ORIGINAL ARTICLE

Comparison of Serum Lactate Dehydrogenase (LDH) with Carbohydrate Antigen 15-3 (CA 15-3) in Breast Cancer Patients

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ABSTRACT

Aim: To evaluating the levels of bloodLDH in different stages (I, II, III& IV) of Breast Cancer (BRCA) patients and comparing them with the gold standard tumor marker CA 15-3.

Methods: Total subjects included were 90, of which 70 females were premenopausal BRCA patients and 20 females were taken as healthy controls.

Results: The BRCA patients showed increased levels of serum CA 15-3, along with serum LDH with respect to controls. These levels increased in parallel with the severity of the disease, CA 15-3 wascorrelated withLDH levelsin all the stages (I,II,III & IV) It was found that CA 15-3 had a positive correlation withserum LDH in BRCA. Furthermore, it was also observed thatLDH were increased in early stages of the disease, unlike CA 15-3 which lacked the sensitivity for early diagnosis.

Conclusions: These results indicate thatserum LDH correlate closely with advancing stages of BRCA. Hence, they may prove to be sensitive, cost effective and relatively simple biochemical parameters for the early diagnosis as well as prognosis of BRCA.

Keywords: Cancer Breast, LDH, CA 15-3

INTRODUCTION

In the world most common female cancer is cancer breast (BRCA)In Pakistani women BRCA incidence is 24.4 which shows that it is most common cancer inPakistani females [1].In Pakistan majority of reported cases fall in the premenopausal age range [2]. and having more chances to develop metastatic cancers.

Numerous studies have shown that most etiological and risk factorsare,early menarche, ,1stpregnancy at late age,menopausal delay (after 55 years),hormonal replacement therapy, genetic susceptibility, body size and obesity, alcohol, physical activity, and possibly diet plus the western lifestyle [3].

Tumor Markers are biochemical substances which are produced by tumors and may released in circulation and appear in serum[4]. The detection of these markers in BRCA helps for early diagnosis, prognosis, monitoring treatment response or resistance after chemotherapy, surgery, or radiation in patients[5].

Role of LDH in Breast Cancer: Increased LDH levels inBRCA patients was estimated by many workers.In a study carried out in India and published in April 2013 which shows raised level of lipid profile and LDH in BRCA patients which. May suggest that

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LDH may be a biomarker for early detectionandprognostic marker for breast cancer and confirm the association between BRCA risk dyslipidaemia and BMI[6] .Similar results have also been reported in another Indian study in 2011. The researchers analyzed and concluded that serum Gamma glutamyl transferase (GGT), LDH and Malondialdehyde (MDA) were significantly increased in BRCA patients. Also, these levels raised significantly with severity of the BRCA. They concluded that LDH may be a potential marker for early detection, assessingprognosis and response to treatment along with clinical findings in BRCA[7].

A study was carried out in China in 2012 and the researchers evaluated serum alkaline phosphatase (ALP),alanine aminotransferase (ALT), aspartate aminotransferase (AST), GGT, LDH, and CA 15-3 levels in BRCA patients with and without liver metastasis

It concluded that these markers were higher in patients with positive liver metastasis than those with no liver metastasis[8].It has been reported in Greece (2009) thatBRCA patientshave raised serum LDH level, and the gene of its one iso-enzymes, LDHA, is up-regulated[9] The researchers concludedthat raised level of LDHmay be aprognostic sign of progression ofdisease [10].

According to another study published in 2003, LDH has a sensitivity score of 84% for the diagnosis of BRCA. Hence, serum LDH levels may be of diagnostic as well as prognostic value in patients with BRCA [11].

Role of CA 15-3 in breast cancer: CA 15-3 is a mucinous carbohydrate antigen product of the mucinous carbohydrate 1 (MUC1) gene. Whichis elevated in up to 70% ofmetastatic diseasepatients[12] and widely used marker for BARCA.

In a study doneon metastatic BRCA patients the researchers evaluated serum tumor markers CA 15-3 CEA,, CYFRA 21-1 and serum non-tumor markers ALP and LDH. From these 86% of patients have increase level of either CYFRA 21-1 or CA 15-3at baseline[13].

