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SERUM OXIDATIVE STRESS PARAMETERS IN BREAST CANCER IRAQI PATIENTS BEFORE AND AFTER RADIOTHERAPY

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Abstract:

Aim: In this study, radiation therapy (RT) effects on some serum oxidant and antioxidant parameters in breast cancer (BC) patients were investigated.
Background: RT, which is used to treat cancer, causes molecular damage to living cells by producing reactive oxygen species. Aqueous free radicals (radiation on water) produce the majority of radiation damage to human tissues since they include 80% water. The primary free radicals produced by aqueous radiolysis are (OH, H, e_{aq}^-, HO_2, H_3O^+). These free radicals damage DNA, RNA, proteins, membranes, and other biological components, causing cell death. Radiation causes these effects in both malignant and normal cells.
Patients and Methods: Sixty BC female patients were involved in this study and received RT at a dose of 40.50 Gray for three weeks, in comparison with a matched (number, mean age, and mean BMI) healthy control group. Blood samples were obtained one day before and after the end of RT from each patient. Serum levels of Malondialdehyde (MDA), Total Serum Bilirubin (TSB), Uric Acid (UA), and Albumin (Alb) were analyzed by full-auto spectrophotometry or ELISA. T-test and a paired t-test were used to compare pre-and post-radiotherapy data with a healthy control group.
Results: Between the patients' group before RT and the control group, there was a non-significant change in MDA, UA, TSB, and Alb concentration levels. In the patients' group after RT and the control group; and before and after RT patients' group, a significant decrease in Alb levels was observed, while a significant increase in MDA levels was found ($p < 0.05$), while the antioxidant defence systems UA and TSB levels had no significant changes ($p > 0.05$) either.

Keywords: Antioxidant, Radiotherapy, Oxidative Stress, Breast cancer.

BACKGROUND

Breast cancer (BC) is the most prevalent cancer in women, comprising (24.5 %) of (9.2 million cases) of all cancers that they are affected within the incident and (15.5%) of (4.4 million cases) in mortality [1]. It's also worth mentioning that BC affects more than two million women each year [2]. According to data, the disease's incidence rate is relatively low in Asian and African countries, although it is rising faster than in other countries [3]. Breast cancer is more common in women over 50 [4]. Because the actual cause of BC is unknown, it is thought to be a complex illness. Several studies have revealed that exposure to numerous carcinogens increases the chance of cancer, with inflammatory variables, dietary parameters, obesity, and genetic alterations being the most well-known potential causes of BC formation. "Currently, surgery, radiotherapy (RT), chemotherapy and hormone therapy are effectively used for the treatment of cancer patients" [5]. After surgery, RT, as one of the most regularly used modalities for cancer therapy, is capable of destroying any leftover cancer cells [6]. Cancer patients require RT for either therapeutic or palliative purposes, but this beneficial treatment comes with a slew of negative side effects [7]. RT has been demonstrated to raise the risk of heart disease in these people [8][9]. Although the goal of RT is to harm just the target organs, skin, bone marrow hematopoietic cells, and other tissues with a high rate of proliferation will be destroyed as well [10][11][12][13]. In tumor cells, RT treatment relies on ROS (reactive oxygen

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species) toxicity, which may damage cellular macromolecules such as DNA (deoxyribonucleic acid), RNA (ribonucleic acid), microRNAs, proteins, and the membrane [14][15][16]. Antioxidants such as catalase, glutathione peroxidase, and superoxide dismutase protect normal cells against radiation damage through various enzymatic systems. Non-enzymatic systems (lipoid acid, glutathione, L-arginine, coenzyme Q10, uric acid, bilirubin, metal-chelating proteins, and others) might also help normal cells scavenge free radicals [17][18]. It has been suggested that radiation can cause a decline in the level of Alb, UA [19][20], and TSB [21] in breast cancer patients. Other studies reported that RT could cause an elevation in the level of MDA [5][20][22].

AIM

RT's impacts on several antioxidant and oxidant systems have been investigated. However, the results are contradictory. RT has been shown to influence the antioxidant and oxidant systems in numerous studies [21][5][20][22]. In contrast, other research have indicated that it has little impact on the antioxidant and oxidant systems [21][23]. As a result, the goal of this study was to see how RT affected malonaldehyde (MDA), uric acid (UA), total serum bilirubin (TSB), and albumin (Alb) levels in a sample of Iraqi women who had BC. To establish the effects of this sort of therapy on biochemical indicators, all the patients were followed up on before and after RT.

