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Meme Kanserinde Oksidatif Stresin Prognostik Değeri ve Önemi

Prognostic Value and Significance of Oxidative Stress in Breast Cancer

[1]İsmail ZENGİN, [2]Belma KOÇER, [3]Tayfur DEMİRAY, [3]Kerem YILMAZ

[1]Bilecik Bozüyük State Hospital, Department of General Surgery, Bilecik, Türkiye
[2]Sakarya University of Faculty of Medicine, Department of General Surgery, Sakarya, Türkiye
[3]Sakarya University, Training and Research Hospital, Clinical Microbiology Laboratory, Sakarya, Türkiye

İsmail Zengin: https://orcid.org/0000-0002-0555-2141
Belma Koçer: https://orcid.org/0000-0002-9888-0661
Tayfur Demiray: https://orcid.org/0000-0003-1161-4684
Kerem Yılmaz: https://orcid.org/0000-0002-1626-5172

ÖZ

Amaç: Meme kanseri hastalarında Total Antioksidan Status (TAS), Total Oksidan Status (TOS), Oksidatif Stres İndeks (OSI) düzeylerini araştırmak ve bunları sağlıklı kadınlarla karşılaştırmaktır.

Materyal ve Metot: Çalışmaya 45 meme kanseri hastası ve sağlıklı 46 kadın dahil edildi. Bu hastaların serumlarında TAS ve TOS değerleri ölçülerek OSİ değerleri hesaplandı. Veriler IBM SPSS 21.0 paket programında değerlendirildi.

Bulgular: Hasta ve sağlıklı kadınların ortalama TOS değerleri karşılaştırıldığında, kontrol grubunun TOS değeri 3,44 µmIU/L, hasta grubunun TOS değeri 11,93 µmIU/L bulundu. TAS'ın ortalama değeri kontrol grubunda 1,74 µmIU/L, hasta grubunda ise 1,63 m/mol/L olarak bulundu. OSİ, meme kanserli hastalarda ortalama 7,23 iken sağlıklı kadınlarda 1,99 olarak belirlendi. Meme kanserli kadın hastalarda, sağlıklı kadınlara göre TOS değeri yüksek, TAS değeri düşük, OSİ değeri anlamlı düzeyde yüksek bulundu ($p<0,01$).

Sonuç: TOS, TAS ve OSİ değerleri meme kanserli hastalar ile sağlıklı kadınların ayrımında kullanılabilecek bir belirteç olabilir.

Anahtar Kelimeler: Meme kanseri, oksidatif stres indeks, prognostik faktör, total antioksidan status, total oksidan status

ABSTRACT

Objective: The aims of this study were to investigate Total Antioxidative Status (TAS), Total Oxidative Status (TOS), and Oxidative Stress Index (OSI) levels in breast cancer patients and compare them to levels in healthy women.

Materials and Methods: In the study, 45 breast cancer patients and 46 healthy women participated. The OSI value was calculated as the % ratio of the TAS and TOS values. The data were analyzed on IBM SPSS 21.0 package software.

Results: When the mean TOS values in patients and healthy women were compared, the control group had a TOS of 3.44 µ mIU/L and the patient group had a TOS of 11.93 µ mIU/L. TAS was found to have a mean value of 1.74 µ mIU/L in the control group and 1.63 m/mol/L in the patient group. OSI was determined to have a mean value of 7.23 in patients with breast cancer and 1.99 in healthy women. In female patients with breast cancer, TOS value was higher, TAS value was lower, and OSI value was significantly higher than healthy women ($p<0.01$).

Conclusion: TOS, TAS and OSI values can be a marker that can be used to differentiate patients with breast cancer and healthy women.

