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Prevalence and Pattern of Mineral Bone Disease in Patients with Chronic Kidney Disease in South-South Nigeria

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Authors' contributions

This work was carried out in collaboration among all authors. Author ONV designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors RIO and PCE managed the analyses of the study. Author FSW managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Background: Mineral bone disease (MBD) is a common complication in patients with chronic kidney disease (CKD). The objective of this study is to determine the prevalence and characteristics of CKD-MBD among adult patients with CKD attending the University of Port Harcourt Teaching Hospital.
Methods: One hundred and fifty subjects with chronic kidney disease patients who fulfilled the inclusion criteria for this study were recruited. Patients had a detailed clinical assessment, biochemical and radiological evaluations for CKD-MBD. Biochemical investigations included serum calcium, phosphate, parathyroid hormone (PTH) and alkaline phosphatase.

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Results: The age range of the patients was 22-80 years, with a mean of 45.1 (±11.9) years. There were 90 males and 60 females with male to female ratio of 1.5:1. The prevalence of CKD-MBD in the study population was 55.3%. Of this, sixty one (73.5%) patients had low turnover bone disease while 22 (26.5%) patients had high turnover bone disease. The mean values for serum PTH, serum calcium, serum phosphate, alkaline phosphatase and caxpo 4 product among the CKD-MBD patients were 205.06±112.6 pg/ml, 2.56±0.73 mmol/l, 1.63±0.63 mmol/l, 109.26±65.57I U/L and 4.07±1.28 mmol2/l2 respectively but the values among non CKD-MBD patients were 123.08±120.99 pg/ml, 2.32±0.46 mmol/l, 1.54±0.57 mmol/l, 108.13±51.84I U/L and 3.52±1.32 mmol2/l2 respectively.
Conclusion: The prevalence of CKD-MBD in our environment is high and low turnover bone disease is the commonest type.

Keywords: CKD; MBD; prevalence; pattern; South-South Nigeria.

1. INTRODUCTION

Chronic kidney disease (CKD) is an impairment of kidney function for three months or more as defined by structural or functional abnormalities of the kidney such as urinary sediment abnormalities or proteinuria with or without reduction in glomerular filtration rate, or estimated glomerular filtration rate (eGFR) of less than 60mls/min/1.73 m^2 for three months or more with or without structural abnormalities [1]. Chronic kidney disease is a leading cause of morbidity and mortality in the world [2]. It is an underrated cause of poverty and it hampers economic growth of many countries [3]. Eighty percent of chronic kidney disease deaths occur in low and middle-income countries [3]. The National Kidney Foundation estimates that 20 million Americans have chronic kidney disease and at least a further 20 million people have an increased risk [4]. The incidence of end-stage renal disease in United Kingdom is within the range of 100-200 per million population per year [5]. In Nigeria, although accurate figures are not available, the size of the problem has been estimated using hospital admission records. In hospital based studies in the South west Nigeria, the frequency of CKD was found to range between 6.7 and 8.0% [6]. Chronic kidney disease is associated with widespread complications and disorders in mineral and bone metabolism are common complications and important causes of morbidity and decreased quality of life [6-9]. These can develop in the early stages of renal disease and may even begin several years before the symptoms and radiological changes appear in the adult [10]. Increasing evidence suggest that these changes are associated with changes in arterial compliance, cardiovascular calcification, bone disorders and all cause cardiovascular mortality [11]. In Africa, studies of CKD-MBD are sparse partly due to limitations in laboratory facilities. There are however few studies on components of CKD-MBD such as secondary hyperparathyroidism, serum calcium, serum phosphate levels and vitamin D. The study was carried out to asses the prevalence and pattern of Mineral Bone Diseases among CKD Patients presenting at the University of Port Harcourt Teaching Hospital.