For detecting and monitoring treatment in BRCA patientsin 2008 in Ghana another study was conductedforsensitivity and specificity of serum CA 15-3 as a markerwhich was76.1 and 100%, respectively. The researchers concluded that serum CA 15-3 was significant for monitoring of treatment as well as early detection and of BRCA[14].Increased levelof CA 15-3 was observedwhen the cancer has spread to the liverand /or to thebones in metastatic breast cancer[15] .

This current study was designed to compare the levels of two biochemical parameters; serum LDH with tumor marker CA 15-3 in diagnosis and also in metastasis of BRCA patients.

MATERIALS AND METHODS

Study subjects included premenopausal BRCA patients (70) and age matched healthy controls (20). The criteria for inclusion were histologically diagnosed cases of BRCA falling in the premenopausal age range (20-50 years). Exclusion criteria was postmenopausal females with breast cancer, patients with benign breast lesions, any malignancy other than breast cancer, any other cause of hyperferritinemia (blood disorders, multiple blood transfusions, chronic hepatitis, alcoholic liver disease, Systemic lupus erythematosus (SLE), hemochromatosis,Rheumatoid arthritis (RA)(Based on history findings). These BRCA patients were selected with theirconsent from the oncology department of INMOL Hospital, Lahore.

Methods: 5ml blood (venous) drawn from each patient..After clotting and centrifugationserum waspreserved at -20°C in labeled tubesfor serum CA 15-3 and serum Lactate Dehydrogenase (LDH).

Biochemical Analysis: The biochemical tests performed on the serum samples were serum CA 15-3, andserum LDH. Serum. CA 15-3was done on "Humareader Plus Make Human GmbH" available in Biochemistry Department, Services Hospital, Lahore. Serum LDH estimation was done on fully automated Dimension AR auto analyzer, available in Biochemistry Depat, Sh. Zayed Hospital, Lahore.

Statistical Analysis: One -Way ANOVA was used

for comparing serum levels of CA 15-3, and in stages I,II,III& IV of BRCA The association between CA 15-3 and other variables was observed by calculating correlation coefficient "r" . A „p" value of less than 0.05 was considered statistically significant.

RESULTS

A study of serum CA15-3 and serum LDH was carried out on breast cancer patients and their resultscompared with selected normal controls. The results of both groups are compared and summarized in Tables.

This study was carried out on 90 individuals, of whom 70 randomly selected cases were included in the breast cancer group and 20 were included in the control group (Table 1). The BRCA patients were divided into four stages (I to IV) according to histological biopsy reports (Table 2).

Serum LDH: In all BARCA patients including stage 1 to stage IVmean serum level of LDH was significantly increased(p < 0.001) as compared to controls. i.e.,. Mean serum LDH in BRCA patients was 494.44±250.11 U/ml andin controls it was 120.63±30.45 U/L (Table 3). In stage I, the mean serum LDH in BRCA patients was 234.52±73.99 U/Las compared to controls which was 120.63±30.45 U/L (Table 4).In stage II, the mean serum LDH in BRCA patients was 401.72±36.12U/L and in controls it was 120.63±30.45 U/L. (Table 5). In stage III, the mean serum LDH in BRCA patients was 566.99±41.50U/L and in controls it was 120.63±30.45 U/L (Table 6). In stage IV, the mean serum LDH in BRCA patients was 780.05±248.83 /L and in controls it was 120.63±30.45 U/L (Table 7).

Serum CA 15-3: Similarly mean serum CA 15-3 in BRCA patients including all four stageswas significantly raised(p < 0.001) when comparing withcontrols. ie. Mean CA15-3 in all BARCA patients was119.39 ± 76.40 U/ml and in controls it was 15.32 ± 4.70 U/ml (Table 3). In stage I, the mean serum CA 15-3 in BRCA patients was 36.08 ± 3.11 U/ml as compared with controls which was 15.32 ± 4.70 U/ml (Table 4).In stage II, the mean serum CA 15-3 in BRCA patients was 78.85±11.47U/ml and in controls it was15.32 ± 4.70 U/ml (Table 5). In stage III, the mean serum CA 15-3 in BRCA patients was 138.36 ± 28.10 U/ml and in controls which was 15.32 ± 4.70 U /ml (Table 6). In stage IV, the mean serum CA 15-3 in BRCA patients was 224.00 ± 30.19 U/ as compared with controls which was 15.32 ± 4.70 U /ml (Table 7).

