ORIGINAL ARTICLE

DO BONE MINERAL METABOLISM PARAMETERS IN CHRONIC KIDNEY DISEASE (CKD) PATIENTS MEET KDOQI GUIDELINES? A TERTIARY CARE HOSPITAL-BASED CROSS-SECTIONAL STUDY.

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ABSTRACT

Background: Chronic kidney disease (CKD) is now a public health problem with a high prevalence in Pakistan. However, there has been very little research on the profile of chronic kidney disease-related bone mineral disorders (CKD-MBD) in Pakistan. We thus aimed to assess the bone-mineral metabolism parameters in patients with CKD who are being followed at the Ziauddin University Hospital (a tertiary care hospital) in the southern city of Karachi, Pakistan.

Methods: A hospital-based cross-sectional study was conducted on 101 patients. The following clinical and biochemical data was collected: age, gender, serum creatinine and stage of CKD, serum PTH, calcium, albumin, phosphorus and Vitamin D levels- all at the same point in time.

Results: The percentages of patients with serum levels within the recommended KDOQI guidelines for stages 3, 4 and 5 were as follows: serum PTH: 11.1, 31.8, 25.8, serum corrected calcium: 88.8, 31.8, 42.9, phosphate: 66.6, 50.0, 57.1, respectively. A significant number of patients were found to have secondary hyperparathyroidism as per the KDOQI criteria. 25-OH Vitamin D deficiency was also noted, as was hypocalcemia especially in CKD stage 5. However, our study demonstrated optimal control of serum phosphate levels for the majority of patients.

Conclusion: This study highlights the difficulty of achieving KDOQI recommended serum PTH levels, and the need for raising awareness for more aggressive management of bone mineral metabolism parameters in order to decrease the morbidity and mortality associated with this disorder.

KEY WORDS: KDOQI, Chronic Kidney Disease (CKD), PTH, calcium, phosphorus

INTRODUCTION

Chronic kidney disease (CKD) is a world-wide public health problem, with increasing prevalence1. The estimated prevalence of CKD on a community based cross-sectional study in Karachi, Pakistan is estimated to be 5.3% (based on an eGFR< 60 ml/min/1.73 m2) 2. As renal function declines, there is a progressive impairment in the regulation of mineral homeostasis leading to altered serum concentrations of calcium, phosphate, parathyroid hormone (PTH) and vitamin D. The major consequences of disordered mineral metabolism in CKD are secondary hyperparathyroidism (SHPT), metabolic bone disease including renal osteodystrophy and vascular calcification. 3,4,5

The end result of these biochemical abnormalities is disordered bone growth and remodeling, and extra-skeletal calcification, collectively known as CKD related mineral bone disorders (CKD-MBD). Numerous cohort studies have shown associations between disorders of mineral metabolism and fractures, cardiovascular disease, and mortality in patients with CKD.6,7,8 The National Kidney Foundation published the Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines9 in an effort to summarize all data available, and established evidence-based recommendations for follow-up and treatment of disturbances of mineral metabolism in CKD patients. These guidelines recommend that all patients with eGFR< 60 ml/min/1.73m2 undergo regular evaluation of serum calcium, phosphorus and iPTH levels (bone mineral metabolism parameters). Despite the high prevalence of CKD related mineral bone disorders (MBDs), there is a paucity of data on CKD-MBD in Pakistan. The aim of this study was to assess if patients with CKD stages 3-5 being followed at the Ziauddin Hospital have their bone mineral metabolism parameters maintained within target ranges as recommended by KDOQI.

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**METHODS**

This was a cross-sectional study conducted in the Department of Medicine, at the two campuses of the Ziauddin Hospital (North and Clifton Campus), between January 2013 and May 2015, after approval by the institutional ethics committee. The sample size was calculated using the WHO sample size calculator, based on the estimated prevalence of CKD of 5.3% in Karachi, Pakistan.  Patients with CKD stages 3, 4 and 5 attending the Department of Medicine were included in the study. The sampling technique was purposive based on the inclusion criteria. The following patients were excluded from the study: (i) patients with acute kidney injury and patients with changing creatinine values within a three month time period (ii) patients with autoimmune diseases, patients receiving bisphosphonates, and patients with primary parathyroid hormone disorders (iii) patients less than 16 years of age. CKD was diagnosed on the basis of history, eGFR< 60ml/min/1.73 m2 by the MDRD formula, biochemical and ultrasonographic/histologic evidence of CKD (as per K/DOQI criteria) 10.

