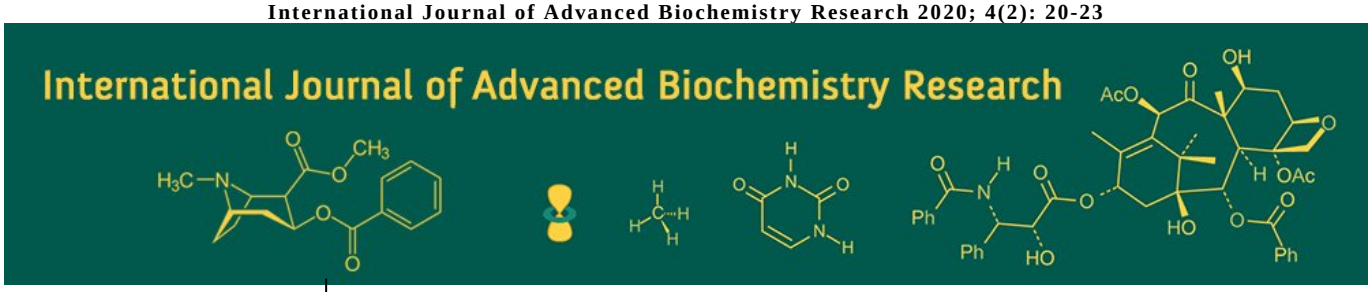

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Study of serum alkaline phosphatase in chronic kidney disease

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Abstract
Introduction: Chronic kidney disease (CKD) now a day becomes an emerging condition with increasing morbidity and mortality. CKD associated with disturbances in alkaline phosphatase levels significantly alters in stage 4 and 5. Serum ALP levels have been shown to have a promoting effect on vascular calcification. So, correlation of ALP with renal failure is also well established.
Aim: To compare the level of serum ALP, urea and creatinine among the CKD patients and healthy controls.
Materials and method: About 50 CKD patients in stage 4 & 5 in dialysis unit and 50 healthy subjects between the age group 30-60 yrs were included in this study carried out from May2018 to January2020 at Noor hospital and IIMSR Medical College, Warudi, Maharashtra. Serum level of ALP, urea and creatinine were measured by fully autoanalyzer. Statistical analysis is done by minitab version 17 software.
Results and conclusion: The results are presented as a mean ±SD and 'P' values of less than 0.05% is considered as significant. In our study ALP, urea and creatinine are increased in stage 4 and 5 CKD patients.

Keywords: Chronic kidney disease, eGFR, alkaline phosphatase, urea and creatinine.

Introduction
Chronic kidney disease (CKD) is a worldwide public health problem with increasing prevalence and potentially lethal adverse outcomes like progressive loss of kidney function, cardiovascular disease and premature death.
According to the kidney Disease Outcomes Quality Initiative (KDOQI) of the National Kidney Foundation (NKF) defines CKD as either kidney damage or a glomerular filtration rate (GFR) <60ml/min/1.73m^2 for 3 or more months with pathological abnormalities or damage, including abnormalities in blood or urine tests [1].
CKD is now recognized as a major medical problem worldwide. The Global Burden of Disease (GBD) study ranked CKD 17th among the cause of death globally (age standardized annual death rate of 19.2 deaths per 100000 populations). In India, GBD 2015 ranks CKD as the eighth leading cause of death.
Death due to renal failure constituted 2.9% of all deaths in 2010-13 among 15-69 years old, an increase of 50% from 2001-03 [2].
In patients with CKD including those undergoing hemodialysis therapy or predialysis CKD stages (1-5) various abnormalities related to mineral and bone disorders with certain enzyme defects have been implicated as novel risk factors of mortality [3].
Serum ALP levels have been shown to have a promoting effect on vascular calcification through the pyrophosphate pathway. In addition to the directly toxic effects of the contrast agent, disturbances in renal blood flow, vasoconstriction of renal vessels, oxidative stress, free radical damage and endothelial dysfunction are thought to be major mechanisms in the development of kidney disease [4].
CKD consists of a wide spectrum of conditions associated with a progressive decline in kidney functions and abnormal glomerular filtration rate (GFR). According to the recent guidelines of the National Kidney Foundation is classified into1-5 stages based on estimated GFR (eGFR).In stage 1 & 2 no symptoms associated with decreasing eGFR. In stage 3, 4 and 5 complications are more common [5].