Keywords: Breast cancer, oxidative stress index, prognostic factor, total antioxidant status, total oxidant status

Sorumlu Yazar / Corresponding Author:
İsmail Zengin
Bilecik Bozüyük State Hospital, Department of General Surgery, Bilecik, Türkiye
Tel: +90 542 442 3113
E-mail: drebzengin@gmail.com

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INTRODUCTION

Free radicals, also known as Reactive Oxygen Species (ROS), are molecules that, by electron exchange, may easily disrupt the structure of other molecules. ROS are the most significant oxygen-based free radicals. Nonetheless, antioxidant defense systems exist to defend against the harmful effects of ROS produced at the physiological level. When important molecules such as proteins, lipids, carbohydrates and DNA enter into oxidative reactions with free radicals in the environment, their structures are deteriorated and they constitute the beginning of many biological problems. The copying of damaged DNA by mitosis and the continuation of this situation may be the beginning of tumor cell transformation. ROS can affect cell functions by altering the plasma membrane structure by protein and lipid peroxidation. Thus, ROS play an important role in the formation of oncogenes and cancer, by affecting membrane-bound protein kinases, growth factors and receptors, by disrupting signal transmission, activating oncogenes and suppressor gene inactivation.[1]

If oxidative stress, which happens when this order is disrupted and free radicals thrive, is not tolerated, numerous diseases such as Alzheimer's, atherosclerosis, coronary heart diseases, diabetes, and cancer develop.[2,3] The products arising from oxidative stress damage were shown to be abundant in research on different malignancies. Total Oxidant Status (TOS) and Oxidative Stress Index (OSI) levels were found to be high, whereas Total Antioxidant Status (TAS) levels were found to be low in the investigations conducted in patients with liver tumors [4] inoperable cases with colorectal tumors,[5,6] patients with colon tumors,[7] patients with prostate cancers.[8,9]

TOS and OSI values were shown to be high in breast cancer patients in studies, while TAS values were found to be low.[10,11] OSI measurements were suggested to be a helpful biomarker in the treatment and follow-up of breast cancer. In the studies carried out in the serum of breast cancer patients diagnosed with infiltrating duct carcinoma,[12] Malondialdehyde (MDA) parameters were found to be high, indicating oxidative stress may have a role in the pathogenesis of breast cancer. MDA levels were discovered to be elevated in tumor tissues from patients with breast cancer. This condition is caused by breast cancer, and it has been shown that oxidative stress can rise in tissue and serum.[13]

The purpose of this study was to determine TAS, TOS, and OSI levels in the blood of breast cancer patients and healthy women, to show the correlation of these values with clinicopathological parameters.

MATERIALS AND METHODS

Ethics Committee Approval: We complied with the ethical principles of the Declaration of Helsinki, all of the research phases. Approval was obtained for this study from Sakarya University Medical Faculty Ethics Committee (date: 09/02/2017, decision no: 71522473/050.01.04/30).

Population and Sample of the Study: A total of 45 patients who were diagnosed with primary invasive breast cancer and 46 healthy women were included in the study. Blood samples were taken consecutively from patients before treatment (neoadjuvant chemotherapy, surgery) and these bloods were stored at -80, and then studied all together. This study was designed retrospective study. While 11 of the 45 breast cancer patients received neoadjuvant chemotherapy, 34 of them did not receive it. The fasting blood samples were collected from 11 patients who were planned to receive neoadjuvant chemotherapy 24 h before chemotherapy, 24 h before the operation, and in the first postoperative month. The serum samples were collected twice from 34 patients without neoadjuvant chemotherapy 24 h before the operation and in the first postoperative month.

The laboratory experiments were conducted at the Microbiology Laboratory of the same hospital. The patients' age, body mass index (BMI) and preoperative staging, type of operation (breast-conserving, mastectomy), type of axillary intervention (sentinel lymph node biopsy, axillary dissection), histopathological typing, tumor diameter, grade, estrogen receptor (ER), progesterone receptors (PR), c-erb B2, pathological stage, lymphatic invasion, vascular invasion, and the extracapsular invasion status were examined during the clinicopathological evaluation of the patients. Patients with BMI > 30 were considered obese. The pathological subtypes were determined by determining the status of ER, PR, and c-erb B2 receptors by immunohistochemical analysis. Next, whether neoadjuvant or adjuvant chemotherapy was administered was evaluated. Patients with pathological diagnoses of invasive ductal, lobular, and mixed (invasive ductal and lobular) carcinoma were included in the study. Breast cancer patients with other pathological diagnoses (ductal and lobular carcinoma *in situ*, sarcoma, mucinous Ca) were not included in the study.

