SERUM LEVELS OF BONE ALKALINE PHOSPHATASE IN BREAST AND PROSTATE CANCERS WITH BONE METASTASIS

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ABSTRACT

BALP activity in the sera of metastatic patients of breast and prostate malignancy has increased significantly. Our studies with patients in India conform the earlier reports that BALP may have a useful complementary role in the early diagnosis of bone metastases.

KEYWORDS: BALP activity, breast cancer, prostate cancer.

INTRODUCTION

Bone alkaline phosphatase is a tetrameric protein that is localized in the plasma membrane of osteoblastic cells (1) entering the circulation as a dimeric protein by phosphatidyl inositol glycanase activity (2) or by formation of membrane vesicles (3). The dynamics of bone metabolism are revealed non invasively with increasing accuracy by the use of newly identified biochemical markers of bone turnover (4,5,6,7).

There are earlier reports on the patterns of liver and bone isoenzymes of alkaline phosphatase to detect early metastasis in patients with a variety of tumors. While Van Hoof et. al. (8) and Steiber et. al. (9) did not find any significant difference in their studies, most of the other studies (10-17) have suggested that serum bone alkaline phosphatase (BALP) levels could play a complementary role in the diagnosis of bone metastasis and could even provide useful clinical information on the degree of skeletal metastasis (13).

There is not much data available in our population and hence this study was undertaken

to analyse the clinical utility of the complementary role of serum BALP in the diagnosis of metastases in patients with carcinoma breast and prostate with bone metastasis as confirmed by scintigraphic studies.

MATERIALS AND METHODS

Fifty apparently healthy persons (25 men and women each) of age range 25 to 60 years for men and 20 to 62 years for women served as controls. None of the persons had a history of serious disease or was taking drugs known to affect bone metabolism. Sixty two patients with breast cancer (Group I) and thirty patients with prostate cancer (Group II), were studied for serum total alkaline phosphatase (TALP) and BALP activity. They were also routinely scanned for the presence of bone metastasis by ^{99m}Tc - methylene bisphosphonate bone scintigraphy.

Group I patients of breast cancer were classed into 29 patients without any pathological findings by bone scintigraphy and 33 patients showing typical signs of bone metastasis.

Group II patients of prostate cancer were classed as 14 patients without any pathological findings and 16 patients showing typical signs of bone metastasis by bone scintigraphy.

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BALP activity in serum was determined by lectin precipitation with use of a commercial test kit. (Test-combination of isoenzymes of alkaline phosphatase, Boehringer Mannheim), and measured at 37°C on Abbott Spectrum CCX Series II. Serum BALP activity was calculated from the difference between serum TALP activity before and after precipitation with wheat germ lectin at 25°C.(12). Wheat germ lectin was used to prevent coprecipitation of the liver isoenzyme of alkaline phosphatase.

Serum BALP activity, expressed as U/L, was calculated by using the following correction factor. $BALP = (1.18 \times TALP \text{ activity}) - 2.35 \times \text{supernatant activity}$. CV'S ranged between 2.5 and 3.8% for intra assay variance and between 3.5 and 4.0% for inter assay variance.

Serum samples are appropriate for measurement of BALP. BALP activity may be affected by the concentrations of divalent cations, and tube containing EDTA or citrate are therefore usually inappropriate. BALP are stable for short period at 4°C and for long period at -20°C and is resistant to repeated freeze thaw cycles.

All specimens were taken between 0800 and 0900 hours. Sera were separated from the blood clot within 2 hours after specimen collection and stored at -20°C until analyses usually within 3 months.

Students 't' test was used to compare the results.

RESULTS AND DISCUSSION

In our study, no significant difference was observed in the mean BALP levels between male and female control subjects. A cut off of 29.0 U/L (mean $\pm$ 1SD) was taken for the control group.

Table 1 shows the TALP and BALP activity in cancer breast and prostate cancer patients compared with controls. Among the 62 breast cancer patients enrolled for the study, 46.8% had a BALP value below 29 U/L (mean 18.9 ± 0.85) and 53.2% of the patients had a BALP value above the cut off value (mean was 57.6 ± 6.25) 33 patients who showed a significant increase in BALP activity

had typical signs of bone metastasis as documented by scintigraphic studies, as against the patients who had normal BALP activity and in whom no bone pathology was noted.

Table 1. TALP and BALP in breast and prostate cancer (mean $\pm$ SE)

Group	TALP activity U/L	BALP activity U/L
CA breast		
BALP		
<29.0 U/L (46.8%)	85.3 ± 5.1 (n = 29)	18.9 ± 0.85 (n = 29)
>29.0 U/L (53.2%)	144.6 ± 13.6 (n = 33)	57.6 ± 6.25 (n = 33)
Controls	77.8 ± 10.9 (n = 25)	22.5 ± 2.3 (n = 25)
CA prostate		
BALP		
<29.0 U/L (46.2%)	142.6 ± 31.42 (n = 14)	18.6 ± 1.79 (n = 14)
>29.0 U/L (53.8%)	555.9 ± 122.9 (n=16)	266.0 ± 70.94 (n=16)
Controls	94.5 ± 7.25 (n=25)	20.1 ± 2.12 (n=25)

Among the 30 patients with prostate cancer, 46.2% had a serum BALP value above the cut off value of 29.0 U/L (mean value 18.6 ± 1.79 U/L) while 53.8% of patients showed increased BALP activity (mean value 266 ± 70.94 U/L). In this group of patients also a positive correlation was noticed between serum BALP activity and bone metastasis as evidenced by scintigraphic criteria.

Our results show significantly increased values for BALP in patients with bone metastasis as compared with those without bone metastasis, the magnitude of increase being more in prostate cancer patients.

Lorente *et. al.* (13) reported similar results in their study of prostate cancer patients and found that the extent of bone disease influenced serum

levels. Wolff et. al. (14) have used BALP as a staging marker to discriminate patients with cancer prostate with bone metastasis from those without bone metastasis. They observed a statistically significant difference between the two groups resulting in a sensitivity and specificity of 71% and 100% respectively. Berruti et. al. (15) measured BALP in various primary malignancies by an electrophoretic technique and reported a good correlation between serum BALP and the number of radiographically confirmed sites of bone involvement. BALP increase was more frequent in prostate cancer as compared to breast cancer and lung cancer patients. Akimoto et. al. (16) reported that serum levels of BALP were significantly higher in patients with prostate cancer and bone metastasis than in patients with benign prostatic hyperplasia and patients with prostate cancer without bone metastasis.

The results of our study support the results of the above studies. However, they are in conflict with those of Van Hoof et. al. (8) as well as Steiber et. al. (9) who did not find such significant differences. This may partly be explained by the different locations of the bone lesions (osteoblastic, osteolytic or mixed) in their patients

as well as the methodology they have used. Burlina et. al. (10) and Withold et. al. (11) have reported that the determination of BALP by wheat germ lectin precipitation is more specific for the identification of bone metastasis than is TALP.

Serum TALP activity is a widely used marker of bone formation, but its clinical usefulness in regard to bone disease is greatly impaired in the presence of hepatobiliary disorders. With the recent advent of more specific immunoassays for measurement of BALP, this isoenzyme has increasingly regained clinical interest, and several studies have indicated that in certain situations BALP might provide a better index of bone formation than measurement of TALP.

In view of the increase in serum BALP levels in metastatic bone disease, there is a possibility of BALP being a good biochemical marker to predict osteoblastic activity and to indicate early and advanced bone involvement. Further studies will be carried out to study the clinical utility of serum BALP as a marker in breast and prostate cancers with and without bone metastasis and metastases at sites other than bone.

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