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Assessment of Bone Mineral Density (BMD) In Children with Advanced CKD (Stage 3 To 5): Experience from Tertiary Care Center, Dhaka, Bangladesh

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Abstract
Background: Chronic kidney disease (CKD) has impact on bone development, remodeling, and modeling. Assessment of bone health is a key element in the management of CKD.
Objective: To assess bone mineral density (BMD) in children with advanced CKD (stage 3 to 5).
Methodology: This cross-sectional study was carried out in the department of Pediatric Nephrology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh from March 2022 to March 2023. A total 45 children with advanced CKD (stage 3 to 5) were included in the study. Serum calcium, phosphate and iPTH were measured and bone mineral density of lumber spine and femoral neck was measured by using dual energy absorptiometry (DEXA).
Results: Total 45 patients were studied. Serum biochemical marker (calcium, phosphate, iPTH and alkaline phosphatase) showed significant changes in CKD stage 5 and 5D (p=0.03, p=0.04, p= 0.001 and p= 0.014 respectively). Eleven patients (24.44%) had skeletal deformities; most were from stage 5D (p=0.01). No significant changes were found in bone mineral density Z score among different stages of CKD and dialysis group.
Conclusion: Bone mineral density did not differ significantly in different stages of CKD in children.

Keywords: Assessment, bone mineral density (BMD), CKD

Introduction
Chronic kidney disease-mineral and bone disorder (CKD-MBD) is a triad of biochemical abnormalities (calcium, phosphate, parathormone, and 1, 25-dihydroxyvitamin D), bone abnormalities (short stature, decreased mineralization, and higher fracture risk), and extra-skeletal calcification [1]. Bone growth, remodeling, and modeling are all impacted by chronic renal disease. Poorly treated CKD causes decreased bone mass accretion and accelerated bone loss [2]. Mineral dysregulation, which causes bone demineralization, causes bone pain, deformities, and fractures in childhood CKD [3]. Pediatric mineral and bone disorders have long-term effects. A study of 249 young adults with pre-adolescent end-stage renal failure followed into adulthood found that 37% had bone disease symptoms (deformities, bone discomfort, aseptic bone necrosis, atraumatic fractures), 18% were disabled, and 61% had severe growth limitation [4]. Serum calcium, phosphate, and iPTH are common biochemical indicators of CKD-MBD, and their derangement is common in advanced CKD. Bone biopsy is needed to determine bone turnover and mineralization. This invasive procedure is the gold standard but rarely employed in clinical practice [5]. Dual-energy X-ray absorptiometry (DEXA) is a widely used method to measure BMD and it is quick, readily available, non-invasive, and has low radiation exposure [6]. So, the aim of the study was to assess bone mineral density (BMD) in children with advanced (stage 3 to 5) CKD using DEXA.

Materials and Methods

This cross-sectional study was carried out in the Department of Pediatric Nephrology, BSMMU, Dhaka, from March 2022 to March 2023. All children with advanced CKD (stage III to V) who attended both in-patient and out-patient in the Department of Pediatric Nephrology, Bangabandhu Sheikh Mujib Medical University (BSMMU), irrespective of primary cause of CKD was included in the study. Patients with following criteria was excluded: 1) Patients who were taking corticosteroids within the last one year, 2) Patients receiving aluminum containing phosphate binder. Patient who did not give consent and did not cooperate also excluded from the study. Total 45 children were included in the study.

Permission from the Institutional Review Board (IRB) of BSMMU was obtained for this study. After selection of the subjects; the objectives, nature, purpose, and potential risk of all procedure used for the study was explained to the parents in detail and informed. Demographic and clinical characteristics were recorded in the predesigned data collection sheet including name, age, sex, residence, etiology of CKD, age at diagnosis of disease, stage of CKD, treatment history, clinical examination which included height, weight, body mass index (BMI), hypertension, and bony change. All patients were getting sodium bicarbonate, calcium carbonate, and calcitriol based on their individual clinical needs. All ESRD patients were getting hemodialysis three times a week and investigations were done on non-dialysis day. Laboratory tests like complete blood count, serum creatinine, urea, electrolytes, calcium, phosphate, iPTH, alkaline phosphatase was done for each patient. eGFR was calculated by revised Schwartz formula as follows- eGFR= 0.413 x (Height/S. creatinine), here height is expressed in centimeter and serum creatinine in mg/dl [7].

BMD was measured in National Institute of Nuclear Medicine and Allied Science (NINMAS), BSMMU by DMS Strator DR Bone Densitometer Dual Emission X-ray Absorptiometry (DEXA) at lumbar vertebra (L1-4) & both femoral neck as bone density in gm/cm². Analysis of data and calculation of Z score from DEXA was computerized & completely automated. Z score more than -2 was regarded as normal bone mass and equal or less than -2 was regarded as low bone mass according to International Society of Clinical Densiometry (ISCD) criteria [8].

