n=58)

Biochemical marker	Stage 4 (n=30)	Stage 5 (n=28)	p-value
Serum calcium (mg/dl)	8.28 ± 0.33	8.09 ± 0.82	0.256
Serum Inorganic Phosphate (mg/dl)	5.14 ± 0.59	5.23 ± 0.69	0.588
Parathyroid Hormone (pg/ml)	371.3 ± 241.6	425.3 ± 197.6	0.357

Table IX: Osteoporosis at different CKD stages (n=58)

CKD stages	Osteoporosis (≤-2.5) (n=30)	Osteopenia (-2.5 to -1) (n=21)	Normal (≥-1) (n=7)
Stage 4	13 (43.3%)	13 (43.3%)	4 (13.4%)
Stage 5	17 (60.7%)	8 (28.6%)	3 (10.7%)
Total	**30 (51.7%)**	**21 (36.2%)**	**7 (12.0%)**

Chi-square test was done to measure the level of significance. Results were presented as frequency (percentage)

Table X: Osteoporosis at different sites (n=58)

Sites	Osteoporosis (≤-2.5) (n=30)	Osteopenia (-2.5 to -1) (n=21)	Normal (≥-1) (n=7)
Lumbar spine	23 (39.7%)	28 (48.3%)	7 (12.1%)
Right femoral neck	22 (37.9%)	26 (44.8%)	10 (17.2%)
Left femoral neck	21 (36.2%)	29 (50.0%)	8 (13.8%)

Table X shows osteoporosis at different sites. Osteoporosis was present in LS (39.7), FN right (37.9%) and in FN left (36.2%) in this study.

Table XI: Sensitivity and specificity at different cut off value of serum calcium in diagnosis of osteoporosis

Serum calcium (mg/dl)	Sensitivity	Specificity
8.02	82.1	46.7
8.06	78.6	46.7
8.15	67.9	50.0
8.25	57.1	60.0
8.35	50.0	70.0

Serum calcium level 8.15 mg/dl is the best cut off value in this study to diagnosis osteoporosis.

Table XII: Sensitivity and specificity at different cut off value of serum phosphate in diagnosis of osteoporosis

Serum Phosphate (mg/dl)	Sensitivity	Specificity
4.75	0.833	0.393
4.85	0.833	0.429
4.95	0.700	0.714
5.05	0.633	0.750
5.15	0.567	0.750

Serum phosphate level 4.95 mg/dl is the best cut off value in this study to diagnosis osteoporosis.

Table XIII: Sensitivity and specificity at different cut off value of parathyroid hormone in diagnosis of osteoporosis

Parathyroid hormone (pg/ml)	Sensitivity	Specificity
318	0.700	0.571
322	0.700	0.643
325	0.700	0.679
328	0.667	0.679
333	0.667	0.714

Parathyroid hormone level 325 pg/ml is the best cut off value in this study to diagnosis osteoporosis.

Table XIV: Osteoporosis diagnosis by DEXA and biochemical parameter (n=58)

Marker	Frequency (n)	Percentage (%)
DEXA	30	51.7
Ca	24	41.4
PTH	30	51.7
PO_4	29	50.0

Table XV: Abnormal biochemical findings in Osteoporosis patients (according to DEXA) (n=30)

Marker	Frequency (n)	Percentage (%)
Ca	26	86.7
PTH	30	100.0
PO_4	28	93.3

Discussion

Metabolic bone disease (BMD) is a common complication of chronic kidney disease and is a part of a broad spectrum of disorder of mineral metabolism and result in both skeletal and extra skeletal consequences. To reduce osteoporotic bone fracture early diagnosis of BMD is essential. This study was performed to assess biochemical bone markers and DEXA in diagnosis osteoporosis. In this study, most of the patients were >40 years old (70.7%). Mean age of the patients was 46.71±7.73 years with a range of 29 – 63 years. In the study of Fidan *et al.* (2016), mean age of the participants was 59.99±11.56.[9] Mean age was more than 53 years in the study of Rix *et al.* (1999).[10] Male to female ratio was 1: 1.1 in this study; similar finding was seen in the study of Fidan *et al.* (2016).[9] In their study male to female ratio was 1:1.02. Regarding CKD stage, 51.7% patients with stage 4 and 48.3% patients with stage 5 were included in this study. Fidan *et al.* (2016) included 22 (26.5%) patients with CKD stage 3, 40 (48.2%) patients with CKD stage 4, and 21 (25.3%) patients with nondialysis CKD stage 5.[9] In this study, smoker was 39.7%. Ketteler, Markus, *et al.* (2018) revealed 14.6% smoker. Regarding biomarkers level of the patients, mean serum calcium, serum inorganic phosphate and parthyroid hormone was 8.19 ± 0.62 mg/dl, 5.18 ± 0.64mg/dl and 397.38 ± 221.24 pg/ml respectively.[11] Tamadon *et al.* (2017) found mean serum Ca, P and PTH were 9.0 ± 0.64 mg/dl, 4.95 ± 0.56 mg/dl and 384.35 ±33.04 pg/ml respectively which are consistent with this study result.[12] Fidan *et al.* (2016) observed parathyroid hormone 308.6± 349.1 with a range of 25.40 to 1866. BMD is a measure of bone strength and can be measured by DEXA.[9] DEXA is the most widely used method due