Elisa Method: Immediately after the blood samples were collected through the peripheral venous puncture, the samples were centrifuged at 3000 *g* for 5 min and then stored at –80°C. The Total Antioxidant Status Assay Kit (Product Code: RL0017) and the Total Oxidant Status Assay Kit (Product Code: RL 0024) (Rel Assay Diagnostic Clinical Chemistry Solutions, Gaziantep, Türkiye) kits were used. On

the day of the study, the TAS, TOS, and OSI index markers were examined with a fully automatic auto analyzer (Abbott Architect brand C160000, USA), and the TAS and TOS measurements were performed using the total antioxidant activity method defined in the literature.[14] The measurement results were unitized as μmol Trolox equivalent/L for TAS, mmol H_2O_2 Equiv./L for TOS. The oxidative stress index (OSI) value was considered as the % ratio of the TAS and TOS values. First, the TAS values were converted to mmol/L. The OSI value was calculated according to the Formula method given below: OSI (Arbitrary Unit) = TOS (mmol H_2O_2 Equiv./L)/TAS (mmol Trolox Equiv./L). The results were expressed in Arbitrary Units (AU).[15]

Test range: TAS: 1.20–1.50 mmol/L (1200–1500 μmol/L), TOS: 4.00–6.00 μmol/L (400–600 μmol/Hl), OSI: TOS/TAS.

Statistical Analysis: Data was transferred and evaluated in IBM SPSS Statistics 21. The Kolmogorov–Smirnov test was performed to determine the normality of the results. Spearman correlation test was applied to determine the correlation between the numerical values. A threshold value (cut-off value) was determined for the TAS, TOS, and OSI values by the ROC graph. The graphs with the area under the curve (AUC) > 0.6 according to these threshold values were considered to be significant. The significance level was considered as $p< 0.05$ while interpreting the results.

RESULTS

The healthy control group in our study had an average age of 58.06±11.72 years (min-max: 37–85 years). The average age of patients with breast cancer was 54.20±12.52 years (min-max: 28–79 years), the mean BMI of breast cancer patients was reported to be 27.68±5.19 (min-max: 17.01–42.24). The mean BMI of healthy women was greater than that of breast cancer patients (p= 0.014) (Table 1).

When the mean TOS values in patients and healthy women were compared, TOS was shown to be substantially greater in breast cancer patients compared to healthy women (p= 0.000). TAS was observed to be decreased in breast cancer patients compared to healthy women (p= 0.003). OSI was shown to be greater in patients with breast cancer than in healthy women (p= 0.000, p< 0.01) (Table 1).

Table 1. Comparison of the total antioxidant status, total oxidant status, and oxidative stress index, age and body mass index values of the patients, who were healthy women.

		N	Mean±SD*	p
TOS	Control	46	3.44 ±1.073	**0.000**
	Patient	45	11.93±19.07	
TAS	Control	46	1.74±0.23	**0.003**
	Patient	45	1.63±0.26	
OSI	Control	46	1.99±0.60	**0.000**
	Patient	45	7.23±11.07	
Age	Control	46	58.06±11.72	0.132
	Patient	45	54.2±12.52	
BMI	Control	46	30.35±5.04	**0.014**
	Patient	45	27.68±5.19	

*: Descriptive analyses were performed to provide information on general characteristics of the study population;
OSI: Oxidative Stress Index; TAS: Total Antioxidant Status; TOS: Total Oxidant Status; BMI: Body Mass Index.

It was determined that the patients with high TAS levels at the time of diagnosis also had high TAS levels assessed after surgery. TAS levels and postoperative TAS levels were shown to have a positive correlation (p= 0.028, R= 0.328). TAS levels were raised as a result of breast cancer treatment (neoadjuvant chemotherapy or surgery) (Table 2).

The TOS levels were significantly correlated with BMI following neoadjuvant chemotherapy (p= 0.010, R= 0.733). Patients' oxidative stress increases as their BMI rises. When serum TOS, TAS, and OSI values from breast cancer patients were compared with clinicopathological parameters, a positive correlation between TAS and obesity was found. Obese patients had greater total antioxidant levels than non-obese ones. The resultant values were observed to be statistically significant (p= 0.014). TOS values were observed to be significantly higher in metastatic breast cancer patients, however, this was not statistically significant (p= 0.067). OSI values in stage four breast cancer patients were found to be statistically significantly higher (p= 0.029). In progesterone receptor-negative patients, the total oxidative level (p= 0.036) and OSI (p= 0.057) were found to be statistically significantly higher. The TOS (p= 0.025) and OSI (p= 0.026) values were observed to be statistically significantly higher in triple-negative patients than in other subtypes. Unfortunately, just one triple-negative patient was present. There was no significant relationship between any of the other clinicopathological parameters (Table 2).

