

Original Article

SIGNIFICANCE OF SERUM TOTAL ALKALINE PHOSPHATASE LEVELS IN BREAST CANCER

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ABSTRACT

Background Breast cancer has shown an increased prevalence worldwide, both in industrialized and developing countries. Unfortunately, most cancers do not produce any symptoms until the tumors are either too large to be removed surgically or metastasis has taken place. Therefore, there is need for simple biochemical investigations, which can be easily assayed, less expensive and can predict stages and prognosis. This study was undertaken to know the usefulness of estimation of serum Alkaline Phosphatase (ALP) in assessing the prognosis and staging of breast cancer in smaller laboratories where sophisticated technology is not available. **Materials & Methods** A total number of 95 subjects participated in the present study which included 60 breast cancer cases and 35 controls. Serum Alkaline Phosphatase levels were estimated in preoperative & postoperative breast cancer subjects of different stages and control. ALP Levels were compared between control and breast cancer. Also comparison was done between different stages and further, ALP levels compared pre and post operatively. **Results** Rise in the ALP was found in breast cancer when compared to controls. ALP levels increased significantly with the stage of cancer. Postoperatively, there was significant decrease in ALP levels in each stage. **Conclusion** Though less sensitive than imaging procedures, measurement of serum ALP is cost effective and may be useful in smaller laboratories for staging, to know the prognosis and monitor the treatment. Serial analysis using plasma Alkaline phosphatase isoenzymes combined with other parameters like Gamma glutamyl transferase (GGT) for the detection of metastasis would seem to be justified.

KEYWORDS

Alkaline phosphatase, Breast cancer, Metastasis, Isoenzymes.

INTRODUCTION

Breast cancer is one of the diseases most feared by women and perceived as fatal world wide. In India breast cancer accounts for 27.0 percent of all malignant cases (an incidence rate of 25.8 per lakh & mortality rate being 12.7/lakh population)^[1]. Breast tumor in women has shown an increased prevalence worldwide, both in industrialized and developing countries. Various theories propounded are based on altered hormonal milieu, personal and demographic factors and certain agents such as radiant energy, oncogenic viruses and chemical carcinogens which induces neoplastic transformation of the cell.^[2]

Educating the women about the value of periodic self examination of the breast will help in detection of breast cancer in early stage. Cancer that is detected early can potentially be cured when the tumor is small enough to be completely removed surgically. Unfortunately, most cancers do not produce any symptoms until the tumors are either too large to be removed surgically or cancerous cells have already spread to other tissues i.e., metastasis has taken

place^[3]. Therefore, there is a need for noninvasive and sensitive methods to detect growths small in size which escape routine examination. This could be achieved to a certain extent by measuring products and metabolites derived from the tumors in the body. There are many non specific markers that are studied in breast cancer when compared to more specific markers like BRCA gene & CA 15-3. However estimation of more specific markers are costlier and is not available in the peripheral labs due to the cost and equipments. Some of the non specific markers that are studied are Lactate dehydrogenase, Alkaline phosphatase, ferritin and gamma glutamyl transpeptidase etc^[4]. Therefore, there is need for simple biochemical investigations, which can be easily assayed, less expensive and can predict stages and prognosis. This study was undertaken to study the importance of ALP in Breast cancer with and without metastasis in women and to know the usefulness of estimation of ALP in assessing the prognosis of breast cancer.

MATERIAL AND METHODS

A total number of 95 subjects participated in the present study which included 60 breast cancer cases and 35 controls. All were in the age group of 25 to 80 years. Study was conducted on inpatients and out patients of Chigateri General Hospital and Bapuji Hospital (both hospitals attached to J.J.M Medical College, Davangere, India) and also from the general population in and around Davangere. Informed consent was taken from each subject and the study was approved by the ethical committee. The patients and controls voluntarily participated in the study.

Cases were histopathologically diagnosed breast cancer cases. Patients with myocardial infarction, jaundice or liver disease, pancreatic disease, diabetes mellitus and those taking anti-epileptic or hepatotoxic drugs during the last three months were excluded from the study. A careful history was taken and thorough clinical examination was conducted in all the cases according to the proforma. Routine investigations was done in all cases. Breast cancer patients were divided into 4 groups according to stage grouping. Stage grouping was based on TNM staging system. About 6ml of blood was drawn in a fasting condition with aseptic precaution from a large peripheral vein (usually cubital vein) and collected in a sterile bulb. Serum was separated by centrifugation and kept at 4°C until analysis was carried out. Serum levels of Alkaline phosphatase was measured preoperatively, and post operatively on 7th day in 60 cases of breast cancer. Total serum alkaline phosphatase activity was determined by recommended method of the committee on the enzymes of the Scandinavian society of clinical chemistry and clinical physiology using 4-nitrophenylphosphate as substrate at 37°C with absorbance reading at 405 nm^[5].

STATISTICAL ANALYSIS

All the measurements were expressed as mean ± SD and range values. Unpaired ‘t’ test was used for finding the significant difference between two groups. One-way ANOVA was used for multiple group comparison. In carcinoma patients, changes in the serum levels of biochemical parameter after surgery was analyzed by paired-t test for each stage. For all the tests p-value of <0.05 was considered as statistically significant.

RESULTS

Table 1. Comparison of mean serum Alkaline phosphatase (ALP) levels in controls & breast cancer patients.