Correlation: Correlation was calculated of serum CA 15-3 withserum LDH in control and stages I(Table 9),II(Table 10),III(Table 11) & IV(Table 12) of BRCA.

CA15-3 did not show any significant correlation with serum LDH in controls (r = -0.233) (Table 9).

Similarly, CA15-3 did not show any significant correlation with serum LDH (r=-0.205)in stage 1 (Table 9) and in stage II BRCA patients (r=0.414) (Table 10).

Significant correlation (p< 0.05) was noted between CA 15-3 and LDH in stage III BRCA patients, positive correlation (r=0.620) (Table 11) andin stage IV BRCA cases (p<0.01) (r=0.692) (Table 12).

Sensitivity and Specificity: The overall sensitivity of serum CA 15-3 in BRCA patients was 78.57% and specificity was 100%, whereas regarding serum LDH the mean sensitivity and specificity was 87.14% and 100% respectively.

The diagnostic sensitivity of CA 15-3 in the current study was 21.05% and specificity was 100% .whereas LDH showed 52.63% sensitivity and 100% specificity.

ANOVA: One-Way ANOVA was used for comparing serum levels of CA 15-3 and LDH in stages I, II, III, IV

Table 1: Distribution of BRCA patients and Controls into different groups.

Group	Frequency	Percentage
Controls	20	22.2
BRCA patients	70	77.8

Table 2: Distribution of BRCA patients into different stages.

Groups	Frequency	Percentage
Stage I	19	27.1
Stage II	17	24.3
Stage III	15	21.4
Stage IV	19	27.1

BRCA. In all the two tumor markers, the results were found to be highly significant with p value <0.001 in stages I vs. II, II vs. III, I vs. IV, II vs. III, II vs. IV and III vs. IV (Table 8).

Table 3: Serum CA 15-3, and Serum LDH comparisonin controls and BRCA groups. Mean ± SD is given.

Group	Controls (20)	BRCA patients(70)
CA 15-3(U/ml)	15.32±4.70	119.39±76.40***
LDH(U/L)	120.63± 30.45	494.44±250.11***

*** p< 0.001 significantly higher as compared to control

Table 4: Serum CA 15-3 and Serum LDHcomparison in controls and Stage I BRCA groups. Mean ± SD is given.

Group	Controls (20)	Stage I(19)
CA 15-3(U/ml)	15.32±4.70	36.08±3.11***
LDH(U/L)	120.63± 30.45	234.52±73.99***

*** p< 0.001 significantly higher as compared to control

Table 5: Serum CA 15-3, and Serum LDH comparisonin controls and Stage II BRCA groups. Mean ± SD is given.

Group	Controls (20)	Stage II(17)
CA 15-3(U/ml)	15.32±4.70	78.85±11.47***
LDH(U/L)	120.63±30.45	401.72±36.12***

*** p< 0.001 significantly higher as compared to control

Table 6: Serum CA 15-3 and Serum LDH comparisonin controls and Stage III BRCA groups. Mean ± SD is given.

Group	Controls (20)	Stage III(15)
CA 15-3(U/ml)	15.32±4.70	138.36±28.10***
LDH(U/L)	120.63±30.45	566.99±41.50***

*** p< 0.001 significantly higher as compared to control

Table 7: Serum CA 15-3, and Serum LDH comparison in controls and Stage IV BRCA groups. Mean ± SD is given.

Group	Controls (20)	Stage IV(19)
CA 15-3(U/ml)	15.32±4.70	224.00±30.19***
LDH(U/L)	120.63±30.45	780.05±248.83***

*** p< 0.001 significantly higher as compared to control

Table 8: ANOVA Statistics Summary: Comparison of CA 15-3 and LDH (U/L) in stage I,II,III& IV of BRCA patients .