Demographic data was recorded for each patient. It was also recorded if the patient was under care of a nephrologist or not. Serum creatinine, albumin, calcium, phosphate (PO4) values were recorded (measured using standard laboratory techniques). Plasma intact parathormone (PTH) and plasma 25-OH vitamin D assays were measured using the solid phase, two-site chemiluminescent assay (Abbott Architect I 1000). The recommended ranges for each stage are described in the KDOQI Clinical Practice Guidelines for bone metabolism and disease in CKD. Statistical analysis was performed using SPSS version 15. P value <0.05 was taken as significant. Continuous variables were analyzed by the Chi-square test. Inter-group significance (ANOVA), was carried out and is detailed later.

**RESULTS**

One hundred and one patients (53 males, 48 females) were included in this study. The mean age of the participants was 58.8 ± 16.6 (range 16–97) years. The duration of chronic kidney disease in these patients ranged from 8 months – 20 years. 63% of the patients were under care of a nephrologist, whereas 18% were under care of a physician.

The patients were subdivided into three subgroups: those with CKD stages 3, 4 and 5. The mean value (%) for serum PTH was 287.57+/−305.5, corrected calcium was 9.04+/−1.64, phosphorus was 4.77+/−1.83 and Vitamin D level 26.38 +/− 21.09 for all patients. Table 1 shows the mean value for each parameter as well as 25 OH vitamin D level for each subgroup of patients.

**Table 1: Laboratory Characteristics of patients with CKD stages 3, 4 and 5**

<table>
<thead>
<tr>
<th></th>
<th>CKD stage 3 (8.9%, n=9)</th>
<th>CKD stage 4 (21.7%, n=22)</th>
<th>CKD stage 5 (69.3%, n=70)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTH (pg/ml)</td>
<td>89.6 +/- 49.47</td>
<td>236.19 +/- 338.17</td>
<td>323.82 +/- 302.89</td>
</tr>
<tr>
<td>Corrected Calcium (mg/dl)</td>
<td>9.68 +/- 1.06</td>
<td>10 +/- 2.1</td>
<td>8.7 +/- 1.37</td>
</tr>
<tr>
<td>Phosphorus (mg/dl)</td>
<td>4 +/- 1.4</td>
<td>3.9 +/- 1.04</td>
<td>5.12 +/- 1.96</td>
</tr>
<tr>
<td>25 OH Vitamin D level (ng/ml)</td>
<td>29.3 +/- 3.22</td>
<td>47.2 +/- 43.9</td>
<td>22.4 +/- 11.1</td>
</tr>
</tbody>
</table>

Mean +/- SD for non-categorical variables

Table 2 The percentage (and number) of patients who accomplish the KDOQI target ranges for the different mineral metabolism parameters: serum PTH, corrected calcium and phosphorus for stages 3-5 of CKD. The number of patients who achieve all mineral metabolism parameters for CKD stages 3, 4 and 5 are: n = 26, 45 and 57, respectively.

**Table 2: PTH, corrected calcium and phosphorus values for different CKD stages**

<table>
<thead>
<tr>
<th></th>
<th>CKD Stage 3 (8.9%, n=9)</th>
<th>CKD Stage 4 (21.7%, n=22)</th>
<th>CKD Stage 5 (69.3%, n=70)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTH reference range (pg/ml)</td>
<td>35-70</td>
<td>70-110</td>
<td>150-300</td>
<td></td>
</tr>
<tr>
<td>above range % (n)</td>
<td>55.6% (5)</td>
<td>40.9% (9)</td>
<td>41.4% (29)</td>
<td></td>
</tr>
<tr>
<td>below range % (n)</td>
<td>33.3% (3)</td>
<td>27.3% (6)</td>
<td>32.9% (23)</td>
<td></td>
</tr>
<tr>
<td>within range % (n)</td>
<td>11.1% (1)</td>
<td>31.8% (7)</td>
<td>25.8% (18)</td>
<td>0.941 (&gt;0.05)</td>
</tr>
<tr>
<td>Corrected calcium reference range (mg/dl)</td>
<td>8.5-10.2</td>
<td>8.5-10.2</td>
<td>8.4-9.5</td>
<td></td>
</tr>
<tr>
<td>above range % (n)</td>
<td>11.1% (1)</td>
<td>36.4% (8)</td>
<td>12.9% (9)</td>
<td></td>
</tr>
<tr>
<td>below range % (n)</td>
<td>00.0% (0)</td>
<td>31.8% (7)</td>
<td>44.3% (31)</td>
<td></td>
</tr>
</tbody>
</table>
The ANOVA test applied to the three different subgroups, no significant difference was observed in PTH and phosphorus values across the groups; corrected calcium was the only value with significant difference between the groups. Figures 1, 2 and 3 show the plots for mean of PTH, corrected calcium and phosphorus respectively.
The parathyroid hormone levels rise progressively from CKD stage 3 to 5, the calcium and phosphorus values reflect mirror images of each other.