Disturbance in mineral metabolism and bone disease are common complications of CKD. CKD affects about 5-10% of the world population and the expected incidence is approximately 5-8% every year [1].

Elevated ALP is associated with increased mortality in patients with predialysis CKD. Low ALP appears to be associated with short term mortality [6].

Serum ALP increases in patient with CKD and high turnover bone disease. Several mechanism link ALP to inflammation. Circulating ALP correlates well with circulating CRP and ALP has been suggesting as a component of hepatic acute phase reactant. Higher ALP has been associated with increased mortality and coronary calcification in dialysis patients.

The ubiquitous expression of ALP and its involvement in several pathophysiological processes with CKD & CVD.

Circulating ALP is better predictor of incident fractures in dialysis patients than bone mineral density. Circulating ALP is a robust and independent risk marker for CVD, mortality in the general population and in CKD [7].

Studies conducted in the general population and in the CKD patients have shown independent associations between ALP and an increased risk of cardiovascular events, hospitalization and death, higher ALP levels are associated with an increased risk of all-cause mortality end stage renal disease (ESRD) [5].

Material and Methods

This study was concluded from April 2018 to Dec 2019 at Noor hospital and IIMSR Medical College, Warudi, Maharashtra. Total 50 patients of advanced chronic kidney disease. (Stage 4 & 5) between the age 35 to 60 years and age match with 50 healthy individuals as control. Blood samples were collected within 12 hours of admission in hospital. Serum level of urea, creatinine and alkaline phosphatase measured by Erba diagnostic kit of fully autoanalyzer Erba EM200.

eGFR is calculated by CKD-EPI formula for staging chronic kidney disease.

Inclusion criteria: Patient in stages 4 & 5 of CKD eGFR where $15^{x}29$ml/min/1.73 m^2 and 15 ml/min/1.73 m^2 of both sexes, age group is 35-60 yrs.

Exclusion criteria: CKD patients those who are on peritoneal dialysis. Exclusion of patients with earlier stages of CKD with eGFR estimated ≥ 60 ml/min/1.73$m^{2.}$ Who had albumin urea and other structure abnormalities.

Statistical analysis was done by Minitab version 17 software. Student 't' test was applied to compare the difference between the two means. The serum parameters in all cases had been measured using fully automated Erba 200 routine chemistry analyzer with commercial kits (Erba diagnostics)

Estimated GFR was calculated in each cases by the formula. Equation from the modification of diet in Renal Disease study eGFR---ml/min/1.73m^2 = 1.86 ^{x} $PCr^{-1.154x}$age-0.203 multiplied by 0.742.

Results

In this study characteristics were summarized according to quarantiles of ALP levels and presented as number percentage for continuous variables with a normal distribution. The reported P values are two –sided and reported as significant at <0.05 for all analyses. For those with a skewed distribution. Differences across quartiles were assessed using analysis of variance

and chi-squared tests for continuous and categorical variables respectively. All analyses were conducted using minitab version 17.

Table 1: Mean and SD of eGFR, urea, creatinine and alkaline phosphatase of cases and controls

Variables	Patients means ±SD N = 50	Controls means ±SD N = 50	P values
Urea mg/dl	76.41±13.23	28.88±5.49	<0.001
Creatinine mg/dl	4.032±1.18	0.83±0.21	<0.001
ALP U/L	431±29±237.11	80.18±0.74	<0.01
eGFR ml/min/1.73m^2	15.66±6.3	92.6 ±24.6	<0.01
Age	47.20±5.42	47.29±4.75	NS

Discussion

Serum ALP is a membrane anchored ectoenzymes that catalyzes the hydrolysis of organic pyrophosphate, which has been shown to be a protective factor for vascular integrity. It has been proposed that ALP may play a role in the pathophysiology of renal dysfunction patients with CKD had relatively higher ALP levels with statistical significance.

The vasculopathic effect of ALP was initially shown in dialysis patients. Vascular calcification is one of the major contributors to atherosclerosis, which leads to vascular hardening, ageing and final significant vascular event. Upregulation of serum ALP levels has been observed in vessels with medical calcification, which supports the mediator role of ALP [4].

Leibovitch *et al*., proposed serum ALP levels have been established as a marker of renal damage. Several studies have reported that the urinary ALP levels may predict early detection of diabetic nephropathy, even with a normal serum creatinine levels. Thus, the serum ALP levels may predict subclinical renal damage [8].