Stage	No	CA 15-3(U/ml)	LDH(U/L)
Control	20	15.32±4.70	120.63±30.45
I	19	36.08±3.11	234.52±73.99
II	17	78.85±11.47	401.72±36.12
III	15	138.36±28.10	566.99±41.50
IV	19	224.00±30.19	780.05±248.83
ANOVA	F	382	87
	P	< 0.001	< 0.001

Stage	CA 15-3(U/ml)	LDH(U/L)
I vs II	HS	HS
I vs III	HS	HS
II vs III	HS	HS
I vs IV	HS	HS
II vs III	HS	HS
II vs IV	HS	HS
III vs IV	HS	HS

P< 0.001, HS (highly significant)

Table 9: Serum CA 15-3 was correlated with Serum LDH in Stage I BRCA pts. Coefficient of correlation (r) is given.

	Control(20)	Stage I(19)
CA 15-3 with LDH	-0.233	-0.205

Table 10: Serum CA 15-3 was correlated withSerum LDH in Stage II BRCA pts. Coefficient of correlation (r) is given.

	Control(20)	Stage II(17)
CA 15-3 with LDH	-0.233	0.414

Table 11: Serum CA 15-3 was correlated with Serum LDH in Stage III BRCA pts. Coefficient of correlation (r) is given.

	Control(20)	Stage III(15)
CA 15-3 with LDH	-0.233	0.620*

* p< 0.05 significantly higher as compared to control

Table 12: Serum CA 15-3 was correlated with Serum LDH in Stage IV BRCA pts. Coefficient of correlation (r) is given.

	Control(20)	Stage IV(19)
CA 15-3 with LDH	-0.233	0.692*

*p< 0.01 significantly higher as compared to control

DISCUSSION

In this study comparison of biochemical parameter LDH and tumor marker CA 15-3 was done for the

diagnosis as well as to assess the prognostic significance and also in metastasis of BRCA. The current study consisted of evaluating serum LDH in all the four stages of BRCA and correlating them with the current tumor marker serum CA 15-3.

In this study BRCApatients were selected according to WHO criteria of TNM staging referred by Bevers T B et al[16]. They were diagnosed both on the basis of mammography and histological conformation. Keeping this in view, only biopsy proven patients were selected forthis study.Total90 study subjects were taken, of which 70 premenopausal females were taken as cases and 20 age matched females taken as control group (Table 1). These cases were further studied in four groups (stages I,II,III & IV) of BRCA (Table 2) according to the TNM staging and grading system[17].

The mean serum CA 15-3 was significantly raised in BRCA patients (p< 0.001) as compared to controls (Table 4). Likewise, a highly significant difference was observed (p<0.001) when mean serum CA 15-3 values were compared in each of the four stages i.e. stage I (Table 4), stage II (Table 5), stage III (Table 6) & stage IV (Table 7) of BRCA with controls. In the current study a prominent difference observed between the controls and patients even in early disease although majority of the studies favor the role of CA 15-3 as a prognostic marker as compared to being a diagnostic one[13,15,18,19]. Some studies show that serum CA 15-3 increases rarely in the early stages of cancer and has no diagnostic significance[5] while others indicate that it often increases in the early stages of BRCA and can prove to be a diagnostic marker[14,20].

The mean serum LDH was significantly raised in BRCA patients (p< 0.001) when compared with controls in the current study (Table 3). Also, a highly significant difference was observed (p<0.001) when mean serum LDH values were compared in each of the four stages i.e. stage I (Table 4), stage II (Table 5), stage III (Table 6) & stage IV (Table 7) of BRCA with controls. Many workers[6,7,8]reported increased level of serum LDH in patients who were suffering from BRCA. Rise in serum LDH level is directly related with fixity and aggressiveness of growth. Also, these levels rise significantly with severity of the BRCA. Based upon the results of the current study, it seems reasonable to assume that serum LDH could be possibly a potential marker in early detection, assessing the prognosis and response to treatment along with clinical findings in BRCA[21].

The results of comparison of mean serum CA 15-3 and serum LDH between control and stages I, II, III & IV have been illustrated. It was observed that the mean level of all the two parameters increased with the advancing stages. This study shows that premenopausal BRCA patients have higher serumLDH level than normal premenopausal women. Moreover the levels of these parameters rise significantly as the disease progresses and as the tumor load increases. So it is our view that serum LDH may be comparable with the gold standard tumor marker CA 15-3 in these cases.

