Association of Serum Phosphorus with Left Ventricular Hypertrophy in Chronic Kidney Disease Patients – A Retrospective Study

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ABSTRACT

Introduction: Chronic Kidney Disease (CKD) has evolved into a major non communicable disease in India due both to increased incidence and recognition . Higher Phosphorus levels was shown to be associated with adverse cardiovascular outcomes in both patients on maintenance hemodialysis and earlier stages of CKD patients. Community based surveys done in Western Countries showed significant association between serum phosphorus and left ventricular hypertrophy. However, from the available literature there are no Indian studies which focused on this linkage. This retrospective study was an attempt to investigate if such an association exists.

Material and Methods: This was a retrospective study conducted on 48 patients diagnosed with Chronic Kidney Disease. We divided them into Predialysis group and hemodialysis group. The study participants were subjected to routine blood investigations including serum phosphorous levels along with 2D ECHO to determine presence of left ventricular hypertrophy , left ventricular mass index.

Results: There were 48 patients in the study cohort. 32 of them belonged to Predialysis stage and 16 of them belonged to hemodialysis group . There was a significant positive association between serum phosphorus level and Left ventricular mass in both Predialysis and Hemodialysis patients. Multiple regression analysis showed that BMI, Diastolic Blood Pressure,Serum Phosphorus and Cholesterol levels could predict LV mass to a significant level.

Conclusion: In this retrospective cohort study involving Pre dialysis and Dialysis patients, hyperphosphatemia is positively correlated with LV mass.

Keywords: Serum Phosphorus, Left Ventricular Hypertrophy, Chronic Kidney Disease

INTRODUCTION

Chronic Kidney Disease (CKD) has evolved into a major non communicable disease in India due both to increased incidence and recognition. It is believed to affect more than 10- of Indian adult population. The incidence of End stage Renal Disease is about 152 per million driven mainly by Diabetes, Hypertension and Chronic glomerulonephritis.[1] A substantial percentage of patients in early stages of CKD suffer from excess cardiovascular morbidity and mortality.[2,3] CKD is now recognised as an independent risk factor for development, progression and adverse events in coronary heart disease. Framingham risk score, which is a common yardstick utilised for measurement of cardiovascular risk loses its accuracy when used in CKD population. When renal parameters such as estimated GFR and Albuminuria were incorporated into the risk score the prediction power for cardiovascular events improved.[4] Cardiac structural and functional alterations begin to develop in the early stages of CKD and worsen in a graded fashion as Glomerular Filtration rate (GFR) worsens. These alterations in cardiac structure and function in CKD patients are attributable not only to conventional risk factors like Age, Hypertension, Diabetes and smoking but also to CKD-related risk factors such as Uremic toxins, Anemia and Divalent cation (calcium, phosphorus) disorders.[5] Alterations in Left Ventricular geometry in the form of Left Ventricular Hypertrophy (LVH) forms the structural basis of heart failure, Arrhythmias and sudden cardiac death encountered in a large number of patients with CKD.[6] Recommended dietary reference intake (DRI) of Phosphorus is 700 mg/day in healthy adults. Recently, interest has centered around the role of phosphorus in cardiovascular health of CKD patients. According to KDOQI recommendations Phsophorus intake should not exceed DRI in patients with early stages of CKD (stage two and three) and to 80% of DRI in CKD stages four and five. Recommended dietary reference intake (DRI) of P is 700 mg/day in healthy adults. The dietary habits of modern society has shown a marked increase in dietary Phosphate intake contributed by fast food industry and ready to eat food items with inorganic Phosphate added to increase taste and shelf life.[5] Serum Phosphorus has emerged as an important cardiovascular risk factor in both the general community and patients with CKD.[6] Higher Phosphorus levels was shown to be associated with adverse cardiovascular outcomes in both patients on maintenance hemodialysis and earlier stages of CKD patients[7]

Community based surveys done in Western Countries showed significant association between serum phosphorus and left ventricular hypertrophy.[6] However, from the available literature there are no Indian studies which focused on this linkage. This restrospective study is an attempt to investigate if such an association exists.

