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ORIGINAL ARTICLE

LEVEL OF SERUM PARATHYROID, CALCIUM, PHOSPHATE AND VITAMIN D AND THEIR CORRELATION IN OCCURRENCE OF MINERAL BONE DISORDER IN CKD PATIENT ADMITTED IN ADULT MEDICINE WARD OF A TERTIARY HOSPITAL IN BANGLADESH

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Abstract:

Background: *Chronic kidney disease (CKD) is a global health problem associated with increased risks of morbidity, premature mortality, and/or decreased quality of life. CKD is usually asymptomatic until progressive damage occurs and produce multiple symptoms and signs. Progressive loss of kidney function in CKD leads to reduced production of 1-á-(OH) 2-D3 (1, 25-dihydroxyvitamin D; calcitriol) and abnormal mineral homeostasis. The aim of the study was planned to assess the mineral and bone disorder in CKD patients admitted in a tertiary care hospital.* ***Methods:*** *A Cross sectional observational study was performed at a tertiary care centre. 100 cases of diagnosed Chronic Kidney Disease patients in indoor of department of Nephrology and Medicine of Sir Salimullah Medical College Mitford hospital from March 2018 to August 2018 were included in this study.* ***Results:*** *Majority of the patients (60%) were of age between 46 and 65 years. 31% of the study population were older than 65 years. 72% of the study population were male and 28% were female. Diabetic nephropathy was the leading cause of CKD, affecting 36% of the study population. Hypertension was the likely cause in 26% of the subjects. Obstructive uropathy and chronic glomerulonephritis affected 7% and 5% of the subjects respectively. There was one (1%) patient with ADPKD, and in 25% of the cases no causative factor was identified. Most (40%) of the study subjects were in the stage 3 of CKD. 34% & 26% of the patients were in the stage 5 & 4 respectively. We did not find any patient with normal vitamin D level. 10% of the patients were in the insufficient range and 90% of the study subjects were deficient in vitamin D. Hyperparathyroidism was prevalent in 75% of the study subjects. 79% of the patients had elevated serum phosphate levels. Hypocalcemia was found in 49% of the patients. 33% of the patients had hyperkalemia during admission. Hyperphosphatasia was prevalent in 39% of the study subjects. However, bone fraction of the ALP was not tested. Among stages 3B, 4 and 5 CKD patients, there were 2% patients in each group that were insufficient in vitamin D. Majority (32% in stage 5, 24% each in stages 3B and 4) were deficient in vitamin D. Deficiency was also prevalent in earlier stages of CKD (10% patients in stage 3A). The difference was statistically significant, that is, the later the stage of CKD the greater*

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the prevalence of vitamin D deficiency was. All the patients in stage 5 and 4 (34% and 26% respectively) had hyperparathyroidism. 0% and 15% of the patients in stages 3A and 3B respectively had hyperparathyroidism. The difference between groups was statistically significant. Serum calcium level correlated well with the stage of CKD. Most of the patients in stage 5 were hypocalcemic (32 among 34). Among the 39% of the total study population with hyperphosphatasia, 24%, 9% and 6% were in stages 5, 4 & 3B respectively. Which were statistically significant. 49% pf the patients had hyperparathyroidism with hypocalcemia, 26% of the patients had hyperparathyroidism and normal serum calcium levels. None of the patients had hypocalcemia and normal PTH level. Among the 90 patients with deficient vitamin D levels, 46 had hypocalcemia also. 70 patients with deficient vitamin D level also had high PTH level. The difference between groups which was statistically significant. ***Conclusion:*** *MBD is a common complication in our CKD patients. Raised PTH, low 25(OH) D, and raised phosphorus levels were the most prevalent markers. 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.*

Keywords: *CKD, hypocalcaemia, hyperphosphataemia, vitamin D deficiency, MBD, PTH*

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Introduction:

Chronic kidney disease (CKD) is a global public health burden[1] and important contributor to the overall non-communicable disease burden.[2] Although the reported prevalence of CKD varies widely across countries and regions 5–10% of world population are affected with this chronic disease and within the paucity of data the estimated prevalence of CKD in Bangladesh is 13.1%.[1,3,4]