Historically, ALP level has only been considered a surrogate of bone metabolism in patients with CKD and ESRD. ALP is derived from various tissues but is mostly concentrated in the liver, biliary duct, bone and placenta. Tissue nonspecific ALP inactivates pyrophosphate an endogenous inhibitors of hydroxyapatite formation, resulting in medical arterial vascular calcification. Under conditions such as hypertension, ageing, diabetes and CKD, vascular cells undergo osteoblastic differentiation and express several bone associated proteins, including ALP. Subsequently, this differentiation leads to mineralization of the endothelium, arterial stiffening and vascular calcification, arterial stiffness might contribute to the progression of CKD.

Elevated ALP levels are associated with an increased risk of ESRD and all cause in CKD patients. These findings, along with previous studies suggest that, clinicians may use ALP as a risk assessments tool to identify patients with higher risk for mortality and/or progression to CKD [9].

Recently emerging evidence from large-scale cohort studies suggests that serum ALP levels are associated with higher risk for mortality not only in the general population but also in CKD patients [6].

However, in CKD patients, renal osteodystrophy could result in a significant increase in the bone isoenzyme of ALP contributing to high serum ALP level. In fact, higher

ALP has been associated with increased mortality in predialysis CKD as well as patients on maintenance hemodialysis [5].

In our study, the serum ALP levels were significantly higher in CKD patients with or without end stage renal disease. (ESRD). Human ALP is produced by tissue nonspecific liver, intestinal and placental type enzymes. A number of studies have provided evidence that, a portion of ALP human kidney is of intestinal type [10].

Recent studies have shown that, non-dialysis dependent CKD populations, higher ALP levels are associated with increased risk for all-cause mortality. In kidney diseases Improving Global Outcomes recommended that ALP measured annually in patients with CKD stage 4 and 5. Higher ALP levels are independently associated with an increased risk for end stage renal disease and death in those with CKD stage 3 and 4. We evaluated the relationship between ALP and CKD for late stage [11].

High serum ALP is associated with increased mortality. An analysis of Dialysis Outcomes and Practices Patterns Study (DOPPS) database found that elevated serum ALP in hemodialysis patients were associated with higher risk of hospitalization and death.

To summarize this study brings significant increase in ALP levels in CKD. All these parameters were found in worse with increase in the stage of CKD highlighting the higher risk of lethal complications secondary to impaired metabolism with poorer renal function [1].

Serum ALP levels are commonly elevated in CKD and dialysis patients. The osteoblast is a prominent source of ALP. As hyperparathyroidism and high turnover bone disease are common is a dialysis patient. A potential mechanism for this increased mortality in vascular calcification. Pyrophosphate in the arterial wall is a potent inhibitor of vascular calcification. By hydrolyzing pyrophosphate, ALP can promote vascular calcification. In addition to vascular calcification, there are other potential mechanisms that may mediate the associations of serum ALP increased might be associated with inflammation. These data suggest that, elevated serum ALP levels might reflect not only altered bone mineral metabolism but also an atherogenic milieu and inflammation. So ALP not only merely a marker of bone mineral metabolism. Higher ALP levels had poorer nutritional status, lower muscle mass and inflammation and thus were more likely to be susceptible to severe infections [12].

Elevated ALP levels are associated with higher risk of adverse clinical outcomes mortality, cardiovascular events, hospitalization. Mortality in dialysis patients suggests their potential value as a treatment target. Further studies are needed to determine if interventions that lower pre ESRD. ALP levels can reduce mortality after dialysis initiation.

Conclusion

Elevated ALP is associated with increased mortality in patients with dialysis CKD. Circulating ALP is better predictor of incident fractures in dialysis patients than bone mineral density. Circulating ALP is a robust and independent risk marker for CVD, mortality in the general population and in CKD. We suggest that, clinician may use ALP as a risk assessment tool to identify patient with higher risk for mortality and end stage renal disease progression.

These abnormalities start in early stages of CKD and worse with disease progression, so understanding of the pathophysiological consequences of the same and planning management strategies to prevent disease progression. Given the prognostic importance of ALP, it may serve as a target for the treatment of hemodialysis patients, further research may be done for the role of novel ALP inhibitors that suppress vascular smooth muscle cell calcification in reducing mortality and morbidity in CKD and CVD.

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