World Journal of Pharmaceutical and Life Sciences
WJPLS
www.wjpls.org
SJIF Impact Factor: 6.129

PREVALENCE AND SEVERITY OF DISORDERED MINERAL METABOLISM IN PATIENTS WITH CHRONIC KIDNEY DISEASE STAGE 3-5(D). A STUDY FROM A TERTIARY CARE HOSPITAL OF BANGLADESH"

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Article Received on 05/01/2021 **Article Revised on 25/01/2021** **Article Accepted on 15/02/2021**

ABSTRACT

Chronic kidney disease (CKD) constitutes a public health problem that is estimated to affect more than 10% of the global population, and the prevalence of which has increased in recent years.Bone mineral metabolism abnormalities, which the KDIGO guidelines recently defined as CKD-mineral bone disorder (CKD-MBD), have been clearly implicated not only in the development of secondary hyperparathyroidism (SHPT) and renal osteodystrophy but have also been associated with the progression of CKD and its complications, including cardiovascular complications and they ultimately contribute significantly to an increase in morbidity and mortality rates among patients with CKD. However, despite high prevalence of MBDs in CKD patients, there are no data on CKD-MBD from Bangladesh. This was a prospective, observational study carried over a period of 1 year(January 2016- December 2016) in Anwer Khan Modern Medical College Hospital. The study population included newly diagnosed CKD Stage 3-5 and prevalent CKD Stage 5D(Dialysis) adult patients of 18 years and above.The biochemical markers of CKD-MBD, namely calcium, phosphate, intact parathyroid hormone(iPTH) and 25-hydroxyvitamin Vitamin D3(250HD) were measured.115 (48 males and 67 females) patients were included in the study with a M:F of 1:1.4. Mean age was 60.07±11.41 years (Range 18-90 years). The most common causes of underlying native kidney diseases were Diabetic nephropathy (31.30%) followed by Hypertension (27.80%), Chronic glomerulonephritis (24.30%), Chronic interstitial nephritis (11.30%) and Autosomal dominant poly cystic kidney disease (5.20%). 44.35%(51) patients were from stage 3 CKD and 32.17%(37), 13.05%(15), 10.43%(12) were from stage 4, stage 5 and stage 5(D) respectively. Out of 51 patients of stage 3 CKD, 82.35% were of Hyperparathyroidism, 9.8% of Hypoparathyroidism and 7.85% were of target range parathormone. Among stage 4 CKD patients (37) of the study group 78.37% were of Hyperparathyroidism and 8.10% and 13.53% were of Hypoparathyroidism Target range respectively. Out of 27 patients of stage 5 and 5(D) CKD, 44.44%, 18.52% and 37.04% were of Hyperparathyroidism, Hypoparathyroidism and Target range. So it is observed that most of the patients (82.35%) of stage 3 CKD presents with Hyperparathyroidism. The mean PTH level of the patient of CKD stage 3,4,5 and 5(D) are 167.70 ±120.79, 235.35±256.08, 292.02±70.34 and 579.31±77.01 respectively. The mean PTH of the patients of stage 5(D) is more among all stages. 97 of all patients were of Hypercalcaemia and 39 of the patients had Hyperphosphataemia, 43 patients had mild Vit D deficiency, 53 had insufficiency and none of them had severe Vit D deficiency. Mean values of serum levels of corrected Calcium(cCa), Phosphate(PO4), creatinine, 25-OHD, intact Parathormone(i PTH) and Albumin are 8±1.06 mg/dl, 4.38±0.89 mg/dl, 3.49±2.6 mg/dl, 20.66±10.05 nmol/L, 318.59±131.05 pg/ml and 24.55±3.13gm/L respectively. There was a high prevalence of CKD-MBD in Bangladeshi CKD patients. CKD-MBD is more common and more severe and has an early onset as compared to the western population.

INTRODUCTION

Chronic kidney disease (CKD) constitutes a public health problem that is estimated to affect more than 10% of the global population, and the prevalence of which has increased in recent years.[1,2] The most important complication of CKD is cardiovascular disease, which is the primary cause of death in these patients. This increase in cardiovascular morbidity/mortality associated with CKD has been described even in patients with no evidence of ischemic heart disease and is the explanation for the high mortality rate among patients in initial stages of CKD (20%, 24% and 46% after 5 years for Stages 2,3 and 4 respectively), which far surpasses the rate for patients who finally require dialysis.[3,4]

Bone mineral metabolism abnormalities, which the KDIGO guidelines recently defined as CKD-mineral bone disorder (CKD-MBD), have been clearly implicated not only in the development of secondary hyperparathyroidism (SHPT) and renal osteodystrophy but have also been associated with the progression of CKD and its complications, including cardiovascular complications and they ultimately contribute significantly to an increase in morbidity and mortality rates among patients with CKD.[5,6,7,8]

CKD-MBD is a systemic disorder that is characterize by abnormal calcium, phosphorous, PTH and Vitamin D metabolism, which in addition to affecting the skeletal system, is related to the appearance of cardiovascular pathologies in patients with CKD.[9,10,11,12] The biochemical abnormalities are common in CKD and are primary indicators by which the diagnosis and management of CKD-MBD is made.