Study objectives were to explore the association of serum

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phosphorus with Echocardiographic evidences of left ventricular hypertrophy and Left ventricular mass index amongst CKD patients in both Predialysis and Dialysis cohorts.

MATERIAL AND METHODS

This study was a retrospective study conducted on 48 patients diagnosed with Chronic Kidney Disease who attended the General Medicine outpatient section and inpatients of R.L.Jalappa hospital and research centre Tamaka, Kolar.

Sampling procedure

This was a retrospective observational cross sectional study of patients aged between 18 to 60 years who were diagnosed as CKD as defined by CKD-EPI formula (< 60 ml/min/1.73 m2) of more than 3 months associated with elevated serum creatinine with or without Albuminuria and with or without structural changes of Kidneys by ultrasonography. We divided them into Predialysis group and hemodialysis group. We excluded patients who had established cardiac diseases in the form of known coronary artery disease, cardiomyopathy, myocarditis and valvular and congenital heart disease. Body mass index was calculated by dividing the Body weight (Kg) by the height (m^2). Clinic Blood pressure was measured by mercury sphygmomanometer. Diabetes mellitus was defined as a fasting plasma glucose ≥ 126 mg /dL or if the patient was already a known diabetic. Venous blood sample was obtained after an overnight fast for biochemical analysis using standard assays. The serum calcium value was corrected for albumin levels. M-mode and 2-Dimensional transthoracic echocardiography were performed using a 2.5-MHz transducer. Parasternal view images were obtained in patients lying in the left decubitus position. Left ventricular end diastolic dimension (LVEDd) and posterior wall thickness (PWT) were evaluated by M-mode echocardiography which were used to calculate left ventricular mass with Devereux formula. LV mass was divided by Body surface area to calculate the Left ventricular mass index (LVMI). Left ventricular hypertrophy (LVH) was defined as LVMI greater than 125 g/m^2 in men and 110 g/m^2 in women. The Study was approved by the Institutional ethical committee.

STATISTICAL ANALYSIS

Statistical analysis was done using descriptive statistics like Mean, Standard deviation for quantitative data and Proportion for qualitative data. The significance of difference in mean and other quantitative measures was done using independent student T-test and difference in proportion by using Chi-square test. P</= 0.05 was considered statistically significant. Pearson Correlation Coefficient and Regression analysis were carried out to analyse the association between various dependent and Independent factors. Statistical analysis was carried out using MS Excel 2016 software.

RESULTS

There were 48 patients in the study cohort. 32 of them belonged to Predialysis stage with a mean GFR of 34 ± 14 ml/min/1.73 m^2. 16 of them belonged to hemodialysis group with a mean GFR of 8.4 ± 1.4 ml/min/1.73 m^2. The demographic data are given in Table -1.

As shown in the Table -1, the demographic parameters are mostly comparable between Predialysis and hemodialysis groups except for Body weight. The lower body weight of dialysis patients could be explained by higher levels of uremic inflammation and protein catabolism in dialysis patients.

As shown in Table-2, there were many parameters which were significantly different between Predialysis and

Parameter	Predialysis[32]	Hemodialysis[16]	Student's t test, P value
No. of Patients	32	16	
Age [y]	57 ± 4.5	56 ± 8.8	0.65 [NS]
Gender – Male	50%	56%	0.83 [NS]
Weight [Kg]	65 ± 4	61 ± 5	0.04 *[S]
BMI [Kg/m^2]	22 ± 2.5	23 ± 2.8	0.42 [NS]
Diabetic status	53%	58%	0.33 [NS]
Smoking	12%	8%	0.67 [NS]
Systolic BP [mm Hg]	152 ± 15	155 ± 11	0.91 [NS]
Diastolic BP [mm Hg]	84 ± 6	88 ± 4	0.08 [NS]

