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RESEARCH ARTICLE

BIO CHEMISTRY

STUDY OF SERUM LEVELS OF GAMMA- GLUTAMYL TRANSFERASE, LACTATE DEHYDROGENASE, MALONDIALDEHYDE AND VITAMIN-E IN BREAST CANCER.

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ABSTRACT

Despite extensive research for many years throughout the world, the etiopathogenesis of cancer still remains obscure. Oxidative stress have been associated with the risk of breast cancer. A total number of 121 subjects are studied, comprising of 35 controls, 26 fibroadenoma and 60 Breast cancer subjects. Breast cancer subjects were further divided depending on stage of the cancer. Serum levels of GGT, LDH, MDA and vitamin E were estimated in all the subjects. 36 postoperative breast cancer subjects were studied.

Serum GGT, LDH and MDA were significantly increased in Breast cancer and fibroadenoma when compared to controls. These levels rised significantly with severity of the Breast cancer. Postoperatively, serum GGT and LDH were increased and decreased respectively. Serum vitamin E levels decreased significantly in Breast cancer when compared to fibroadenoma and controls.

Serum Gamma-glutamyl transferase and lactate dehydrogenase may be a better marker in early detection, assessing the prognosis and response to treatment along with clinical findings in Breast cancer. Determination of malondialdehyde and vitamin E may be useful in evaluating oxidative damage in patients with benign and malignant tumors of the breast.

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KEYWORDS

Gamma-glutamyltransferase; Lactate dehydrogenase; Malondialdehyde; Vitamin E; Breast cancer; Fibroadenoma.

INTRODUCTION

Breast cancer is one of the diseases most feared by women and perceived as fatal world wide. 75,000 new cases are estimated in India every year. Incidence of breast cancer is 23.2 per 100,000 in India, however in Mumbai the incidence of breast cancer is 30.4 per 100,000. 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.[1]

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. 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. However, the analytical method of many of these are unapproachable for general population as the facilities for these are available only at sophisticated and well-equipped centers with latest technology and are expensive. Therefore, there is need for simple biochemical investigations, which can be easily assayed, less expensive and can predict stages and prognosis.[2]

Hence, this study was undertaken to evaluate the importance of assessing the serum levels of gamma-glutamyl transferase (γ-GT) and lactate dehydrogenase (LDH). And also, to correlate the probable relationship between the serum levels of these tumor markers and stages of breast cancer. To determine the extent of oxidative stress by measuring malondialdehyde (MDA) and vitamin E, and to evaluate the relationship between oxidative stress and different clinical stages in breast cancer patients.

MATERIALS AND METHODS

A total number of 121 subjects participated in the present study which included 60 breast cancer cases, 26 fibroadenoma 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 of our college. The patients and controls voluntarily participated in the study.

Cases were histopathologically diagnosed breast cancer and fibroadenoma 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 were done in all cases.

Breast cancer patients were divided into 4 groups according to stage grouping. Stage grouping was based on TNM staging system.

Collection of Blood Sample :

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 4^0C until analysis was carried out. Serum levels of Gamma-GT, LDH, MDA and Vitamin E were measured preoperatively, and post operatively on 7^{th} day in 36 cases of breast cancer.

METHODS:

1)Estimation of serum lactate dehydrogenase by semi-micro methods.[3]

2)Estimation of serum gamma-glutamyl transeferase activity by optimized SZASZ method.[4]

3)Estimation of serum malondialdehyde(MDA) by thiobarbituric acid method.[5]

4)Determination of serum tocopherol by baker and frank method.[6]

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 parameters after surgery was analyzed by paired-t test for each stage. Pearson's correlation coefficient was used to assess the relationship between two parameters.

For all the tests p-value of <0.05 was considered as statistically significant.

RESULTS

Table 1

Comparison of serum levels of GGT, LDH, MDA and vitamin E in controls, fibroadenoma and breast cancer.

