

Biochemical parameters and comparison with CA 15-3 in premenopausal females with BRCA

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Objective: To find the correlation of CA 15-3 with serum Ferritin and serum LDH in different stages BRCA.

Methodology: A case control study was designed and included 70 patients with different stages of BRCA. Twenty normal subjects with no history of any disease or malignancy were taken as healthy controls. Estimation of serum LDH, serum CA 15-3 and serum ferritin was carried out by standard methods.

Results: The levels of CA 15-3 along with serum ferritin and serum LDH were progressively

increased in BRCA women from stage IV to stage 4. A significant correlation was observed between CA 15-3, serum LDH and serum Ferritin in advanced stages of BRCA.

Conclusion: Levels of serum CA 15-3, serum ferritin and serum LDL are associated with tumor extent as their significantly increased values were observed in BRCA. A significant correlation was observed between and advanced stages of BRCA. (Rawal Med J 202;45:790-793).

Keywords: Tumor markers, LDH, ferritin.

INTRODUCTION

Cancer cells and other benign tumors of the human body produce tumor markers. Though most of these clinical indicators are made by normal cells in addition to cancer cells, they are synthesized at much elevated rates during malignancy. Hence, these tumor markers are used for evaluation of the patient's response to treatment and for the detection of metastasis and recurrence.¹ BRCA is one of the most prevalent malignancies in females. CA 27-29, CA 15-3, carcinoembryonic antigen (CEA), and HER-2 are the most expressed tumor markers in it. They play a critical role in the diagnosis, monitoring the response to therapy, detection of metastasis and recurrence.² Therapeutic criteria are associated with good understanding of mechanisms that take part in the initiation of BRCA and its progression.³

The increased level of CA 15-3 is observed different malignancies; however, it is a marker of metastasis of BRCA and used to find the progression of problem and success of treatment. This marker cannot be used for the detection of cancer as it is less sensitive.⁴ Increased level of CA 15-3 between the period of 4 and 6 weeks after starting the new mode

of treatment shows poor prognosis.⁵ Ferritin is produced in spleen, liver, placenta, myocardium and has a role in storage of iron. Its level is increased in hemochromatosis, inflammation or infection, neurodegenerative problems, malignancies and destruction of liver tissues.⁶ Its level may be altered in BRCA, but its exact mode of action is conflicting.^{7,8}

Serum Lactate Dehydrogenase (LDH) is an established marker of BRCA and one of its isoenzymes is increased due to gene up regulation. Hence it may be used as a prognostic marker of BRCA.⁹ A sharp increase in number of malignant cells may modulates the level of LDH in cell cytoplasm mainly due to its gene up regulation.¹⁰ In malignant cell, this increased level is helpful for completion of metabolic related requirements like glycolysis in anaerobic phase of tumor cells. The level of serum LDH also communicates with TNM staging of cancer.^{11,12} CA 15-3 is established biomarker for advanced stage of BRCA with less sensitivity for primary stage BRCA patients. For the detection of metastatic BRCA, there is a need of combination of tumor markers which may increase the sensitivity for detection of metastatic BRCA.

The aim of this study was to find the correlation of CA 15-3 with serum ferritin and serum LDH in different stages BRCA.

METHODOLOGY

Study subjects included premenopausal BRCA patients (70) and age matched healthy controls (20). The criteria for inclusion were premenopausal histologically diagnosed cases of BRCA. Exclusion criteria were postmenopausal females with BRCA, patients with benign breast lesions, any other malignancy, and any other causes of hyperferritinemia. These patients were selected from the oncology department of INMOL and Shaikh Zayed Hospital, Lahore.

Height was measured in centimeters (cm) on a standard height scale and weight was measured in kilograms (kg) on Camry weight scale. The Body Mass Index (BMI) in kg/m² was calculated. Blood pressure (BP) was measured by mercurial sphygmomanometer after the patient rested for 5 minutes in sitting position. Blood sample was collected for serum CA 15-3, serum ferritin and serum LDH. Serum CA 15-3 (Human Gesellschaft für Biochemica and Diagnostica Germany, was done on "Humareader plus Make Human GmbH". Serum Ferritin (Monobind Inc. LakeForest, USA, using Accubind Elisa microwells, Ferritin was performed on fully automatic Elisa system model "ELISYS UNO". Serum LDH estimation was done on fully automated Dimension AR auto analyzer. Quality control was maintained by using control sera by Human.

