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Characteristic Abnormalities In Serum Biochemistry In Patients With Breast Cancer

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ABSTRACT

Introduction: Free radicals play an effective role in the pathogenesis of different pathological diseases together with cancer which is the second leading cause of cancer death in women worldwide and the main aim of this study was to estimate the of Thrombospondin (TSP-1),TAS, malondialdehyde (MDA) , Paraoxonase(PON-1), and arylesterase (ARE) ,selenium (SE), and G6PD as antioxidant capability in breast cancer patients and to compare with apparently healthy individuals.

Methods: A total of 150 subjects were recruited which included 75 patients (age range 25 to 45 years) with BC attending the Kirkuk Teaching Hospital (Kirkuk province), were enrolled in this study, in a period from 15 December 2019 to 20 March 2020.and 75 controls (age and sex matched). The analysis of covariance was used to identify any significant differences and statistical significance was set at $P<0.05$.

Results: The activity of TSP-1, PON-1,ARE, SE, and TAS were significantly lower in patients compared to control group. The level of MDA, and G6PD were significantly higher in patients versus the healthy group.

Conclusion: Breast cancer patients demonstrate raised oxidative stress compared to healthy subjects.

Keywords: Breast cancer; Oxidative stress; Thrombospondin.

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INTRODUCTION

Cancer is characterized by loss of control of cellular growth and development leading to excessive proliferation and spread of cells (Sarhat *et al*,2019). Breast cancer is one of the most relevant of women's health issues worldwide, it is the leading cause of death from malignant tumors in women (Janina Didžiapetrienė, 2020). Its etiology and causative factors are complex and interlinked (Eman El-Attar, 2020).

Thrombospondin (TSP)-1, a typical matricellular protein-450 kDa-. TSP-1 is an extracellular matrix glycoprotein , widely expressed in diverse tissues such as endothelial cells, monocytes and macrophages, smooth muscle cells, fibroblasts and adipocytes, Its mechanism of action include activation of CD36, p59Fyn, and caspase resulting in apoptosis, as well as activation of transforming growth factor β (Rodrı´guez-Manzaneque *et al*,2001; Ma *et al*.2013; Sarhat *et al*,2019).

Oxidative stress which is formed by the breakdown of the balance between free radicals and antioxidants in favor of free radicals. The harmful effects of an increased oxidative load are reduced by antioxidant enzymes that convert ROS to less harmful molecules. When the production of excessive ROS overcomes the natural antioxidant defense system, an unstable environment may emerge for the cells and tissues(Sarhat *et al*,2018; Alev Özer *et al*,2016; Khalid *et al*,2018). Breast tumors display greater dependence on ROS detoxification systems, which increases gradually as the tumor progresses and becomes metastatic(Benito *et al*, 2017).

The main purpose of the present study was to evaluate TSP-1, oxidative stress and antioxidant capability in patients with BC and control subjects.

MATERIALS AND METHODS

Study design

One hundred fifty patients (mean age: 42 ± 10 years) with clinically proven breast cancer were chosen for the study as study subjects (patients). Normal healthy age matched women volunteers were taken as controls.The present study was carried out in Kirkuk Teaching Hospital (Kirkuk Province), in a period from 15 December 2019 to 20 March 2020, that conducted on 75 patients (mean age: 42 ± 10 years) with clinically proven breast cancer were chosen for the study as study subjects (patients).All the patients underwent standard preoperative malignancy investigations including mammography, ultrasound examination and fine needle aspiration cytology (FNAC) of the lesion. 75 subject will be age and sex matched healthy volunteers as control group. The control group will be taken from patient's attendants, staff, students and may be from private labs which conduct routine serum checkup of healthy persons. The study was approved by the local ethics committee, and all subjects gave written informed consent before taking part in the study. All the blood samples were collected between 8:00-10:00am, and the blood samples were collected from the patients and controls by venous arm punctures ,it was allowed to clot, centrifuged at 2500xg and the serum was aspirated and stored in aliquots at -20^{0}C.

Paraoxonase and arylesterase PON1 activity were assayed spectrophotometrically by using synthetic paraoxon (diethyl-p-nitrophenyl phosphate) ,and phenyl acetate as substrate respectively. TAC was assayed spectrophotometrically using a Biodiagnostics® kit .An ELISA (United Kingdom) was used to determine concentrations of TSP1 in serum.

Statistical analyses

Statistical analysis were performed using SPSS version 21.Values are expressed in means ± standard deviations, Student's *t*-test was used to compare the mean values

between patients and controls. In all cases, a p value < 0.05 was considered significant.

RESULTS

This study reveals that the mean serum level of TSP-1 in women with breast cancer 16.1±8.87ng/mL was significantly lower than that of the control 8.169±4.60 ng/mL, as evident in the following Figures 1-3.