When TOS, TAS, and OSI values were classified and compared to the patients' clinicopathological parameters, TOS positivity was statistically signifi-

cantly higher in patients with a negative PR value (p = 0.05). 23 patients with positive PR value (76.7%) and five patients with negative PR value (33.3%) had a high TOS value. TAS positivity was statistically higher in obese patients than non-obese patients (59.0% & 36.5%, p = 0.034). Unfortunately, no significant correlation was found between the TOS, TAS, and OSI positivity and any clinicopathological parameters (Table 2).

Table 2. Comparison of clinicopathological parameters with serum total antioxidant status, total oxidant status, and oxidative stress index values.

Parameters			N	TOS	TAS	OSI
				Mean±SD	**Mean±SD**	**Mean±SD**
OBESITY		Absent	30	11.95±18.23	1.57±0.15	7.99±12.52
		Present	15	11.89±21.31	1.77±0.36	5.71± 7.56
		p*		0.81	**0.014**	0.942
STAGE		Stage 1	13	9.41±10.67	1.58±0.17	6.41± 8.11
		Stage 2	26	11.17±18.56	1.67±0.31	6.3± 9.24
		Stage 3	4	7.82±3.27	1.62±0.09	4.76± 1.88
		Stage 4	2	46.35±58.77	1.58±0.03	29.55±37.58
		p		0.067	0.974	**0.029**
PR		Absent	30	13.84±21.48	1.65±0.29	8.05±11.67
		Present	15	8.12±12.77	1.59±0.17	5.59±9.95
		p		**0.036**	0.866	0.057
SUBTYPE		Luminal A	23	6.41 ±3.90	1.61±0.23	4.02±2.56
		Luminal B	13	23.23 ±30.49	1.68±0.34	13.19±16.48
		Her2 +	8	4.36 ±2.32	1.66±0.17	2.61±1.28
		Triple Negative	1	52.58	1.29	40.63
		p		**0.025**	0.222	**0.026**
		TOS		**TAS**	**OSI**	**Postop TAS**
TOS	r**	1.00		-0.035	0.982	0.038
	p	-		0.819	**0.000**	0.804
TAS	r	-		1.00	-0.168	0.328
	p	-		-	0.270	**0.028**
OSI	r	-		-	1.00	-,036
	p	-		-	-	0.814

*: Mann-Whitney U test; **: Spearman Correlation Analysis; OSI: Oxidative Stress Index; TAS: Total Antioxidant Status; TOS: Total Oxidant Status.

To calculate a threshold value for TOS, TAS, and OSI values, the ROC curve was plotted for all three parameters. The value with maximum 1-sensitivity + 1- specificity was selected as the threshold value based on this examination. The threshold (cut-off) value for TOS was >4.319 µ mIU/L. The values greater than 4.319 µ mIU/L was considered positive (Figure 1a). The threshold (cut-off) value for TAS was ≤1.676µ mIU/L. The values less than 1.676 µ mIU/L were regarded as positive (Figure 1b). TAS such as "small values show cancer status". The OSI threshold (cut-off) value was set at >3.307 (Figure 1c, Table 3).

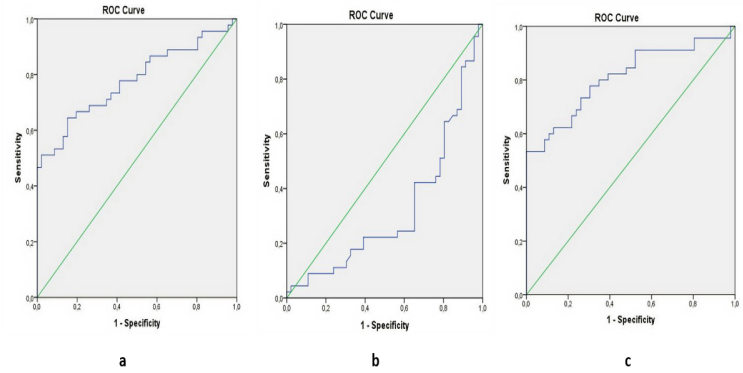

Figure 1. a) Receiver operating characteristic (ROC) curve analyses of TOS value for the differentiation of breast cancer patients from healthy women. **b)** Receiver operating characteristic (ROC) curve analyses of TAS value for the differentiation of breast cancer patients from healthy women **c)** Receiver operating characteristic (ROC) curve analyses of OSI value for the differentiation of breast cancer patients from healthy women.

