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Original Article

Biochemistry Section

Increased Serum Alkaline Phosphatase and Serum Phosphate as Predictors of Mortality after Stroke

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ABSTRACT

Context: Serum Alkaline phosphatase (ALP) & phosphate are considered to be indicators of vascular calcification. Link between bone metabolism, vascular calcification, cardiovascular events have been well studied in chronic kidney disease and ischemic heart disease.

Aims: To determine that increased serum phosphate and alkaline phosphatase are predictors of mortality rates and recurrent vascular events in stroke.

Materials and Methods: Sixty patients admitted with acute stroke (ischemic & haemorrhagic) were included in the study. Their baseline clinical characteristics and biochemical parameters including serum ALP and phosphate were noted. All patients were followed up for a period of one year. The all- cause mortality, the mortality due to cardiovascular events and recurrent vascular events without death were noted during the follow up. Statistical analyses were done to look for any correlation between mortality and baseline levels of serum ALP and phosphate.

Results: Of the 60 patients, 8 (13.3%) patients were lost for follow up. Fourteen (26.9%) patients died; of which 12 deaths were due to vascular causes and 2 deaths were due to non vascular causes. Increasing levels of serum ALP and phosphate correlated with all cause mortality and recurrent vascular events without death

Conclusion: Serum ALP and phosphate prove to be cost effective prognostic indicator of mortality and recurrent vascular events in stroke. This finding has to be confirmed with studies including larger population. Further research on ALP inhibitors, Vitamin D analogues and phosphate binders to improve mortality in stroke population can be encouraged.

Keywords: Alkaline phosphatase, Phosphate, Recurrent vascular events, Vascular calcification

INTRODUCTION

Stroke is one of the most disabling neurological disorders and remains the second most common cause of death. It is estimated to produce 5.5 million deaths per year worldwide and 44 million disability adjusted life years (DALYs) are lost [1]. In India, the prevalence ranges from 84-262/100,000 in rural areas and 334-424/ 100,000 in urban areas [2].The case fatality rate in India ranges from 27.2% [3] to as high as 42% [4] in some of the studies. Patients with stroke have several vascular risk factors which may predispose to cardiovascular morbidity also. It is essential for us to look for cost-effective methods which can predict the morbidity and mortality in these patients.

Several studies in the past decades have highlighted the role of serum Alkaline Phosphatase (ALP) and serum phosphate as predictors of mortality in Chronic Kidney Disease (CKD) [5-7], hypertension [8], metabolic syndrome [9] and previous myocardial infarction [10,11]. Recently, there have been studies showing significance of increased serum ALP and phosphate in stroke population also [12,13]. These are biochemical parameters which can be easily obtained in most of the centres and cost effective, even in developing countries like India. They may be useful as predictors of prognosis in patients with stroke.

ALP is an enzyme which catalyses hydrolysis of organic pyrophosphate, which is an inhibitor of vascular calcification [14]. ALP is noticed to be a regulator or indicator of accelerated vascular calcification. Vascular calcification causes vascular hardening and aging, consequently contributing to atherosclerosis [15]. So, increased ALP may also be associated with poor vascular fate in cases of stroke.

Studies have shown that patients with kidney failure have an increased risk of cardiovascular mortality that may be due in part to vascular calcification. Intense attention has been focused on potential link between bone metabolism, vascular calcification, and cardiovascular events in patients with kidney failure [16].

Serum phosphate has been known to be associated with cardiovascular mortality in both uremic [17] and non-uremic patients [18]. In fact, it has been implicated in atherogenesis. Its role now seems to be much more significant than thought previously, that few authors call it “the new cholesterol” [19]. They suggest that phosphate binders may act like statins in prevention of atherosclerosis.

Serum ALP and Phosphate, if proven to be useful prognostic indicators, will be very useful cost-effective test in our settings. This study was aimed at determining if increased serum phosphate and alkaline phosphatase are predictors of mortality rates and recurrent vascular events in stroke.

MATERIALS AND METHODS

Sixty patients (>18 years) admitted with acute stroke within 2wks of symptom onset were included in the study. Patients were recruited from June 2011 to November 2011. All patients were followed up for a period of atleast 1yr and the last follow up was made on November 2012. Patients were those admitted in medicine and neurology wards in Victoria Hospital within 1wk of symptom onset. Both ischemic and haemorrhagic strokes were considered. Patients with subarachnoid haemorrhage, liver disease (total bilirubin > 1.3), history of malignancy, and alcohol consumption (within past 3mnths) were excluded from the study.