Table 3 shows the number percentage of patients in each CKD subgroup with Vitamin D level < 30 ng/ml. Vitamin D levels had not been checked for all patients. 66.7% of patients with CKD Stage 3 (n=3), 45.5% of patients in CKD Stage 4 (n=11) and 83.3% of patients in CKD Stage 5 (n=50) were found to be vitamin D deficient.

DISCUSSION

The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF KDOQI)TM has provided evidence-based clinical practice guidelines for all stages of chronic kidney disease (CKD) and related complications since 200210. Recognized throughout the world for improving the diagnosis and treatment of kidney disease, the KDOQI Guidelines have changed the practices of numerous specialties and disciplines and improved the lives of thousands of patients with kidney diseases.

This study highlights the difficulty in achievement of KDOQI recommended target values for PTH and calcium levels in CKD, though phosphorus values were found to be within target range for the majority of patients. Despite the high prevalence of chronic kidney disease in Pakistan of 5.3%, there is a lack of data from Pakistan regarding bone-mineral metabolism parameters in CKD patients. The only recent study in Pakistan done on this subject included an assessment of bone mineral metabolism derangements in hemodialysis patients in Rawalpindi which was not inclusive of patients with CKD stages 3 and 4 (i.e. patients not on dialysis)15. This study had shown that hyperparathyroidism leading to secondary hyperparathyroidism was the main mineral abnormality. Another study done in Spain in a large CKD population (Stages 1-5) also showed that the PTH recommended levels are difficult to attain with the current treatment options12. A high prevalence of 25(OH)D deficiency, hypocalcemia and hyperparathyroidism in patients with CKD stages 4 and 5 has also been reported14.

The mean age of the patients in our study was 58±16.6 years. The demographic profile also showed a slight male predominance which has been seen in studies among the CKD population, including the studies quoted above. Another study also observed that males outnumbered females 15, and yet another community based study 16 showed similar findings. One reason may be that more males in the Indo-Pakistan subcontinent visit hospitals compared to females. Our study shows much higher number of patients with CKD Stage 3 (n=70), compared to CKD Stage 4 (n=22), and CKD Stage 5 (n=9). Since the patients were randomly selected, this points to the fact that most patients with kidney disease are already very far advanced when they visit the hospital, reflecting the general lack of awareness about referral to nephrology in earlier stages of CKD.

The PTH level was elevated for the majority of patients for CKD stages 3, 4 and 5 (55.6%, 40.9% and 41.4%, respectively). In CKD Stage 5, 32.9% of patients also had a value for PTH which was lower than that suggested by KDOQI guidelines. A significant number of patients with CKD stage 4 (44.3%) were found to be hypocalcemic, while hypercalcemia was seen in a majority (36.4%) of patients in the CKD Stage 4 subgroup, and most (88.8%) of the CKD Stage 3 patients were normocalcemic. This difference was significant between the three subgroups. As regards the serum phosphorus levels, the majority of patients had normal phosphate values.

Due to decreased GFR and altered endocrine function of kidneys, the parathyroid-vitamin-D-renal axis gets deranged which results in phosphate retention, hypocalcemia, decreased active vitamin D, and secondary hyperparathyroidism in majority of patients.17-21. Thus, from a pathophysiological point of view, early calcitriol supplementation should be the treatment of choice.13 Decreasing serum calcium levels and rising serum phosphate levels in advanced stages of CKD also contribute to the hyperparathyroidism progression13. We also found PTH level to be below KDOQI reference range for 32.9% patients with Stage 5 CKD, which is a marker of malnutrition, adynamic bone disease and other pathological conditions; they also represent a subset of hemodialysis patients with higher morbidity and mortality14.