The bone mineral metabolism abnormalities start during first stages of CKD as renal function decreases, long before the need for renal replacement therapy and can be positively or negatively influenced by the treatment strategy employed. As such, it is recommended that attending physicians monitor and control biochemical parameters early in the development of CKD before the need for dialysis.[3,4,5,13] However, despite high prevalence of MBDs in CKD patients, there are no data on CKD-MBD from Bangladesh.

MATERIALS AND METHODS

This was a prospective, observational study carried over a period of 1 year(January 2016- December 2016) in Anwer Khan Modern Medical College Hospital. The study population included newly diagnosed CKD Stage 3-5 and prevalent CKD Stage 5D(Dialysis) adult patients of 18 years and above. Patients with the following characteristics were excluded from the study: (i) CKD stage 3-5 patients taking calcium supplement, phosphate binder, Vitamin D and its active metabolites and analogs, calcimimetic; (ii) patients on glucocorticoid, bisphosphonate, nonsteroidal antiinflamatory drugs, phenytoin or warfarin; (iii) patients having rheumatologic diseases such as rheumatoid arthritis and ankylosing spondylitis or primary PTH disorders; and (iv) those having liver disease or history of bone fracture in preceding 6 months. Institute ethical committee approved this work. CKD was defined and classified as per kidney disease outcome quality initiative (KDOQI)[14] The estimated glomerular filtration rates were calculated from serum creatinine level using the Cockcroft-Gault equation. The diagnosis of underlying basic kidney disease was made on clinical evidence.

The biochemical markers of CKD-MBD, namely calcium, phosphate, intact parathyroid hormone(iPTH) and 25-hydroxyvitamin Vitamin D3(250HD) were measured. When serum albumin concentrations are reduced, a corrected calcium(cCa) concentration was calculated by adding 0.8mg/dl to the total calcium level for every decrement in serum albumin of 1.0gm/dl below the reference value of 4gm/dl for albumin. The definitions for hypocalcemia (cCa<8.5 mg/dl), hypercalcemia (cCa>10.5 mg/dl), hyperphosphatemia (phosphate>4.5mg/dl), hypophosphatemia (phosphate <2.5mg/dl), hyperparathyroidism (iPTH>65pg/ml), hypoparathyroidism (iPTH<10pg/ml) and Vitamin D deficiency (25OHD level of <30ng/ml) were used.

Different iPTH levels outside of the range established by the KDOQI guidelines were used.[15] For subgroup analysis of Vitamin D deficiency, common clinical cut-points were used with 25OHD levels of 16-30, 5-15, and <5 ng/ml classified as insufficient, deficient, and severely deficient, respectively.[16,17]

Plasma iPTH was measured using the solid phase, two-site chemiluminescent enzyme-labeled immunometric assay (immulite/immulite 1000). Plasma 25OH Vitamin D (25OHD) assay was done using the equilibrium radioimmunometric assay (DiaSorin I125 RIA Kit).

Statistical analysis

Descriptive statistics including means, standard deviation, and percentages were used to describe the demographic and clinical data. Comparison between groups was performed by Chi-square or Fisher's exact test for categorical data and Student's t-test, Mann–Whitney U-test, or analysis of variance (ANOVA) with post hoc Bonferroni test, and nonparametric Kruskal–Wallis H-test as appropriate for continuous data. Pearson's correlation testing was used to look for associations between different parameters. Multivariate binary logistic regression analysis was done for factors predictive of an elevated iPTH. $P < 0.05$ was considered statistically significant. All statistics were carried out using SPSS, version 16 (SPSS, Chicago, IL, USA).

