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Clinical Biochemistry

ROLE OF OXIDATIVE STRESS MARKERS IN THE DEVELOPMENT OF BREAST CANCER IN WOMEN OF MARATHWADA, INDIA.

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ABSTRACT **Background:** Malondialdehyde (MDA) is the principal and most studied product of polyunsaturated fatty acid peroxidation. These products have the ability to provoke oxidative damage. Antioxidants are the body's defence mechanisms against oxidants that maintain redox status and remove reactive species. The balance of redox reactions plays an important role in the body. The present study evaluated the role of oxidative stress marker malondialdehyde (MDA)and antioxidant enzyme superoxide dismutase (SOD) in the breast cancer (BC) patients in Marathwada, India. **Material and Methods:** Present case control study was carried out on 104 breast cancer women and 104 healthy controls at SRTRGMC, Ambajogai. Serum MDA was measured by Satho method and serum SOD was measured by Markland and Markland method in patients with BC and healthy women. The difference in serum levels between cases and controls were evaluated by using statistical methods. **Results:** The mean age of patients and controls was 46.49 ±10.82 and 41.7 ± 10.2 respectively. The results showed that the Serum levels of MDA were significantly higher in BC patients when compared with healthy controls. (1.45± (1.07) Vs 0.75 ± (0.25), $p<0.05$). The serum levels of SOD were significantly decreased in BC cases than healthy controls. (15.74 ± (5.88) Vs 45.14 ± (16.69), $p<0.05$). **Conclusion:** Significantly increased serum MDA levels indicate increased oxidative stress in BC patients and significantly decreased levels of SOD in BC patients indicates lowered antioxidant defence in BC.

KEYWORDS : Breast Cancer, Oxidative Stress, MDA, Antioxidants, SOD

INTRODUCTION

Mutations in DNA converts proto-oncogenes into oncogenes.[1]Cancer is an important barrier to increasing life expectancy in every country in the world. In 2020 there were an estimated 19.3 million new cases and 10 million deaths worldwide. Incident rates are higher in developed countries than in developing countries.[2]

In 2022, 2,296,840 new cases of female BC were reported globally. cases there were an estimated 666,103 BC related deaths globally. India reported the highest number of BC related deaths (15%of global deaths) followed by China (11%).[3]

In Indian women newly diagnosed cases are in premenopausal stage; peak age is in between 40-50 years. This situation is worrying because early onset of BC is more aggressive and prognosis is also poor than late onset. In India diagnosis of BC in women is late, only approximately 1% to 8% women are diagnosed at the stage 1 of the disease, 6% to 24% with the stage IV of the disease and 29% to 52% are diagnosed at stage III. Mortality associated with BC is increasing in India.[4]

The etiology of breast cancer is multi factorial, demographic factors like age, gender, early menarche, delayed menopause, use of contraceptives or hormone therapy, family history, history of benign breast disease, obesity, life style, the mentioned risk factors show their effects through oxidative stress.[1]

Oxidative stress (OS) is an imbalance in the ratio between oxidants and antioxidants. It is the condition in which the body's redox and oxidation reactions create problems. Increasing imbalance between production and removal of free radicals and reactive species in the body causes disorders. Many cellular processes including cell metabolism, signalling pathways, pathways regulating gene expressions, cell proliferation and apoptosis are affected by OS. Damage caused by OS is involved in many types of diseases, most importantly types of cancers including breast cancer.[1] OS plays an important role in the initiation, progression, and invasion of breast cancer.[5]

Malondialdehyde measurement is an indicator of lipid peroxidation, which used as a biomarker for oxidative stress. It is one of the major end products of the peroxidative degradation of polyunsaturated fatty acids.[6] It is a normal ketoaldehyde, one of the biproducts of arachidonate metabolism. Excessive amount of MDA is formed due to tissue injury, which can bind with the free amino groups of proteins to form MDA-modified protein complex, which is an immunogenic.[7]