Serum CA 15-3 wascorrelated with serum LDH levels in the 4 stages. No significant correlation was found between the two parameters in stages I and II. However, CA 15-3 and LDH correlated well with each other in stages III (r=0.620,p<0.05, Table 11) & IV (r= 0.692,p<0.01, Table 12)

The meanvalues of CA 15-3 were higher in stage I as compared to controls and further increased as the stages advanced. These findings are similar with previous studies that showed the positive relationships between CA 15-3 levels and advancing BRCA[5,15,18,20].

A strong positive correlation was observed in a study carried out on CA 15-3 levels and advancing stages of BRCA (r = 0.518)[14].The "r" value in the current study was 0.269.

The second main objective of the study was to compare the sensitivity and specificity of serum LDH against CA 15-3 in BRCA patients. In this study, the overall sensitivity of serum CA 15-3 in BRCA cases was 78.57% and specificity was 100%. The diagnostic sensitivity of CA 15-3 was 21.05% and specificity was 100%. It was also observed that CA 15-3 has a low diagnostic sensitivity but a high specificity. Similar results were observed in some previous studies. As emphasized by Keyhani et al[22] CA 15-3 has a diagnostic sensitivity of 14% and specificity of 92.3%. Another study also reports low diagnostic sensitivity 19.3% with a high specificity 94.8% [23]. Similarly in a third study it was reported as 23.2% sensitivity and 95.3% specificity[20]. In contrast to these findings, there are studies who show high diagnostic sensitivity and specificity of serum CA 15-3 i.e. 76% and 100%[14] .This difference in results may be due to different environmental or genetic factors.

Similarly, the overall sensitivity of serum LDH in BRCA cases was 87.14% and specificity was 100% in this study, whereas, the diagnostic sensitivity of LDH was 52.63% and specificity was 100%. Both overall and diagnostic sensitivity of LDH was slightly better when compared to serum ferritin. The observed results are in close agreement with the results of Seth et al[11] who reported that LDH has a sensitivity of 84% in BRCA patients.

One - Way ANOVA was used for comparing serum levels of CA 15-3, LDH and in stages I, II, III & IV of BRCA. In all the two tumor markers, the results were highlysignificant with p value <0.001 in stages I vs. II, II vs. III, I vs. IV, II vs. III, II vs. IV and III vs. IV

(Table 8).

Thus it seems likely that alterations in serum LDH and CA 15-3 levels are characteristics of patients with BRCA.On the bases of results of the current study it is recommended that serum LDH may be used as diagnostic as well as prognostic markers for BRCA. CA 15-3 along with CEA are no doubt the most reliable tumor markers for BRCA patients according to the American Society of Clinical Oncology (ASCO). However, the analytical method of these advanced tumor markers are not only expensive, but unapproachable for general population, because these facilities forare available only at well-equipped and latest centers.

CONCLUSIONS

1. Serum LDH were seen to be significantly raised in the early stages (I, II) of BRCA, proving their worth as very sensitive markers for the early diagnosis. Also, they both showed more diagnostic sensitivity than CA 15-3 which is currently known to be the gold standard cancer marker of BRCA.
2. CA 15-3 is not onlyexpensive parameter, but unapproachable for people, as It is not available at primary and secondary care hospitals. This suggests that serumLDH measurements might become useful, sensitive and inexpensive parameters for the diagnosis as well as the prognosis of BRCA patients.

