Prevalence of CKD-MBD in pre-dialysis patients using biochemical markers in Enugu, South-East Nigeria

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Abstract

Background: As kidney function declines, there is a progressive deterioration in mineral homeostasis with disruption of normal serum and tissue concentration of phosphorus and calcium, and changes in circulating levels of hormones-parathyroid hormone (PTH), calcitriol (1,25(OH)2 D), and Fibroblast growth factor-23 (FGF-23).

Objective: This study was aimed at determining the prevalence of markers of CKD-MBD in pre-dialysis patients.

Methods: We evaluated consecutively 168 subjects made up of 85 CKD patients and 83 healthy controls, who were attending the renal clinics and medical outpatient of University of Nigeria Teaching Hospital, Enugu. GFR was estimated and serum calcium, phosphorus, alkaline phosphatase, PTH, and 25(OH) D levels assayed.

Results: The prevalence of various mineral bone disease abnormalities were 70% hyper-phosphatemia, 85% hyper-parathyroidism, and 100% low levels of 25 (OH) D among the patients. Estimated GFR correlated negatively with both serum phosphorus, and PTH. Age of the patients ranged from18-76 years with a male to female ratio of 1.7:1. Chronic Glomerulonephritis (CGN), hypertension and diabetes mellitus caused CKD in 75% of the patients. There was no significant decrease in serum calcium levels of patients compared to controls. The patients did not have pathologically raised alkaline phosphatase, although their mean level was significantly higher than that of the control group.

Conclusion: Low 25 (OH) D levels (insufficiency/deficiency), hyperparathyroidism, and hyper-phosphatemia were the obvious markers of CKD-MBD in our pre-dialysis patients. These should be evaluated at presentation in these patients.

Key words: CKD-MBD, Predialysis, biochemical markers, Southeast Nigeria.

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Introduction

Chronic kidney disease (CKD) is an international public health problem affecting 5-10% of the world population.[1] It is classified according to severity from stages 1-5. Chronic kidney disease mineral bone disorder (CKD-MBD) is a systemic disorder. The broadened concept of CKD-MBD, includes abnormal mineral metabolism (the focus of this study), abnormalities in bone morphology and extra skeletal calcifications. These are closely inter-related and together make major contribution to morbidity, and mortality of patients with CKD.

The metabolic changes that occur in patients with CKD have a profound influence on mineral and bone metabolism. CKD results in altered levels of serum phosphorus, calcium, vitamin D, PTH, and Fibroblast Growth Factor-23 (FGF-23). Beginning in CKD stage 3, the ability of the kidneys to excrete a phosphorus load is diminished leading to raised phosphorus and PTH, and decreased 1,25 $(OH)_2D$ levels associated with elevated FGF-23 levels. The conversion of 25 (OH) D to 1, 25 $(OH)_2D$ is impaired, reducing intestinal calcium absorption. The kidneys fail to respond adequately to PTH which normally promotes phosphaturia and calcium reabsorption; and to FGF-23 which enhances phosphate excretion. There is in addition, at the tissue level a down regulation of vitamin D receptors and resistance to the action of PTH.

Bone abnormalities are found almost universally in patients with CKD stage 5 and in majority of patients with stages 3-5.[2] The biochemical abnormalities form the primary routine indicators in management of CKD-MBD, though there are limitations. Diagnosis for CKD-MBD using the invasive bone biopsy for bone turnover, mineralization, and volume; or arterial, valvular or coronary calcification score using gold standards such as electron beam CT, or multi-slice CT; or

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measuring bone mineral density (BMD) by Z score of dual energy X ray absorptiometry (DXA), ultrasound or echocardiography to assess tissue calcification, are not necessary in routine clinical practice especially in a developing country as ours. Therefore, changes in serum calcium, phosphorus, PTH, 25 (OH) D, and total alkaline phosphatase were used in this work to assess CKD-MBD in the study group. These changes contribute to increased cardiovascular mortality in affected patients. It is also important to quantify MBD as a complication of CKD even before renal replacement therapy (RRT) and during treatment. Interventions are aimed at controlling hyperphosphataemia, hyperparathyroidism, vitamin D deficiency among others, and include phosphate binding, supplementation with vitamin D analogues, use of calcimimetics, parathyroidectomy, and even kidney transplant.

Their pattern in pre-dialysis and especially in black CKD patients in developing countries is not clear. This study, using the biochemical methods explored the prevalence of these markers in black Ibo patients of South Eastern Nigeria.