Antioxidants are the body's defence mechanisms against oxidants that maintain redox status and remove reactive species. The balance of redox reactions plays an important role in the body. The most important and frequent antioxidants are catalase, glutathione peroxidase, superoxide dismutase and nonenzymatic antioxidants like vitamin E, vitamin C, vitamin A, flavonoids, albumin, glutathione, thioredoxins, uric acid etc.[1]

Antioxidants act as a radical scavenger, hydrogen donor, electron donor, peroxide decomposer, singlet oxygen quencher, enzyme inhibitor, synergist and metal chelating agents. Both enzymatic and non-enzymatic antioxidants exist in the intracellular and extracellular environment to detoxify reactive oxygen species. (ROS). Endogenous antioxidants play a crucial role in maintaining optimal cellular functions and thus, systemic health and wellbeing. However, there are some conditions under which oxidative stress is increased in that condition endogenous antioxidants may not be sufficient and dietary antioxidants may be required to maintain optimal cellular functions.[8]

Superoxide dismutase (SOD) is an enzyme catalysing dismutation or disproportion of superoxide radical to dioxygen and hydrogen peroxide.

$M_3^+ + O_2^- \text{------} M_2^+ + O_2$

$M_2 + O_2^- + 2H^+ \text{------} M_3 + H_2O_2$

SOD is found in many organisms, from microorganism to plant and animals. Superoxide radicals are toxic to living cell. They oxidize and degrade biologically important molecules, such as lipids and proteins. Based on the requirement of metal species at the active site, several types of SOD have been reported.

a) Manganese containing Superoxide dismutase (Mn SOD).
b) Copper and Zink containing Superoxide dismutase (Cu-Zn SOD).
c) Iron containing Superoxide dismutase (Fe SOD).
d) Ni-containing Superoxide dismutase[9]

MnSOD is considered to be one of the most important antioxidant enzymes. It is cytoprotective and plays an antiapoptotic role against oxidative stress, ionizing radiation and inflammatory cytokines.[10]

Cu-Zn SOD have potential effect on mammary tumorigenesis, in addition to this it may also play a role in sustaining mammary tumours. The increased resistance of breast cancer cells to oxidative stress compared with normal cells may partially due to activity of this SOD.[11]

Many studies have revealed the critical role of oxidative stress in carcinogenesis. It is suggested that, SOD may regulate cancer progression and hence, can be used as a novel target for cancer treatment. [12]

Therefore, to know the effect of oxidative stress and role of antioxidants in the development of BC we evaluated an association of oxidative stress marker MDA and an antioxidant enzyme SOD in the serum of BC patients and healthy controls.

MATERIAL AND METHODS

One hundred and four female BC patients at SRTR Govt. Medical college and Hospital, Ambajogai, Marathwada, Maharashtra, were included as cases in the study. One hundred and four normal OPD volunteers were included as controls. The age of the cases and controls were between 20 to 70 years. Information form regarding age, the menstrual cycle, family history of malignancy, oral contraceptives was filled along with written informed consent was taken. Controls were closely matched to BC cases. The study was approved by the Medical Ethics Committee of research centre.

Blood Sample Collection

3 ml blood was collected from each individual in a plain vacutainer without anticoagulant. kept it aside for 1-2 hours or centrifuged after an hour for serum separation. Samples were processed for MDA and SOD estimation.

a. Serum MDA was estimated by Satho method[13]
b. Serum SOD was estimated by Markland and Markland[14]

Statistical Analysis

All the data were analysed by Open Epi version 2.3 and MyStat -12 as a statistical software. P<0.05 was considered as statistical significance. Odds ratio (OR) and P value were calculated to estimate the association between risk of BC and genotype. We used t-test for comparison of means of two groups and Chi square test for categorial variables.