PATIENTS AND METHODS

Study Population

This study was carried out on 60 BC patients who had had pathological exams that were deemed satisfactory. Each patient's demographic and clinical information was documented, such as age, clinical stage, BMI, and histology grade. The tumor node metastasis (TNM) approach was used to assess the BC stage [24], as illustrated in table (1,2). All patients were given RT two months after finishing chemotherapy, and their hematological and biochemical markers were normal at the start of the trial. For three weeks (five days weekly), they were given RT at a dosage of 40.05 Gray with a fraction size of 2.67 Gray each day. Blood samples were taken from all patients twice: one day before and one day after the completion of RT. The samples were centrifuged, and the serums were kept at a temperature of -24 °C until the final analysis.

Table (1): Distribution of Study Participants According to Their Health Status in Relation to Breast Cancer, Mean Age, and Body Mass Index.

Study group	Frequency	Percent	Age Mean∓ SD	40 ≥	40 <	BMI Mean∓SD
Breast Cancer group	60	50	43.47∓9.44	28	32	28.8∓5.02
Healthy Control group	60	50	42.21∓9.61	28	32	28.6∓5.03
Total	120	100				

Table (2): Characteristics of Breast Cancer Patients Who Participated in This Study.

	N	%
Clinical Stage		
Stage I	2	3.33
Stage II	20	33.34
Stage III	36	60
Stage IV	2	3.33

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Estradiol Receptor		
Positive	46	76.67
Negative	14	23.33
Progesterone Receptor		
Positive	40	66.67
Negative	20	33.33
Her-2		
Positive	16	26.66
Negative	44	73.34
Histology Type		
IDC	52	86.68
ILC	4	6.66
IDC+ILC	4	6.66
Notes: Age and BMI are expressed as mean ± standard deviation (SD); BMI: Body mass index (kg/m²); Her-2: human epidermal growth factor receptor; IDC: invasive ductal carcinoma; ILC: invasive lobular carcinoma.		

Measurement of Some Antioxidant Status Parameters (Alb, TSB, and UA) by Coulometric Method

In this study, some biochemical parameters of antioxidant status (Alb, TSB, and UA) were evaluated by using a full-auto spectrophotometer from Mindray, China.

Serum total Bilirubin (TSB) was analyzed according to the VOX (vanadiate oxidation) method. At a pH of 3, the sample's bilirubin is oxidized to biliverdine in this test. The bilirubin-specific yellow absorbance reduces as a result. As a result, measuring absorbance before and after vanadate oxidation can provide information on blood bilirubin concentrations. The TSB concentration was expressed in (mg/dL).

Alb was analyzed with the dye-binding methods. The method uses bromocresol green (BCG). A blue-green dye complex is formed when the anionic dye bromocresol green (BCG) binds to Alb at pH 4.2. Blood albumin content is closely correlated with blue-green color intensity. The rise in absorbance between 580 and 630 nm is used to determine the Alb concentration, that was expressed in (g/dL).

UA was determined with Uricase-Peroxidase (Uricase-POD) method. By using ascorbic oxidase to eliminate the interference of ascorbic acid, the UA is catalyzed to produce H_2O_2, which oxidizes the 4-Aminoantipyrine to yield a colored dye of quinoneimine. The absorbency decrease is directly proportional to the concentration of UA. The UA was expressed in (mg/dL)

MDA Measurement by Sandwich Enzyme-linked immunosorbent assay (ELISA)

The level of MDA, as the level of lipid peroxidation, was measured by ELISA kit on an ELISA reader from (Sunlong – China), by Sunlong Biotech Co., Ltd ELISA kit, China (catalogue numbers: REF-SL1135Hu) employing the quantitative sandwich enzyme immunoassay technique. The analysis was performed according to the manufacturer's instructions. The MDA was expressed in (ng/ml).

Statistical Analysis

SPSS version 20 (PASW, USA) was used to conduct statistical analysis. The mean± standard deviation was used to express the demographic and clinical data. The control group was compared to the patients' group before radiation and the patients' group after radiotherapy using the T-test. To compare before and post RT data, a paired t-test was employed, with statistical significance (p 0.05) taken into account.

RESULTS AND DISCUSSION

Tables (2,3 and 4) and Figures (1,2,3 and 4) show serum levels of the antioxidant and oxidant parameters for the patients' group before RT (G2) and the patients' group after the RT (G3) in comparison with the healthy control group (G1)

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Table (3): Results for Control Group (G1) and Patients Group Before Radiotherapy (G2)

Groups	Test Name	Sample Size	Mean	SD	P-Value
G1	Alb	60	3.924	0.2573	0.732
G2		60	3.943	0.3481	
G1	UA	60	3.831	0.7738	0.532
G2		60	3.730	0.9780	
G1	TSB	60	0.618	0.1223	0.959
G2		60	0.617	0.1304	
G1	MDA	60	50.250	13.5400	0.361
G2		60	52.580	14.2900	

Table (4): Results for Control Group (G1) and Patients Group After Radiotherapy (G3).