Method

Eighty five adult CKD patients (in stages 3-5) and 83 healthy control subjects presenting for the first time at the renal clinic and medical outpatient clinic of the University of Nigeria Teaching Hospital (UNTH), Ituku/Ozalla, Enugu, between December 2010 and May 2011, were recruited consecutively for the study.

Ethical clearance was obtained from Ethics Committee of UNTH, Enugu.

All subjects were physically assessed, and had serum PTH, 25 (OH) D, Calcium, Phosphorus, total alkaline phosphatase, Bicarbonate, Potassium, and Creatinine measured. Glomerular filtration rate (eGFR) was estimated based on 4 variable MDRD formula.

PTH and 25 (OH) D were analyzed using ELISA based International Immuno-Diagnostics-USA; PTH EIA (Lot # 1386) and Vitamin D 25 (OH) EIA (Lot K2110-100722) kits for iPTH and 25 (OH) D assays respectively. The measurement of serum 25 (OH) D is regarded as the best measure of vitamin D status, because of its long half-life of approximately 3 weeks i.e. the storage form of the vitamin. The active form 1, 25 (OH)2D3(-Calcitriol) has short half-life of 4-6 hours.

Excluded were patients on dialysis, taking phosphate binders, calcium supplements, or vitamin D analogues; or having chronic liver disease, and patients with primary hyperparathyroidism or parathyroid surgery.

Statistical analysis

Analysis was performed using Statistical Package for Social Sciences (SPSS) version 20 and results were presented as means and standard deviation. Student t test was used to compare patients' variables with controls. X2 for trend, Spearman's coefficient of correlation as well as multiple regression analysis were used to assess correlations of parameters. A p value of < 0.05 was considered significant.

Results

The baseline characteristics of the study population were summarized in Table 1. There were 85 patients and 83 controls. Majority, 63.1% were males. The subjects were aged between 18 and 86 years. There was no difference between the mean age, body mass index, and serum calcium level of the patients and controls. The weight of the controls was significantly higher than the patients. The mean systolic blood pressure (SBP), diastolic blood pressure (DBP), serum creatinine, serum potassium, phosphate, alkaline phosphatase, and parathyroid hormone were significantly higher in the patients compared to controls. On the other hand, eGFR, serum bicarbonate and 25(OH) D levels were significantly lower in the patients compared to controls. The median serum PTH and 25 (OH) D levels of the patients were 196.8pg/ml and 25nmol/l respectively.

Table 1: Characteristics of study population

Variable	Mean, (Median)		p value	95% CI
	Patients: N=85	Controls: N=83		
Age (yrs)	48.0±15	44.7±11.4	NS	
Weight (kg)	65.2±10.8	73.3±10.6	<0.001	-11.39 - - 4.83
BMI (kg/m²)	24.5±3.4	25.5±4.4	NS	
SBP (mmHg)	154.1±31.7	120.2±8.8	<0.001	26.7- 41.0
DBP (mmHg)	92.7±19.1	76.5±7.6	<0.001	11.7- 20.6
SCr (μmol/l)	351.9±172.7	83.6±16.4	<0.001	230.8-305.9
eGFR (ml/min/1.73m²)	24.4±0.30	106.0±27.7	<0.001	-88.2- -75.1
HCO_3 (mmol/l)	20.3±5.1	25.9±2.0	<0.001	-6.8- - 4.4
K (mmol/l)	4.9±0.84	3.8±0.34	<0.001	0.88 - 1.3
Ca (mmol/l)	2.42±0.30	2.49±0.10	NS	
PO_4	1.87±0.70	1.14±0.22	<0.001	0.58 - 0.90
ALP (U/l)	78.7±33.1	66.9±18.8	0.005	3.58 - 20.0
PTH (pg/ml)	318.6±276.5 (196.8)	26.6±17.2	<0.001	231.9 - 351.7
25(OH)D(nmol/l)	28.4±11.3 (25)	93.2±31.6	<0.001	-72.0 - -57.7

The various features of the patients are shown in Table 2. Chronic Glomerulonephritis, hypertension and Diabetes mellitus were the main causes of chronic kidney disease. Also, 25.9%, 50.6%, and 23.5% were in stages 3, 4, and 5 CKD respectively. While 55.3% had acidosis , 41.2% had hyperkalemia.

Table 2: Various characteristics of the Patients.

