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CA 15-3 and lipid profile in preoperative breast cancer patients

Siddiqua Jamall[1], Mohammad Ishaq[1], Junaid Mahmood Alam[2] and Misbah Khadim[1]*
[1]Department of Biochemistry, University of Karachi, Karachi, Pakistan,
[2]Department of Biochemistry and Chemical Pathology, Liaquat National Hospital, Karachi, Pakistan

Abstract: The transmembrane glycoprotein CA 15-3 is the most widely used serum tumor marker in breast cancer. At present the main uses of CA 15-3 are in pre-clinically detecting recurrent breast cancer and monitoring the treatment of patients with advanced breast cancer. The aim of this study was to define the role of preoperative concentrations of serum CA 15-3 as prognostic factor and to determine its sensitivity. Serum and plasma samples from breast cancer patients and normal individuals under fasting condition were used to estimate CA15-3 and lipid profile. The lipid profile was done in order to assess the impact of plasma lipid on the progression of breast cancer. The serum concentration of the tumor marker CA15-3 in preoperative breast cancer patients was found to be significantly higher ($p<0.001$) as compared to the normal individuals. The plasma cholesterol (TC), triglyceride (TRG) and total lipid (TL) levels in breast cancer patients were found to be significantly higher ($p<0.01$) for TC, TRG and TL as compared to the normal individuals. Moreover, plasma LDL-C levels in breast cancer patients were found to be significantly higher ($p<0.01$) compared to the normal individuals.

Keywords: CA 15-3, breast cancer, lipid profile, cholesterol, triglycerides, total lipids, lipoproteins.
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***Author for Correspondence:** sidjam@hotmail.com

INTRODUCTION

Breast cancer is the most common type of cancer in women; about 80-90 % of all breast cancers are infiltrating ductal carcinoma[1,2]. The precise cause of breast cancer is unknown; however, the female sex hormone estrogen is reported to be the main cause since it promotes the cellular growth in the tissues of the breast and reproductive organ[3-5]. In addition, the environmental factors like exposure to radiation and chemicals may trigger the onset of breast cancer[6,7]. The risk for breast cancer increases with a high fat diet[8], obesity[9], use of contraceptives[10], lack or short duration of breast feeding and family history of breast cancer[11]. The discovery of the tumor suppressor genes BRCA1 and BRCA2 in families with breast cancer history implicated the genetic risk factors[12-14].

A variety of tumor markers with varying sensitivity and specificity are used for diagnosis of different malignancies[15-17]. CA 15-3 (also known as MUC1) is the most widely used serum tumor marker in breast cancer. It is a large transmembrane glycoprotein, which is frequently over expressed[18-22] and aberrantly glycosylated in cancer[23]. At present the main uses of CA 15-3 are in pre-clinically detecting recurrent breast cancer and monitoring the treatment of patients with advanced breast cancer[20,22,24-30].

Preoperative serum CA 15-3 levels were an independent prognostic factor for disease free survival[31]. Elevated preoperative serum CA 15-3 levels correlated with early relapse and death from disease[32-33]. CA 15-3 is a prognostic marker in node negative breast cancer and the risk of relapse increased progressively from approximately 10 U/ml[27,34] and values above 30 U/ml preceded clinical diagnosis of relapse with a median time of nine months[35]. The combination of increased serum CA 15-3 and increased serum Her-2/neu predicted a worse prognosis[36-38]. The direct relationship with estrogen receptor status indicated that serum CA 15-3 diagnostic sensitivity in the early detection of disease recurrence could be greater in estrogen receptor positive patients than in estrogen receptor negative patients and they would be more sensitive to hormone manipulation than those with normal serum CA 15-3 values[39]. Compared to other tumor markers like CA 27.29 and carcinoembryonic antigen (CEA), serum levels of CA 15-3 is the most effective marker[40], while CA 27.29 is the most sensitive one. Both markers can therefore be used in combination for the detection of possible metastasis during follow ups[41,42].

In addition to the prognostic markers, studies have shown an evidence of direct association between lipids and incidence of breast cancer[43-48]. Plasma lipids and lipoproteins are under environmental control and have epidemiological and biological characteristics that suggest that they may be relevant to breast cancer risk.

The aim of the present study was to define the role of preoperative concentrations of serum CA 15-3 as prognostic factor and to determine its sensitivity. Furthermore, we have attempted to correlate the CA 15-3 levels and plasma lipid levels with breast cancer.

