Original Research Paper

Volume - 13 | Issue - 02 | February - 2023 | PRINT ISSN No. 2249 - 555X | DOI : 10.36106/ijar

Biochemistry

"SERUM ADENOSINE DEAMINASE (ADA) ENZYME LEVELS AS AN INFLAMMATORY MARKER IN FEMALES WITH BREAST TUMOR."

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ABSTRACT Cancer is one of the major causes of mortality worldwide. It is the most frequent cancer of women and account for 25% of all cancers. This burden is increasing significantly and in near future it is predicted to be 22 million new cancer cases and 13 million cancer-related deaths occurring annually by 2030. Chronic inflammation is associated with several human cancers and that pro-inflammatory cytokines and other immuno-modulatory molecules can be produced by cells in cancerous tissue to favour tumour growth, infiltration and metastasis. The relationship between chronic inflammation and cancer is complex and bidirectional. This gives idea to take this a comparative study to find out Inflammatory marker in Benign and Malignant Breast cancer in female. This study was carried out on total 450 female subjects from Western Rajasthan, age ranging between 21 to 70 years. As Inflammation progressed with the advancement in growth of tumor, levels of this inflammatory marker were found significantly higher compared to age matched control. So, this marker can be used as a important diagnostic tool for early diagnosis of breast cancer to prevent its seriousness.

KEYWORDS : Serum Adenosine Deaminase (ADA), Inflammatory Biomarker, Benign and Malignant Breast

INTRODUCTION

Cancer is one of the major causes of mortality worldwide. Fairly accurate about 18.1 million new cancer cases and 9.6 million cancer deaths in 2018, as data presented by the International Agency for Research on Cancer (IARC), after focusing on geographic variability across 20 world regions. [1] This burden is increasing significantly and in near future it is predicted to be 22 million new cancer cases and 13 million cancer-related deaths occurring annually by 2030. The reason for increase in this magnitude of cancer is a consequence of population growth and aging, but with these consequences societal, economic, and lifestyle change are also linked due to increasing human development and are likely to additionally increase the scale and alter cancer trends in the next decades [2].

It is the most frequent cancer of women and account for 25% of all cancers. The major types of cancer are carcinoma, sarcoma, melanoma, lymphoma, and leukaemia. The most commonly diagnosed carcinoma originate in the skin, lungs, breasts, pancreas, and other organs and glands. Breast cancer (BC) is the leading cause of cancer death in women. It can be benign and malignant type. Breast cancer is the commonest cancer and leading cause of cancer death in women worldwide, with an estimated 1.7 million cases and over 520,000 deaths in 2012, accounting for 25% of all female cancers and 15% of all female cancer deaths.[3]

As long ago as 1863, Rudolf Virchow proposed that cancers originate at sites of chronic inflammation [4]. It is now clear that chronic inflammation is associated with several human cancers and that pro-inflammatory cytokines and other immuno-modulatory molecules can be produced by cells in cancerous tissue to favour tumour growth, infiltration and metastasis [5]. The relationship between chronic inflammation and cancer is complex and bidirectional. This gives idea to take this a comparative study to find out Inflammatory marker in Benign and Malignant Breast cancer in female. Although the research conducted on breast cancer is done but studies to show relation Inflammatory with Benign and Malignant Breast cancer in female in pre-menopause and post menopause are very less in western Rajasthan. So the present study was planned for this mentioned aim.

MATERIAL & METHODS

The present study was conducted in the Department of Biochemistry and Department of Sugary Dr. S. N. Medical College, Jodhpur and Associated Groups of Hospitals. The current study is a case control study and was aimed with primary objective of estimation of Serum Adenosine Deaminase (ADA) Enzyme, Levels in newly diagnosed breast cancer tumor (Benign or Malignant) and to correlate it with the condition of benign.

Study Design: Case control study
Sample Size: This study was carried out on total 450 female Subjects.

Inclusion Criteria

Females who are willingly participating, aged between 21-70 years., had significant findings of solid breast lump and with confirmed diagnosed case of breast tumour either benign (neoplastic) or malignant and were going for lumpectomy were included.

Exclusion Criteria

All Females who were not willingly participating , less than 21 years and more than 70 years of age, pregnant and lactating mothers, ongoing menstruation phase of uterine cycle, addicted to smoking, alcohol & tobacco etc, had any history of breast trauma, breast abscess, cystic changes breast diseases and other inflammatory conditions, had any history of breast surgery conducted at least six months, had any history of oral contraceptive drugs at least six months, had any history taking anti-inflammatory drug at least one month, had any history of other chronic diseases presenting with breast lumps, had any history of estrogen and progesterone therapy, particularly that of hormone replacement therapy (HRT treatment for menopausal conditions), and who have any short history of cancer chemotherapy and taking any other cancer treatment like Ayurvedic, Homeopathic etc. and also male were excluded from current study.

Study Groups:

Subjects was categorised into three groups as Healthy, Benign and Malignant and 150 subjects was enrolled in each group for this present study.

Group –I: Healthy Control Females (HC: Healthy Control =150)
One hundred fifty (150) control females aged between 21-70 years

having normal vital organ functions and confirmed by routine biochemistry tests were selected from Out Patient Clinics of Hospitals, associated to Dr. S. N. Medical College, Jodhpur.

Group –II: Subjects with Benign Breast Tumour: (BG: Benign Group =150)

This group included clinically diagnosed cases of hundred and fifty (150) females subjects of Benign Breast Tumour confirmed by histopathological investigations either needle or excision biopsy performed in Clinical laboratories of Department of Pathology.