2. METHODS

2.1 Study Area

This cross-sectional study was conducted in the Department of Internal Medicine, University of Port Harcourt Teaching Hospital (UPTH) Port Harcourt, Rivers State, Nigeria. University of Port Harcourt Teaching Hospital is a tertiary institution with more than 600 in-patient beds located in Port Harcourt, the capital city of Rivers State, Nigeria. The Department of Internal Medicine has 160 beds with average annual renal admission of 220 patients. The hospital serves as a referral centre for patients from Rivers, Bayelsa, Abia, Imo, Cross River, Akwa Ibom and Ebonyi States.

2.2 Sample Selection

The study was a descriptive, cross-sectional study of 150 consecutive patients with chronic kidney disease who met the inclusion criteria for the study. Chronic kidney disease was defined as eGFR less than 60 mls/min/1.73 m^2 for three months or more with concomitant evidence of kidney damage such as urinary abnormalities (proteinuria, haematuria), structural abnormalities (e.g abnormal renal imaging) and genetic disease (e.g autosomal dominant polycystic kidney disease).

2.2.1 Inclusion criteria

1. Adults aged 18 years and above.
2. Chronic kidney disease patients who grant informed consent.
3. Chronic kidney disease patients in stages 3-5.

2.2.2 Exclusion criteria

1. Acute or chronic bone disorders including metastatic bone disease.
2. Patients on calcium and vitamin D therapy, or any other drug that may interfere with calcium, phosphate and vitamin D metabolism.
3. Patients who have had renal transplant.
4. Patients with chronic liver disease or other significant organ dysfunction.
5. Patients on long-term steroids.
6. Post-menopausal women.

2.3 Specimen Analysis

All samples were analyzed at the University of Port Harcourt Teaching Hospital Clinical Chemistry and Haematology laboratories.

The assay for the serum parathyroid hormone level was done in the Research Laboratory using immunochemiluminometric assay method (ICMA). The reference values of PTH in CKD stage 3-5 was 16.5-72.7pg/ml but 145-654pg/ml for CKD stage 5D (2-9 times the upper limit of normal for assay)[91].

In this study therefore, CKD-MBD was defined as follows:

Stages of CKD	Low turnover bone disease	High turnover bone disease
Stage 3-5	PTH < 16.5pg/ml	PTH >72.7pg/ml
Stage 5D	PTH < 145pg/ml	PTH >654pg/ml

2.4 Data Analysis

Data obtained were analyzed using a commercially available statistical data management soft ware-Statistical package for social sciences package 21. Results were presented as mean±standard deviation for continuous variables and percentages for categorical variables. Tables were also used to illustrate results where appropriate. Continuous variables were compared by the students't-test and Mann-Whitney U test. Categorical parameters were compared with the chi-square test and two tailed fisher's exact test as appropriate. A p-value of less than 0.05 was considered statistically significant.

3. RESULTS

The study consisted of 90 males (60%) and 60 females (40%) with male to female ratio of 1.5:1. The age range of the patients was 22-80 years with mean age of 45.1±11.9 years. The age and sex distribution of the patients are shown in Table 1. The mean duration of CKD was 17.2±15.5 months with a range of 3 to 120 months. Eighty two (54.7%) patients were on haemodialysis. The median duration of haemodialysis was 6.3 months. Among the patients on haemodialysis, kt/v was less than 1.2 in 77 (93.9%) and ≥1.2 in 5 (6.1%) of the patients. The prevalence of CKD-MBD in this study was 55.3%. Of this 61 (73.5%) had low turnover bone disease while 22 (26.5%) had high turnover bone disease (Tables 2 and 3 repectively). There was a significant difference in the prevalence and pattern of CKD-MBD across various stages of CKD ($p<0.001$). (Tables 4 and 5 respectively). There was no statistical significant difference on comparison of CKD-MBD and non CKD-MBD by socio-demographic characteristics (Table 6). A significant difference