Group	No.		GGT (U/L)	LDH (U/L)	MDA (n mol / ml)	Vit. E (mg/L)
1) Controls	35	Mean ± SD	16.4 ± 2.5	222.6 ± 34.1	3.93 ± 0.22	10.5 ± 1.8
		Range	11.1 – 22.0	170.6 – 299.3	3.52 – 4.35	7.9 – 14.1
2)Fibroadenoma	26	Mean ± SD	33.3 ± 6.1	261.0 ± 26.0	4.27 ± 0.17	10.19 ± 0.28
		Range	22.2 – 43.4	212.3 – 311.6	3.92 – 4.62	9.62 – 10.64
3)Breast cancer	60	Mean ± SD	150.2 ± 81.2	604.2 ± 216.7	6.47 ± 1.31	7.54 ± 1.35
		Range	38.0 – 311.3	288.0 – 1102.2	4.30 – 8.64	5.16 – 9.30

ANOVA, F, p value		73.8, < 0.001	84.7, < 0.001	100.3, < 0.001	66.5, < 0.001
Controls vs Fibroadenoma	t p	15.1 < 0.001	4.88 < 0.001	6.66 < 0.001	0.88 NS
Controls vs Breast cancer	t p	9.83 < 0.001	10.43 < 0.001	11.47 < 0.001	32.6 < 0.001
Fibroadenoma vs Breast cancer	t p	7.39 < 0.001	9.41 < 0.001	9.97 < 0.001	11.57 < 0.001

p > 0.05, NS (not significant)
p < 0.001, HS (highly significant)

Table 2
Comparison of GGT, LDH, MDA and vitamin E in different clinical stages of breast cancer patients.

Stage	No.	GGT (U/L)	LDH (U/L)	MDA (n mol / ml)	Vit. E (mg/L)
I	11	51.0 ± 8.90	332.6 ± 31.5	4.54 ± 0.18	9.11 ± 0.17
II	18	106.0 ± 10.5	496.0 ± 25.9	6.00 ± 0.10	8.45 ± 0.11
III	18	158.0 ± 17.2	623.0 ± 23.3	6.66 ± 0.22	7.28 ± 0.22
IV	13	284.2 ± 18.0	957.8 ± 84.4	8.51 ± 0.09	5.33 ± 0.09
ANOVA	F p	607.3 < 0.001	427.2 < 0.001	1318.4 < 0.001	1365.5 < 0.001
I vs II		HS	HS	HS	HS
I vs III		HS	HS	HS	HS
I vs IV		HS	HS	HS	HS
II vs III		HS	HS	HS	HS
II vs IV		HS	HS	HS	HS
III vs IV		HS	HS	HS	HS

P < 0.001, HS (highly significant)

Table 3
Pre and Post operative levels of GGT, LDH, MDA and vitamin E levels in breast cancer

Parameters	Pre operative n = 36	Post operative n = 36	Difference	t*	P
GGT (U/L)	152.2 ± 81.2	181.0 ±	28.9 ± 22.5	7.7	< 0.001

		94.1			
LDH (U/L)	619.0 ± 226.7	551.7 ± 216.2	67.3 ± 37.1	10.9	< 0.001
MDA (n mol / ml)	6.53 ± 1.29	6.51 ± 1.30	0.01 ± 0.07	1.02	0.31, NS
Vitamin E (mg/L)	7.51 ± 1.36	7.54 ± 1.34	0.03 ± 0.12	1.63	0.11, NS

**** Paired t-test***

Table 4

Pre and post operative levels of GGT and LDH in different clinical stages of breast cancer