CKD is a complex and progressive condition[4], characterized by either kidney damage or a decreased glomerular filtration rate (GFR) of less than 60 mL/min/1.73 m2 for 3 or more months[5-6], which is associated with serious consequences and increased risk of mortality.[2] Almost one million deaths were reported worldwide in 2013 due to CKD and labeled as the 13th leading cause of death.[7] Moreover, the societal direct and indirect costs of CKD and end-stage renal disease (ESRD) are substantial and increase throughout disease progression.[8] Economic cost associated with CKD is higher and developed countries dedicate more than 1% of the total health budget to the approximately 0.1% of the population that has ESRD.[9] However, ESRD management in low middle income countries is too expensive to meet the burden of treatment, such as, a study reported that 80% of kidney-failure patients could not afford treatment prior to 2003.[10] In addition, in Southeast Asia, renal replacement therapy (RRT) or dialysis costs are more than 10 times the annual per capita income of approximately USD 400, and health insurance coverage is low or non-existent for RRT/CKD treatment.[11]

CKD-associated mineral and bone disorders (also termed as metabolic bone disease, MBD) or CKD-MBD is one of the common complications, appeared with progression of CKD comprising the abnormalities in mineral and bone metabolism having both skeletal and extra skeletal consequences.[3,12] Progressive loss of kidney function leads to reduced production of calcitriol (1,25-dihydroxyvitamin D; active vitamin D), an imbalance in serum calcium (Ca) and phosphorus (P) levels and as well as changes in circulating levels of parathyroid hormone (PTH) and elevated fibroblast growth factor 23 (FGF23) levels).[13-14] In addition, multifactorial hypocalcemia and resistance to parathyroid hormone (PTH) can lead to prolonged[3] and excessive synthesis and secretion of PTH, eventually leading to development of secondary hyperparathyroidism and abnormalities in bone architecture (renal osteodystrophy)[14] which can be caused by either a high bone turnover state or a low bone turnover state. In pre-dialysis patients, high bone turnover bone disease is most prevalent. In contrast, low bone turnover predominates in dialysis patients.[15] On the other hand, three novel cardiovascular risk factors (hyperphosphatemia, vascular calcification, and elevated fibroblast growth factor 23 (FGF23) levels) have been discovered within

the CKD-MBD and their risk factor status confirmed in the general population.

So, CKD-associated mineral bone disorders significantly increase mortality in CKD patients[16] and patients on hemodialysis with high plasma phosphorus level have a 40% higher mortality rate.[17-19] Thus, the CKD-MBD manifests a disruption in the systems biology between the injured kidney, skeleton, and cardiovascular system that has a profoundly negative impact on survival in CKD.[20] However, despite high prevalence of mineral and bone disorders in CKD patients[4], there are limited data on CKD-MBD in our country. Therefore, the objective of this study is to find out the frequency of MBD in CKD patient admitted in adult Nephrology and Medicine ward of SirSalimullah Medical College Mitford Hospital.

Methods:

A hospital based cross sectional observational study was performed in indoor patientsin Nephrology and Medicine department of Sir Salimullah Medical College Mitford hospital. All the in patients (>18years) who were diagnosed with CKD stage 3-5 between March 2018 to August2018 were included in this study. History, clinical features, Investigation and treatment given was collected from the records. Patients on dialysis,on steroids and other drugs which have effect on bone,with primary bone diseases and patients who have kidney transplantwith were excluded from the A total of 100 patients were included in the study. Stage of CKD and MBD were determined by analyzing data and statistical analysis was done.

Statistical analysis:

Results for variables were expressed as means and percentages. To establish relationship in between variables chi-square analysis, student t test and Fisher's Exact test were done andthe p value of less than 0.05 was considered statistically significant. The SPSS 25 software was used for statistical analysis.

Results:

Demographic Characteristics:

Majority of the patients (60%) were of age between 46 and 65 years. 31% of the study population were older than 65 years.

72% of the study population were male and 28% were female.

Diabetic nephropathy was the leading cause of CKD, affecting 36% of the study population. Hypertension was the likely cause in 26% of the subjects. Obstructive uropathy and chronic glomerulonephritis affected 7% and 5% of the subjects respectively. There was one (1%) patient with ADPKD, and in 25% of the cases no causative factor was identified (Table-I).

Most (40%) of the study subjects were in the stage 3 of CKD. 34% & 26% of the patients were in the stage 5& 4 respectively (Table -II).

No patient with normal vitamin D level was found. 10% of the patients were in the insufficient range and 90% of the study subjects were deficient in vitamin D (Table-III).