MATERIALS AND METHODS

Sample collection

Serum and plasma samples were prepared from blood collected from consenting 36 preoperative breast cancer patients and 37 age and

sex matched normal individuals under fasting condition and stored at -20°C till further use.

Estimation of CA 15-3

COBAS CORE CA 15-3 EIA is an *in vitro* diagnostic test for the quantitative detection of CA 15-3 in human serum or plasma. It is a two-step, solid phase enzyme immunoassay based on the sandwich principle (using monoclonal 115D8 and DF3 antibodies). Briefly, polystyrene beads were coated with 115D8 antibodies to which CA 15-3 from the specimen was bound. After washing with PBS, horseradish peroxidase conjugated anti CA 15-3 antibody (DF3) was added. Unbound antibody was removed by washing with PBS and the bound enzyme was reacted with COBAS CORE substrate. The intensity of the existing colour was proportional to the amount of CA 15-3 in the specimen.

Estimation of lipid profile

Plasma samples were analyzed for cholesterol, low density lipoprotein cholesterol (LDL cholesterol), high density lipoprotein cholesterol (HDL cholesterol), triglycerides and total lipids using kits purchased from Randox (Randox Laboratories Ltd., UK). The relative ratios of plasma LDL and HDL were analyzed by densitometer after separation of lipoproteins by agarose gel electrophoresis.

Statistical analysis

The Statistical Package for Social Sciences (SPSS) software was used to analyze the data. The data was analyzed using student t-test.

RESULTS

Tumor marker CA 15-3

The serum concentration of the CA15-3 in preoperative breast cancer patients were found to be significantly higher ($p<0.001$), i.e. 60.43±44.90 U/ml, as compared to the normal healthy individuals, i.e. 12.73±4.50 U/ml (Table 1, Figure 1).

Plasma lipid profile

Results of the plasma lipid profile are shown in Table 1 and Figure 2. The plasma cholesterol levels in breast cancer patients were found to be significantly higher ($p<0.01$) i.e. 246.61±96.00 mg/dl, as compared to the normal healthy individuals, i.e. 173.78±34.82 mg/dl. The triglyceride levels in breast cancer patients were found to be significantly higher ($p<0.001$) i.e. 224.55±127.78 mg/dl as compared to the normal healthy individuals, i.e. 105.32±40.02 mg/dl. The plasma levels of total lipids in breast cancer patients were significantly higher ($p<0.001$) i.e. 791.23±286.23 mg/dl, as compared to normal healthy individuals, i.e. 623.19±94.38 mg/dl.

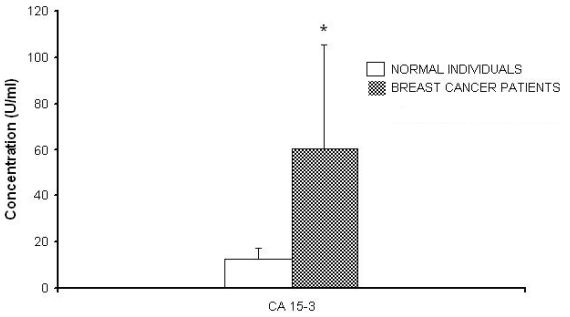

Figure 1: Comparison of the CA 15-3 levels of breast cancer patients with normal individuals. Values are mean±SD, the number of individuals is given in the results section of the text. The normal individuals were compared with the breast cancer patients; the significance of difference is indicated by p values calculated by independent t- test.

Plasma HDL-C levels in breast cancer patients were found to be non- significantly lower ($p>0.05$) i.e. 48±11.51 mg/dl as compared to the normal healthy individuals i.e. 49±10.51 mg/dl. In contrast, the plasma LDL-C levels in breast cancer patients were found to be significantly higher ($p<0.01$) i.e. 112.18±52.59 mg/dl as compared to the normal healthy individuals, i.e. 101.95±28.59 mg/dl.

Table 1: Comparison of lipid profile and CA 15-3 in normal individuals and breast cancer patients.