Table 1. Age and sex distribution of the study subjects

Age (years)	Frequency n=150 (%)	Male n=90 (%)	Female n=60 (%)
≤ 30	16 (10.7)	9 (6)	7(4.7)
31-40	40 (26.7)	24(16)	16(10.6)
41-50	50 (33.3)	18(12)	32(21.3)
51-60	26 (17.3)	22(14.6)	4(2.7)
>60	18 (12.0)	17(11.4)	1(0.7)
Total	**150(100)**	**90(60)**	**60(40)**

Table 2. Prevalence and pattern of ckd-mbd among the study population

Study population	Frequency n=150	Percentage (%)
CKD-MBD	83	55.3
NO CKD-MBD	67	44.7

Table 3. Pattern of CKD-MBD in study subjects

Pattern of CKD-MBD	n=83	(%)
Low turnover bone disease	61	73.5
High turnover bone disease	22	26.5

Table 4. Prevalence of CKD-MBD across various stages of CKD

All stages of CKD n =150(%)	CKD-MBD n =83(%)	No CKD-MBD n =67(%)	Chi-square (p-value)
Stage 3 n=13(8.7)	0(0)	13(19.4)	27.08 < 0.001*
Stage 4 n=29(19.3)	10(12)	19(28.4)	
Stage 5 n=26(17.3)	16(19.3)	10(14.9)	
Stage 5D n=82(54.7)	57(68.7)	25(37.3)	

**Statistically significant*

Table 5. Pattern of CKD-MBD across various stages of CKD

Stages of chronic kidney disease	Low-turnover bone disease n=61(%)	High-turnover bone disease n=22(%)	Chi-square (p-value)
Stage 4 (n=10)	4 (6.6)	6 (27.3)	
Stage 5 (n=16)	2 (3.3)	14 (63.6)	51.79
Stage 5D (n=57)	55(90.1)	2(9.1)	<0.001*

** Statistically significant*

Table 6. Prevalence of CKD-MBD By sociodemographic characteristics

Socio-demographics	CKD-MBD n=83(%)	No MBD n=67(%)	Chi-square	p-value
Age group				
≤30	9 (10.8)	7 (10.4)		
31-40	20 (24.1)	20 (29.9)		
41-50	25 (30.1)	25 (37.3)	4.354	0.36
51-60	19 (22.9)	7 (10.4)		
>60	10 (12.0)	8 (11.9)		
Gender				
Males	51 (61.4)	39 (58.2)		
Females	32 (38.6)	28 (41.8)	0.162	0.687
Duration of illness				
3 to 24 months	71 (85.5)	55 (82.1)		
25 to 48 months	10 (12.0)	11 (16.4)		
49 to 72 months	2 (2.4)	0 (0.00)	-	0.39**
73 to 96 month	0 (0.00)	0 (0.00)		
97 to 120 months	0 (0.0)	1 (1.5)		

***=Fisher's exact test*

was observed in the pattern of CKD-MBD across the various age groups (p=0.014) as shown in Table 7.

4. DISCUSSION

The study population was made up of more male than females with male to female ratio of 1.5:1. There was male preponderance in both CKD-MBD and non CKD-MBD patients, though this difference was not statistically significant.This male preponderance in this study is consistent with the findings of the work done in Benin by Onyemekeihia [12] that reported 58% of male, and that of Sanusi, et al. [13]. The males are the breadwinners and by the nature of their lifestyle and occupation they are constantly being exposed to stress and more likely to adopt a western type of diet with consumption of high cholesterol foods, use of alcohol and smoking resulting to increased prevalence of various risk factors of CKD such as hypertension, diabetes and hyperlipidemia, and therefore eventually prone to subsequent complications of

CKD including CKD-MBD. Male preponderance may also reflect the fact that females are less likely than male to go to the hospital for cultural and financial reasons rather than a difference in incidence [14]. About 80.7% of the study population were 50 years and below, the economically active age group. Thus the study population consisted of mainly young and middle age patients and therefore preponderance of young and middle age among CKD-MBD patients. This is similar to findings from other developing countries but contrasts with that seen in developed countries [15-17].

