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Role of Serum Alkaline Phosphatase Levels as an Early Marker of Disease Progression in Chronic Kidney Disease

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ABSTRACT

Introduction: Chronic kidney disease (CKD) is an emerging condition with increasing morbidity and mortality. In chronic kidney disease (CKD), disturbance of several metabolic regulatory mechanisms cause premature ageing, accelerated cardiovascular disease (CVD), and mortality. CKD is associated with disturbances in alkaline phosphatase levels significantly in stage 4 and 5. Serum ALP levels has been shown to have a promoting effect on vascular calcification which leads to atherosclerosis and cardiovascular complication.
Aims and Objectives: To estimate the serum ALP levels and to correlate its association with CKD patients Material & methods: 50 cases of CKD and 50 controls were included in the study. Serum Urea, creatinine, alkaline phosphatase were measured in both cases and controls. Statistically significant increases in levels of all parameters were seen. The levels of alkaline phosphatase were also increased in cases but it was not statistically significant.
Conclusion: Elevated ALP levels are associated with an increased risk of End Stage Renal Disease and all-cause mortality in patients with CKD. Alkaline phosphatase levels can be used as an alternate marker for early identification of complications in CKD.

Key words: CKD-Chronic kidney disease, ALP-Alkaline phosphatase, ESRD-End stage renal disease

INTRODUCTION

Chronic kidney disease (CKD) is a worldwide public health problem, affecting between 8% to 16% of the population worldwide, with potentially lethal outcomes like loss of kidney function and cardiovascular diseases.**[1]**

CKD is most commonly attributed to diabetes and hypertension but other causes such as glomerulonephritis other infections and exposure to environmental toxins also plays a role.**[2]**

Early detection and treatment are important as progression of CKD is associated with increased mortality.**[3]**

Alkaline phosphatase is primarily secreted by the liver and bone. Small amounts are also secreted by intestine, kidneys and leukocytes. The osteoblasts are prominent source of alkaline phosphatase. ALP is an indicator for high bone turnover mainly in patients with CKD and are associated with increased mortality in CKD patients. **[4,5,6]**

The mechanism of increased ALP and increased mortality is due to their role in vascular calcification. Enzyme Pyrophosphate is an endogenous inhibitor of hydroxy apatite formation which is present in the arterial wall and is a potent inhibitor of vascular calcification and hence a protective factor for maintaining vascular integrity.**[7]**

Alkaline phosphatase is known to promote vascular calcification, by hydrolysing pyrophosphate. **[6]** Apart from vascular calcification, inflammation, and insulin resistance are other potential

mechanisms for the association between higher serum alkaline phosphatase levels and increased mortality. **[8,9]**

In presence of co-morbid conditions like hypertension, ageing and diabetes the vascular cells undergo osteoblastic differentiation and express several bones associated proteins which include alkaline phosphatase. This leads to mineralization of the endothelium, arterial stiffening and vascular calcification. Vascular calcification is one of the major contributors to atherosclerosis and leads to vascular hardening, ageing and significant vascular events contributing to the cardiovascular disease and mortality.**[10]**

The Proposed mechanism of renal damage from arterial stiffness include highly pulsatile blood pressure and flow to the low resistance renal vascular bed and defects in the filtration barrier leading to intraglomerular hypertension, hyperfiltration, and eventual nephrosclerosis. **[11]**

Several Studies have shown that, circulating ALP is a robust and independent risk marker for CVD and mortality in CKD. **[12]**

Hence this study was taken up to see the association of alkaline phosphatase levels in chronic kidney disease patients.

Aims and Objectives

To estimate the serum ALP levels and to correlate its association with CKD patients.

MATERIALS AND METHODS

The study was conducted at Vydehi Institute of Medical Sciences and Research Centre, Bangalore, Karnataka. After a written informed consent, 50 patients diagnosed with CKD were included in the study. Patients with history of auto immune disorders and congenital renal disorders were excluded from the study. The basic personal details of patients were documented. A detailed clinical, personal, family history was taken from each patient. Healthy individuals were included as controls in the study. Blood samples were collected in vacutainers and transported to the laboratory and analysed.**[13]**

The investigations like Serum urea, creatinine, Alkaline phosphatase were analysed. Beckman coulter Unicell DXC 600 was used to analyse all chemistry analytes. Bio Rad Controls were used for all parameters.

