Association of mineral levels with Chronic Kidney Disease (CKD-MBD) – A hospital based retrospective study

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Abstract

Background: There is a deep association between mineral & bone disorders in chronic kidney disease. High phosphate levels in CKD-MBD have been associated with increased all-cause mortality & cardiovascular morbidity & mortality. This study aims to find association of mineral levels with CKD-MBD. Objective is to get data of serum calcium & phosphorus levels in known CKD-MBD patients & evaluate their association with CKD-MBD.

Methodology: This is a retrospective analytical study carried out at Dhiraj Hospital, Piparia, Vadodara. Total 71 consented indoor patients were enrolled in study out of 317 requested for consent in provided time period of 6 months, 45 (63.3%) patients with known CKD-MBD & 26 (36.6%) without CKD-MBD were taken as control group. Various laboratory parameters were evaluated & compared.

Results: Out of 50 male & 21 female participants total 36 (80%) were found to have low calcium levels & 39 (86.67%) were found to have high phosphorus levels among known CKD-MBD patients which were classified according to eGFR.

Conclusion: Low calcium & high phosphorus levels are associated in patients with CKD-MBD. There should be multi-disciplinary approach towards maintenance of mineral levels in patients to meet the K/DOQI guidelines.

Keywords: CKD-MBD (Chronic Kidney Disease-Mineral & Bone Disorder), K/DOQI, S. Phosphorus, S. Calcium, eGFR (Estimated Glomerular Filtration Rate)

1. Introduction

A CKD-MBD is emerging as one of the major public health problems across the world & its incidence is rising day by day.\textsuperscript{1} CKD may lead to End-stage Renal Disease (ESRD) & is also associated with increased risk of cardiovascular disease, heart failure, & increased healthcare expenditures.\textsuperscript{2}

Epidemiological studies show that serum phosphate levels are linearly & independently associated with all-cause & cardio-vascular mortality in patients on hemodialysis\textsuperscript{3} & pre-dialysis patients with CKD-MBD.\textsuperscript{4} Block et al. highlighted the association between hyperphosphataemia & mortality in a cross-sectional study of hemodialysis patients using the United States Renal Data System & reported a 17.5% increased population attributable to risk from abnormalities of mineral metabolism, largely as a result of high phosphate level.\textsuperscript{3} Hyperphosphataemia may also directly affect vascular health by
increasing reactive oxygen species, thereby causing oxidative damage & endothelial dysfunction.\textsuperscript{5,6,7}

Serum Calcium levels are invariably associated with CKD-MBD with fall in calcium levels as disease progresses. The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (K/DOQI) clinical practice guidelines advise maintaining serum levels of total calcium (tCa), corrected for albumin level, within the “normal” range for the laboratory.\textsuperscript{[8]}

Thus calcium & phosphorus, major minerals, metabolism regulation of which is associated closely with renal function, makes their serum levels closely dependent on proper renal function.\textsuperscript{9} Aim of this study was to find out relation of mineral levels among CKD-MBD patients, also to evaluate & discuss possible outcomes of analysis.

2. Material & Methods

Present Retrospective study was performed in Dhiraj Hospital, Piparia, Vadodara after receiving ethical approval from institutional ethical committee. 71 consented adult indoor patients were enrolled in study, out of these 45 (63.3\%) patients were known to have CKD-MBD on basis of clinical diagnosis & 26 (36.6\%) patients were taken as control group. Patients having following criteria were excluded from the study: age<20 years, GI disorders, patients taking mineral supplements & hormonal therapy, Type 1 Diabetes, malignancy & post surgery patients.

Baseline data were collected from paper documentation & electronic medical records of hospital. Diabetes & Cardio Vascular disease were defined as per clinical diagnosis. GFR was estimated from baseline creatinine levels using abbreviated equation developed for the Modification of Diet in Renal Disease Study\textsuperscript{10} & patients were categorised according to K/DOQI: Evaluation, Classification & Stratification.\textsuperscript{8} Measurements of various parameters were done with appropriate methods on fully automated biochemistry analyser (ERBA EM-200) like creatinine with modified jaffe’s, calcium with arsenazo III, phosphorus with UV phosphomolybdate ensuring minimal analytical errors. Normal values were taken 0.6-1.4mg/dl for creatinine, 8.8-10.2mg/dl for calcium, 2.1-5.6mg/dl for phosphorus according to reference range established by laboratory.

3. Statistical Methods

Statistical analyses were performed with the SPSS v20. Continuous variables were expressed as mean & SD (Standard Deviation) & categorical variables were expressed as proportions. Descriptive analyses were used to characterize the study population by demographics, including sex, age, & by medical status, including mean creatinine, calcium & phosphorus levels & presence of CKD status with its categories. Association of CKD status with values of minerals, stratified by categories were examined using chi-square statistics.

