ORIGINAL ARTICLE

Correlation between Cardiac Markers and Serum Phosphate Levels in Patients with Newly Diagnosed Chronic Kidney Disease

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ABSTRACT

Aim: To determine the correlation between cardiac markers and serum phosphate levels in patients with newly diagnosed stage 4 and 5 Chronic Kidney Disease not yet undergoing hemodialysis.

Methodology: It was a Cross-sectional study done in Department of Medicine, Mayo Hospital, Lahore from July to December 2015. A total of 100 newly diagnosed patient of stage 4 and 5 Chronic Kidney Disease not yet undergoing hemodialysis were enrolled through outpatient department of Medicine, Mayo Hospital, Lahore. Blood samples were obtained for the assessment of serum cardiac troponin T level, creatinine kinase-MB (CKMB) and serum phosphate. Reports were assessed and levels were noted.

Results: Out of 100 cases, 48(48%) were male and 52(52%) were females, the mean age was calculated as 48.21±6.99 years, correlation between mean serum phosphate level and cardiac troponin T levels was calculated which showed r value as 0.9273. Correlation between mean serum phosphate level and CK-MB levels was calculated which showed r value as 0.7545.

Conclusion: We concluded that the correlation is positive between cardiac markers and serum phosphate levels in patients with newly diagnosed stage 4 and 5 Chronic Kidney Disease not yet undergoing hemodialysis.

Keywords: Cardiac markers, Serum phosphate levels, Chronic Kidney Disease.

INTRODUCTION

Chronic kidney disease (CKD) has been found as an independent risk factor for coronary artery disease[1]. Patients with CKD carry 10-20 times higher cardiovascular disease (CVD) mortality as compared to the general population[2]. So far, the pathogenesis of cardiovascular injury in CKD has remained unclear[3]. Hyperphosphatemia is commonly present in patients with CKD. Studies have shown that Hemodialysis (HD) patients with serum phosphate >2.1 mmol/L had 41% greater risk of death occurring due to CVD as compared to patients with serum phosphorus levels ranging from 0.7 to 2.1 mmol/L[4]. Even in patients with normal renal function, hyperphosphatemia has been associated with increased cardiovascular morbidity and mortality[5].

Cardiac markers (CMs), such as cardiac troponin T (cTnT) and creatinine kinase-MB (CK-MB) have been used clinically as sensitive diagnostic markers of myocardial necrosis.[6,7] Interestingly, it has been found that CMs were elevated in patients with various degrees of renal failure,[8,9] however majority of those patients never presented with acute coronary syndrome (ACS)[10,11].

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Cardiac troponin T may be helpful in detecting asymptomatic coronary artery disease (CAD), especially multivessel disease, and as a predictor of mortality in CKD patients.[12] Hayashi T et al used Cardiac TnT as a marker to identify occult CAD in 142 CKD patients at the initiation of their renal replacement therapy. Of 60 patients at the time of evaluation, 35 (43.8%) had obstructive CAD and 27 had multivessel CAD as assessed by invasive coronary angiography[13]. Many studies have supported the value of Cardiac TnT as a predictor of unfavorable CAD events in CKD patients. Cardiac TnT was found to be equivalent in differentiating short-term prognosis in patients with CKD suffering a non-ST-segment elevation myocardial infarction[12].

Therefore, the rationale of this study was to see the correlation between cardiac markers and serum phosphate levels in patients with newly diagnosed stage 4 and 5 chronic kidney disease, not yet undergoing hemodialysis. It has been noticed through literature that phosphate level is significantly correlated with cardiac markers in non-cardiac CKD patients. This showed that if phosphate level of CKD patients would increase, the cardiac markers would definitely increase significantly, although this correlation was found to be weak. So, through this study we tried to explore the role of serum phosphate in CKD patients with elevated cardiac markers. It was the first local study of its kind showing the

relationship between cardiac markers and serum phosphate levels in patients with newly diagnosed stage 4 and 5 CKD that was supposed to help in understanding the relationship and providing a valuable insight to the future management of CKD.