Methodology

Serum Urea was measured by enzymatic Conductivity rate method **[14]**, serum Creatinine was measured by modified rate Jaffé method **[15]** and serum Alkaline phosphatase activity was measured by a kinetic rate method.**[16]**

Statistical analysis

Descriptive and inferential statistical analysis has been carried out in the present study. Results on continuous measurements are presented on Mean ± SD (Min-Max) and results on categorical measurements are presented in Number (%).

Significant figures

+Suggestive significance (P value: $0.05<P<0.10$), *Moderately significant (P value: $0.01<P\leq0.05$), **Strongly significant (P value: $P\leq0.01$.

Statistical software

The Statistical software namely SPSS 15.0, was used for the analysis of the data and Microsoft word and Excel have been used to generate graphs, tables etc. **[17,18]**

RESULTS

For our study, the following results were obtained.

Samples were matched according to their age. Maximum number of patients, 32% were in the age group of 51-60 years, followed by 24% patients in 31-40 yrs. The mean age in patients is 47.26±12.73 years, whereas in controls age is 43.83±15.12 years.

Samples are gender matched. 70% of cases are males and 30% are females. In controls 62% are males and 38% are

females. Among the study population, 66% were diabetic and 63% were hypertensive.

Table 1: Gender distribution in cases and controls studied

Gender	Cases		Controls	
	No	%	No	%
Male	35	70	31	62
Female	15	30	19	38
Total	**50**	**100.0**	**50**	**100.0**

Samples were gender matched

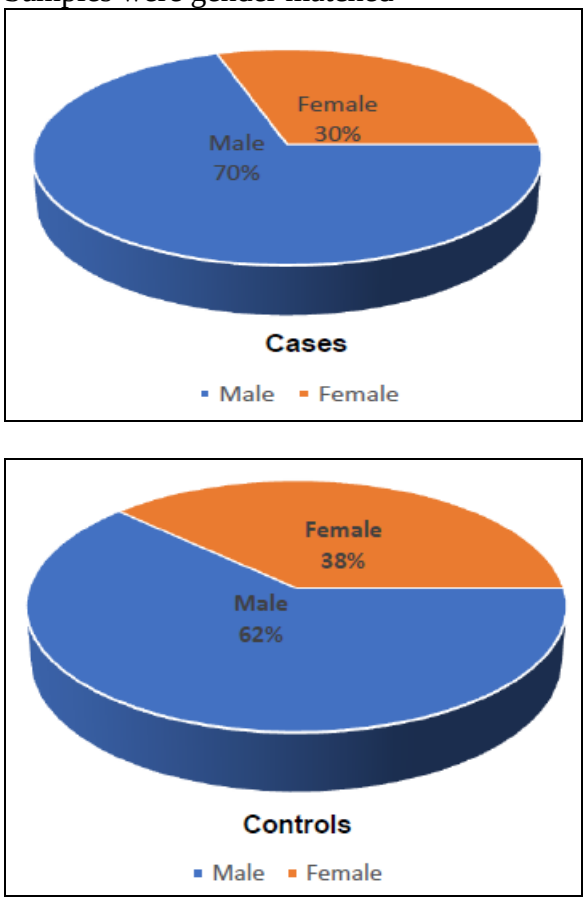

Figure 1: Gender distribution in cases and controls studied

Samples are gender matched. 70% of cases are males and 30% are females. In controls 62% are males and 38% are females.