Stage	GGT				LDH			
	Pre op (U/L)	**Post op (U/L)**	**Difference**	**p***	**Pre op(U/L)**	**Post op (U/L)**	**Difference**	**p***
I	53.3 ± 9.2	63.7 ± 6.7	10.4 ± 3.6	t = 7.1 p < 0.01	326.7 ± 26.4	305.3 ± 24.5	21.3 ± 7.1	t = 7.3 p < 0.01
II	100.9 ± 10.5	119.4 ± 16.6	18.5 ± 8.3	t = 7.0 p < 0.001	495.6 ± 27.0	387.8 ± 24.6	107.8 ± 14.3	t = 23.8 p < 0.001
III	157.0 ± 17.3	194.1 ± 34.3	37.2 ± 30.3	t = 4.3 p < 0.01	622.1 ± 23.3	581.2 ± 29.3	40.9 ± 18.0	t = 7.9 p < 0.001
IV	282.9 ± 15.3	326.3 ± 19.3	43.5 ± 13.5	t =9.15 p <0.001	987.8 ± 58.7	896.9 ± 54.0	90.8 ± 10.0	t = 25.7 p < 0.001

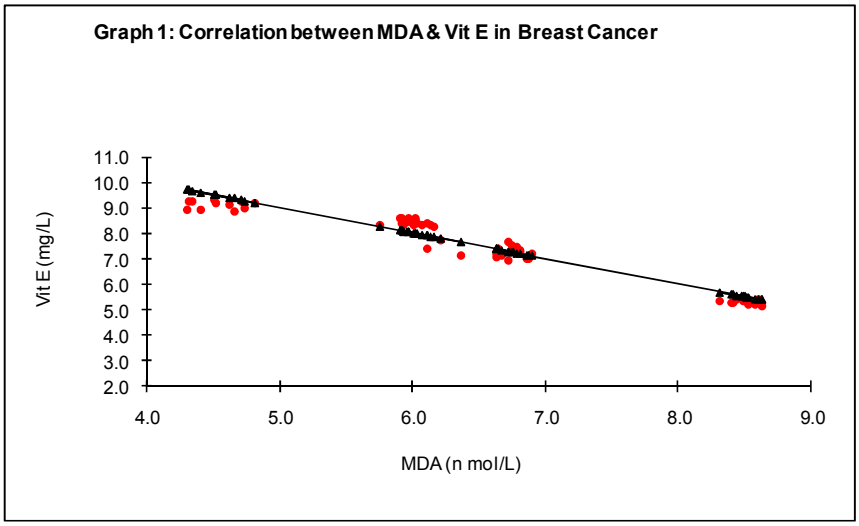
**** paired t-test***

Table 5

Pearson's correlation coefficients between MDA and vitamin E in breast carcinoma

Parameter	Controls		Fibroadenoma		Carcinoma	
	r	**p**	**r**	**p**	**r**	**P**
MDA vs vitamin E	-0.06	0.72 NS	-0.12	0.57 NS	-0.97	< 0.001 HS

r – Pearson's correlation coefficient



DISCUSSION

Breast carcinoma is one of the commonest malignancies in females with its increasing incidence. Despite the extensive research for many years throughout the world, the etiopathogenesis of cancer still remains obscure. Oxidative stress plays an important role in the pathogenesis of chronic diseases, such as cancer and atherosclerosis. For the early detection of carcinoma of various origins, a number of biochemical markers have been studied to evaluate the malignancy. Tumor associated markers reflect behavioural changes from tissue to blood, resulting in changes in levels of enzymes, proteins and hormones both in cancerous tissue and blood because of unchecked proliferation of cells. Therefore, alteration in particular enzyme contents in serum could be a good index of malignancy in its early and best manageable stage.