4. Results

Total 71 patient data were taken into account for results among them 50 were males & 21 were females. With this 45 were clinically diagnosed as having CKD-MBD while 26 were patients without CKD-MBD. Mean age was 51.66±12.3 with minimum 22 & max 65 years. Mean levels of creatinine, calcium & phosphorus were 6.9±6.7 mg/dl, 8.5±1.4 mg/dl & 6.2±2.2 mg/dl respectively. Taking cut off values for low calcium as 8.8mg/dl, high phosphorus as 5.6mg/dl & high creatinine as 1.4mg/dl; we found that 42(59.2\%), 42(59.2\%) & 57(80.3\%) were having low calcium level, high phosphorus level & high creatinine levels respectively.

| Sr. No. | Variable     | CKD-MBD | Total | p-Value |
|---------|--------------|---------|-------|---------|
|         |              | Yes     | No    |         |
| 1.      | S. Creatinine| High    | 45    | 12      | 57      | <0.05   |
|         |              | Normal  | 00    | 14      | 14      |         |
| 2.      | S. Calcium   | Low     | 36    | 06      | 42      | <0.05   |
|         |              | Normal  | 09    | 20      | 29      |         |
| 3.      | S. Phosphorus| High    | 39    | 03      | 42      | <0.05   |
|         |              | Normal  | 06    | 23      | 29      |         |
Further patients were categorised into CKD stages & were found to be having proportion as depicted in chart. (Fig 1)

Fig 1: patients category into CKD stages

![Pie chart showing distribution of patients among CKD stages]

26(37%) were non CKD-MBD patients while 8(11%), 25(35%), 9(13%) & 3(4%) patients were of CKD stages 2, 3, 4 & 5 respectively.

Among all patients 36(51%) were diagnosed as having Diabetes clinically. Statistically correlation between CKD-MBD patients & Diabetes was insignificant.

Phosphorus & calcium values among participants were plotted against each other it showed linear correlation between them. As phosphorus level increased calcium level was decreasing in linear manner. (Fig. 2)

Fig. 2. Phosphorus & calcium values among participants

![Graph showing linear correlation between phosphorus and calcium levels]

Table II : Demographics of Study Population

| Characteristic                | Value    | Normal Range |
|-------------------------------|----------|--------------|
| Male/Female                   | 50/21    | -            |
| CKD Status                    | 45/26    | -            |
| Diabetes Status               | 36/35    | -            |
| Age                           | 51.66±12.3 (22 to 65) | - |
| Creatinine                    | 6.9±6.7 (0.8 to 31.0) | 0.6 to 1.4 |
| eGFR among CKD-MBD Patients   | 43.9±16.9 (10.4 to 72.1) | - |
| S. Calcium                    | 8.5±1.4 (5.2 to 12.1) | 8.8 to 10.2 |
| S. Phosphorus                 | 6.2±2.2 (2.7 to 11.8) | 2.1 to 5.6 |
5. Discussion

In present study we evaluated the levels of minerals (calcium & phosphorus) among the patients of CKD of various stages. These abnormalities start developing in earlier stages of CKD & they are associated with higher mortality in patients with ESRD. The impact of phosphorus level on progression of CKD & on mortality has been examined, with two studies showing different results, but the effect of bone-mineral abnormalities on kidney function is unclear. Our study shows that higher serum phosphorus was associated with significantly higher risk for progression of CKD, these findings complements earlier primary studies that showed a beneficial effect of dietary phosphorus restriction on progression of CKD in experimental animals & in humans. Our findings of a significant quantitative interaction between serum phosphorus & calcium levels supports the hypothesis that tissue calcification may be reason behind observed association. The association of phosphorus level with progression of CKD in our study also seemed to be more pronounced in patients with diabetes, although the interaction did not reach any statistical significance. Diabetes affected the association of serum phosphorus with mortality in patients with ESRD in the study by Block et al (risk for mortality being higher in patients with diabetes), & serum phosphorus was not associated with mortality in a study that was performed in patients who had CKD-MBD & were not yet on dialysis, who almost exclusively did not have diabetes. Mechanism of action behind the observed effect by diabetes is unclear & requires more thorough research.

We found association between lower calcium levels & progressive CKD in unadjusted analyses by evaluating calcium with eGFR & phosphorus levels, suggesting that lower serum calcium level may be a supportive marker of lower GFR rather than an independent risk factor. It is of note that being associated with lower eGFR, low calcium may be associated with higher parathyroid hormone (PTH) levels, which were not available to us for analysis; therefore, additional association is very likely possible.

Several shortcomings of our study have to be acknowledged. Our study population consisted very small number of patients who were taken from limited geographic area & were from single clinical setup; therefore our results may not apply to patients from other geographic areas. Being retrospective nature of this study, we could determine only the presence of associations but cannot establish causality. Impact of other important variables that are known to affect progression of CKD has to stressed in this regard. First, we could not get data on amount of protein intake in our patients as it is highly associated with favourable outcome in CKD. Second, we could not account for the confounding effect of PTH levels, which were not available to us. Higher PTH levels could be associated with both lower calcium & higher phosphorus levels; so, we cannot rule out a residual effect related to hyperparathyroidism. Third, although we have used eGFR, true assessment of GFR in a historical retrospective study is not possible; therefore, the association between phosphorus levels & progression of CKD may have been affected by residual results stemming from differences between eGFR & true GFR. Other limitations are conferred by the use of baseline available data to predict future outcomes & the non-concurrent historical cohort design.

6. Conclusion

Our study shows an association between higher levels of phosphorus & lower levels of calcium with unfavourable outcome in CKD-MBD patients. We suggest better monitoring of mineral levels on periodic time schedule & also monitoring of other parameters like PTH & Vitamin-D in patients of CKD-MBD. Also we suggest proper timely follow up of patients as suggested by K/DOQI guidelines. Further research needs to be done to find relation of other proposed variables with CKD-MBD.

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