Table 2: Comparison of mean levels of various bio chemical parameters in cases and controls

Biochemical parameters	Cases	Controls	P value
Urea mg/dl	76.60±69.77	23.54±7.46	<0.001**
Creatinine mg/dl	4.11±4.25	0.56±0.10	<0.001**
Alkaline Phosphatase IU/L	90.92±46.37	82.91±21.78	0.285

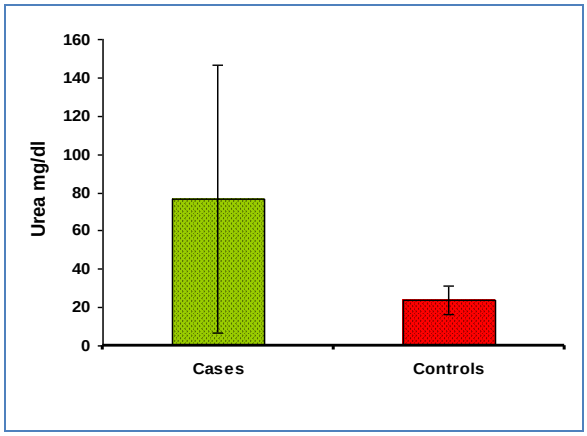

Fig 2: Mean Urea levels in cases and controls

Statistically significant increase in urea levels was seen in cases as compared to controls (p<0.001). The mean level in cases is 76.60±69.77 and control is 223.50± 7.46(p<0.001).

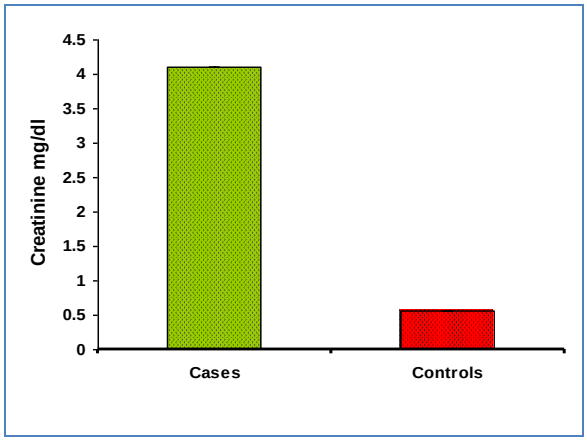

Fig 3: Mean creatinine levels in cases and controls

Statistically significant increase in creatinine levels was seen in cases as compared to controls (p<0.001). The mean level in cases is 4.11±4.25 and control is 0.56± 0.10(p<0.001).

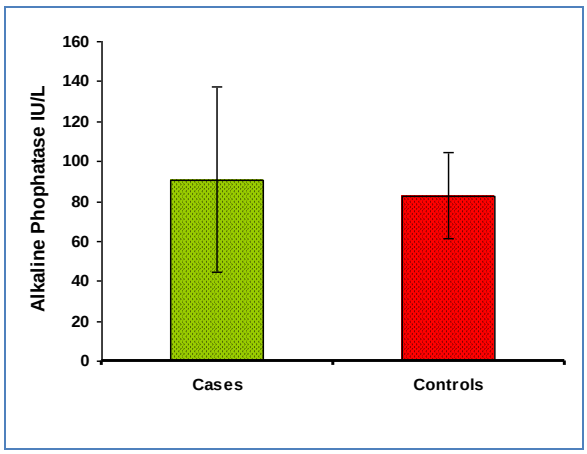

Fig 4: Mean Alkaline Phosphatase levels in cases and controls.

There is elevation in Alkaline Phosphatase levels in cases as compared to controls but the increase was not statistically significant. The mean level in cases is 90.92±46.37 and control is 82.91± 21.78(p=0.285).

Distribution of Alkaline Phosphatase in two groups studied

Alkaline Phosphatase levels were measured in cases and controls.

The normal range is 56-153 IU/L. 94% of patients had alkaline phosphatase levels between 56-153 IU/L where as 98% of controls had in the same range.

6% of cases had levels >153 IU/L and only 2% of controls had in the same range.