Demographic features of all the patients and the following clinical characteristics were noted: NIHSS score, smoking status, alcohol consumption, history of diabetes and hypertension, systolic and diastolic blood pressure, drugs used- ACE inhibitors, beta blockers, and aspirin. The following investigations were done in all patients: fasting and post prandial blood sugars, systolic and diastolic blood

	<60	60-79	80-99	100-119	>120	p-value
Gender	3	15	5	3	9	0.36
Previous Stroke	0	4	1	2	3	0.85
Hypertension	2	13	4	8	10	0.046
Diabetes	2	7	5	3	4	0.68
Current Smoking	2	8	3	0	6	0.12
Heart Disease	0	7	2	5	4	0.32
NIHSS	3.5±0.5774	5.87± 3.6	6.0± 2.93	13.86±6.56	9.27± 6.42	0.0008
HBA1C	6.3±0.75	6.82±1.14	7.5±1.18	7.64±2.44	6.6±0.98	0.299
LDL	193.25±13.84	164.86±28.55	173.0± 19.25	156.86± 33.01	137.09± 55.0	0.06
Triglycerides	201.5±96.04	159.38±59.32	183.12±79.60	147.75±37.36	157.18±52.71	0.5
HDL	36.5±4.65	38.14±4.46	37.37±2.19	38.62±4.40	36.36±6.43	0.8
Systolic BP	147.5±23.63	159.52±30.54	153.75±23.26	180±15.11	170±24.9	0.15
Albumin	3.95±0.98	3.88±0.32	3.73±0.28	3.67±0.38	4.15±0.47	0.062
Calcium	8.66±0.22	8.83±0.22	8.7±0.41	8.7±0.2	8.66±0.38	0.56

[Table/Fig-1]: Baseline characteristics of the patients with reference to serum ALP levels

	<3.5	3.5-4.0	>4.0	p-value
Gender	15	16	4	0.99
Previous Stroke	2	7	1	0.17
Hypertension	15	17	5	0.36
Diabetes	11	9	1	0.50
Current Smoking	7	10	2	0.76
Heart Disease	8	10	0	0.25
NIHSS	6.06±3.48	9.58± 6.37	10± 8.33	0.07
HBA_1C	6.9 ± 1.16	7.17± 1.16	6.3±0.5	0.425
LDL	175±21.53	157.12± 39.33	117.2 ±47.83	0.003
Triglycerides	188.21± 66.46	141.36 ± 51.66	116 ± 50.9	0.007
HDL	37.73± 3.95	44.75± 34.99	54 ±36.63	0.36
Systolic BP	158.26 ± 27.41	165.25 ± 25.33	170±31.62	0.50
Albumin	3.81 ±0.34	3.88 ±0.40	4.3± 0.48	0.045
Calcium	8.78± 0.34	8.76± 0.43	9±0.2	0.44

[Table/Fig-2]: Baseline characteristics of the patients with reference to serum phosphate levels

Serum ALP	All Cause Deaths	Vascular Deaths	Vascular Events Without Death	Non Vascular Deaths
<60	-	-	-	
60-79(21)	2	2	1	-
80-99(9)	2	1	1	1
100-119(7)	5	4	1	1
>120(11)	5	5	6	-
	p=0.01	p=0.02	p=0.008	p=0.15
Serum Phosphate	All Cause Deaths	Vascular Deaths	Vascular Events Without Death	Non Vascular Deaths
<3.5(23)	3	2	3	1
3.5-4.0(24)	10	9	2	1
>4.0(5)	1	1	4	0
	p=0.038	p=0.11	p=0.002	p=0.99

[Table/Fig-3]: Correlation between increasing serum ALP/ phosphate levels, recurrent vascular events and mortality

pressure, Glomerular filtration rate (GFR) (calculated by Cockcroft-Gault formula) [20], urine proteins, ECG (to look for ischemic changes, arrhythmias, 2D-ECHO (to look for LV clot, LV ejection fraction), hemoglobin, fasting lipid profile- LDL, HDL, TGs, HbA1C, serum albumin, calcium, bilirubin, liver enzymes (SGOT, SGPT), C-reactive protein, serum ALP and phosphate.

All patients were followed up at intervals of 3 months upto a period of 1year in person or on phone, in case they did not turn up for their allocated visit. In each follow up, drug compliance and lifestyle modifications were assured (which could be confounding factors). Patients were assessed for any new vascular events. If death was informed, the cause for death was obtained and classified into either vascular or non vascular event. Vascular event may be stroke, myocardial infarction, heart failure, pulmonary embolism, cardiac arrhythmia, or other definite vascular causes.

Data were analysed to look for any correlation between increasing serum levels of ALP and phosphate, mortality and recurrent vascular events. The statistical tests used were chi-square test, ANOVA and Fisher's exact test.