Groups	Test Name	Sample Size	Mean	SD	P-Value
G1	**Alb**	60	3.924	0.2573	**0.003****
G3		60	3.790	0.2168	
G1	UA	60	3.831	0.7738	0.994
G3		60	3.830	0.6796	
G1	TSB	60	0.618	0.1223	0.207
G3		60	0.650	0.1535	
G1	**MDA**	60	50.250	13.5400	**0.000****
G3		60	74.910	19.2800	

Table (5): Results for Patients Group Before Radiotherapy (G2) and Patients Group After Radiotherapy (G3).

Groups	Teat Name	Sample Size	Mean	SD	P-Value
G2	**Alb**	60	3.943	0.3481	**0.017***
G3		60	3.790	0.2168	
G2	UA	60	3.730	0.9780	0.522
G3		60	3.830	0.6800	
G2	TSB	60	0.617	0.1304	0.128
G3		60	0.650	0.1535	
G2	**MDA**	60	52.580	14.2900	**0.000****
G3		60	74.910	19.2800	

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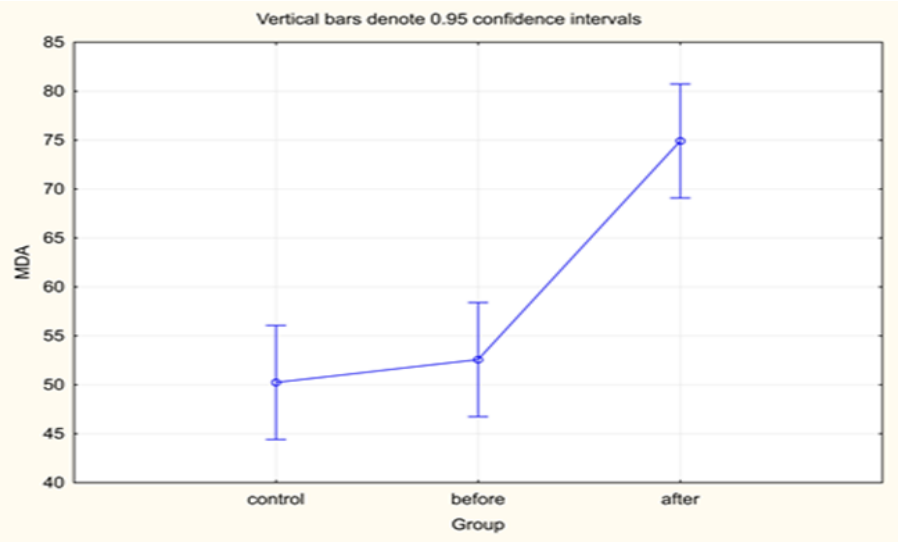

Figure (1): MDA Mean Concentration Levels (ng/ml) for Control Group, Patients Group Before RT, and Patients Group After RT.

The mean distribution of MDA serum levels for studied groups are listed in tables (3, 4 and 5) and graphic demonstration in figure (1).

The results of MDA concentration levels in G2 and G1 showed there was a non-significant change, and that was in agreement with a study done by (Taha I. Hewala , Moustafa R. Abo Elsoud, 2019) [23]. Table (4) illustrates the effects of RT (which produces FRs and promotes lipid peroxidation), which explains why the results show a significant increase in MDA in the G3, and this is in agreement with the two follow-up studies conducted before and after RT: the first, conducted by (M. Khalil Arjmandi, et al.) [5], and the second, conducted by (H. Youssef and H. Salem) [22]. When comparing the same patients, the effect of RT on MDA was also found to be statistically significant, as shown in table (5); this agreed with (Aqeel Shakir Mahmood, 2019), that found, "The result shows a high significantly increase of MDA levels ($p<0.01$) when comparing (after radiotherapy group) with the same group (before radiotherapy)". Increased MDA levels after radiation have been shown to strengthen erythrocyte membranes by forming cross-connections with first amino groups of proteins or membrane phospholipids. The increase in MDA in cancer is linked to oxidative stress, which reduces polyunsaturated fatty acid (PUFA) in the plasma membrane, and causes mitochondrial malfunction [20]. Breast cancer and lipid peroxidation have been proven to positively correlate in other research, with lipid peroxidation assessed as MDA being greater in the breast cancer group than in healthy women in numerous investigations [19][25].