Table-I

Distribution of study patients according to etiology of CKD (n = 100)

Aetiology	Frequency (%)
Chronic Glomerulonephritis	5(5)
Hypertension	26(26)
Diabetes Mellitus	36(36)
Obstructive uropathy	7(7)
Unknown	25(25)
ADPKD	1(1)

Table II

Distribution of study patients according to Stage of CKD (n = 100)

	Frequency	Percentage
Stage 3A	7	7.0
Stage 3B	33	33.0
Stage 4	26	26.0
Stage 5	34	34
Total	100	100

Table-III

Distribution of study patients according to Vitamin D level (n = 100)

	Frequency	Percentage	Cumulative percentage
Insufficient	10	10.0	10
Deficient	90	90.0	100
Total	100	100	

Hyperparathyroidism was prevalent in 75% of the study subjects (Table-IV).

79% of the patients had elevated serum phosphate levels (Table-V).

Table-IV

Distribution of study patients according to Serum PTH level (n = 100)

	Frequency	Percentage	Cumulative percentage
Normal	25	25.0	25
Hyperparathyroid	75	75.0	100
Total	100	100	

Table-V

Distribution of study patients according to Serum Phosphate (n = 100)

	Frequency	Percentage	Cumulative percentage
Normal	21	21.0	21
Hyperphosphataemia	79	79.0	100
Total	100	100	

Hypocalcemia was found in 49% of the patients (Table VI).

Among stages 3B, 4 and 5 CKD patients, there were 2% patients in each group that were insufficient in vitamin D. Majority (32% in stage 5, 24% each in stages 3B and 4) were deficient in vitamin D. Deficiency was also prevalent in earlier stages of CKD (10% patients in stage 3A). The difference was statistically significant, that is, the later the stage of CKD the greater the prevalence of vitamin D deficiency was Table VII.

All the patients in stage 5 and 4(34% and 26% respectively) had hyperparathyroidism. 0% and 15% of the patients in stages 3A and 3B respectively had hyperparathyroidism. The difference between groups was statistically significant (Table-VIII).

Table VI

Distribution of study patients according to Serum Calcium (n = 100)

	Frequency	Percentage	Cumulative percentage
Normal	51	51.0	51
Hypocalcaemia	49	49.0	100
Total	100	100	

Table VII

Correlation between Vitamin D level&Stage of CKD (n = 100)

		Stage 3A	Stage 3B	Stage 4	Stage 5	Total
Vitamin D	Insufficient	4	2	2	2	10
	Deficient	10	24	24	32	90
Total		14	26	26	34	100

Table VIII

Correlation between Serum PTH level & Stage of CKD (n = 100)

		Stage 3A	Stage 3B	Stage 4	Stage 5	Total
PTH	Normal	13	12	0	0	25
	Hyperparathyroid	0	15	26	34	75
Total		13	27	26	34	100

Chi-Square Tests

	Value	df	Asymptomatic Significance (2-sided)
Pearson Chi-Square	60.967[a]	4	.000

Table IX

Correlation between Serum calcium level&Stage of CKD (n = 100)

		Stage 3A	Stage 3B	Stage 4	Stage 5	Total
Ca	Normal	13	4	14	2	51
	Hypocalcaemia	1	22	12	32	49
Total		14	26	26	34	100

Chi-Square Tests

	Value df	df	Asymptomatic Significance (2-sided)
Pearson Chi-Square	49.637[a]	4	.000

Serum calcium level correlated well with the stage of CKD. Most of the patients in stage 5 were hypocalcemic (32 among 34).

Table X

Correlation between Serum ALP level&Stage of CKD (n = 100)

		Stage 3A	Stage 3B	Stage 4	Stage 5	Total
ALP	Normal	14	20	17	10	61
	Hyperphosphataesia	0	6	9	24	39
Total		14	26	26	34	100

Chi-Square Tests

	Value df	Df	Asymptomatic Significance (2-sided)
Pearson Chi-Square	26.192[a]	4	.000

Serum calcium level correlated well with the stage of CKD. Most of the patients in stage 5 were hypocalcemic (32 among 34).

Table-XI

Correlation between Serum PTH and Calcium levels (n = 100)

		Normal	Hypocalcaemia	Total
PTH	Normal	25	0	25
	Hyperparathyroid	26	49	75
Total		51	49	100

Chi-Square Tests

	Value df	Df	Asymptomatic Significance (2-sided)
Pearson Chi-Square	32.026[a]	1	.000

49% pf the patients had hyperparathyroidism with hypocalcemia, 26% of the patients had hyperparathyroidism and normal serum calcium levels. None of the patients had hypocalcemia and normal PTH level (Fig.-1).