There is a high prevalence of infections/ infestation and these contributes to the development of chronic glomerulonephritis which is the leading cause of CKD in developing countries among young individuals [18]. The second commonest cause of CKD in the tropics is hypertension and this tends to run a more aggressive course in blacks [19]. Diabetic nephropathy occurs at a younger age and is more aggressive in blacks than in Caucasian population [20]. The prevalence of HIV associated nephropathy is also high in developing world and the prevalence is higher among the younger population [21].

Table 7. Pattern of CKD-MBD by socio-demographic characteristics

Socio-demographics	Low turnover bone disease n=61(%)	High turnover bone disease n=22(%)	Chi-square	p-value
Age group				
≤30	7 (11.5)	2 (9.1)		
31-40	18 (29.5)	2 (9.1)	-	0.014**
41-50	20 (32.8)	5 (22.7)		
51-60	8 (13.1)	11 (50.0)		
>60	8 (13.1)	2 (9.1)		
Gender				
Males	35 (57.4)	16 (72.7)		
Females	26 (42.6)	6 (27.3)	1.61	0.205
Duration of illness				
3 to 24 months	52(85.2)	19 (86.4)		
25 to 48 months	7 (11.5)	3 (13.6)	-	1.00**
49 to 72 months	2 (3.3)	0 (0.0)		

***= Fisher's exact test*

Table 8. Comparison of biochemical markers of CKD-MBD across various stages of CKD

Biochemical markers	CKD–MBD (n=83)			F – test	p-value
	Stage 4 n=10 mean±SD	Stage 5 n=16 mean±SD	Stage 5D n=57 mean±SD		
PTH(pg/ml)	86.47±81.36	190.33±167.37	225.51±95.40	1.447	0.241
Calcium(mmol/L)	2.41 ±0.341	2.34± 0.46	2.65 ±0.83	1.355	0.264
Phosphate(mmol/L)	1.48 ±0.21	1.171 ±0.43	2.65 ±0.83	0.791	0.457
ALP(IU/L)	101.90 ±57.39	112.5±47.53	109.64 ±71.75	0.082	0.922
Ca x PO_4($mmol^2/L^2$)	3.67 ±0.72	3.92 ±0.93	4.18 ±1.43	0.797	0.454

Table 9. Comparison of biochemical markers of CKD-MBD among CKD-MBD and non CKD-MBD

Biochemical markers	CKD-MBD n=83 mean±SD	No CKD-MBD n=67 mean±SD	t-test	p-value	95% C.I
PTH(pg/ml)**	205.06±112.6	123.08 ±120.99	-	0.205	-
Calcium(mmol/L)	2.56 ±0.73	2.32 ±0.46	2.28	0.024*	0.03 to 0.44
Phosphate(mmol/L)	1.63 ±0.46	1.54 ±0.57	1.01	0.31	-0.08 to 0.25
ALP(IU/L)	109.26 ±65.57	108.13 ±51.84	0.11	0.91	-18.29 to 20.55
Ca xPO_4 ($mmol^2/L^2$)	4.07 ±1.28	3.52 ±1.37	2.50	0.01*	0.11 to 0.97

**Statistically significant*

***PTH is not normally distributed, therefore was analyzed with Mann-Whitney U test*

Table 10. Comparison of biochemical markers of CKD-MBD among low turnover and high turnover bone disease

Biochemical markers	Low turnover n=61 mean±SD	Highturn over n=22 mean±SD	t-test	(p-value)	95% C.I
PTH (pg/ml)**	48.89±35.63	340.66±289.32	-	0.001*	-
calcium(mmol/L)	2.68±0.79	2.24±0.37	3.39	0.001*	0.13 to 0.18
Phosphate(mmol/L)	1.61±0.47	1.67±0.46	-0.50	0.62	0.11 to -0.29
ALP(IU/L)	109.40 ±69.99	108.86 ±52.80	0.03	0.97	14.39 to -28.37
Ca x PO_4 ($mmol^2/L^2$)	4.20±1.39	3.68±0.82	1.64	0.11	0.32 to -0.11