Statistical analysis was performed by IBM SPSS (statistical program for social science) software for Windows version 26, 2019. Appropriate statistical tests (Chi-square test, Fisher Exact test, Kruskal Wallis test) were applied for data analysis. A p value less than 0.05 was considered as significant.

Results

Table 1: Demographic and clinical variables of the study population (n=45)

Characteristics	CKD stage 3 (n=4)	CKD stage 4 (n=10)	CKD stage 5 (n=12)	CKD stage 5D (n=19)
Age in years (mean ±SD)	13±1.13	8.9±3.35	13.19±3.66	13.83±3.02
Gender (%)				
Male	3 (75%)	8 (80%)	11 (91.7%)	12 (63.2%)
Female	1 (25%)	2 (20%)	1 (8.3%)	7 (36.8%)
Residence (%)				
Urban	1 (25%)	4 (40%)	3 (25%)	10 (52.6%)
Rural	3 (75%)	6 (60)	9 (75%)	9 (47.4%)
Age at diagnosis of CKD in years (mean ±SD)	12.02±1.60	7.95±2.93	7.5±5.01	11.57±3.28
Anemia (%)	1 (25%)	5 (59%)	8 (66.7%)	18 (94.7%)
Hypertension (%)	1 (25%)	2 (20%)	5 (41.7%)	14 (73.7%)
Height for age Z score (HAZ)	-2.45±1.77	-2.22±1.74	-3.36±2.33	-2.76±1.80
BMI in kg/m2 (mean ± SD)	17.58±3.34	13.83±2.98	16.39±4.60	16.69±3.40
Skeletal deformities (%)	1 (25%)	1 (10%)	2 (16.67%)	7 (36.84%)

Demographic and clinical characteristics were described in table 1. Mean age at diagnosis of CKD in stage 3 was 12.02±1.60, in stage 4 was 7.95±2.93, in stage 5 was 7.5±5.01 and in stage 5D was 11.57±3.28 year. Most patients with CKD stage 5D had anaemia and hypertension (94.7% and 73.7% respectively). A higher number of children from stage 5D presented with skeletal changes. There were no significant changes in height for age Z score (HAZ), BMI, or TCO2 level among different stages of CKD.

Table 2: Etiology of CKD among the study population (n=45)

Etiology	Number	Percentage
Posterior urethral valve	19	42.22%
Hypoplastic kidney	8	17.8%
Pelviureteric junction obstruction	1	2.2%
Glomerulonephritis	3	6.7%
Polycystic kidney disease	2	4.4%
Single kidney	1	2.2%
Horseshoe kidney	1	2.2%
Primary VUR with recurrent UTI	2	4.4%
Neurogenic bladder with recurrent UTI	1	2.2%
Alport Syndrome	3	6.7%
Unknown etiology	4	8.9%

Most common cause was posterior urethral valve (n=19, 42.22%). Other causes were hypoplastic kidney (n=8, 17.8%), glomerulonephritis (n=3, 6.7%), Alport syndrome (n=3, 6.7%), polycystic kidney disease (n=2, 4.4%), primary

VUR with recurrent UTI (n=2, 4.4%), pelviuretic junction obstruction, single kidney, horseshoe kidney, neurogenic bladder with recurrent UTI and unknown etiology (Table 2).

Table 3: Biochemical parameter in different stages of CKD (n=45)

Variable	Stage 3 Median (IQR)	Stage 4 Median (IQR)	Stage 5 Median (IQR)	Stage 5D Median (IQR)	p value
S. Calcium (mg/dl)	9.8 (9.4-10.05)	9.1 (8.93-9.28)	7.95 (6.68-9.28)	8.2 (7.6-9.2)	0.033
S. PO4 (mg/dl)	4.2 (3.67-4.28)	5.00 (3.70-5.85)	5.98 (3.93-7.20)	6.93 (4.5-8.4)	0.04
S. iPTH (pg/ml)	78.5 (29.98-125.75)	99.7(49.38-134.80)	716.45 (145.78-999.95)	486 (204.0-817.0)	0.001
S. alkaline phosphatase (mg/dl)	120.0 (98.25-341.25)	155.0 (129.5-238.75)	342.0 (214.5-484.5)	254.0 (206.0-438.0)	0.014
TCO2 (mmol/L)	23.50 (21.60-25.25)	18.00 (15.93-20.00)	19.65 (14.80- 23.08)	22.0 (16.00-24.90)	0.209

Independent sample Kruskal Wallis test was done and $p<0.05$ significant

There was significant difference in serum calcium, PO4 and iPTH level in different stages of CKD ($p<0.05$) (Table 3).