Among the 90 patients with deficient vitamin D levels, 46 had hypocalcemia also 70 patients with deficient vitamin D level also had high PTH level. The difference between groups was statistically significant.

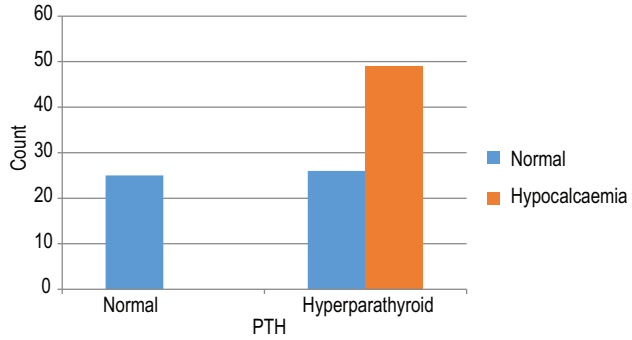

Fig.-1: *Bar Chart*

Table XII

Correlation between Serum 25(OH)D and Calcium levels (n = 100)

		Normal	Hypocalcaemia	Total
Vitamin D	Insufficient	7	3	10
	Deficient	44	46	90
Total		51	49	100

Chi-Square Tests

	Value	df	Df	Asymptomatic Significance (2-sided)
Pearson Chi-Square	1.605[a]		1	.205

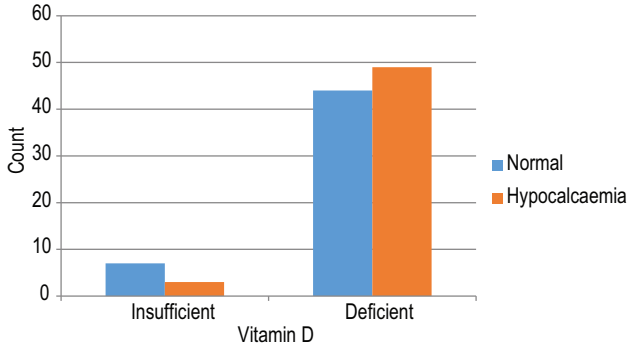

Fig.-2: *Bar Chart*

Table-XIII

Correlation between Serum 25(OH)D and PTH levels (n = 100)

		Normal	Hypocalcaemia	Total
Vitamin D	Insufficient	5	5	10
	Deficient	20	70	90
Total		25	75	100

Chi-Square Tests

	Value	df	Df	Asymptomatic Significance (2-sided)
Pearson Chi-Square	3.704[a]		1	.054

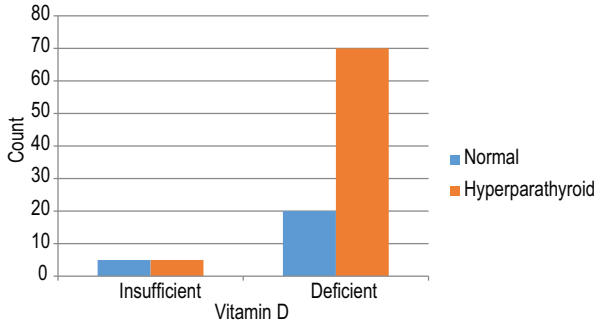

Fig.-3: *Bar Chart*

Discussion:

The study was done on 100 patients diagnosed as a case of Chronic Kidney Diseae after considering the exclusion and inclusion criteria described in the previous chapters.

In this study, majority of the patients (60%) were of age between 46 and 65 years. 31% of the study population were older than 65 years. 72% of the study population were male and 28% were female. In a study done by Julius U. Okoye, Ejikeme B. et al in Nigeria, 63.1% were males. The subjects were aged between 18 and 86 years.[21]

Diabetic nephropathy was the leading cause of CKD, affecting 36% of the study population. Hypertension was the likely cause in 26% of the subjects. Obstructive uropathy and chronic glomerulonephritis affected 7% and 5% of the subjects respectively. There was one (1%) patient with ADPKD, and in 25% of the cases no causative factor was identified. In the study done by Julius U. Okoye, Ejikeme B. et al in Nigeria, Chronic Glomerulonephritis, hypertension and Diabetes mellitus were the main causes of chronic kidney disease.[21]

In our study, most (40%) of the study subjects were in the stage 3 of CKD. 34% & 26% of the patients were in the stage 5 & 4 respectively.In a study in BIRDEM[22] 16%, 29.4%,54.6% were in stages 3,4,5 CKD respectively.In the Nigerian study, 25.9%, 50.6%, and 23.5% were in stages 3, 4, and 5 CKD respectively.[21]