Variables	n(%)	Variables	n(%)	Variables	n(%)
Etiology of CKD		**Clinical features**		**Laboratory parameters**	
*CGN	27(31.8)	Pallor	71(83.5)	Bicarbonate<22	
*HTN	20(23.5)	Edema	60(70.6)	(mmol/L)	47(55.3)
*DM	17(20)	Hypertension	62(72.9)	Potassium>5	
*UO	7(8.2)	* S-3 CKD	22(25.6)	(meq/L)	35(41.2)
UNKNOWN	6(7)	*S-4 CKD	43(50.6)	Calcium<2.1	
*ADPKD	3(3.5)	*S-5 CKD	20(23.5)	(mmol/L)	5(5.9)
*SCN	2(2.4)			Phosphorous>1.49	
H+N	2(2.4)			(mg/dl)	59(69.4)
				ALP>95iu/L	21(24.7)
				PTH>65	72(84.7)
				Vit. D deficiency	53(62.4)
				Vit. D insufficiency	32(37.6

Key: *CGN-Chronic Glomerulonephritis, HTN- hypertension, DM-diabetes mellitus, UO-obstructive uropathy, ADPKD-autosomal dominant polycystic kidney disease, SCN- sickle cell nephropathy, H+N-HIV with nephropathy, S-3, 4, 5 - stages 3, 4, 5 CKD.

For the markers of CKD-MBD, all patients had low levels of 25 (OH) D, 62.4% had vitamin D deficiency, while 37.6% had insufficient vitamin D. 84.7% of the patients had hyperparathyroidism, 69.4% hyperphosphataemia, 24.7% high levels of alkaline phosphatase, while only 5.9% had hypocalcaemia. No patient had combination of hypocalcaemia, hyperphosphataemia, high alkaline phosphatase, low vitamin D, and hyperparathyroidism. Only 3 patients (3.5%) had combined hypocalcaemia, hyperphosphataemia, low vitamin D levels, and hyperparathyroidism, while 15.3% had combined high alkaline phosphatase levels with high phosphorus, high PTH, and low vitamin D levels. 63.5% had combined hyperphosphataemia, hyperparathyroidism and low vitamin D levels and even higher numbers, 84.7% had hyperparathyroidism and low 25 (OH) D levels.

There was a progressive increase observed in serum potassium, phosphorus, and PTH from stage 3 to 5 CKD, while the converse was noted for serum bicarbonate and 25 (OH)D(table 2).

Table 3 showed the correlation values of serum PTH and serum phosphorous levels with various variables in the patients. Serum PTH levels correlated positively with diastolic BP, serum potassium and phosphorus, but negatively with eGFR, and serum bicarbonate levels. Upon correcting for eGFR (β =-0.318, p =0.011), and diastolic BP (β =0.252, p =0.012) with multiple regression analysis, the observed correlation disappeared. Serum phosphorus correlated negatively with eGFR and serum bicarbonate but positively with serum potassium. However, on multiple regression, only eGFR (β =-0.449, p =0.0001), and serum Potassium (β =0.222, p =0.019) demonstrated significant correlation. 25(OH) D did not correlate with other parameters.

Table 3: Correlations of serum PTH and serum phosphorous with various variables.

Correlations for PTH		
Variable	Coefficients (r)	p value
DBP	0.289	0.007
K	0.281	0.009
PO_4	0.386	0.0001
eGFR	-0.533	0.0001
HCO_3	-0.293	0.007
Correlations for PO_4		
K	0.399	0.019
eGFR	-0.643	0.0001
HCO_3	-0.468	0.0001

Table 4 showed the prevalence of various vitamin D abnormalities in the different stages of CKD. Vitamin D deficiency worsened as CKD stage increased. However, prevalence of vitamin D insufficiency (relative higher Vitamin D levels) appeared to fall with worsening renal function. The changing pattern of vitamin D insufficiency and deficiency with increasing CKD stage was assessed using X^2 test for trend.

Table 4: Prevalence of 25 (OH) D levels in various CKD stages.

25 (OH) D levels	CKD 3.(%)	CKD4.(%)	CKD5.(%)	Total
>75nmol/l(Normal)	0	0	0	0
30-75 ,, (Insufficient)	54.5	37.2	20	37.6
<30 ,, (deficient)	45.5	62.8	80	62.4
Total	100	100	100	100

This showed a strong evidence that the odds of vitamin D deficiency increased significantly with increasing CKD stage (table 5).