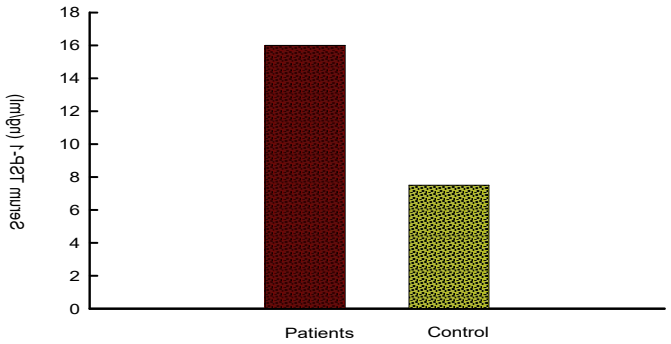

Figure (1):-The level of Serum TSP-1 (ng/ml) in breast cancer group and the control group.

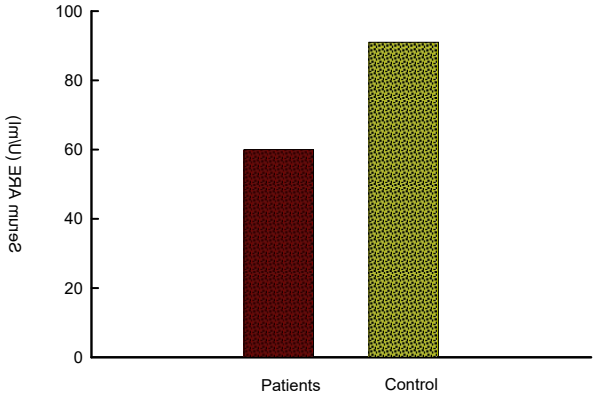

Figure (2):-The level of Serum ARE (U/ml) in breast cancer group and the control group.

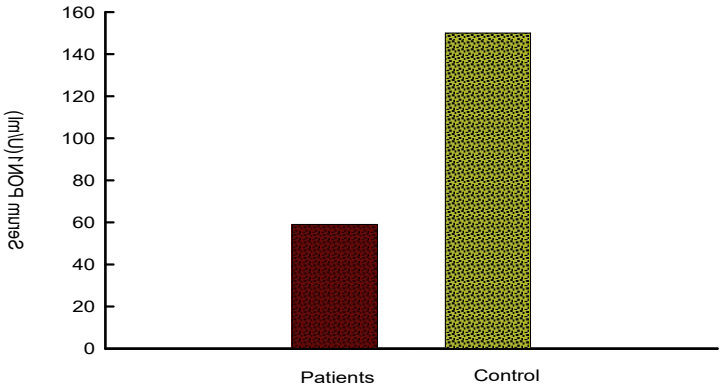

Figure (3):-The level of Serum PON1 (U/ml)in breast cancer group and the control group.

As shown in Table 1, this results reveals that serum level of MDA, and G6PD were significantly elevated in breast cancer women was (13.83±2.63 µl/l), and (16.33±1.65 U/g Hb), respectively as compared with apparently healthy women which was (7.32 ± 1.52 µl/l: $P < 0.05$), and (10.109±1.81 U/g Hb: $P < 0.05$), respectively. While the mean serum of TAS, Se, in women with BC was TAS (1.2 ± 0.27mmol/l), and (101.24 ± 17.27 mg/dL), respectively, compared with apparently healthy women (1.61±0.28:P<0.0001), and (115.36±13.31mg/ dL : $P < 0.001$) respectively.

Table 1: Baseline characteristics of the study population

Parameters	Serum		*P* value
	Group A(Control)	Group B	
TAS (mmol/l)	1.61 ± 0.28	1.2 ± 0.27	*P*<0.0001
Se, mg/dL	115.36 ± 13.31	101.24 ± 17.27	*P* < 0.001
MDA (µl/l)	7.32 ± 1.52	13.83±2.63	*P* < 0.05
G6PD (U/g Hb)	10.109±1.81	16.33±1.65	*P* < 0.05

DISCUSSION

Arylesterase is an endogenous inhibitor of angiogenesis, it might be due to directly by interacting with VEGF and indirectly by engaging several endothelial cell TSP1 receptors (Sukhbir Kaur *et al*,2010). It activates the macrophage TGFβ and the NFκB pathway by binding CD36.On the one hand, endothelial cells activated by TSP-1 influence the inflammatory reaction and promote carcinogenesis((Hideya Kashihara *et al*, 2017).The present study is the first to determine serum TSP-1 concentrations in patients with BC. We found that serumTSP-1 levels were higher in BC patients than those in healthy control due to both pro- and anti-angiogenesis and up-regulation of tissue TSP-1 expression(Stéphanie Filleur *et al*, 2013). THBS1 as a prognostic factor in breast cancers(Rice *et al*, 2002). Stromal THBS1 expression in breast cancer was inversely related to lymph node involvement (Ioachim *et al*, 2012).Evidence indicates that the failure of THBS1 to protect in breast cancer is due to an escape mechanism involving increased VEGFA expression (Fontana *et al*, 2005).