Table 3. The receiver operating characteristic (ROC) curve and diagnostic scan values in each total oxidant status, total antioxidant status, and oxidative stress index.

	Cut-off	Sensitivity (%)	Specifity (%)	AUC	95% Confidence Interval	p
TOS	> 4.319	64.44	84.78	0.777	0.679-0.875	0.000*
TAS	< 1.676	75.56	65.22	0.321	0.208-0.433	0.003*
OSI	> 3.307	53.33	100.0	0.810	0.719-0.901	0.000*

*: ROC analysis was performed on independent variables; OSI: Oxidative Stress Index; TAS: Total Antioxidant Status; TOS: Total Oxidant Status.

DISCUSSION AND CONCLUSION

According to the results of this study, it was observed that TOS and OSI values increased and TAS values decreased in women diagnosed with breast cancer compared to healthy women. The study conducted by Yang et al. (2021), presented similar results with this study.[9,16,17]

In this study, no change was observed in TAS, TOS and OSI values after neoadjuvant chemotherapy. In one study, TOS and OSI values were found to be high and TAS values to be low in samples taken in the first hour after neoadjuvant therapy.[18] In another study, TAS levels were found to be high in women with postmenopausal breast cancer after neoadjuvant chemotherapy.[19] In another study, TAS levels were found to be low in women diagnosed with breast cancer before and after radiotherapy.[20] Under normal conditions, because antineoplastic agents increase the peroxidation of unsaturated fat acids in membrane phospholipids, a decrease in TAS levels is expected. In this study, this situation was explained by the fact that the effect of antineoplastic agents taken for neoadjuvant treatment may have disappeared due to the fact that the samples were taken in the preoperative period.

In this study, a positive correlation was found between preoperative serum TAS values and postoperative TAS values in patients diagnosed with breast cancer ($p< 0.05$, $r= 0.328$). Surgical removal of the tumor and elimination of the oxidative stress caused by the tumor can increase antioxidant levels in patients. However, in the study reviewed in the literature, it was demonstrated that if the samples were taken in the early postoperative period, the oxidative stress due to the operation increased, the TAS value decreased while in the later periods, the oxidative stress was lower and the TAS value increased.[21] This study is not similar to the literature.

In this study, TAS levels of obese female patients with breast cancer were found to be higher than those of patients in normal weight. Studies have found that obesity causes a decrease in plasma TAS levels,[22] and there is no relationship between increased oxidative stress indicators and obesity in patients with a diagnosis of obese breast cancer.[23] The findings of previous studies do not show any similarity with the findings of this study.

In this study, it was observed that TOS and OSI levels were significantly higher in breast cancer patients with progesterone receptor deficiency. Although the importance of estrogen receptor and progesterone receptors in breast cancer was demonstrated,[24,25] no study was found in the literature that mentioned the relationship between oxidative stress and progesterone receptors.

In conclusion, in patients diagnosed with breast cancer, TOS and OSI values were found to be higher and TAS value lower than in healthy women. It was concluded that neoadjuvant chemotherapy increased the TAS values of patients with breast cancer. TOS, TAS and OSI values can be a marker that can be used to differentiate patients with breast cancer and healthy women. Examination of these markers next to clinicopathological features in larger studies would reveal significant variations.

Ethics Committee Approval: Our study was approved by the Sakarya University Ethics Committee (Date: 09/02/2017, decision no: 71522473/050.01.04/30). The study was carried out in accordance with international declaration, guideline, etc.

Conflict of Interest: No conflict of interest was declared by the authors.

Author Contributions: Concept – IZ, BK; Supervision – IZ, BK; Materials – IZ, BK; Data Collection and/or Processing –IZ, BK, KY, TD; Analysis and/or Interpretation – IZ, BK; Writing – IZ, BK.

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