RESULTS

115 (48 males and 67 females) patients were included in the study with a M:F of 1:1.4. Mean age was 60.07±11.41 years (Range 18-90 years). The most common causes of underlying native kidney diseases

were Diabetic nephropathy (31.30%) followed by Hypertension (27.80%), Chronic glomerulonephritis (24.30%), Chronic interstitial nephritis (11.30%) and Autosomal dominant poly cystic kidney disease (5.20%) (Table 1) 44.35%(51) patients were from stage 3 CKD and 32.17%(37), 13.05%(15), 10.43%(12) were from stage 4, stage 5 and stage 5(D) respectively. (Table 2) Out of 51 patients of stage 3 CKD, 82.35% were of Hyperparathyroidism, 9.8% of Hypoparathyroidism and 7.85% were of target range parathormone. Among stage 4 CKD patients(37) of the study group 78.37% were of Hyperparathyroidism and 8.10% and 13.53% were of Hypoparathyroidism Target range respectively. Out of 27 patients of stage 5 and 5(D) CKD, 44.44%, 18.52% and 37.04% were of Hyperparathyroidism, Hypoparathyroidism and Target range (Table 3). So it is observed that most of the patients (82.35%) of stage 3 CKD presents with Hyperparathyroidism (Table 3)

The mean PTH level of the patient of CKD stage 3,4,5 and 5(D) are 167.70 ±120.79, 235.35±256.08, 292.02±70.34 and 579.31±77.01 respectively. The mean PTH of the patients of stage 5(D) is more among all stages (Table 4) 97 of all patients were of Hypercalcaemia and 39 of the patients had Hyperphosphataemia, 43 patients had mild Vit D deficiency, 53 had insufficiency and none of them had severe Vit D deficiency (Table 5)

Mean values of serum levels of corrected Calcium(CCa), Phosphate (PO4), creatinine, 25-OHD, intact Parathormone (i PTH) and Albumin are 8±1.06 mg/dl, 4.38±0.89 mg/dl, 3.49±2.6 mg/dl, 20.66±10.05 nmol/L, 318.59±131.05 pg/ml and 24.55±3.13gm/L respectively (Table 6)

Table 1: Distribution of Patients according to causes of CKD (Chronic Kidney Disease).

Causes	No	%
Diabetic Nephropathy	36	31.30
Hypertension	32	27.80
Chronic Glomerulonephritis	28	24.30
CIN (Chronic Interstitial Nephritis)	13	11.30
ADPKD (Autosomal Dominant Polycystic Kidney Disease)	06	5.20
Total	115	100.00

Table 2: Distribution of Patients according to staging of CKD (Chronic Kidney Disease).

Stages	No	%
Stage 3	51	44.35
Stage 4	37	32.17
Stage 5	15	13.05
Stage 5 (D)	12	10.43
Total	115	100.00

Table 3: Distribution of Patients according to PTH (Parathormone) Level.

Stages	Total	PTH Level Increase	PTH Level Decrease	Target Range (PTH)
	No (%)	No (%)	No (%)	No (%)
Stage 3	51 (44.35%)	42 (82.35%)	5 (9.80%)	4 (7.85%)
Stage 4	37 (32.17%)	29 (78.37%)	3 (8.10%)	5 (13.53%)
Stage 5 & 5 (D)	27 (23.48%)	12 (44.44%)	5 (18.52%)	10 (37.04%
Total	115 (100.00%)	83 (72.17%)	13 (11.30%)	19 (16.53%)

Table 4: Distribution of Patients according to Mean PTH Level in different stages of CKD 3-5D

Stages	Mean PTH
Stage 3	167.70 ± 120.79
Stage 4	235.35 ± 256.08
Stage 5	292.02 ± 70.34
Stage 5 (D)	579.31 ± 77.01

Table 5: Distribution of Patient according to biochemical parameter.
5-A

Minerals	Increase Calcium (>10.5mg/dl)	Decrease Calcium (<8.5mg/dl)	Normal
	No (%)	No (%)	No (%)
Serum Calcium	4 (3.83%)	97 (84.35%)	14 (11.82%)

5-B

Minerals	Increase Phosphate (>4.5mg/dl)	Decrease Phosphate (<2.5mg/dl)	Normal
	No (%)	No (%)	No (%)
Serum Phosphate	39 (33.91%)	1 (0.87%)	75 (65.22%)

5-C

Vitamin	Severe Vit D Deficiency (<5ng/ml)	Mild Vit D Deficiency (5-15ng/ml)	Vit D Insufficiency (16-30ng/ml)	Normal (30-100ng/ml)
	No (%)	No (%)	No (%)	No (%)
Serum Vit D	0 (0%)	43 (37.39%)	53 (46.08%)	19 (16.53%)

Table 6: Lab results of the study population (n – 115).