RESULTS:

Table 1 Basic demographic

Subjects	Control Mean ±(SD)	Cases Mean ±(SD)	P value
NO. of Cases	n=104	n=104	----
Age in years	41.7 ± (10.2)	46.49 ± (10.82)	P<0.05
Sr. MDA	0.75± (0.25)	1.45± (1.07)	P<0.05
Sr. SOD	45.14 ± (16.69)	15.74 ± (5.88)	P<0.05

Table 2

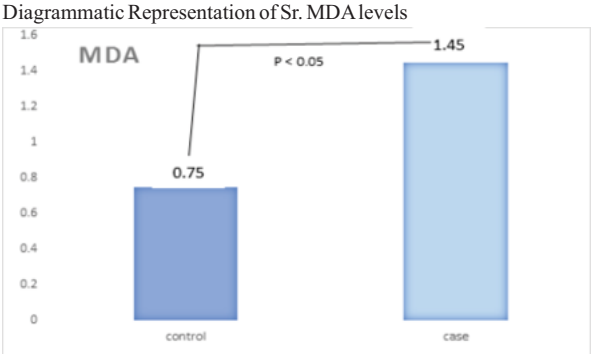
Subject		Controls n (%)	Cases n (%)	P value	OR (95%CI)
Premenopausal		66 (63.46%)	41(39.42%)	P<0.05	OR=0.37
Postmenopausal		38(36.53%)	63 (60.57%)	P<0.05	OR=2.67
BMI	Normal	92(88.5%)	75(72.1%)	P<0.05	OR=2.96
	High	12(11.5%)	29(27.9%)		
Family History		2(1.92%)	12 (11.53%)	P<0.05	OR=6.65

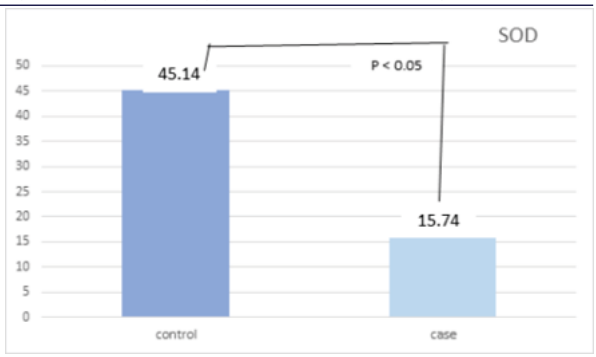
Age showed statistically significant difference in cases when compared to controls. There was a statistically Significant increase in serum MDA levels in BC cases than in controls. (Table 1)

And statistically significant decrease in serum SOD levels in cases compared to healthy controls.

Similarly, it was seen that, Among premenopausal women 39.42% cases and 63.46% controls. Premenopausal status showed significantly lower odds ratio compared to controls (x^2=12.03, OR=0.37; p=0.0005). Among postmenopausal women 60.57% BC cases and 36.53% healthy controls (X^2=12.03,OR=2.66;95%CI:1.52-4.67;p=0.0005) The association between menopausal status and BC is statistically significant. There is a significant difference between cases and controls about the distribution of BMI (X^2=8.77, p=0.003). Women with higher BMI were frequently observed in cases (27.9%) than in controls. (11.5%). Women with high BMI showed increased chances of developing BC compared to women with normal BMI (OR=2.96;95%CI:0.1.42-6.20). We observed a positive association between family history and BC. The association was statistically significant (x^2=7.66, OR=6.65;95%CI:1.45-30.51, P=0.005) (Table 2)

Diagrammatic Representation of Sr. MDA levels





Diagrammatic Representation of Sr. SOD levels

DISCUSSION

Free radicals (FR) are unstable molecules that are formed as natural byproducts in the body during biological processes and lead to oxidative stress (OS). Reactive oxygen species (ROS) and reactive nitrogen species (RNS) helps to sustain redox homeostasis at the cellular level in the normal healthy tissues. Over production of ROS and RNS leads to OS which cause damage to protein, nucleic acids to form harmful products like lipid peroxides and lipid adducts,[8] MDA has a potential toxicity and at elevated levels it can stimulate the immune and inflammatory response. MDA is used as a biomarker for OS.[15]