	Parameters	Normal individuals Mean±SD (n)	Breast Cancer patients Mean±SD (n)
1	Cholesterol (mg/dl)	173.78±34.82 (37)	246.61±96 (36)*
2	Triglyceride (mg/dl)	105.32±40.02 (37)	224.55±127.78 (36)*
3	Total lipids (mg/dl)	623.19±94.38 (37)	791.23±286.23 (36)*
4	HDL-C (mg/dl)	49.38±10.51 (37)	48±11.51 (11)*
5	LDL-C (mg/dl)	101.95±28.59 (37)	112.18±52.59 (11)*
6	CA15-3 (U/ml)	12.73±4.50 (37)	60.43±44.90 (36)*
7	LDL-C (%)	62.90±10.55 (37)	77.03±22.97 (36)
8	HDL-C (%)	37.10±10.55 (37)	22.34±24.91 (36)

*$p<0.01$ as compared to normal individuals.

Agarose gel electrophoresis of plasma lipoproteins of both normal individuals and breast cancer patients showed two bands corresponding to

LDL and HDL in the plasma of normal individuals and breast cancer patients. The relative concentration of LDL was greater in the band obtained in case of breast cancer patients as compared to that of the normal healthy individuals, i.e. 77.03±24.97% and 62.90±10.55% respectively. However, in the case of HDL the relative concentration is lowered in breast cancer patients as compared to that of normal individuals, i.e. 22.34±24.91% and 37.10±10.55% respectively.

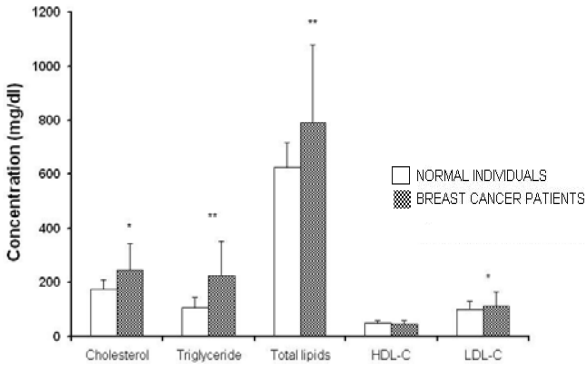

Figure 2: Comparison of lipid profile of breast cancer patients with normal individuals. Values are mean±SD; the number of individuals are given in the Results section of the text. The normal individuals were compared with the breast cancer patients; the significance of difference is indicated by p values calculated by independent t- test. *denotes significance at $p<0.01$ and **denotes significance at $p<0.001$.

DISCUSSION

CA 15-3 is the most significant tumor marker and a powerful predictor of survival after breast cancer. It is highly sensitive as an early indicator of relapse (degeneration). In this study CA 15-3 levels were detected by the ELISA technique. Our results indicated that CA15-3 levels were significantly higher ($p<0.001$) in the serum of preoperative breast cancer patients as compared to the normal individuals. These elevated levels may be due to the over expression of the gene MUC1 which encodes CA15-3. Our findings concurred with those of previous studies which reported that CA 15-3 levels are higher in breast cancer patients and are positively correlated with the number of lymph nodes of level I/II[49-51]. High preoperative levels of CA 15-3 indicated a worse outcome than low preoperative levels of CA 15-3[52,53]. CA 15-3 was more sensitive in detecting recurrences of breast cancer in pre- and post-chemotherapy stages[54]. Therefore it is suggested that CA 15-3 is a useful tumor marker and can be used as a prognostic factor in breast cancer thus it can indicate the status, risk or the presence of secondary breast cancer or metastasis.

The plasma cholesterol, total lipids and triglyceride levels in breast cancer patients were found to be significantly higher as compared to the normal healthy individuals. The plasma HDL-C levels in breast cancer patients were non-significantly lower while the plasma LDL-C levels in breast cancer patients were significantly higher as compared to the normal healthy individuals. The electrophoresis of the plasma lipoproteins indicated that the relative concentration of LDL is greater while the relative concentration of HDL is lower in the breast cancer patients as compared to normal individuals. Studies have shown a strong relationship of plasma lipids and lipoproteins alteration with risk of breast cancer[55-61]. The possibility that lipid abnormalities in cancer patients might represent an acute-phase response caused by the delivery of cytokines produced by inflammatory cells around the tumor or by the tumor cell itself, should be evaluated further. Changes in the lipid profile could also be explained by an increased estrogen activity, which is believed to be involved in the development of breast cancer and in the modulation of lipid metabolism[62]. Hence our findings are consistent with these studies.

In conclusion our study suggested that CA15-3 and circulating lipids can act as tumor markers of breast cancer and can be useful in detecting the recurrences, status, risk or the presence of secondary breast cancer or metastasis.

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