	Mean ± SD	Range
Corrected Serum Calcium (mg/dl)	8 ± 1.06	6.2 – 11.5
Serum Phosphate (mg/dl)	4.38 ± 0.89	1.8 – 6.5
Serum Creatinine (mg/dl)	3.49 ± 2.6	1.19 – 16.9
Serum Vit D (ng/ml)	20.66 ± 10.05	8.5 – 65
Intact PTH (pg/ml)	318.59 ± 131.05	10.2 -1603.8
Serum Albumin (gm/L)	24.55 ± 3.13	20.3 - 28.5

DISCUSSION

Disordered mineral metabolism, SHPT (Secondary Hyperparathyroidism), and deficiencies of Vitamin D are common complications of CKD.[18,19] A high prevalence of biochemical abnormalities of CKD-MBD was found in this observational study involving CKD Stage 3–5D patients. The Vitamin D deficiency (83.47%), SHPT (72.17%), hyperphosphatemia (33.9%), hypocalcemia (84.35%), and hypercalcemia (3.83%) were the major disorders seen in our patients.A highprevalence of disorders of mineral metabolism has been reported from the Western countries.[18-24]

In the study of Sanjoy Vikrant and Anupam Parashar, 2016, Vitamin D deficiency (90.4%), SHPT (82.7%), hyperphosphatemia (55.4%), hypocalcemia (23.8%), and hypercalcaemia(5.4%) were the major disorder which are similar to our study.[25]

Vitamin D deficiency was the most common biochemical abnormality of CKD-MBD seen in our patients. Vitamin D deficiency in patients with CKD Stages 3 and 4 is associated with increased PTH and low bone mineral density (BMD).[22,23,24,26] In CKD 5D patients, Vitamin D deficiency is associated with mortality in incident dialysis patients and increased cardiovascular events in PD patients.[27,28] These studies support the concern raised by the National Kidney Foundation KDOQI guidelines that low 25OHD levels in patients with CKD may contribute to the etiology of SHPT.[15]

A high (72.17%) prevalence of SHPT was found in our study subjects. Further, a high proportion (70.6%) had an iPTH above target range is of concern. The majority (58%) of CKD Stage 5 and 5D and a quarter of CKD Stage 4 had iPTH >400 pg/ml, representing high risk for high turnover bone disease. They need aggressive treatment to suppress PTH. Further, study results indicate that even in early stage Indian CKD patients, there is high prevalence of high turnover bone disease. It is speculated that in them, the biochemical abnormalities of CKD-MBD begin before CKD Stage 3 and coupled with widespread Vitamin D deficiency contributed to high prevalence of high turnover bone disease. It is suggested that in Bangladeshi CKD patients, monitoring for CKD-MBD should begin in CKD Stage 2 earlier than recommended by the guidelines.

Suppression of PTH to normal values is also not desirable (below 150 pg/ml) since it is associated with a higher prevalence of adynamic bone disease, in which bone turnover is low.[13] In our study, 18.52% of CKD Stage 5 and 5D subjects had low iPTH levels. A higher proportion (31.3%) of subjects in CKD Stage 5D had low iPTH; all were on PD. Multiple risk factors for adynamic bone disease have been identified, including increased age and diabetes. The principal factor underlying adynamic bone disease appears to be oversuppression of PTH release, which may be induced by the relatively high doses of Vitamin D analogs and possibly of calcium-based phosphate binders.[29] Adynamic bone disease is a significant concern in patients on PD compared to those on HD. One of the factors for this increased occurrence is the iatrogenic factor of giving a high or normal calcium dialysate in the PD.[30]

This study had several limitations. First, most important is the cross-sectional nature of the study which permits examination of association but not causal or temporal relationship. Information on dietary intake of calcium and phosphorus was not collected. A bone biopsy was not carried out. Nonetheless, studies have shown biochemical parameters to correlate well with the bone histology and this study gives a clinically relevant overview of what we could expect in our day to day clinical practice. Finally, although study reports a high

prevalence of disordered mineral metabolism, only randomized trials could definitively determine whether early screening and treatment of these abnormalities may have a salutary effect on CKD, bone, or cardiovascular endpoints.

CONCLUSION

To conclude, this study found a spectrum of CKD-MBD in CKD Stage 3–5D. It showed that SHPT, hyperphosphatemia, hypocalcemia, and Vitamin D deficiency were quite common in Bangladeshi CKD subjects. The most common type of MBD was SHPT. The disorders of mineral metabolism, particularly SHPT and 25OHD deficiency, were more common, more severe, and develop earlier in the course of CKD in Bangladeshi CKD patients as compared to that in western populations. Monitoring for CKD-MBD should begin at early CKD stage. However, to know the impact of early screening and treatment of the abnormalities on CKD and its complications, more studies are required.

Conflict of Interest

There are no conflicts of interest.

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