Table 4: Bone mineral density Z score in different stages of CKD (n=45)

Site	Stage 3	Stage 4	Stage 5	Stage 5D	*P* value
Lumber spine (mean ± SD)	-1.35±0.51	-1.32±1.2	-1.98±2.44	-1.39±1.63	0.625[a]
Right femoral neck (mean ± SD)	-1.00±1.31	-1.15±1.52	-2.27±2.01	-1.14±1.43	0.246[a]
Left femoral neck (mean ± SD)	-1.30±1.28	-1.11±1.56	-2.23±1.85	-1.25±1.42	0.306[a]

A ANOVA was done to measure the level of significance. p value <0.05 significant

Table 5: Comparison of bone mineral density Z score in non-dialysis and dialysis patients (n=45)

	Non-dialysis group (n=26)	Dialysis group (n=19)	p value
Lumber spine (Mean ± SD)	-1.78±1.84	-1.39±1.63	0.467[a]
Right femoral neck (Mean ± SD)	-1.64±1.78	-1.14±1.43	0.331[a]
Left femoral neck (Mean ± SD)	-1.66±1.69	-1.25±1.42	0.399[a]

A Independent sample t test was done to see the level of significance. p value <0.05 significant.

The bone mineral density Z score of both femoral necks was lower in stage 5 than in other stages, but it was not statistically significant (Table 4). There were no significant changes between bone mineral density Z score of non-dialysis and dialysis group (Table 5).

Discussion

Forty-five children from stages 3 to 5D were included in this research. Four patients were from stage 3, 10 patients from stage 4, 12 patients from stage 5 and 19 patients were receiving hemodialysis. Mean age at diagnosis of CKD in stage 3 was 12.02±1.06 yr, in stage 4 was 7.95±2.93 yr, in stage 5 was 7.5±5.01 yr and in stage 5D 11.57±3.28months (Table 1). A recent epidemiological study performed in Lithuania showed CKD stage 5 was diagnosed in 21.2% of the study population and CKD-related cause was determined at the age of 4.25±5.11 years on average [9]. In another series 58% of children with renal failure had ESRD at presentation [10, 11]. The data from the North American Pediatric Renal Transplant Co-operative Study (NAPRTCS) also found 70% of children registered for CKD were from the advanced stage of CKD [12]. In the current study, most of the patients were from stage 5 and 5D (Table 1).

In a series of 305 children, median age 8 years, presenting with CKD at a tertiary care hospital in India, the cause of renal failure in 75% of cases was obstructive nephropathy, reflux nephropathy or chronic glomerulonephritis [13]. In the current study, the age of diagnosis of CKD was much higher (Table 1). This may be due to the absence of any screening guidelines for children with CKD who may not have received any medical attention earlier. In many developed countries, the leading cause of CKD is congenital anomaly of kidney and urinary tract (CAKUT) [10, 14]. The data of the United States, Italian, Belgian, and Serbian CKD registries, where CAKUT accounted for 48%, 58%, 59%, and 58% of all CKD causes respectively [10, 15]. Whereas in developing countries, acquired causes mainly glomerulonephritis predominates [10]. According to published data from Bangabandhu Sheikh Mujib Medical University, the leading causes of CKD stages 4 and 5 in children were glomerulonephritis (26.08%), obstructive uropathy (17.39%), hypoplastic kidney (19.56%), neurogenic bladder and reflux (8.68%), and unclear etiology ((21.73%) [16]. In this study leading causes of CKD were posterior urethral valve (42.22%) and hypoplastic kidney (17.8%) (Table 2). This information is different from earlier published statistics from the same institute, but it is comparable to that of developed nations. This might be as a result of recent advancements in the management of glomerulonephritis, which have slowed the development of CKD and made CAKUT the leading cause. Moreover, a decreased infection rate brought on by the extensive use of antibiotics, extensive immunization, and improved socioeconomic conditions may contribute to a decrease in the frequency of glomerulonephritis. In each stage of CKD, male accounted for most of the patients (Stage 3- 75%, stage 4- 80%, stage 5- 91.7%, stage 5D- 63%) (Table 1). As the most frequent causes of CKD in this study were the posterior urethral valve (42.22%), there was male predominance. Recent UK data also showed higher prevalence CKD among boys in comparison to girls and this was largely due to congenital urinary tract disorder [17]. In Chronic Kidney Disease in Children (CKiD) study, patients with a GFR less than 30 ml/min/1.73 m2 had a fourfold to fivefold higher risk of anemia compared to those with a GFR of 50 ml/min/ 1.73 m2 or greater [18]. Pediatric Renal Trials and Collaborative Studies (NAPRTCS) have demonstrated that the prevalence of anemia in children is 73% at stage 3 CKD, 87% at stage 4 and >93% at stage 5 [19]. In this study, a higher percentage of patients with CKD stage 5 (66.7%) and stage 5D (94.7%) were anemic which are comparable to other studies showing that the risk of anemia increased with advancing CKD stage