Oxidative stress parameters can potentially facilitate the development of biomarkers of cancers, including breast cancer(Xiang *et al*, 2019). Malondialdehyde is one of the most important marker of the oxidative stress in patients with breast cancer, its low-molecular-weight aldehydes derived from lipid peroxidation processes, and is one of the many reactive electrophile species that cause toxic stress in cells (Sarhat *et al*,2019; Jasmina Gradaščević-Gubaljević, *et al*; Intesar Jasim *et al* ,2021). Higher activity of MDA were observed in breast cancer patients as compared to the levels in control subjects. The reason for this increase could be due to increased generation of reactive oxygen species or suppression of the antioxidants defense mechanism in the metabolically active tissues(Subramanyam *et al* ,2013).

Paraoxonase (PON1, EC 3.1.8.1) is a member of the paraoxonase family (PON1, PON2, PON3), bound to the apolipoprotein A1- containing HDL fraction is basically synthesized by the liver and secreted into the blood .PON1 is an HDL associated antioxidant enzyme protecting cells against ROS by preventing LDL and HDL from oxidation and destroy active lipids in mildly oxidized LDL(Sarhat *et al*,2018; AyŞe *et al*,2015; Sarhat *et al*,2015).

The mean activity of PON-1 were decreased in patients with BC as compared to apparently healthy controls due to at least two mechanisms: First, PON1 activity decreased by increased oxidative stress , since the PON1 active site for LP hydrolysis requires a free sulfhydryl group at cysteine 284; PON1 degrades lipid peroxides by reacting covalently with this site which leading to enzyme inactivation .Second, the activity of enzymatic decrease in is related to a decrease in the serum concentration of the enzyme, suggesting an inhibition hepatic synthesis of PON1(Rodríguez-Tomàs, *et al*,2005).

Selenium, as an essential trace element for human health, serves as a key component of several functional selenoproteins [e.g., glutathione peroxidases (GPx), thioredoxin reductases, iodothyronine deiodinases and selenoprotein P ,as well as it is involved It functions as a redox center as part of the family of selenium-dependent glutathione peroxidases (GPx), transforming hydrogen peroxide and damaging lipid and phospholipid hydroperoxides into harmless products that protect tissues and membranes from oxidative stress and control the cell redox status (Joachim Bleys, *et al*,2007; Kong *et al*,2016; Wang *et al*,2016).

Se-containing gene that encodes for Se-containing proteins and its various polymorphisms may lead to decreased element absorption (Charalabopoulos, *et al*,2006).Selenium has roles that support immune function and, through specific cellular pathways, may play a preventive role in both the initiation and promotion of specific cancer (Basma T, 2010)The findings in this study show significantly lower serum level of selenium in BC patients the results of this study were in line with the results of studies conducted by (Hashemi *et a,* 2017). The exact mechanism responsible for the reduction in blood concentration of selenium in BC patients is yet to be fully understood, the findings in this study also show significantly lower serum level of selenium in BC patients. but it has been suggested that cancer cells use antioxidants more effectively than healthy cells, thus depleting circulating antioxidants agents(Franca, 2011).

Glucose-6-phosphate dehydrogenase (G6PD or G6PDH) (EC 1.1.1.49) is is the rate-limiting enzyme of the pentose phosphate pathway. (PPP).In the erythrocytes the PPP is the only source of NADPH, G6PD provides a source of reducing power against oxidative damage(Lele Hou *et al*,2017). PPP activity and G6PD itself are often up regulated in cancer and are associated with aggressiveness, drug resistance and poor prognosis((Mele, *et al*,2019).G6PD silencing increases the glycolytic flux, reduces lipid synthesis and increases glutamine uptake in breast cancer cells, whereas TKT silencing reduces glycolysis flux(Jin,,2019). G6PD inhibition leads to an increase in 5′-AMP-activated protein kinase (AMPK) signaling, a decrease in lipid biosynthesis and the inhibition of breast cancer cell growth and survival(Yang,,2018). BC patients in our study showed lower levels of G6PD as compared to controls might be interpret by elevation free radical production occurring in this condition due to low activity of antioxidant enzymes by inducing oxidative stress.Antioxidants are capable of reducing oxidative stress by scavenging free radicals (Sarhat *et al*,2018). Total antioxidant status (TAS) indicates the total summation of the individual enzymatic and non-enzymatic antioxidants present in a sample known as ferric reducing antioxidant power (Sadri, *et al*, 2017; Sarhat *et al*, 2019). In this study, significantly lower concentrations TAS were observed in BC patients compared to controls. may be due to their increased consumption of plasma antioxidants by enhanced

ROS/RNS production in women with breast cancer(Maria, *et al*, 2013). Our finding is in accordance with these previous study reports(Ashrafi, *et al*,2018).

The activity antioxidants reduced in the existence of a low level of TAS resulting in compensatory rise of SOD Activity. A possible mechanism for the decreased level of TAC could be that due to malnutrition and the scavenger antioxidants were consumed by the increased free radical activity (Sarhat *et al*,2019).

CONCLUSIONS

The findings from this study show that patients with BC demonstrate increased oxidative stress compared to the control groups. Further studies are needed to assess whether the observed associations are causal.

Conflict of Interests

The authors of this paper declares that he has no financial o personal relationships with individuals or organizations tha would unacceptably bias the content of this paper an therefore declare that there is no conflict of interests.

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