METHODOLOGY

It was a Cross-sectional study done in outpatient department of Medicine, Mayo Hospital, Lahore from July to December 2015. Non-probability/consecutive sampling was used. After taking approval from Institutional review board (IRB), 100 Patients having age 18-65 years, of either gender and already diagnosed case of CKD stage 4 & 5 (based on National Kidney Foundation CKD classification)[14] were included in the study. Patients with known ischemic heart disease or who present with central chest pain at presentation, patients with malignancy, active tuberculosis, inflammatory diseases, diabetic ketoacidosis, history of chronic vomiting and/or diarrhea and patients having malignant hypertension, surgery, trauma, blood infusion and erythropoietin use in the last 6 months prior to recruitment were excluded.

The demographic details (name, age, gender, CKD stage and duration of CKD) were also noted. Blood samples were sent to the laboratory for the assessment of serum cardiac troponin T level, CK-MB and serum phosphate. Reports were assessed and levels were noted. All data was arranged and analyzed using SPSS version 20. Mean and standard deviation was calculated for quantitative variables like age, duration of CKD, serum phosphate, cardiac troponin T level and CK-MB. Frequency and percentage was calculated for qualitative variables like gender and CKD stage. Pearson correlation coefficient was calculated between serum phosphate level and cardiac troponin T levels and CK-MB. p-value <0.05 was taken as significant. Data was stratified for age, gender, CKD stage and duration of CKD.

RESULTS

Age distribution of the patients was done, it showed that 23(23%) were between 18-40 years of age while 77(77%) were between 41-65 years of age, Mean±SD was calculated as 48.21±6.99 years. Patients were distributed according to gender, it showed that 48(48%) were male and 52(52%) were females. Frequency of stage of CKD was calculated as 62(62%) for stage 4 and 38(38%) for stage 5. Mean duration of CKD was calculated as 7.92±3.29 months. Mean serum phosphate (mmol/L) was calculated as 1.70±0.32mmol/L. Mean cardiac troponin T level was calculated as 0.59±0.41 ng/mL. Mean CK-MB level was calculated as 46.9±9.86 U/L.

Correlation between mean serum phosphate level and cardiac troponin t levels was calculated which showed r value as 0.9273. It is a strong positive correlation, which means that high Phosphate levels correlates with high Cardiac Troponin T levels (and vice versa) (Table 1).

Correlation between mean serum phosphate level and CK-MB levels was calculated which showed r value as 0.7545. It is a strong positive correlation, which means that high Phosphate levels correlates with high CK-MB levels (and vice versa) (Table 2).

Table 1: Correlation between mean serum phosphate level and cardiac troponin t levels

Phosphate/Cardiac Troponin T levels	Mean	SD
Phosphate	1.70	0.32
Cardiac Troponin T levels	0.59	0.41

P value 0.0001, r value 0.9273

Table 2: Correlation between mean serum phosphate level and ck-mb levels

Phosphate/CK-MB levels	Mean	SD
Phosphate	1.70	0.32
CK MB	46.90	9.86

P value 0.0001, r value 0.7545

DISCUSSION

Cardiac biomarkers are used in conjunction with symptoms, in patients with chronic kidney disease (CKD). Cardiac biomarkers are also used to predict short- and long-term adverse outcomes. The current study was planned with the view to determine the correlation between cardiac markers and serum phosphate levels in patients with newly diagnosed stage 4 and 5 chronic kidney disease. Phosphate levels are significantly correlated with cardiac markers in non cardiac CKD patients. Through this study we tried to explore the role of serum phosphate in CKD patients with elevated cardiac markers.

In our study, out of 100 cases newly diagnosed stage 4 and 5 Chronic Kidney Disease not yet undergoing hemodialysis, 48(48%) were male and 52(52%) were females, the mean age was calculated as 48.21±6.99 years, correlation between mean serum phosphate level and cardiac troponin t levels was calculated which shows r value as 0.9273. Correlation between mean serum phosphate level and CK-MB levels was calculated which shows r value as 0.7545.