Antioxidants block the initiation of FR chain reactions. SODs are enzymatic antioxidant produced by organism itself.[16] SODs are a group of key enzymes functioning as the first line of antioxidant defence with the ability to convert highly reactive superoxide radicals into hydrogen peroxide and molecular oxygen.[8] it is suggested that the antioxidant properties of SOD supplementation are useful to protect the immune system in a variety of pathophysiological conditions.[17]

In the present study, we found statistically significant rise in the serum levels of MDA (p<0.05). Our results support the previous findings reporting that, increased formation or inadequate removal of ROS may lead to the cancer.[7,18,19,20]

H. Alagol[21] etal and Omar Abdel Salem[22] et al found lower plasma levels of MDA in advanced BC patients and in patients with BC undergoing chemotherapy respectively.

We observed statistically significant decrease in the serum levels of SOD (p<0.05) in the breast cancer cases when compared with healthy controls.

Our study is in agreement with these studies.[15,16,20,23]

Some studies showed increased levels of SOD in BC, are not agree with our study[5,6,11] C. Ambrosone[24] reported that, BC risk is greatest among women who consumed a smaller number of dietary antioxidants. Decreased action of Cu,Zn-SOD and Mn-SOD has been reported in cancer by Khanzode[25] et al.

Increased MDA levels in the serum of breast cancer patients may be in response to the aggregation of ROS, which might result in extensively elevated lipid peroxidation. In newly diagnosed BC patients, the increased levels of oxidative factors can be an indicator of early stages of cancer progression.[5]

The study indicated increased levels of oxidative stress marker MDA in BC patients may be due to disease process itself and tissue injury. Excess production of ROS causes tissue injury. However, tissue injury itself causes excessive ROS leading to increased MDA levels. Anticancer drugs themselves can induce oxidative stress and thereby MDA levels. free radical trapping capacity of plasma gets reduced which results in increased plasma MDA levels.[22]

The low activity of antioxidant enzyme might be due to increased Oxidative stress and depletion of antioxidant system increased ROS production, and consequently oxidative stress, and decreased antioxidants such as SOD, increases the susceptibility to BC.

In the present study, Postmenopausal status was significantly associated with increased BC risk, This may be because of prolonged

exposure to environmental carcinogens.[26] Women with a positive family history of BC had higher probability to develop BC and was statistically significant. Family history is a well- established risk factor for BC[1,27,28,29] and it shows inherited genetic susceptibility as well as common environmental influence. In the present study, we may suggest that, the women with higher BMI had increased susceptibility to BC compared to women with normal BMI. In premenopausal women estrogens are not influenced by aromatization, so higher BMI or obesity does not play a significant role in carcinogenesis but postmenopausal women have high activity of aromatase in adipose tissue results in higher estrogen levels and thereby increased chances to develop BC.[30] Elevated OS in high BMI or Obesity can have direct and indirect effects on DNA ability and thereby tumorigenesis. It has an important role in cell transformation and cancer development. In obesity breast tissue is exposed to a surplus of estrogen, ROS and inflammation factors.[31]OS and obesity linked to breast carcinogenesis by promoting genomic instability and epithelial cell proliferation. Obesity also linked with poor prognosis in women diagnosed with BC.[32]

Reports from World health organisation (WHO) (who.int 14 Aug.2025) and several studies showed the association of these risk factors and BC.[1,27,28,29,30]

CONCLUSION

Thus, in association with risk factors, increase in Free radicals and oxidative stress thereby increasing MDA levels and decreased antioxidant defence due to OS, both may play an important role in developing of BC.

Abbreviations:

BC = Breast cancer;
MDA = Malondialdehyde;
ROS =Reactive oxygen species;
Frs = Free radicals
BMI = Body mass index.
SOD = Superoxide Dismutase
OS = Oxidative Stress

Limitations of Study.

There are some limitations of this study. The sample size was multicentric. Other demographic parameters such as Diet, Smoking, alcohol intake were not included. Further studies with larger population are needed to confirm the results.

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