There is more data available from India compared to
Pakistan with regards to CKD-MBD. Agarwal described hypocalcemia in 29.9% and 49.6% in CKD stage 4 and 5, respectively, and hyperphosphatemia in 45% and 41.8%, respectively, hyperparathyroidism in 57.8% of patients with CKD stage 4 and in 39.4% of patients with CKD stage 5. Hypocalcaemia was also found to be associated with hyperparathyroidism.14 Jabbar, et al. observed prevalence of hyperparathyroidism in 60% of their patients in CKD stage 4 and 5 taking a cutoff of iPTH= 300 pg/mL for both stages.15 Banerjee and colleagues found a high incidence of secondary hyperparathyroidism and hyperphosphatemia in stages 4 and 5 of CKD. In Pakistan, Khan and colleagues described 47.4% of patients with stage 5 CKD with hyperparathyroidism, and they also found this population to have significant hypercalcemia and hyperphosphataemia as well. In Pakistan, bone mineral metabolism parameters are often not checked in patients with early stages of CKD, so that by the time they reach advanced CKD, several of them have already developed hyperparathyroidism, when it becomes more difficult to control. The fact that the phosphate level was within normal limits for most of our patients might be due to the fact that the majority of patients were on calcium based phosphate binders and nutritional factors may also be contributing. Sevelamer chloride as a phosphate binder is finding wider use in Pakistan, although calcium based binders would be recommended for patients with hypocalcemia.

Although monitoring of 25-OH vitamin D levels is not part of the KDQQI guidelines, its deficiency plays an important role in modifying and preventing CKD-MBD and its presence has a deep rooted nutritional, genetic and socio-economic basis.14 This includes poor dietary fortification and darker skin pigmentation requiring longer exposure to ultraviolet rays to achieve adequate 25-OH vitamin D levels.15 25-OH vitamin D deficiency is common in CKD stage 3–5. Levels of 25-OH vitamin D level were less than 75 nmol/L in 83% of patients with CKD stage 4,16 83.13% of patients with CKD stage 4 and 5 had vitamin D level less than 30 ng/mL. Concurrent with the study of LaClair, et al. and Banerjee et al.; our study also established the majority of patients to be vitamin D deficient. Although supplementation of cholecalciferol may improve secondary hyperparathyroidism without the need for the active compound (calcitriol or other analogues), this issue has not been addressed adequately till now.24-27

One of the strengths of this study is that it is the first of its kind in Pakistan to assess if bone mineral disease is being followed according to KDQQI guidelines in patients with chronic kidney disease Stages 3-5. As it is a hospital-based survey, it may not be representative of the actual population with CKD as it consists only of the referred (and relatively more affluent) population.

In summary, the majority of patients with CKD stage 3-5 had PTH values that deviated by far from the KDQQI recom-mended guidelines the most. The phosphate levels were generally within target range, but a significant number of patients with CKD Stages 4 and 5 had hyperphosphataemia (31.8% and 30% respectively). Calcium levels were gener-ally above range for the majority of stage 4 patients, and below range for the majority of stage 5 patients. Moreover, vitamin D deficiency was also quite prevalent in CKD patients, especially Stages 3 and 5. The abnormalities in calcium, phosphate levels and lack of use of activated Vitamin D (when VITD3) contributes to secondary hyperparathyroidism in the CKD population. This study highlights the need for more studies in this field in Pakistan, so that efforts can be made to achieve target values for bone-mineral metabolism parameters for patients with CKD, which will greatly improve morbidity (reduction of fractures, vascular events) and mortality. This can be made through dietary modifications (including education of patients, doctors and dieticians), as well through more frequent monitoring of these parameters, replacement of Vitamin D deficiency (especially in CKD stages 3 and 4), use of appropriate phosphate binders, Vitamin D analogues and/or calcimimetic agents according to the patient’s requirements as determined by the laboratory values. Moreover, efforts should be made to educate general practitioners about early referral to nephrologists so that patient management can be started early, before bone disease and vascular calcification sets in.

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REFERENCES