Table-1: Demographic Data of patients with CKD

Parameter	Predialysis[32]	Hemodialysis[16]	P value (Student's t test)
Hemoglobin [g /dL]	11.2 ± 1.2	8.8 ± 2.3	0.004* [S]
B.Urea [mg /dL]	68 ± 9	97 ± 8	0.02* [S]
S.Creatinine [mg /dL]	3.5 ± 1.4	5.4 ± 2.1	0.04 * [S]
Fasting glucose [mg/dL]	125 ± 12	132 ± 14	0.12 [NS]
S.Albumin [g/L]	3.4 ± 1.6	3.2 ± 1.2	0.21 [NS]
S.Cholesterol [mg /dL]	176 ± 14	157 ± 8	0.03 * [S]
S.Phosphorus [mg/dL]	4.4 ± 0.26	5.8 ± 1.3	0.001* [S]
S.Calcium [mg/dL]	8.3 ± 1.5	7.8 ± 1.2	0.06 [NS]

Table-2: Biochemical Parameters

Parameter	Predialysis	Hemodialysis	P Value (Student's t test)
LV Mass [g/m ^{2}]	234.6± 25.6	271.7 ±13.7	0.001* [S]
LV Mass Index	130.6± 15.5	161.6 ± 5.9	0.001 * [S]

Table-3: Echocardiographic Parameters

	Coefficients	Standard Error	t Stat	P-value	Lower 95%	Upper 95%
Intercept	142.36	154.99	0.92	0.36	-171.40	456.13
Age	0.71	0.80	0.89	0.38	-0.90	2.33
BMI*	4.81	2.11	2.28	0.03	0.54	9.08
SBP	0.30	0.44	0.68	0.50	-0.60	1.20
DBP**	1.67	0.64	2.62	0.01	0.38	2.97
HB	-7.57	3.93	-1.93	0.06	-15.52	0.39
P***	16.46	5.00	3.29	0.00	6.35	26.57
Ca	-5.67	7.41	-0.76	0.45	-20.68	9.34
Cholesterol****	-0.86	0.31	-2.82	0.01	-1.49	-0.24
Albumin	-18.17	9.91	-1.83	0.07	-38.23	1.89

Table-4: Multiple Regression analysis between LV mass and various independent variables.

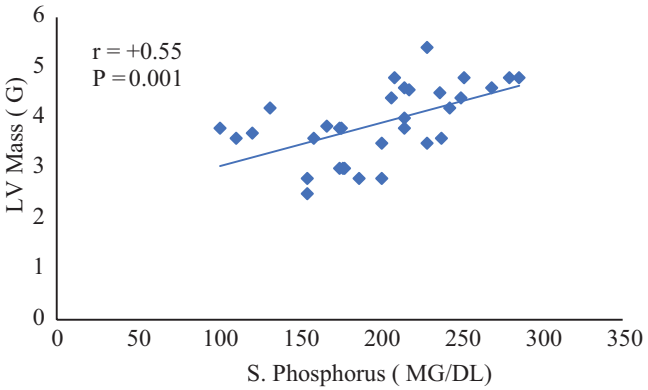

Figure-1: Association between Serum Phosphorus and LV mass in Predialysis cohort.

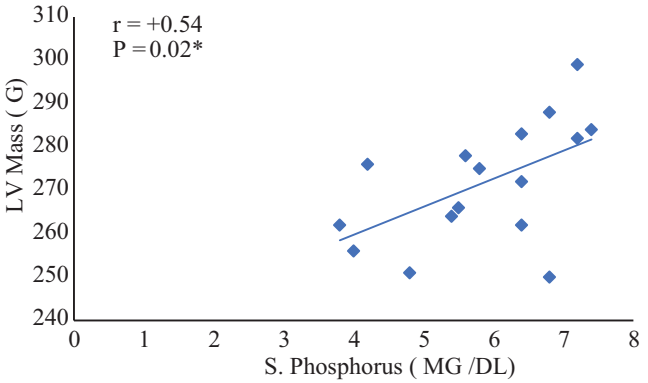

Figure-2: Association between Serum Phosphorus and LV mass in Hemodialysis cohort.

hemodialysis patients. Hemoglobin and serum cholesterol levels were lower while Blood Urea, serum creatinine and serum Phosphorus levels were significantly higher in hemodialysis group.

