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Cracking the code: Is Alkaline Phosphatase a Hidden Predictor of Cardiovascular and Cerebrovascular events

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Abstract

Introduction: Alkaline phosphatase (ALP) is a group of isoenzymes that is found in the kidney, placenta, bone, ileal mucosa, and liver. In clinical practice, it is commonly used in as a biomarker of hepatobiliary and skeletal diseases. Moreover, the elevation of this enzyme has been reported to be associated with various cardiovascular and cerebrovascular disorders. Very few studies have discussed about the association of ALP with Cardio and cerebrovascular events.

Objective: The aim of this study was to evaluate the potential association of serum ALP levels with cardiovascular and cerebrovascular disorders.

Material and methods: In this retrospective study, case records of patients who were investigated for liver enzyme levels of ALP for the past 6 months were screened and the data was documented. Statistical analysis was performed using SPSS software version 24.

Results: The results revealed that patients with cardiovascular disorders had higher ALP values than patients with cerebrovascular disorders. This could be due to the hydrolysis of PPi to inorganic phosphate by serum ALP leading to microcalcification related vascular events. ALP levels not significantly altered in

Conclusion: This study signifies the ALP levels as one among the vascular biomarkers in predicting the micro calcification related acute vascular events. Further studies are required

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to evaluate the same in prospective long-term analysis on survival benefit in cardiovascular disease patients.

Keywords: Alkaline phosphatase, cardiovascular disorders, cerebrovascular disorde

Introduction:

Alkaline phosphatase (ALP) is a group of isoenzymes present in various organs like the liver, kidney, placenta, bone, and the ileal mucosa. These are categorized into tissue-specific and tissue nonspecific types. The tissue-specific forms are found in the intestine, placenta, and germinal tissue. The tissue-nonspecific type form most of the fraction circulating in body serum. [1] The exact physiological function of this enzyme is still unclear. However, reports suggest that serum ALP activity is commonly used in clinical practice as a biomarker of hepatobiliary and skeletal diseases. ALP is an inflammatory mediator similar toC-reactive protein (CRP) which acts as a novel risk marker for cardiovascular disease (CVD).Thus, both ALP and CRP have been reported to have a direct association with each other owing to the fact that they share common biological pathways.[2] In relation to cardiovascular disorders, a high level of serum ALP is associated with an increased risk of mortality and myocardial infarction.

ALP hydrolyses inorganic pyrophosphate, which strongly inhibits calcium phosphate deposition, this leads to increase in coronary artery calcification, which is an important marker of cardiovascular atheroma and various cardiovascular events.[3] Studies suggest that ALP is elevated in patients with Subcortical Ischemic Vascular Disease (SIVD) and there is a significant positive relationship with cognitive impairments in SIVD patients. These findings are clinically important for detecting possible cognitive impairments during early stages of SIVD.[4] Serum ALP level is increased in patients with Acute Ischemic Stroke. However, it is considered as a low-potency biomarker for the diagnosis of this condition.[5].

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Few studies have been conducted on association of ALP with different cardiovascular and cerebrovascular disorders. The aim of this study was to evaluate the potential association of serum ALP levels with cardiovascular and cerebrovascular disorders.