Table 5: X^2 test for trend of 25 (OH) D in various CKD stages.

25(OH) D status value	Stage 3	Stage 4	Stage 5	Total	X^2 for trend	p
Deficiency	10(45.5%)	27(62.8%)	16(80%)	53(62.4%)		
Insufficiency	12(54.5%)	16(37.2%)	4(20%)	32(37.6%)		
Total	22(100%)	43(100%)	20(100%)	85(100%)	19.97	<0.001*

Discussion

The individuals studied were all Ibo Nigerians, of the black race: an adverse risk factor for kidney diseases.[3] They were mostly middle aged as against the geriatric CKD patients seen in developed countries. Studies in the past in Nigeria, and in most sub- Saharan African countries, showed that kidney diseases occur in relatively younger age group.[4,5,6] Most of the patients had pallor (83.5%) even at stage 3 disease, most also had peripheral edema (70.6%) and half of them had other symptoms of uremia at first presentation. Haemoglobin estimation would have given a more objective estimate of those that are pale. However, this was not included in our protocol as it has no direct bearing on the objectives of the study. Majority of our patients present late, (50.6%) presented at stage 4 in this study. Late presentations/ referrals contributed to poor outcomes in our CKD patients. This finding is similar to other studies that noted late presentation and severe illness at first presentation.[5,7,8,9] The predominant causes of ESRD in Africa are essentially CGN and hypertension, with both sharing the lead in most study series.[6] This study found CGN the predominant cause of CKD. However, a rise of the percentage contribution of diabetes has been noted in various centers, consistent with urbanization and improvement in the living standards in African countries.[10] Diabetes was the 3rd most common cause of CKD in this study, accounting for 20% of cases.

Markers of CKD-MBD

Studies have shown that decreases in calcitriol levels occurred in patients with early CKD and preceded increases in serum PTH levels.[11] These are in agreement with this study in which none of the patients had sufficiency of 25 (OH) D (from FGF-23 inhibition), while about 15% of them had normal levels of PTH. Though most of these patients (76%) were not in end stage renal disease, there was still a high prevalence of these markers of CKD-MBD. This may explain the high mortality rates even in earlier stages of CKD. This study showed low levels of vitamin D, with high rates of hyperparathyroidism and hyperphosphataemia.

In SEEK study[12], where pre-dialysis patients were similarly studied, it was found that blacks had significantly lower levels of 25(OH) D but higher levels of calcium, phosphorus and PTH. This high secondary hyperparathyroidism (SHPT) and 25(OH) D deficiency occurs early in the course of CKD, irrespective of age, gender, diabetes mellitus, eGFR, calcium and phosphorus. Some studies have suggested that this high prevalence might be due to blacks having reduced calcium sensing capacity,[13] or due to greater skeletal resistance to PTH among blacks.[14]

The patients and controls had normal mean serum calcium levels which were not significantly different between them. Again, in the CHOICE study,[15] serum calcium level at the commencement of dialysis was 2.34 mmol/L, similar to values in our study. Llach et al,[16] also found from their work that serum calcium, phosphorus, and ALP are usually normal, until late in the course of CKD. Our study like the one by Gutierrez et al[12] has shown that raised PTH and phosphorus levels, do occur with normal calcium and low vitamin D levels, especially among blacks. In-fact calcium is said to be frequently but not consistently abnormal with reduced GFR.[17] Since the results in our study are cross sectional, causal relationships between dependent variables (kidney function) and independent variables (PTH, Vitamin D metabolites, calcium and phosphorous) cannot be defined. No longitudinal data has been reported here,

thus relationships between the variables and different eGFR levels may change over time in different individuals.

There was a 69.4% hyperphosphataemia in this study. This high prevalence is similar to those found in Benin, Nigeria by Onyemekeihia et al[18] (79%) and Sanusi et al[19] at Ife, Nigeria (60%). The high prevalence of hyperphosphataemia occurs despite the fact that Africans are likely to have lower daily intake of dairy products and other sources of calcium and phosphorus.[12] This might be due to renal resistance to the phosphaturic stimulus of raised PTH seen in blacks.[17]