to its short scan time, low cost, and low radiation dose. DEXA can quantify bone mass and measure BMD in patients with CKD (Nickolas *et al.,* 2013; Coresh *et al.,* 2003; Jamal *et al.,* 2012).[7,13,14] Osteoporosis can be diagnosed by BMD measurements (Kanis *et al.,* 1994), however, unlike in the non-CKD population, there has been limited evidence to prove that DEXA can provide significant predictive value of increased bone loss in predialysis patients with CKD.[15] Several studies demonstrated that BMD measurements obtained by DEXA can predict bone loss and fracture risk in patients with CKD (Nickolas *et al.,* 2013; Coresh *et al.,* 2003; Jamal *et al.,* 2012).[7,13,14] According to the WHO criteria, patients were categorized into normal BMD (T-score≥−1.0), osteopenia (T-score=−1.0 to −2.5) and osteoporosis (T-score <−2.5) groups (NIH Consensus Development Panel, 2001).[16] In this study, overall Osteoporosis was 30 (51.7%) and Osteomenia was 21 (36.2%). Incidence of Osteoporosis was higher in stage 5 patients. Osteoporosis was present in LS (39.7), FN right (37.9%) and in FN left (36.2%) in this study. The prevalence of T-scores ≤-2.5 SD was 28.6%, 35.1% and 13.0% according to the LS, FN and three bone sites T scores respectively (Tamadon *et al.,* 2017). Mean BMD (T-score) of lumbar vertebrae, right femoral neck and left femoral neck was -2.22 ± 0.62, -2.10 ± 0.74 and -2.12 ± 0.71 respectively in this study. Tamadon *et al.* (2017) found (T-score = -1.92 ± 1.29) at the femoral neck (FN), (T-score = -1.79 ± 1.25) at the total hip (TH) and (T-score = -1.55 ± 1.84) at the LS. Serum inorganic phosphate and parthyroid hormone level increased and serum calcium level reduced with reduced of BMD (T-score) level.[12] There were significant differences in serum calcium, serum inorganic phosphate and parathyroid hormone among osteoporosis, osteopenia and healthy controls. Regarding biochemical marker in CKD stage 4 and stage 5, there were no significant differences in serum calcium (8.28±0.33mg/dl vs 8.09±0.82 mg/dl; p>0.05), serum inorganic phosphate (5.14±0.59 vs 5.14±0.59 mg/dl; p>0.05) and parathyroid hormone (371.27±241.65 vs 425.35±197.60 pg/ml; p>0.05) between stage 4 and stage 5. But in the study of Rix *et al*. (1999), the mean serum levels of the different biochemical markers increased with the more advanced stage of renal impairment.[10] Area under curve derived from ROC curve for detecting accuracy of serum calcium in diagnosis of Osteoporosis was 0.689 and sensitivity and specificity were 67.9% and 50.0% respectively at 8.15 mg/dl cut off value of serum calcium. Area under curve derived from ROC curve for detecting accuracy of serum inorganic phosphate in diagnosis of Osteoporosis was 0.680 and sensitivity and specificity were 70.0% and 71.4% respectively at 4.95 mg/dl cut off value of serum inorganic phosphate. Area under curve derived from ROC curve for detecting accuracy of parathyroid hormone in diagnosis of Osteoporosis was 0.705 and sensitivity and specificity were 70.0% and 67.9% respectively at 325 pg/ml cut off value of parathyroid hormone. None of the above biochemical markers shows good sensitivity and specificity in diagnosis of osteoporosis. Specific biochemical markers of bone turnover have been studied extensively over the last decade, but the actual concept in the bone research field is that these biochemical markers are of no certain diagnostic use in the single patient, but might be of some use in following the results of clinical trials (Barco, Carmen M, 2012; Seibel *et al.,* 1997).[17,18] The reasons for the limitation in the daily clinical use are a substantial intra-individual variability

(Stevenson *et al.,* 1997) and a poor correlation between the markers and the rate of bone loss (Keen *et al.,* 1996).[19,20] Osteoporosis was found 51.7%, 41.4%, 51.7% and 50.0% according to DEXA, Ca, PTH and PO4 respectively. Abnormal Ca was found in 86.7% cases, PTH was in 100.0% cases and PO4 in 93.3% cases.

Conclusion

None of the biochemical markers (serum calcium, serum inorganic phosphate and parathyroid hormone) shows good sensitivity and specificity in diagnosis of osteoporosis. DEXA remains the only available test for diagnosis of osteoporosis by measuring BMD (T score ≤ -0.25). Bone biopsy provides definitive and quantitative diagnosis of renal bone disease. Bone biopsy is not routinely performed in clinical practice because of the invasive nature of the procedure. So, DEXA should be considered for diagnosis of osteoporosis because of its preciseness, rapidness and non-invasiveness.

Limitations

Single cantered. Limited sample. Gold standard test for BMD – bone biopsy is not available in Bangladesh. We did not obtain similar data in healthy control group. DEXA provides a two-dimensional assessment of a three-dimensional structure; therefore, it may not discriminate cortical and trabecular bone, this may restrict the usefulness of DEXA in chronic renal disease patients.

Recommendations

To find the efficacy of biochemical markers and Dexa to diagnosis osteoporosis bone biopsy is mandatory. Large sample size and multicenter study is required. There is need for further studies on novel BMD measurement techniques and novel serum bone turnover markers to determine bone loss quantity in predialysis patients with CKD.

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