(Table 1). Anemia in CKD has bidirectional relation with CKD-MBD. Iron and erythropoietin deficiency exerts its effect on bone mineralization by increasing FGF23 activity. On the other hand, FGF23 and hyperparathyroidism affect erythropoiesis [20]. Abnormalities in mineral metabolism and bone structure are almost individual findings in progressive CKD [21]. Skeletal symptoms, including limb deformities, bone pains and fractures, or radiological signs of bone disease have been reported in 15% of children on peritoneal dialysis [22]. Another study reported significant bone pain hindered daily activities of 58% of children with advanced CKD (i.e., stage 4-5) (2). In this study, only 11 patients (24.44%) had bony changes; most were from stage 5D (n = 7, 63.64%) (Table 1). This may be lower than the actual number because this study did not look at radiological abnormalities like signs of rickets, broken bones, etc. Although HAZ and BMI did not differ significantly in different stages of CKD, both parameters were below the target range of normal growth and nutrition (Table 1). This indicates the poor nutritional status of all the study subjects. Abnormalities in calcium, phosphate and PTH are common in patient with CKD. Changes in the laboratory parameter of CKD-MBD may begin in the CKD stage 3 but the presence of abnormal values, the rate of change and the severity of abnormalities are highly variable among patients [23]. In most of the cases severity increase with decrease GFR. In the present study, significant changes in serum calcium, phosphate, iPTH and alkaline phosphatase were observed in stage 5 and 5D CKD (Table 3). Despite receiving treatment, the severity of the disease and potential adherence issues with medications and dietary restrictions can explain these findings. Patients with chronic kidney illness frequently have metabolic acidosis, which can cause demineralization of the bones. Serum bicarbonate levels are typically assessed for determining whether a patient has metabolic acidosis, and serum TCO2 can be utilized as a substitute for this measurement [24]. Serum TCO2 was employed in this study to measure metabolic acidosis and no significant differences between CKD stages were detected (Table 3). As a result of receiving treatment, all patients maintained normal levels of TCO2. However, a precise determination of metabolic acidosis necessitates the assessment of systemic pH and HCO3. Renal osteodystrophy is known to be accompanied by pathophysiological changes in phosphate excretion, vitamin D metabolism, hypocalcemia, elevated PTH, and acid-base abnormalities. Due to these conditions, bone microarchitecture is destroyed and bone mass is lost [25]. According to Ziolkowska *et al*. 48.4% of children with CKD had lumbar spine Z-scores that were less than -2. Two-thirds of these patients were receiving dialysis, whereas one-third had conservative care [26]. Children on dialysis and predialysis who had CKD had reduced BMD at the lumbar spine (Z-score -1.6 at lumbar spine), according to another study [27]. The same authors also observed that children and adolescent with ESRD receiving dialysis have lower BMD (Z-scores -1.47) in comparison to the general population [28]. Groothoff *et al*. measured BMD at the lumbar spines in 247 young people who had ESRD between the ages of 0 and 14 years. They showed that these patients' mean Z-scores were -2.12±1.4 [4]. The mean lumbar spine BMD of children with CKD did not differ from healthy controls, according to Moon RJ, *et al* [29]. Sixty two percent of children with CKD and 59% of children with ESRD had osteopenia (Z score <-1), according to Bakr *et al* [25] and this was not related to severity of CKD. Pluskiewicz *et al*. also reported that the severity of skeletal alteration in children and adolescents was similar in the early phase (predialysis) and end stage (dialysis) of CKD [27]. Despite lacking statistical significance, in this study the Z score for bone mineral density was observed to be lower in individuals with stage 5 chronic kidney disease (Table 4). Also, no significant changes were found in bone mineral density Z score in non-hemodialysis and hemodialysis group (Table 5). This probably means that the skeletal changes occur early and that later bone status is rather stable. Also, poor compliance to drug and dietary restriction could be a possible reason. Methods of BMD measurement also different in different studies. In this study, there was lack of dietary information, drug doses, vitamin D level, and other factor such as pubertal stage and level of physical activity which have significant effect on bone mineral density in children with CKD.

Conclusion

This study concluded that bone mineral density did not differ significantly in different stages of CKD in children. This should be validated by long-term investigations that collect large samples from multiple centers.

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