STAGES	N	MEAN±SD	RANGE
CONTROL	35	94.85±25.13	41.2 – 140.3
I	11	135.36±22.11	111.2 – 180.1
II	18	167.16±13.59	148.1 – 188.8
III	18	298.21±18.44	271.0 – 333.5
IV	13	415.08±30.35	374.1 – 456.2

TABLE 2: Comparison of serum ALP between the stages of cancer preoperatively (PRE-OP) (ANOVA TEST)

GROUPS COMPARED	MEAN DIFFERENCE	SIGNIFICANCE	F - VALUE
STAGE 1 – STAGE 2	31.80	0.001, HS	497.88
STAGE 1 – STAGE 3	162.84	<0.001, HS	
STAGE 1 – STAGE 4	279.71	<0.001, HS	576.74
STAGE 2 – STAGE 3	131.04	<0.001, HS	
STAGE 2 – STAGE 4	251.33	<0.001, HS	t-VALUE: 12.34 *
STAGE 3 – STAGE 4	116.87	<0.001, HS	

***INDEPENDENT/UNPAIRED t TEST**

TABLE 3. Comparison of serum ALP levels in PRE-OP AND POST-OP in different stages (PAIRED t TEST)

STAGES	N	MEAN±SD	t - VALUE	SIGNIFICANCE
I	PRE-OP	11 135.36±22.11	1.58	0.145, NS
	POST-OP	11 130.76±27.85		
II	PRE-OP	18 167.16±13.59	10.97	<0.001, HS
	POST-OP	18 129.97±7.45		
III	PRE-OP	18 298.21±18.44	22.75	<0.001, HS
	POST-OP	18 211.56±9.54		
IV	PRE-OP	13 415.08±30.35	14.96	<0.001, HS
	POST-OP	13 265.51±17.65		

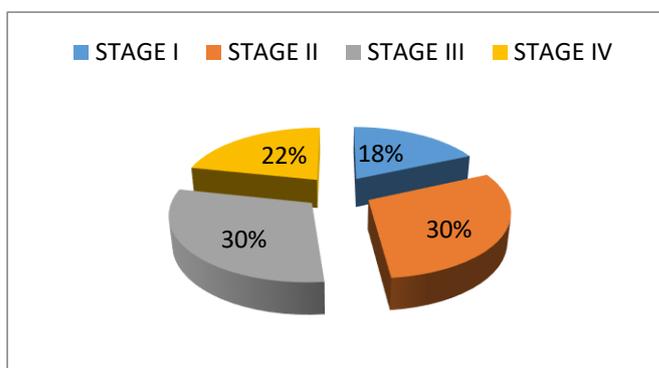


Figure 1. Showing number of cases in different stages

DISCUSSION

Alkaline phosphatase (ALP) is a serum enzyme whose total levels reflect the combined activity of several isoenzymes found in the liver, bone, kidney, and intestinal lining^[6]. ALP has consistently been shown to predict bone metastases, and to some extent liver metastases, as expected on the basis of its biologic activity. While some studies have reported fairly high sensitivity of ALP for bone and overall metastases detection, these studies included the use of specific

isoenzymes in addition to total ALP^[7]. Elevation of serum ALP occurs because of the accelerated de novo synthesis of the enzyme and subsequent regurgitation into the serum^[8,9,10].

The present study showed increased total ALP in breast cancer when compared to control. And also, serum ALP levels increased significantly as the stage of the cancer progressed. The increased ALP noticed in our study also indicates that the disease had metastasized to bone or liver. According to the study conducted by the International Breast Cancer Study Group (IBCSG), ALP alone was abnormal in a high proportion of breast cancer patients with bone metastases and/or liver metastases, and was more effective than AST and GGT in distinguishing patients with relapse from those without^[11]. Coombes et al^[12] also suggested that, of all the biochemical determinants available in the clinical laboratory, measurement of plasma total alkaline phosphatase, gamma-glutamyltransferase activity, and carcinoembryonic antigen (CEA) concentration are the most useful for detecting overt metastatic deposits.

Vanhoof et al. (1992)^[13] and Stieber et al. (1992)^[14] did not find any significant difference in ALP levels in non-metastatic breast cancer, despite the fact that some others have also revealed a significant rise in ALP in metastasis (Ramaswamy et al. 2000^[15]; Lamerz et al. 1993^[16]) suggesting involvement of bone and liver. Findings in present study is similar to recent study of A K Sing et al (2013)^[17] also found significant rise of ALP levels in different stages of cancer. Mishra et al (2004)^[18] also found persistent rise of ALP levels in metastasis.

From our study it is observed that serum alkaline phosphatase analyzed 7 days after surgery showed significant decrease in serum levels. This may be due to removal of cancer tissue. B. Prabasheela et al (2012)^[19] and Keshaviah et al^[6] have noticed increased ALP activity in some of the cases after surgery, which might be due to recurrence. However, in the present study 7 days of surgery is a very short duration of follow up. To establish prognostic importance, a longer duration follow up is needed.

CONCLUSION

Our study reveals higher ALP levels in breast cancer when compared to controls. Progressive increase in serum ALP in the study may be due to metastasis. Serial analysis using plasma Alkaline phosphatase isoenzymes combined with other parameters like Gamma glutamyl transferase (GGT) for the detection of metastasis would seem to be justified. Such measurements, though less sensitive than imaging procedures, can assist in screening for, early detection of a considerable proportion of metastasis and to monitor the treatment in breast cancer. Study indicates measurement of serum ALP is cost effective and may be useful in smaller laboratories where sophisticated laboratory and reliable cancer marker are not available.

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