Group – III: Subjects with Malignant Breast Tumour (MG: Malignant Group =150)

This group included clinically diagnosed cases of hundred and fifty (150) females subjects of Malignant Breast Tumour confirmed by histopathological investigations either needle or excision biopsy performed in Clinical laboratories of Department of Pathology.

Data collection: Female subjects from Western Rajasthan, age ranging between 21 to 70 years and who visited the OPD and enrolled in IPD ward Department of Sugary, for breast tumour surgery either benign or malignant. It was a case control observational study, as an equally number subjects was studied in healthy and breast cancer groups. A blood sample was taken from antecubital vein with all aseptic conditions. The collected samples were immediately carried to the biochemistry lab and were processed to assess serum ADA levels. The prior ethical permission was taken from the institutional ethical committee and a detailed informed consent form signed wilfully by all the study participants was accepted.

RESULTS:

In current study levels of ADA also increase as we go from the healthy control (15.26±4.2 U/L) group to the benign group (20.38±7.10 U/L), and this further increases in the malignant group (33.28±8.78 U/L). The mean ADA levels difference between healthy control group and benign group was found to be significant F (2, 447) = 267.26 (p <0.001). Table No. 1.

TABLE – 1 ANOVA-One Way for mean levels of serum ADA among Various Study Groups

Study Group	ADA (U/L)					
	N	Mean	SD	df	F value	P value
Healthy Control	150	15.26	4.20	2/447	267.26	0.001
Benign Group	150	20.38	7.10			
Malignant Group	150	33.28	8.78			
Total	450	22.97	10.29	449		
= 0.05, at 95% confidence level. F crit = 3.016						

The healthy control group mean value is within reference range and for benign group it is just near to upper range of physiological reference range of serum ADA activity (4 – 17 IU/L). The mean difference of ADA between healthy control vs malignant group and benign group vs malignant group were found to be statistically significant as shown below table no.2

Post Hoc -Tukey HSD Tests of Inflammatory Marker: ADA (U/L)

TABLE – 2 Multiple Comparisons (Post Hoc -Tukey HSD Tests) Dependent Variable: ADA (U/L)

(I) Group	(J) Group	Mean Diff. (I-J) *	Std. Error	P-value	95% Conf. Interval	
					Lower Bound	Upper Bound
Healthy Control	Benign Group	-5.12	0.80	0.001	-7.01	-3.23
	Malignant Group	-18.02	0.80	0.001	-19.91	-16.13
Benign Group	Malignant Group	-12.90	0.80	0.001	-14.79	-11.01
* The mean difference is significant at the 0.05 level.						

DISCUSSION:

In the present study we have found the mean ADA levels were 15.26 ± 4.20 U/L in the healthy control group. Similar findings of mean ADA levels (14.92 ± 3.73 U/L) of healthy control subjects have been reported in a study conducted in the Pakistani population by Wajahat Ullah Khan et al[6] as well study conducted by Mohmoud Aghaei et al.[7] in Iranian population.

A study conducted by Choudhari Archana et al[8] 2013, in India on 30 healthy control subjects reported mean values of 21.6 ± 4.62 U/L, the findings are slightly higher to the present study. Similarly, the mean difference of ADA between benign group and malignant group found to be highly significant ($p < 0.001$). Mahajan Mridula et al[9] observed a mean value of 49.7±15.5 U/L in 60 control subjects of Punjab population.

Study conducted by Faisal A et al[10] 2012, in Iranian population between healthy control and malignant groups, the mean results are near to present study of respective groups. While in another study conducted in Pakistani population by Wajahat Ullah Khan et al[6] reported there is no statistically significance mean difference between control and malignant group. In another study conducted in Iranian population showed significance difference between controls and benign cases as well controls and malignant cases (14.01 vs 24.0 U/L, 14.01 vs 24.76 U/L) but no significance difference found between benign and malignant tumor cases of female breasts (24.0 vs 24.76 U/L).

Inflammation due to prevalence of oxidative stress seen in benign and malignant tumours and it is evidence of increased adenosine purine nucleotide in tissue. This is an important signalling molecule that exerts major anti-inflammatory action.[11] The enzyme ADA catalysed adenosine into inosine which finally converted into uric acid. Growing tumours have high concentration of adenosine which could inhibit the process of infiltrating of tumours.[12] As Inflammation progressed with the advancement in growth of tumor in either benign and malignant condition, levels of inflammatory marker were found significantly higher compared to age matched control. ADA activities seemed to be improved i.e., they get normal after mastectomy indicating relatively less inflammation and better condition after surgery.

ADA is found in the tissues and body fluids and its activity is linked to lymphoid tissue. It helps in proliferation, maturation, and differentiation of lymphocytes, this has been shown that the radioactivity increases with rapid proliferation of cells which is the case in breast tumours[13].

For a long time, ADA has been an inflammatory marker in the diagnosis of Pulmonary tuberculosis. Similarly, ADA has also been reported linked to the breast tumor pathologies. The role of the ADA has been extensively studied in the pulmonary tuberculosis patients but stress upon the levels of this marker in breast tumor patients has not been thoroughly studied.[14] In present study the mean differences are statistically significant but in case of benign group this mean value is just near to upper limits of physiological reference so we can use ADA as one of the diagnostic tools for assessing breast status in females.

CONCLUSION:

In the present study, we included 450 females, 150 for each study group based on inclusion and exclusion criteria and we found that ADA levels were statistically more significant increases in malignant group as compare to control group than other two group comparison (Control vs Benign and Benign vs Malignant). But in case of benign group this mean value is just near to upper limits of physiological reference so ADA has less weight age than other biomarkers for early diagnosis of benign tumor while for malignant tumors it can be used for early diagnosis of cancerous tumor of breast as well as a tool to shown prognosis of disease.

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