Gamma-GT :

GGT is a membrane bound glycoprotein which catalyzes the transfer of gamma-glutamyl groups between peptides or aminoacids. It may be involved in the transport of aminoacid across the cell membrane.[7] Although the highest concentration of GGT is found in the brush borders of the epithelial cells that line the proximal convoluted tubules of the kidney, the enzyme has been demonstrated in a variety of other human tissues.[8]

Gamma GT is an oncofetal protein, a glycoprotien whose levels have been shown to be altered during development and carcinogenesis. In most of the liver diseases, both malignant and non malignant, GGT estimation has been reported to be a sensitive but non specific indicator of the disease.[9] Some studies have shown that GGT levels are also elevated in malignant tumors of the other tissues.[10]

In the present study the mean levels of GGT in control group and in breast cancer are in the range of 16.4 $\pm$ 2.5 U/L and 150.2 $\pm$ 81.2 U/L respectively. This difference is statistically significant ($P<0.001$)[11,9,12]. This increase in serum GGT activity is due to rapid turnover of malignant cells, which release the enzymes into blood streams.[13]

In the present study, patients with carcinoma of breast were classified into 4 stages, according to TNM classification. The rise in serum GGT was found to be directly proportional with the advancing stage (disease)[9,11]. The steady increase in serum GGT from stage I to stage IV may indicate GGT as a better biochemical marker.

Mean serum GGT levels were increased significantly ($p < 0.001$) in fibroadenoma when compared to controls. It was also noticed that activity of GGT increased after surgery in the present study. The increased activity of serum GGT after surgery might be due to increased shedding of the membrane constituents into the surrounding milieu.[9]

Lactate dehydrogenase (LDH) :

Lactate dehydrogenase is an oxidation reduction enzyme which reversibly catalyses the reaction between pyruvic acid to lactic acid. It is distributed widely in body tissues and is raised in variety of physiological and pathological status. LDH is thus derived from the tissues and its high levels in serum indicates, the destruction of the cells.[14]

In the present study, mean levels of lactate dehydrogenase was 222.6 ± 34.1 U/L, 261.0 ± 26.0 U/L and 604.2 ± 216.7 U/L in controls, fibroadenoma and breast cancer patients respectively. The mean values of lactate dehydrogenase in breast cancer cases was found to be significantly raised (3-fold), when compared to controls [14,15,16,,17]. There was significant rise ($p < 0.001$) in LDH levels in breast cancer than in fibroadenoma patients. When serum LDH levels was compared in different stages of breast cancer, the enzyme levels rised significantly with increase in severity (stage) of the disease [14,15,17]. It has been reported that tumour cells excrete large amounts of lactic acid, because glucose is metabolized via the anaerobic glycolytic pathway to lactic acid when compared to normal cell. And serum levels of glycolytic enzymes were found to be increased in patients with breast carcinoma.[15] Raised levels of LDH are seen in malignancies because of high rate of glycolysis, increased production of enzyme by tumour cells, change in the permeability of cells, allowing leakage of soluble enzyme into circulation and because of tumour blockade of the duct system through which enzyme passes.[18] Induction of LDH synthesis in the normal tissues of the host by the tumour also contribute to raised LDH levels.[14]

Post treatment serum enzyme studies on the 7th day in the cancer group showed that, the enzyme levels tend to decline but do not touch the base line. 7 days of surgery seems to be too short a period for serum LDH levels to touch the base line and a longer follow up is needed[2]. But, removal of primary tumour load is definitely beneficial.[15]

Thus LDH levels are a good adjunct in the diagnosis, are an indicator of the stage of the disease, response to treatment and prognosis of the patient.[14]

Malondialdehyde :

Oxidative stress plays an important role in the pathogenesis of chronic diseases, such as cancer and atherosclerosis. In these pathological states, the increased production or ineffective scavenging of oxidants may play a crucial role in determining tissue injury. Prime targets of reactive oxygen species are the polyunsaturated fatty acids in cell membranes and their interaction results in lipid peroxidation. Enhanced lipid peroxidation and impairment in antioxidant defense mechanisms were demonstrated in patients with lung and breast cancers.[19]

In the present study serum MDA levels in controls, fibroadenoma and carcinoma of breast was found to be 3.93 ± 0.22 n mol/ml, 4.27 ± 0.17 n mol/ml and 6.47 ± 1.31 n mol/ml respectively. Serum MDA levels were significantly elevated in breast cancer when compared to controls[19,20,21,22,23,24]. Levels of

serum MDA were significantly increased in cancer patients when compared to fibroadenoma[25]. According to disease severity, serum MDA levels were significantly ($p < 0.001$) elevated from stage I to stage IV.