In this study, we did not find any patient with normal vitamin D level. 10% of the patients were in the insufficient range and 90% of the study subjects were deficient in vitamin D. In the Nigerian study, all patients had low levels of 25 (OH) D, 62.4% had vitamin D deficiency, while 37.6% had insufficient vitamin D.[21]

Other studies done in USA[23,24] and UK[25] showed similar findings. Wolf et al[24] found 78% of patients they studied, had low 25(OH) D i.e. <75 nmol/L, with blacks being more deficient than whites. Gonzalez et al[23] found that 86% of 43 CKD patients they studied had inadequate 25(OH) vitamin D. Kosmadakis et al [25]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). 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.[26] They studied 3011 predialysis patients, found that those with 25(OH) D levels < 37.5 nmol/L had increased risk for all-cause mortality, compared to those with vitamin D sufficiency.

Other studies have shown that decreases in calcitriol levels occurred in patients with early CKD and preceded increases in serum PTH levels.[27] 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 25% of them had normal levels of PTH.

Though none of our patients 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. Hypocalcemia was found in 49% of our patients during admission. But the Nigerian study differs in this aspect as only 5.9% of the cases there had hypocalcemia.[21]

In SEEK study[28], 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,[29] or due to greater skeletal resistance to PTH among blacks.[30]

In our study, hyperparathyroidism was prevalent in 75% of the study subjects. In the Nigerian study, 84.7% of the patients had hyperparathyroidism. 79% of the patients had elevated serum phosphate levels in our study. In the Nigerian study, 69.4% had hyperphosphataemia. In Ananna's[22] study significantly low rate (44.8%-56.2%) of raised serum ALP was seen in CKDMBD cases compared to 72.5%-83.2% rate of raised iPTH in those cases. Also, there were no increase in the rate of raised serum iPTH and ALP with worsened CKD stages

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 in addition 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.[30] Also, calcium in these compounds has a stimulatory effect on the secretion of FGF23 which further sustains the MBD. This however is not the case with Sevelamer or Lanthanum carbonate.[31]

In our study, 33% of the patients had hyperkalemia during admission. In the Nigerian study, 41.2% had hyperkalemia.[21]

Hyperphosphatasia was prevalent in 39% of our study subjects. However, bone fraction of the ALP was not tested. In the Nigerian study, 24.7% had high levels of alkaline phosphatase.[21]

Among the 34 patients in the stage 5 CKD, 24 (24%) were male and 10 (10%) were female. 7% and 22% of the patients in stage 3A and 3B CKD respectively were male, with 0% and 11% being female in those groups respectively. The sex difference between groups were not statistically significant.

In this study, among stages 3B, 4 and 5 CKD patients, there were 2% patients in each group that were insufficient in vitamin D. Majority (32% in stage 5, 24% each in stages 3B and 4) were deficient in vitamin D. Deficiency was also prevalent in earlier

stages of CKD (10% patients in stage 3A). The difference was statistically significant, that is, the later the stage of CKD the greater the prevalence of vitamin D deficiency was. This finding is similar to the Nigerian study, which saw worsening Vitamin D deficiency 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.[21]

All our patients& in stage 4 and 3b (34% and 26% respectively) had hyperparathyroidism. None, 1% and 14% of the patients in stages 1, 2 and 3A 39 respectively had hyperparathyroidism. The difference between groups was statistically significant. Serum calcium level correlated well with the stage of CKD. Most of the patients in stage 5 were hypocalcemic (32 among 34). Among the 39% of the total study population with hyperphosphatasia, 24%, 9% and 6% were in stages 5, 4 & 3B respectively. The difference between groups were statistically significant. 49% pf the patients had hyperparathyroidism with hypocalcemia, 26% of the patients had hyperparathyroidism and normal serum calcium levels. None of the patients had hypocalcemia and normal PTH level. Among the 90 patients with deficient vitamin D levels, 46 had hypocalcemia also. 70 patients with deficient vitamin D level also had high PTH level. The difference between groups was statistically significant.

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. 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:

The study was done on 100 cases only due to time and resource constraint. It was done in only one centre in Dhaka, which may not reflect the wholesome picture of our country. 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.

Conflict of Interest:

The authors stated that there is no conflict of interest in this study.

Ethical consideration:

The study was conducted after approval from the ethical review committee. The confidentiality and anonymity of the study participants were maintained.

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