**Statistically significant*

***PTH is not normally distributed, therefore was analyzed using Mann-Whitney U test*

The duration of chronic kidney disease is 24 months or less in the majority of those with CKD-MBD in this study. This high prevalence of CKD-MBD among CKD patients with short duration of illness is consistent with findings in other studies from Africa [22,23] This could be due to the fact that many CKD patients in our environment do not sustain treatment for long periods of time due to poverty and therefore do not live long enough for these manifestations to develop. The prevalence of CKD-MBD in this study was high as reported by other investigations in Nigeria [21,22]. This high frequency of CKD-MBD may be explained by a poor control of phosphate balance due to inability to have adequate dialysis. Most of our patients are poor and majority of them had dialysis less than three times a week.

Over the past few years, the spectrum of CKD-MBD has changed, and low turnover bone disease has been increasingly recognized. This study found low turnover bone disease in the majority of the patients. This is in agreement with the findings of reports from Ile-Ife where low turnover bone disease was found in the majority of the study population [22]. Factors associated with low turnover bone disease may include short dialysis history, male gender and malnutrition [23]. However, these findings were in contrast to that of Onyemekeihie [12] in Benin who observed high turnover bone disease in majority of his patients; PTH was not assessed and alkaline phosphatase was used as surrogate for PTH.

A Libyan study reported high turnover bone disease and low turnover bone disease in 28.9% and 27.1% of their patients respectively while in Senegal the prevalence of high turnover and low turnover bone disease was 48.3% and 17.8% respectively [19-20]. These disparities observed in the pattern of CKD-MBD compared to our study may be due to their smaller sample size and the exclusion of non dialysis patients in their studies. Agarwal, et al. [24] found high turnover bone disease in 57.8% of patients with CKD-MBD consistently with London, et al. [25] who observed prevalence of high turnover bone disease in 60% of their patients with CKD-MBD. This is in complete contrast to our findings. As reported by Jabber, et al. differences in dietary habits, body composition, and racial and genetic background, influences the exhibition of different pattern of abnormalities in CKD-MBD, while estimating the intact PTH (iPTH), total deoxypyridinoline (tDPD), BAP and 25 (OH) vitamin D levels, and measured BMD in a cohort of Indian CKD patients [25]. Agarwal, et al. [24] and London, et al. [25], defined hyperparathyroidism as PTH > 300pg/ml for CKD stage 5 using K/DOQI guideline. However hyperparathyroidism was defined in this study using recent KDIGO guideline (>9x the upper limit of normal for assay used, for CKD stage 5D) [25].

Thus, the high prevalence of low turnover bone disease and low prevalence of high turnover bone diseases in dialysis patients is of concern. Alkaline phosphatase also signifies high turnover bone disease when elevated. In this study, the mean value of alkaline phosphatase for dialysis patients was higher compared to non dialysis patients and this may suggest that more patients in CKD stage 5D may have high turnover bone disease than suggested by the high cutoff value of PTH in this study. Indeed, KDIGO recommended that treatment of CKD-MBD be based on trend in changes of biochemical parameters rather than on abnormalities at a single point in time [25].

5. CONCLUSION

This study revealed that CKD-MBD is common among patients with CKD in our environment and low turnover bone disease was the most common type of mineral bone disease in these CKD patients.

6. LIMITATIONS

In Africa, studies of CKD-MBD are sparse partly due to limitations in laboratory facilities. There are however few studies on components of CKD-MBD such as secondary hyperparathyroidism, serum calcium, serum phosphate levels and vitamin D.

CONSENT AND ETHICAL APPROVAL

As per international standard or university standard guideline participant consent and ethical approval has been collected and preserved by the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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