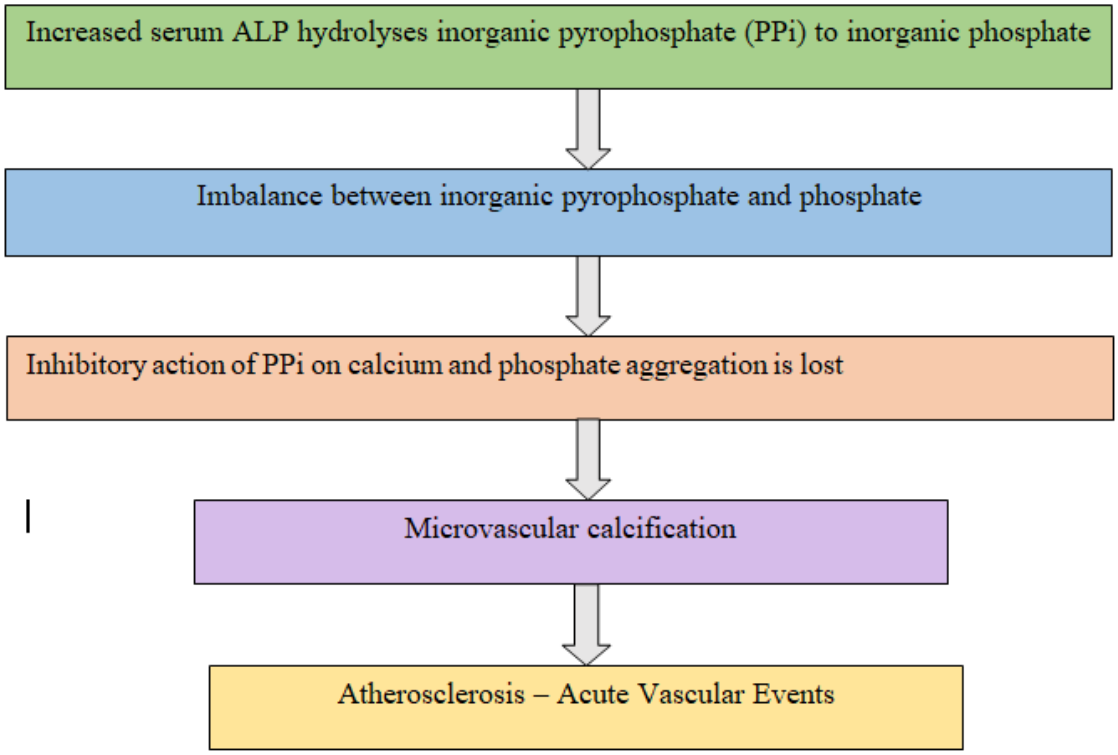

Fig.1: Pathway depicting the High serum Alkaline phosphatase link with microcalcifcation leading to Atherosclerosis

Material and methods

After obtaining ethical approval 19/243, a retrospective study where in 150 case records of patients who had been investigated for liver enzyme levels were assessed and the data were documented. The study took place in a tertiary care hospital of Coimbatore. Case sheets of patients with cardiovascular and cerebrovascular disorders who had been investigated for liver enzymes for the were included in the study**.** Case sheets of patients who were diagnosed with endocrine, bone and hepatic abnormalities as well as pregnant patients were excluded from the study. The data recorded were age, sex, diagnosis, and laboratory levels of serum ALP. Additionally, serum ALP levels of patients with the above-mentioned disorders that were on

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statin therapy were also recorded and tabulated separately. All these data were documented and entered in excel sheets. Data analysis was done using Microsoft excel and R i386 3.6.3. Continuous variables were represented by mean ± standard deviation. Categorical variables were represented by frequency tables. Categorical data compared using chi-square test with simulation. $p<0.05$ considered as significant.

Results: A total of 150 cases with mean age 63.27 ± 13.05 years were included in the study among which 108 were male and 42 were female.

It has been observed that, among 19 patients aged between 20-50 years, 1 (5.26%) had ALP > 140 U/L which indicates very high ALP, 3(15.79%) had high normal, 13(68.42%) had ALP ranging from 50 -100 U/L and 2 (10.53%) had ALP less than 50 U/L. Whereas in 131 patients of age group 50 years and above, 20 (15.27%)had very high ALP , 27 (20.61%) had high normal ALP, 79 (60.31%)had normal ALP and 5 (60.31%)had ALP less than 50. Even though high ALP levels exist with increasing age group, but statistically using chi-square test, it has been concluded that distribution ALP is not significantly different over age group in patients with cardiovascular or cerebrovascular disorder($p=0.3693$).

Among 108 male cases, 16(14.81%) had very high ALP and 16 ((14.81%) high normal ALP, 71 (65.74%) had normal ALP and 5 (4.63%) had ALP less than 50 U/ L while among 42 female cases, 5(11.9%) had very high ALP, 14 (33.33%) had high normal ALP, 21 (50%) had normal ALP and2 (4.76%) had ALP less than 50. Using chi-square test with simulation, it has been concluded that distribution of ALP is not significant different over gender in cases with cardiovascular or cerebrovascular disorder ($p=0.0805$).

Among 82 patients with CAD/IHD/Acute coronary syndrome, 15 (18.07%) had very high ALP, 16 (19.28%) had high normal ALP, 50 (60.24%) patients had ALP ranging from 50-100

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U/L and 2 (2.41%) patients had ALP less than 50 U/L. In 4 patients with cardiomyopathy and related disorders, 2 (50%) patients had very high ALP, 2 cases (50%) had ALP ranging from 50-100 U/L.