The mean plasma MDA levels were not found to be significantly altered after 7 days of surgery when compared with the preoperative values.

Increased lipid peroxidation in serum and tissues has been reported in breast cancer patients. The lipid peroxidation products such as MDA can structurally alter DNA, proteins and other biomolecules.

Our findings are in agreement with most of the earlier studies suggesting that breast cancer patients might be at risk from oxidative cell damage. Oxidative stress arises when there is an imbalance between oxygen-free radical (OFR) formation and scavenging by antioxidants. Excess generation of free radical can cause oxidative damage to biomolecules resulting in lipid peroxidation. OFR-induced lipid peroxidation has been implicated in neoplastic transformation.[22] The increase in the rate of lipid peroxidation, causes the increased production of MDA that leaks into the blood stream, consequently causing increased levels of MDA in patients with breast cancer.

Vitamin E :

Vitamin E as a lipophilic antioxidant molecule is able to react with lipid peroxyl radicals, eventually terminating the peroxidation chain reaction, and thereby reducing oxidative damage.[19]

In the present study, serum vitamin E was found to be 10.5 ± 1.8 mg/L, 10.19 ± 0.28 mg/L and 7.54 ± 1.35 mg/L in controls, fibroadenoma and breast cancer respectively. There was no significant change in serum vitamin E levels in fibroadenoma and controls.

Serum vitamin E levels were significantly ($p < 0.001$) decreased in breast cancer when compared to controls [19,23,22,25,26]. The mean plasma vitamin E concentration in patients with stage I was found to be significantly lowered when compared with the mean values of control group ($P<0.001$). The decrease in plasma vitamin E concentration was proportion with the increasing stages of cancer. Further, the preoperative levels remained unchanged after 7 days of surgery. It could be due to the possibility of a short duration of follow up which may not be sufficient to bring the vitamin E levels back to normal.[2]

Decrease in vitamin E in patients with breast cancer could be due to the possibility that vitamin E reacts very rapidly with molecular oxygen and free radicals, the role of which has been implicated in carcinogenesis.[2] It is suggested that vitamin E acts as a scavenger protecting polyunsaturated fatty acids from peroxidation reaction in cancer.[27]

As vitamin E was found to decrease in breast cancer patients, they may not be sufficient enough to counter free radical attack, thereby resulting in oxidative stress. In the present study a negative correlation was found between MDA and vitamin E.[19]

CONCLUSION

Breast cancer is one of the most common cancer in women of developed and developing countries. Despite the extensive research for many years throughout the world, the etiopathogenesis of cancer still remains obscure. For the early detection of carcinoma of various origins, a number of biochemical markers have been studied to evaluate the malignancy.

The presence of an association between oxidative stress and breast cancer was observed in the present study. Because only longitudinal studies could confirm causality by providing data on the chronology of the changes observed, the increase of MDA could be a result of the

presence of breast cancer, but oxidative stress may not be implicated in its development. Changes in circulatory lipid peroxides and antioxidants seen in breast cancer patients were also evident in fibroadenoma patients placing them in a "high-risk" category. Thus determination of lipid peroxidation and antioxidants in circulation may be useful in evaluating patients with benign and malignant tumours of the breast.

The determination of GGT and LDH enzymes in malignant breast has been helpful. And also, these can be easily assayed and are less expensive. Not only are these enzymes able to differentiate malignant growths from benign tumours, but also assist in assessing the extent and therefore prognosis of this malignancy along with clinical findings. Serum GGT and LDH may be better biomarkers in carcinoma of breast and may help in early detection of the disease. It is difficult to ascertain their diagnostic importance in cancer patients, yet their prognostic importance cannot be undermined.

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