Statistical Analysis: Statistical analysis was performed using SPSS version 20. Student's test was used for comparison between two groups. The association between CA 15-3 and other variables was observed by calculating correlation coefficient "r". p<0.05 was considered statistically significant.

RESULTS

The levels of CA 15-3 were progressively increased in BRCA women from stage I to stage IV. Contrarily, there is sharp rise in the levels of serum ferritin and serum LDH in women with stage I to stage IV (Table 1).

Table 1. Comparison of CA 15-3, serum ferritin and LDH in stage I, II, III, IV of BRCA patients.

Stage	No	Serum CA 15-3 (U/ml)	Serum ferritin (ng/ml)	Serum LDH (U/L)
Control	20	15.32±4.70	50.13±4.70	120.63±30.45
I	19	36.08±3.11**	240.68±120.39**	234.52±73.99**
II	17	78.85±11.47**	442.56±23.82**	401.72±36.12**
III	15	138.36±28.10**	536.76±17.86**	566.99±41.50**
IV	19	224.0±30.19**	669.42±39.48**	780.07±248.83**
	F	382	306	87
	P	<0.001	<0.001	<0.001

**P<0.001 = highly significant

Table 2. Correlation of CA 15-3 with serum ferritin and serum LDH in stage I, II, III, IV of BRCA patients.

Variable	Stage I (19)	Stage II (19)	Stage III (15)	Stage IV (19)
CA 15-3 with ferritin	r= 0.062	r= 0.154	r=0.208	r= 0.529
CA 15-3 with LDH	r= -0.205	r= 0.414	r=0.620	r= 0.692

A non-significant correlation was observed between CA 15-3 and serum ferritin in women with stage I to stage III. Moreover, a significant correlation was observed between CA 15-3 and serum ferritin in women with stage IV. A non-significant correlation was observed between CA 15-3 and serum LDH in women with stage I to stage II. Also, a significant correlation was observed between CA 15-3 and serum LDH in women with stage II and stage IV (Table 2).

DISCUSSION

Many studies demonstrated that increased level of CA 15-3 before the surgery was associated with size of tumor, involvement of axillary node and stage III to IV of BRCA.^{13,14} Moreover, it is found that prognosis of BRCA women with raised level of CA 15-3 in blood circulation was worse. Additionally, some studies stated that sequential postoperative improvement in the levels of CA 15-3 in the period of follow up may be helpful in for early discovery of recurrent cancer of breast.^{15,16}

A study estimated the levels of CA 15-3 levels in 1300 BRCA women and found that 69% of patients had raised values of CA 15-3 and found that is significantly related with decreased survival of patients.¹⁶ A study is observed an increased level of LDH in circulation in patients with BRCA and correlated with clinical TNM stage and bulk of tumor.¹⁷ Another study concluded that estimation of

level of serum LDH may help in monitoring the treatment of cancer.¹⁸

In this study, we observed high level of serum ferritin which may increase from stage I to stage IV. A study demonstrated that iron is the major regulator of synthesis of ferritin and hypoxia observed in malignant tissue may stimulate the synthesis of ferritin independent of iron status.¹⁹ Levels of serum ferritin may be a prognostic marker in patients of breast and lung cancer. Studies also found an association of serum ferritin with BRCA but this issue is still conflicting.^{20,21}

We observed a non-significant correlation between CA 15-3 and serum ferritin in women with stage I to stage III. However, a significant correlation was observed between CA 15-3 and serum ferritin in women with stage IV. Our study is in line with a study who found no correlation of CA 15-3 with the levels of serum ferritin in patients with initial stage of BRCA.²² According to a study, CA 15-3; a tumor marker did not give information of prognosis. However, estimation of CA 15-3 may take part to multivariate predictive representation.²³ BRCA prognosis as well as therapeutic interventions mainly depend upon the biochemical features and clinic pathological features of the cancer cells and have huge variations due to the varied nature of the disease.²⁴ Due to financial and time limited constraints, it was a single center study with a relatively smaller sample size.

CONCLUSION

Levels of serum CA 15-3, serum ferritin and serum LDL are associated with tumor extent with significantly increased values observed in BRCA. Serum LDH monitoring may be taken as a prognostic biomarker in BRCA.

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