Out of the 72 cases with cerebrovascular disorder diagnosed with Stroke and TIAs, 7 (9.72%) patients had very high ALP, 15 (20.83%) patients had high normal ALP, 45 (62.5%) patients had ALP ranging from 50-100 U/L and 5 (6.94%) patients had ALP less than 50 U/L.

In 94 patients with cardiovascular or cerebrovascular disorders who are on Statin therapy, 13 (13.83%) patients had very high ALP, 18 (19.15%) patients had high normal ALP, 59 (62.77%)patients had ALP ranging from 50-100 U/L and 4 (4.26%) patients had ALP less than 50 U/L.

In 56 patients with cardiovascular and cerebrovascular disorders who are not on Statin therapy, 8 (14.29%) patients had very high ALP, 12 (21.43%) patients had high normal ALP, 33 (58.93%) patients had ALP ranging from 50-100 U/L and 3 (5.36%) patients had ALP less than 50 U/L.

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Factor	Sub-category	ALP (U/L)			
		>140	101-140	50-100	<50
Age group	20-49	1 (5.26%)	3 (15.79%)	13 (68.42%)	2 (10.53%)
	50 years and above	20 (15.27%)	27 (20.61%)	79 (60.31%)	5 (3.82%)
Gender	Male	16 (14.81%)	16 (14.81%)	71 (65.74%)	5 (4.63%)
	Female	5 (11.9%)	14 (33.33%)	21 (50%)	2 (4.76%)
Cardiovascular disorder	CAD/IHD/Acute coronary syndrome	15 (18.07%)	16 (19.28%)	50 (60.24%)	2 (2.41%)
	Cardiomyopathy and related disorders	2 (50%)	0 (0%)	2 (50%)	0 (0%)
Patients with cerebrovascular disorder (Stroke & TIA only)		7 (9.72%)	15 (20.83%)	45 (62.5%)	5 (6.94%)
Statin therapy	Patients with cardiovascular or cerebrovascular disorders on Statin therapy	13 (13.83%)	18 (19.15%)	59 (62.77%)	4 (4.26%)
	Patients with cardiovascular or cerebrovascular disorders not on Statin therapy	8 (14.29%)	12 (21.43%)	33 (58.93%)	3 (5.36%)

Table1: Frequency distribution of classified ALP levels status according to the demographic details, comorbid cardiovascular & cerebrovascular conditions and on statin drug therapy.

Discussion:

A high level of ALP activity is independently and positively associated with the incidence of coronary artery calcification. [3] Complete inhibition of calcium and phosphate deposition which leads to micro calcification is achieved by a physiological concentration of PPi. In case of high ALP levels in the body, inhibitory effect of inorganic pyrophosphate (PPi) on vascular calcification is lost due to its hydrolysis by ALP. [6, 7] Epidemiological studies also have shown that high ALP levels are associated with cardiovascular events in the general population as well as in patients with secondary cardiovascular prevention. [8, 9]

Kabootari M, *et al* has reported that ALP level >179 IU/L is associated with >30% higher risk of CVD (including CAD and stroke events), independent of established traditional CVD risk factors. [10] In this study, 60% patients with CAD, and 50% patients with cardiomyopathy

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and 62.5% patients with stroke or TIA related cerebrovascular disorders had their ALP values in the range of 50-100 IU/L which gives the insight that irrespective of established cardiovascular and cerebrovascular disorders, patients on their proper medical management has normal ALP levels subjecting to low risk primary and secondary cardiovascular and cerebrovascular events. [10]

Wannamethee SG, *et al* showed that in older men with high ALP value >140 IU/L and no previous event of acute MI or stroke, was associated with increased risk of CAD and CVD events; this could be partially explained by its association with inflammation and established risk factors. [11] Abramowitz M, *et al* in their study found that higher serum ALP is associated with increased mortality and hospitalization due to CVD. [12] In this study it was found that among 131 patients of age group 50 years and above, 20 (15.27%) had ALP levels >140 IU/L and 27 (20.61%) had ALP level ranging around 101-140 IU/L suggesting similar risk of CAD and CVD events as evidenced in the previous studies compared to younger aged people, which in force the need of proper medical management in order to avoid risk of CAD and CVD events. Among 19 patients aged less than 50 years, only 3 patients had high ALP values whereas remaining 16 (78%) patients had normal ALP levels in which in turn falling in low risk category of CAD and CVD events. These results suggest that definite age factor related association with ALP levels, but not statistical significant (p=0.3693) which was analyzed using chi-square test. However, elderly people with cardiovascular and cerebrovascular disorder should keep an eye on ALP levels in order to avoid risk of micro calcification leading to atherosclerosis related acute events.