Table 3: Distribution of Alkaline Phosphatase in two groups studied

Bio chemical parameters	Cases (n=50)		Controls (n=50)	
	No	%	No	%
Alkaline Phosphatase IU/L				
• <56	6	12	5	10
• 56-153	41	82	44	88
• >153	3	6	1	2

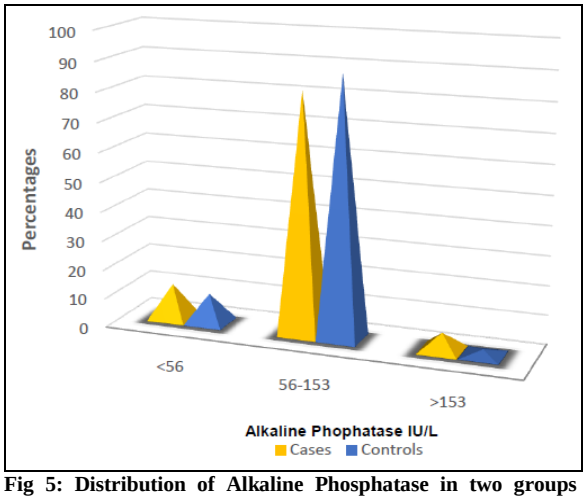

Fig 5: Distribution of Alkaline Phosphatase in two groups studied

DISCUSSION

Chronic kidney disease (CKD) is a state of imbalance of several important physiologic regulatory mechanisms, among them mineral balance, acid– base balance, nutritional balance, and energy balance, resulting in accelerated cardiovascular disease (CVD) and mortality.**[19,20]**

Elevated ALP may be causally involved in the cardiovascular calcification of CKD.**[7]**

High serum alkaline phosphatase is associated with increased mortality. An analysis of the Dialysis Outcomes and Practice Patterns Study (DOPPS) database found that elevated serum alkaline phosphatase levels in hemodialysis patients were associated with higher risk of hospitalization and death. The potential mechanisms for this observation remain unclear.**[21]**

ALP has been shown to be associated with arterial calcification in the coronary, carotid, and aorta, and superficial femoral artery and therefore ALP has been suggested as a surrogate for arterial stiffening.**[22]**

In our study increase in serum alkaline phosphatase levels were observed in cases as compared to controls and the rise was of significant only in stage 5.

Lee et al studies concluded saying, that alkaline phosphatase can promote vascular calcification by hydrolyzing pyrophosphate in the arterial wall.**[23]**

Sigrist et al conducted a longitudinal study and found elevated levels of alkaline phosphatase in stage IV and V of CKD, they found that higher levels of serum alkaline phosphatase were associated with progressive arterial calcification.**[22]**

Our findings are in agreement with study done by Freethi et al. who also found that the mean activity of serum Alkaline phosphatase was significantly higher in chronic kidney disease patients compared to the Healthy subjects (controls) (p<0.0001).**[24]**

Beddhu et al. reported that doubling of ALP was associated with a 55% increase rate in all-cause mortality in the African American Study of Kidney Disease and Hypertension (AASK) cohort. There was no association noted between ALP and the composite of death, dialysis, or GFR event.**[25]**

Another study including a veteran population with CKD stages 1–5 reported a 17% risk of death for every 50 U/L increase in ALP. After multivariate adjustment, the higher (>105 U/L) and lower (<66U/L) were

associated with all-cause mortality and a composite of pre-dialysis mortality and ESRD.**[26]**

Improving Global Outcomes (KDIGO) guidelines recommends monitoring chronic kidney disease, mineral and bone disorder biochemical markers, including PTH, calcium, phosphorus, and ALP, in patients with moderate-to-severe chronic kidney disease.**[27]**

Serum alkaline phosphatase levels were found to be elevated in diabetes, hypertension, and cardiovascular disease. Thus, serum alkaline phosphatase in CKD could reflect an inflammatory and atherogenic sequence. **[10]**

These might be potential mechanisms for the observed increased mortality associated with elevated serum alkaline phosphatase seen in CKD patients.

CONCLUSION

Elevated ALP levels are associated with an increased risk of ESRD and all cause mortality in patients with CKD. This readily available, inexpensive biomarker ALP can be used by clinicians as a risk assessment tool to identify patients with higher risk for mortality or ESRD progression. Hence, ALP is a predictor of mortality in CKD patients.

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