Di Marco GS et al had proved that phosphate overload can directly lead to apoptosis of human vascular endothelial cells.[15] In a cross-sectional study done by Wang S and associates, 151 patients with

different kidney functions were enrolled to scrutinize the relation of serum phosphate with cardiac markers (CMs), including myoglobin, cardiac troponin T, brain natriuretic peptide (BNP) and creatine kinase-MB (CK-MB). They found that phosphate and CMs slowly raised as the glomerular filtration rate decreased in CKD patients ($p<0.01$). They also found that rise in serum CMs was much higher and cardiac functioning was poor in chronic kidney disease patients who had high serum phosphate ($p<0.05$). It was established that levels of phosphate in blood directly correlated with cardiac troponin T, myoglobin, and brain natriuretic peptide in CKD patients ($p<0.001$). They concluded that hyperphosphatemia induced damage of myocardium in patients of CKD, possibly by initiating apoptosis of human cardiomyocytes, could cause the elevated cardiac markers in CKD patients. Our study also showed strong positive correlation between mean serum phosphate level and cardiac troponin t levels ($r=0.9273$, p value= 0.0001) and also between mean serum phosphate level and CK-MB levels ($r= 0.7545$, p value= 0.0001) which means that high phosphate levels correlates with high cardiac troponin T and CK-MB levels[16].

Phosphate is a vital mineral for the structure and energy requirements of the cell. About 29% of phosphate resides in the bones, 1% circulates in the serum and about 70% of phosphate is mainly intracellular[17]. As suggested by Hruska et al. the three sites collectively make the "exchangeable phosphorus pool"[17]. Kidneys majorly controls the phosphate levels in the body. Phosphate is initially filtered in the glomerulus. It is then reabsorbed in the proximal tubules under the influence of many hormones. In patients with normal renal function or marginally reduced glomerulus filtration rate (GFR), the serum phosphate levels are chiefly controlled by the amount of reabsorbed phosphate.

In case of chronic kidney disease, the kidneys fail to remove phosphate out of the body and this results in a positive phosphate balance. However, the skeleton contributes to this hyperphosphatemic state, through the disorders of the bone accompanying CKD, as it cannot handle the phosphate excess. This results in increase in need for a new phosphate reservoir. The soft tissue organs including vasculature act as a phosphate reservoir in such cases.[17] The end result is vascular calcification that is commonly found in CKD. Experimental evidence suggests phosphate is responsible for the complete process of vascular calcification resulting in a new consensus that has renamed the old term of “renal osteodystrophy” with CKD mineral bone disorder” (CKDMBD) and it emphasizes upon the almost neglected role of skeleton in such pathological states[17].

McGovern AP et al did a study in a large community-based population to see the association of serum phosphate with cardiovascular events in people with and without CKD. They found that in people with CKD stages 3-5, hyperphosphatemia (>1.50mmol/l) was associated with increased cardiovascular risk; OR 2.34 (95% CI 1.64-3.32; $p<0.001$). They concluded that Serum phosphate was associated with cardiovascular events in people with CKD[18].

The current guidelines and recommendations emphasis that levels of serum phosphate should be kept between 2.7 to 4.7 mg/dl in patients with Stage 3 and 4 CKD and between 3.5 to 5.5mg/dl in patients of stage 5 CKD by dietary restriction of phosphate or by drugs like with phosphate binders[17,19] . Although few old studies suggest a beneficial effect of low phosphate containing diet, the latest evidence shows that this method involves high risk of malnutrition and should be avoided[20,21].

Our findings revealed that phosphate level of CKD patients increased and the cardiac markers also increased significantly and the correlation was observed to be positive. So through this study we explored the role of serum phosphate in CKD patients with elevated cardiac markers. It was the first local study of its kind where the relationship between cardiac markers and serum phosphate levels in patients with newly diagnosed stage 4 and 5 CKD was determined. It is not only helpful in understanding the relationship but also provided a valuable insight to the future management of CKD.

CONCLUSION

We concluded that there is a positive correlation between cardiac markers and serum phosphate levels in patients with newly diagnosed stage 4 and 5 Chronic Kidney Disease not yet undergoing hemodialysis. However, further trials are required to validate our findings.

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