REFERENCES

1. Rasool MI, Malik IA, Luqman MK. The clinicopathologic study of carcinoma of breast .A preliminary report. Pak J Med Res.1987; 26:135-9.
2. Sohail S, Alam SN. Breast cancer in Pakistan - awareness and early detection. J Coll Physicians Surg Pak.2007; 17 (12): 711-2.
3. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. CA Cancer J Clin. 2005; 55(2):74-108.
4. Mishra S, Sharma DC, Sharma P. Studies of biochemical parameters in breast cancer with and without Metastasis. Indian Journal of Clinical Biochemistry.2004; 19 (1): 71-5.
5. Duffy M J. Serum tumor markers in Breast Cancer: Are they of clinical value? Clinical Chemistry. 2006; 52(3):345-51.
6. Swetha N, Arul Senghor KA, Ramachandran K. Serum lactate dehydrogenase and lipid profile in breast cancer. International Journal of Pharmacy and Biological Sciences.2013; 3(2): 423.
7. ChandrakanthKH ,Nagaraj, Jayaprakashmurthy DS, Satish kumar D, Anandpyati. Study of serum levels of gamma glutamyl transferase, lactate dehydrogenase,
8. Rui C, Li-ping W. Serological Diagnosis of Liver Metastasis in Patients with Breast Cancer. Cancer Biol Med. 2012; 9: 57-62.
9. Koukourakis MI, Kontomanolis E, Giatromanolaki A, Sivridis E, Liberis V. Serum and tissue LDH levels in patients with breast/ gynaecological cancer and benign diseases. GynecolObstet Invest. 2009; 67(3):162-8.
10. Bogdanović V, Turšijan S, Đorđević M, Nikolić A, Mrđanović J, Jakimov D, Trajković V. Activity of lactate dehydrogenase and superoxide dismutase in the circulation of patients with breast carcinoma. Archive of Oncology. 2008;16(3-4):39-41.
11. Seth RK, Kharb S, Kharb DP. Serum biochemical markers in carcinoma breast. Indian Journal of Medical Sciences. 2003; 57(8): 350-4.
12. Duffy MJ. Biochemical markers in breast cancer: which ones are clinically useful? ClinBiochem 2001; 34: 347-52.
13. Bidard FC, Hajage D, Bachelot T, Delaloge S, Brain E, Pierga JY. Assessment of circulating tumor cells and serum markers for progression-free survival prediction in metastatic breast cancer: a prospective observational study. Breast Cancer Research. 2012 Feb 13;14(1):R29.
14. Agyei Frempong MT, Darko E, Addai BW. The use of carbohydrate antigen (CA) 15-3 as a tumor marker in detecting breast cancer. Pakistan journal of biological sciences.2008;11(15):1945-8.
15. Bast RC, Ravdin P, Hayes DF. 2000 update of recommendations for the use of tumor markers in breast and colorectal cancer: clinical practice guidelines of the American Society of Clinical Oncology. J ClinOnc .2001; 19:1865-78.
16. Bevers T B, Anderson B O, Bonaccio E, Buys S, Daly M B, Dempsey P J. Breast Cancer Screening and Diagnosis. J NatlComprCancNetw. 2009; 7:1060-96 .
17. Edge S B, Byrd D R, Compton C C, Fritz AG, Greene F L, Trotti A (Eds). AJCC Cancer Staging Manual.7th ed. Springer; 2010.
18. Ghoraishian SM, Jalali BA, Mozayan MR. Serum Level of CA15.3 and CEA in Women Affected with Breast Cancer. International Digital Organization for Scientific Information.2006;1(1): 48-51.
19. Gang Y, Adachi I, Ohkura H, Yamamoto H, Mizuguchi Y, Abe K. CA 15-3 is present as a novel tumour marker in the sera of patients with breast cancer and other malignancies. GanTo Kagaku Ryoho. 1985 ;12(12):2379-86.
20. Arslan N, Serdar M, Deveci S, Ozturk B, Narin Y, IlganS,Ozturk E, Ozguven M A. Use of CA15-3, CEA and prolactin for the primary diagnosis of breast cancer and correlation with the prognostic factors at the time of initial diagnosis. Annals of nuclear medicine .2000 ; 14(5) 395-9.
21. Kher A, Moghe G, Deshpande A. Significance of serum ferritin and lactate dehydrogenase in benign and malignant disease of breast. Indian J Pathol Microbiol. 1997 Jul; 40(3):321-6.
22. Keyhani M., Nasizadeh S, Dehghannejad A. Serum CA15-3 measurement in breast cancer patients before and after mastectomy. Arch Iranian Med. 2005; 8 (4): 263- 6.
23. Wojtacki J, Dziewulska-Bokiniec A, Skokowski J, Ciesielski D. Evaluation of CA15-3 tumor marker in the diagnosis of breast cancer. A pilot study. Neoplasma.1994 ; 41(4): 213

Also in the middle column continuing reference 7:
malondialdehyde and vitamin-e in breast cancer.2011; 2(4): 489-98.