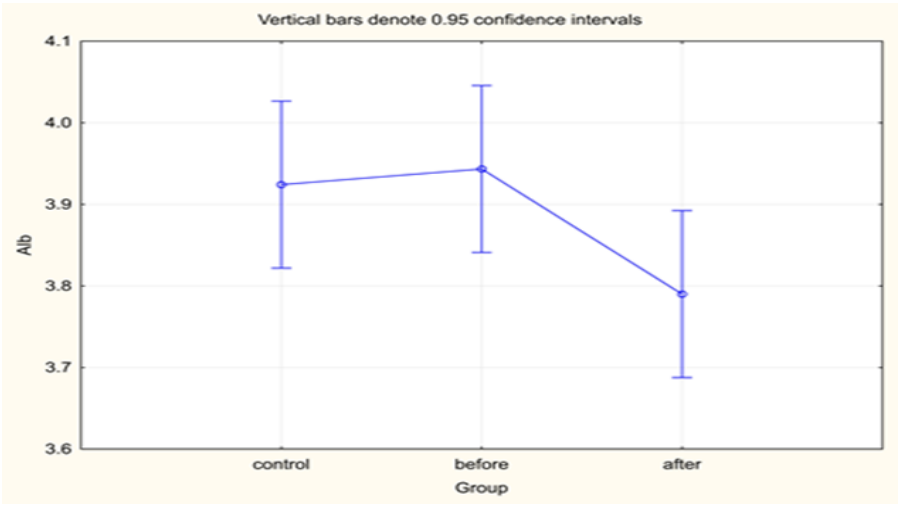

Figure (2): Alb Mean Concentration Levels (g/dL) for Control Group, Patients Group Before RT, And Patients Group After RT.

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The mean distribution of Alb serum levels for studied groups are listed in tables (3, 4 and 5) and graphic demonstration in figure (2).

Low serum Alb has previously been shown to be an independent predictor of poor survival in cancers such as gastrointestinal cancer, lung cancer, ovarian cancer, nasopharyngeal carcinoma, and breast cancer. The lowering of Alb following RT was seen during RT exposure in the case of radiation therapy. The structure and activities of plasma proteins were altered by free radicals. It has been discovered that the modifications generated by Alb radicals are linked to antioxidant property degradation and can result in severe changes in protein stability [20]. In this study, there was not a significant variation in Alb when comparing G2 with G1. At the same time, there was a significant decrease in G3 compared with G1; this result agrees with (A A. R. Mahmood, M. R. Abdullah, and H. S. Khalaf) research. In response to oxidative stress in cells, the body may burn up its stores of antioxidants faster than it can produce them, lowering their concentration. Toxins, including tumor necrosis factor (TNF) and interleukin 6 (IL-6), have been shown to decrease Alb synthesis and enhance acute-phase protein production in isolated hepatocytes, which may explain the decreased Alb content [19]. Also, there was a significant decrease in Alb concentration before and after RT, and this was in agreement with (Aqeel Shakir Mahmood,2019) study [20] and That was expected for Alb as an antioxidant [26], can be due to the free radicals that were generated from RT [24][27].

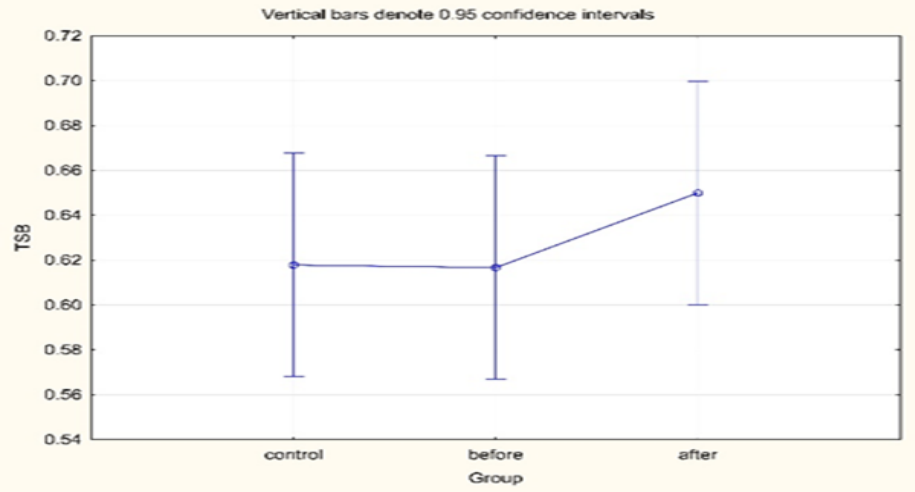

Figure (3): TSB Mean Concentration Levels (mg/dl), for Control Group, Patients Group Before RT, and Patients Group After RT.