There is currently a phosphate-centric paradigm for the pathophysiology and therapy of CKD. In our environment, serum phosphorus is routinely assayed in patients. There is, the tendency to treat hyperphosphataemia with available calcium containing phosphate binders inaddition to vitamin D analogues. Also patients are dialyzed with high calcium containing dialysate. Without concomitant assays of serum PTH, vitamin D, and FGF-23, this practice no longer enjoys a favorable review, and predisposes patients to Adynamic bone disease (ABD) which worsens vascular calcification type of MBD as noted, in the work by Sanusi et al.[18] Also, calcium in these compounds has a stimulatory effect on the secretion of FGF-23 which further sustains the MBD. This however is not the case with Sevelamer or Lanthanum carbonate.[20]

Though ALP levels, were significantly higher in patients than controls, absolutely high levels of total ALP (>95U/L) were insignificant in both groups and showed that this affordable assay is not a valid surrogate marker for CKD-MBD in pre-dialysis patients. The bone fraction (bALP), however might be. Raised ALP has been shown to have a linear and incremental association with both all cause and cardiovascular disease mortality[21] because it reduces the pyrophosphate/phosphate ratio. Pyrophosphate is an inhibitor of vascular calcification.

All patients in this study had low 25(OH) D levels. The study showed that majority of the patients (62.4%) had 25 (OH) D deficiency, worse in stage 5 than 3, and the remaining 37.6% had insufficiency, more in stage 3 than 5. The progressive deficiency in the stages was found to be significant by X2 for trend. The Gutierrez et al[12] study found low levels of 25(OH) D as well, in Blacks. Other studies done in USA[22,23] and UK[24] showed similar findings. Wolf et al[23] found 78% of patients they studied, had low 25(OH) D i.e. <75nmo/L, with blacks being more deficient than whites. Gonzalez et al,[22] found that 86% of 43 CKD patients they studied had inadequate 25(OH) vitamin D. Kosmadakis et al,[24] studied stages 3 and 4 CKD patients, found 25(OH) D insufficiency with values not much different in the 2 stages (39.8±24 versus 38.3±22.3nmol/L). This feature was similar to our findings. The finding of low 25 (OH) D in our study is significant considering the increased all-cause mortality noted in patients with deficiency as was documented by Mehrota et al.[25] They studied 3011 predialysis patients, found that those with 25(OH) D levels <37.5nmol/L had increased risk for all-cause mortality, compared to those with vitamin D sufficiency.

Levin et al,[11] found a high SHPT prevalence of 56% in mainly stages 3 and 4 pre-dialysis patients. The mean PTH levels were noted to be 71.7±59.08, and 185.5±159.88pg/ml respectively. They did not study stage 5 disease patients. The higher prevalence and higher values in our study could be explained by various factors. The patients in this study were younger and purely blacks and both factors have been documented as causes of high SHPT.[26] Furthermore, our study also included stage 5 CKD patients. PTH level > 300pg/ml is associated with Blacks, long duration of ESRD and varies inversely with age.[27] Similar to this index study, Levin el al[11] found no correlation between hyperparathyroidism and serum calcium, and ALP especially in stage 3 disease. This underscores the need to assay PTH levels for diagnosis of MBD early in CKD as calcium, ALP, and phosphorus may be normal even with elevated PTH.

It was instructive that as expected, both hyperparathyroidism and hyperphosphataemia correlated inversely with eGFR, even in multiple regression analysis. However, that vitamin D levels did not correlate with eGFR could be explained by its inhibition caused early by increased FGF-23 in the course of MBD. Unfortunately FGF-23 was not assayed in the study.

Conclusion

The findings of this study suggest that MBD as a complication is common in our CKD patients. Raised PTH, low 25(OH) D, and raised phosphorus levels were the most prevalent markers, even in this population of

pre-dialysis patients. Total alkaline phosphatase was not found to be a good surrogate marker for CKD-MBD in our predialysis patient population. It did not correlate with early markers - serum PTH and vitamin D. This cheap MBD marker may therefore not be ideal in pre-dialysis CKD patients. Majority of our patients presented, or were referred late. Clinical features of MBD in CKD were poor guides to the presence of MBD in our pre-dialysis patients. It therefore may not be proper for practitioners to wait for symptoms and signs to manifest.

Limitations of the study

Due to the cross-sectional nature of this study, patients were assessed only at presentation. There is a chance of changes in CKD stages estimation on further patient follow up. There are also diurnal variations in the metabolites assayed, some variations occur with meals, and different coefficients of variation of assays exist. Bone fraction (bALP) ALP and FGF-23 levels could not be assayed in this study.

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