In the present study, it was found that patients with cardiovascular disorders showed higher ALP values as compared to cerebrovascular patients. In reference to previous studies [3], the underlying reason for its association with cardiovascular diseases is attributed to the

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hydrolysis of inorganic pyrophosphate (PPi) to inorganic phosphate by serum ALP. PPi is an inhibitor of calcium and phosphate aggregation. Thus, an increased serum ALP activity induces an imbalance between inorganic pyrophosphate and phosphate, leading to ectopic vascular calcification which may result in premature atherosclerosis and various other cardiovascular events. [3] According to the evidence, the increased ALP is a result of liver dysfuction secondary to coronary artery disease especially related to heart failure due to CAD, congestive heapatopathy, ischemic hepatitis due to poor blood flow from the heart. Hence the primary focus of treatment is to address the underlying cardiac condition to prevent the further progression of disease and to restore the proper blood flow to the liver.

Ryu WS, *et al* conducted a study to assess the relationship between serum alkaline phosphatase and stroke. The study concluded that an increased level of ALP is a predictor of mortality after acute ischemic stroke. [13] In the present study, among the 72 patients with cerebrovascular disorders, most of the patients almost 50 had ALP level ranging from 50-100 U/L which is under the normal standard levels. In this study overall the expression of cerebrovascular disease patients were less compared to cardiovascular disease patients. So as per the present study we could not evidence the increase ALP among the cerebrovascular disorder patients. But, previous clinical studies have reported ALP as a diagnostic and prognostic marker for the assessment of stroke risk by correlating the indices of ALP activity, stroke severity and hypertension. [14, 15]. Studies also have reported that increased ALP in associated with risk of cardiovascular disease which is one of the risk factors for stroke as well [10, 16]. Hence the findings related to increased ALP levels and its correlation in cerebrovascular disorders outcome needs confirmation with a prospective, follow up studies on long term survival benefits.

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In this present study, among the 94 patients with Cardiovascular or Cerebrovascular disorders on statin therapy , the ALP levels was high in 31 (32%) compared to 56 patients of Cardiovascular or Cerebrovascular disorders with not on statin therapy in which ALP levels were found to be high in 20 (35%) patients. In reference to previous studies [17], it could be due to the paradoxical effect of statins through which it stimulates calcification of osteoblasts and paradoxically inhibits myofibroblast calcification in the cardiac valve. Statins have been reported to be associated with hepatic injury that causes an increase in various liver enzymes including ALP. [18] The mechanisms involved in hepatocellular injury associated with statin are not fully established yet; however, animal studies suggest that the decrease in mevalonate or one of its sterol intermediates may be involved in the elevation of liver enzymes. Furthermore, asymptomatic elevation without histopathologic changes may occur due to changes in the composition of hepatocyte membrane lipid leading to increased permeability and leakage of the liver enzymes. Statin-induced liver toxicity may also occur due to intake of high oral dose of statin daily, which may result in extensive hepatic metabolic activity and lipophilicity, ultimately causing drug-induced liver injury. [19] This implies that inspite of stating various pathways of statin increasing the ALP levels, most of the patients on statin therapy in this study have normal ALP levels 50-100 UI/L.

Conclusion:

The study revealed that patients with cardiovascular disorders had higher ALP values as compared to cerebrovascular patients indicating the risk of arterial micro calcification to progression of arthrosclerosis related acute events. This shows that ALP levels are altered in the long term cardiovascular disorder secondary to liver dysfunction. Hence proper medical intervention is required to prevent liver dysfunction secondary to cardiovascular diseases which is the root cause for the elevated ALP level. The study also revealed that no significant

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increase in ALP among patients on statin therapy. This study signifies the ALP levels a one among the vascular biomarkers in predicting the micro calcification related acute vascular events. The study had some limitations as it could not identify any causal relationship of serum ALP levels with the definite underlying disorder. Further studies are required to evaluate the same in prospective long-term analysis on survival benefit in cardiovascular disease patients.

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