The mean distribution of TSB serum levels for studied groups are listed in tables (3, 4 and 5) and graphic demonstration in figure (3).

Total bilirubin concentration reflects the liver's functional transport capability and has strong antioxidant effects. This might be attributed to lower hepatocyte damage and no increase in haemoglobin breakdown in BC patients. The production of apolipoprotein D by unconjugated bilirubin reduced BC cell line proliferation in a dose-dependent way, which might explain the small decrease of bilirubin reported in BC patients with high triglyceride levels in an attempt to minimize BC cell growth [28]. This study showed insignificant change in TSB concentration between the G1 and G2, the G1 and G3, and the G2 and G3. As shown in tables (3,4 and 5) and figure (3), and our results in agreement with (G. Krishna Veni et al. (2011)) [21], that was observed an insignificant change in the levels of TSB. The study was done by (N. So, S. O. Nwozo, et al.,2013) also reported that TSB was a non-significant decrease in the bilirubin level when compared with control. Despite taking a group of patients on chemotherapy/radiotherapy and immune booster supplements (a combination of essential vitamins and minerals), this study agreed with it. Because, following surgery, most cancer patients receive a combination of radiation and/or chemotherapy, which might increase oxidative stress.[28]

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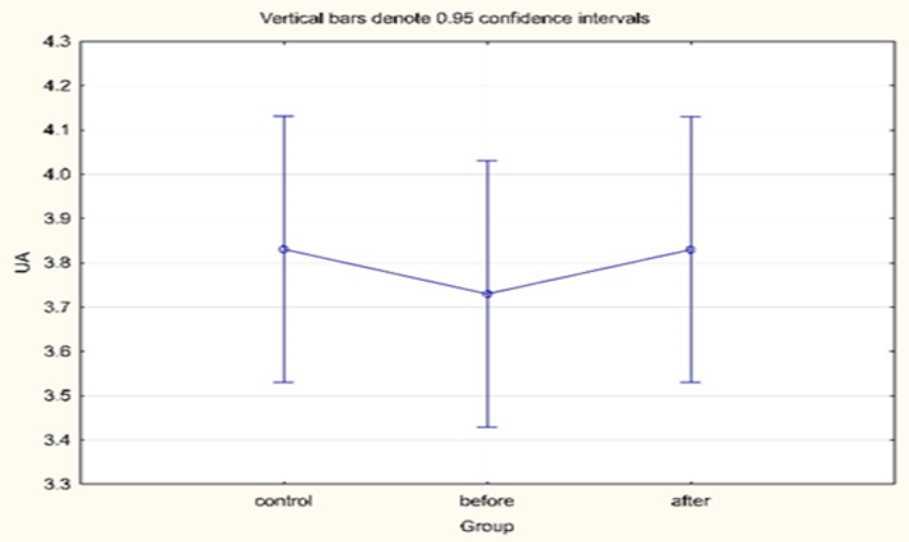

Figure (4): UA Mean Concentration Levels (mg/dl) for Control Group, Patients Group Before RT, and Patients Group After RT.

The mean distribution of UA serum levels for studied groups are listed in tables (3,4 and 5) and graphic demonstration in figure (4).

This study showed a statistically non-significant change in UA concentration between the G1 and G2, the G1 and G3, and the G2 and G3. UA is derived exclusively from xanthine and hypoxanthine by xanthine oxidoreductase (XOR), and it is in agreement with (Mahmood AR, Abdullah MR, and Khalaf HS (2018)), who observed a non-significant increase in G1 and patient groups (P>0.05) [19]. And this was in disagreement with (G. Krishna Veni et al. (2011)) that observed a significant increase in the levels of UA [21]. In contrast, in (Aqeel Shakir Mahmood 2019) study, he observed A significant change (decrease) in UA concentration levels at ($p<0.05$) in comparison of the RT group with the before RT group. Assuming UA is an effective antioxidant and protective agent, it might help prevent cancer by avoiding the creation of oxygen radicals, which in turn would help prevent the incidence of cancer. In scientific research, uric acid and cancer have been linked several times [20].

CONCLUSIONS

This study revealed some interesting outputs that we summarise: an increase in the oxidative stress biomarker and a decrease in the levels of antioxidants that arise from exposure of body cells to radiotherapy.

RECOMMENDATIONS

Antioxidants should be used after RT for BC patients to reduce the danger of activating another carcinogenic process and ultimately increase the patient survival rate. To obtain obvious correlations, the sample size should be increased in any future work. Also, dose dependents follow up study should be done to obtain a detailed change in biomarker

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