RESULTS

Of the 60 patients in the study, 8 (13.3%) lost for follow-up. Fourteen (26.9%) patients died during the one year follow up. Twelve patients died due to vascular causes and 2 patients due to non- vascular causes. Nine patients had recurrent vascular events without mortality.

Patients were divided depending on the serum ALP levels (<60; 60-79; 80-99; 100-119; >120 U/l) and also depending on serum phosphate levels (<3.5; 3.5-4.0; > 4.0 mg/dl). [Table/Fig-1,2] depict the baseline characteristics of the patients with reference to serum ALP and phosphate levels respectively.

Stroke severity (p=0.008) and hypertension (p=0.046) were higher in patients with higher ALP. LDL (p=0.003), triglyceride (p=0.007), albumin (p=0.04) levels were higher in patients with higher serum phosphate.

The [Table/Fig-3] shows that the patients with higher ALP had higher incidence of all cause deaths, vascular deaths and recurrent vascular events. Patients with higher serum phosphate had significantly higher incidence of all cause deaths and recurrent vascular events.

DISCUSSION

This study proves that the serum ALP and phosphate can predict mortality and also recurrent vascular events in patients with stroke.

Vascular calcification has been considered an active process. There are multiple circulating promoters and inhibitors involved in this process. Phosphate is one such promoter which helps in osteogenic and chondrogenic differentiation and hence in vascular calcification.

Pyrophosphate (PPi) homeostasis is an important determinant of soft tissue mineralisation. PPi is an inhibitor of vascular calcification [21]. ALP is an enzyme involved in hydrolysis of PPi. So an increase in ALP indicates decreased inhibition of vascular calcification.

Vascular calcification can lead to plaque instability, vascular stiffness, valvular heart disease and calciphylaxis. This will further lead to cardiovascular events and eventually mortality [22].

A study from National database of all DaVita MHD (Maintenance Hemodialysis) patients in the US showed that patients on hemodialysis with higher ALP were found to have higher mortality rates - both vascular and non vascular causes of death [16]. Another population based study done on patients with previous history of myocardial infarction showed similar results irrespective of renal status of the patient [11].

Following this, there have been several studies evaluating serum ALP and phosphate as predictors of morality in disorders like CKD and myocardial infarction. Such studies have been limited in stroke population. One such study was carried out in Korea in patients with stroke [12] to evaluate serum ALP and phosphate as predictors of mortality and recurrent vascular events. It proved that serum ALP and phosphate can be predictor of mortality in stroke, both ischemic and haemorrhagic.

In an interesting study [13] the authors prospectively evaluated the incidence of stroke based on levels of serum ALP. There was a J-shaped association and not only people with higher levels of serum ALP were associated with stroke but those with lower levels also. It is difficult to compare these results with our study as we had evaluated mortality rather than incidence of stroke.

ALP is an acute phase reactant [23]. It also indicates poor nutritional status and increased susceptibility to infection. These above reasons could also contribute to the mortality in these patients. However, these reasons cannot account for the increase in recurrent vascular events occurring at a later time, which is most probably due its involvement in vascular calcification.

This was a prospective study and we could ensure compliance of drugs and other confounding factors during follow up. We evaluated recurrent vascular events also, apart from mortality, which was not done in the previous study [12]. By this observation, we can derive that serum ALP and phosphate definitely indicate vascular morbidity apart from the other mechanisms mentioned above.

There are several limitations for this study. The most important one being the small sample size and shorter follow up. This study may need to be further carried out in a larger population. A longer follow up of the patients would have yielded much more information regarding long term mortality also. Apart from these, there were nearly 13% of the patients who were lost to follow up.

Baseline characteristics which could be confounding factors were evaluated. Stroke severity by NIHSS was higher in patients with higher ALP levels. Whether the stroke severity was a confounding factor or patients with more vascular calcification tend to have severe stroke has to be determined.

Serum albumin was found to be higher in patients with higher serum phosphate. This could not be a confounding factor as higher albumin levels are not likely to lead to increased mortality. Increased incidence of hypertension in patients with higher ALP and increased cholesterol levels in patients with higher serum phosphate levels could be confounding factors. Other factors like vitamin D and parathyroid hormone levels have not been taken into account in this study.

Serum ALP and phosphate are markers of vascular calcification. They provide cost effective prognostic indicators of mortality and recurrent vascular events in stroke.

Further research on ALP inhibitors, Vitamin D analogues and phosphate binders to prevent vascular calcification can be encouraged. This might prevent mortality and recurrent vascular events in stroke population.

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