As shown in Table -3 Echocardiographic measurement of LV Mass disclosed a higher value for hemodialysis group.

As shown in Figure -1 and 2, there is a significant positive association between serum phosphorus level and Left ventricular mass in both Pre dialysis and Hemodialysis patients (r= + 0.55 and +0.55 respectively).

As shown in Table-4, a multiple regression analysis was performed taking LV mass as the dependent variable and various independent variables such as Age, BMI, Blood Pressure, Hemoglobin, S.Phosphorus, Calcium, Cholesterol and Albumin. It showed that BMI, Diastolic Blood Pressure,Serum Phosphorus and Cholesterol levels could predict LV mass to a significant level.

DISCUSSION

Our Study is the first one to demonstrate the highly significant association between serum Phosphorus levels and Left Ventricular mass in patients with CKD. Though association does not always equate with causality, there are strong experimental support for such a nexus. Multiple confounding causes of LVH may exist in CKD patients including hypertension, Renin Angiotensin excess and sodium overload. A latest addition to the list is serum Phosphorus. Serum levels of Phosphorus are not raised in the earlier stages of CKD such as stage 2 and 3 but show an upward trend in Stage 4 and 5. It is a misconception that hyperphosphatemia is less of an issue in Indian population given their predominant Agro based food habits. Publications show that upto 60% of stage 4 and 75% of stage 5 D Indian CKD patients are hyperphosphatemic.[8] The structural basis of high cardiovascular mortality in CKD is Left Ventricular hypertrophy resulting in sudden death, arrhythmias and myocardial infarction. Eddington et al., have shown that higher phosphorus levels are associated with higher risk of death in CKD patients.[9] Serum Phosphorus also is linked to alterations of Left ventricular geometry leading onto eccentric remodelling.[10] Disordered release and function of two hormones namely, FGF-23 and Parathormone could underlie the positive correlation between raising phosphorus levels and LV mass. When healthy volunteers were fed on a phosphorus loaded diet, serum fibroblast growth factor-23 (FGF-23) level increased.[11] FGF-23 is a phosphaturic hormone released from Osteocytes in response to minor elevations of serum Phosphorus. It inhibits the Sodium Phosphate Co- transporter in the renal proximal tubules

ensuring phosphaturia. However, it induces cardiomyocyte hypertrophy via FGF receptor-dependent activation of the calcineurin-NFAT signaling pathway. Studies done on mice models have shown that serum phosphorus has an independent association with Left ventricular hypertrophy.[10] This unique pathway was not dependent on klotho, which is the coreceptor for FGF23 in the kidney and parathyroid glands.[12] A second hemodynamic mechanism may operate in hyperphosphatemia to facilitate LVH. Aortic stiffness increases with hyperphosphatemia which leads to increased afterload and LVH.[13] Secondary hyperparathyroidism of CKD is a potent risk factor for aortic calcification. Hyperphosphatemia increases PTH secretion by as yet unidentified pathway. The hormone PTH is another potential adverse factor inducing Left Ventricular hypertrophy. Measurement of these hormones in our cohort could have thrown more light on the association of serum Phosphorus levels and LV hypertrophy. The therapeutic implications of such an association between serum Phosphorus and LVH are important for the clinician. Clinical practice guidelines support normalizing serum phosphate levels using dietary restriction and phosphate binders. However, the benefits of normalizing serum phosphate are unproven, the optimal serum phosphate target remains unknown and potential harms of aggressive treatment have not been determined. Phosphate binder Sevelamer use is associated with decreased mortality among CKD patients when compared to calcium based phosphate binders in a meta analysis.[14] Animal studies vouch for the benefits of phosphate lowering in ameliorating cardiac hypertrophy.[15] Placebo controlled trial of Phosphate reduction in reducing all cause and cardiovascular mortality is ongoing which is likely to resolve much of the controversy surrounding this area.

CONCLUSION

In this retrospective cohort study involving Pre dialysis and Dialysis patients, hyperphosphatemia is positively correlated with LV mass. Further exploration of this pathway is likely to improve the dismal cardiovascular outlook of patients with CKD.

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