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Oxidative stress markers in breast cancer

Meme kanserinde oksidatif stres belirteçleri

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Abstract

Purpose: The aim of this study was to compare serum Total Antioxidant Status (TAS), Total Oxidant Status (TOS), Oxidative Stress Index (OSI) and Ischemia Modified Albumin (IMA) levels in breast cancer patients and healthy women and to determine whether there is a relationship between oxidative stress markers and breast cancer.

Materials and methods: Newly diagnosed 106 breast cancer patients at the Bozyaka Training and Research Hospital General Surgery Clinic and 30 healthy women were included in the study. Serum levels of IMA, TAS, TOS were analyzed by spectrophotometric methods.

Results: IMA, TOS and OSI values were found significantly higher in the breast cancer group. Although the TAS values in patients with breast cancer were lower than the control group, the difference was not statistically significant.

Conclusions: In our study, it was seen that oxidative stress levels increased in breast cancer patients due to decreased TAS, and significantly increased IMA, TOS and OSI results. There was no correlation of histopathologic findings with IMA, TOS and OSI levels in terms of tumor grade and size. Disturbed oxidative stress status and IMA may contribute to the pathogenesis of breast cancer and more comprehensive studies are needed for prognostic value.

Keywords: Breast cancer, biomarkers, ischemia-modified albumin, oxidative stress.

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Öz

Amaç: Çalışmamızda oksidatif stres ile meme kanseri arasında ilişki olup olmadığını araştırmak için, meme kanseri hastalarında ve sağlıklı kadınlarda serumda Total Antioksidan Seviye (TAS), Total Oksidan Seviye (TOS), Oksidatif Stres İndeksi (OSİ) ve İskemi Modifiye Albumin (İMA) değerlerinin karşılaştırması amaçlandı.

Gereç ve yöntem: Bozyaka Eğitim ve Araştırma Hastanesi Genel Cerrahi Kliniği'nde yeni tanı almış ve henüz tedavi almamış 106 meme kanseri hastası ve sağlıklı 30 kadın çalışmaya alındı. Serum TAS, TOS ve İMA düzeyleri spektrofotometrik yöntemle analiz edildi.

Bulgular: Meme kanseri grubunda İMA, TOS ve OSİ düzeyleri, istatistiksel olarak anlamlı yüksek bulundu. TAS değerleri ise, meme kanserli hastalarda kontrol grubuna göre düşük olmasına rağmen, aradaki fark istatistiksel olarak anlamlı değildi.

Sonuç: Çalışmamızda meme kanseri hastalarında azalmış TAS, anlamlı derecede artmış İMA, TOS ve OSİ sonuçları sebebiyle oksidatif stres düzeylerinin arttığı anlaşılmaktadır. IMA, TOS ve OSI meme kanseri patofizyolojisinde önemli bir belirteç olup prognostik değer için daha kapsamlı çalışmalara ihtiyaç duyulmaktadır.

Anahtar kelimeler: Meme kanseri, biyobelirteçler, iskemi modifiye albumin, oksidatif stres.

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Introduction

Breast cancer is known as the most prevalent form of cancer in women, constituting approximately 30% of all cancers in women. Breast cancer is the second leading cause of deaths associated with cancer, following lung cancer [1]. The exact cause of breast cancer is unknown, but many factors such as genetics, environmental factors, age, diet, reproductive features, body weight, physical activity, alcohol use, endogenous and exogenous hormonal factors are thought to play a role in its etiology [2].

Metabolic and physiological processes in the body produce free radicals but they are removed by antioxidant mechanisms. Excessive production of free radicals or insufficient antioxidant system causes oxidative stress which plays a vital role in many health problems such as inflammation, ischemia reperfusion injury, diabetes mellitus, lung diseases, atherosclerosis, muscle diseases, kidney diseases and especially cancer [3-5]. Endogenous and exogenous antioxidants can prevent the development of diseases by neutralizing the free radicals or preventing their effects [6]. Reactive oxygen species (ROS), which are composed of oxygen, are the most important free radicals in biological systems and affect different stages of cancer formation. There are studies showing that ROS has many roles in cancer formation [7, 8].

Under normal physiological conditions, the organism has an antioxidant defense system that combats endogenous or exogenous free radicals and oxidative stress. By-products of free oxygen molecules synthesized in the body endogenously make the biggest contribution to total oxidant capacity [9]. Total antioxidant capacity is composed of mainly from antioxidant molecules in plasma such as uric acid, bilirubin, albumin, ceruloplasmin, transferrin, vitamins E and C, as well as chain-breaking antioxidants that bind free radicals [10]. The N-terminal end of albumin consists of the amino acid sequence aspartate-alanine-histidine-lysine amino acid chain, which is a high affinity binding site for transition metals such as cobalt, copper and nickel. It has been observed that it shows strong binding capacity for cobalt (Co^{+2}) compared to other metal ions. In the case of ischemia and reperfusion, cellular changes, especially due to free radical production and oxidative damage, have been shown to cause structural modifications at the N-terminal end by deletion or N-acetylation of one or more amino acids [11]. These modifications decrease the albumin binding capacity and a new molecule formed is ischemia modified albumin (IMA) [12, 13].

Our aim was to compare the serum IMA, Total Antioxidant Status (TAS), Total Oxidant Status (TOS), Oxidative Stress Index (OSI) levels in women with breast cancer and healthy control group to investigate whether there was any relationship between oxidative stress and breast cancer.

Materials and methods

One hundred and six women who were recently diagnosed as breast cancer and have not yet started medical or surgical treatment and 30 healthy women who did not have any pathology in their annual routine mammography and ultrasonography, were included as control group in the study. Tru-cut biopsies were performed via the same surgeon accompanied with the same radiologist. After the biopsies were taken, histopathological diagnosis was made by the same pathologist to prevent the difference between the observers. Eighty-nine of breast cancer patients were diagnosed as invasive ductal carcinoma. Stage 1 and 2 carcinomas constitute most of the patient group while stage 3 patients are few and stage 4 patients are absent in our study. Patients with cardiovascular disease, hypertension, diabetes mellitus, any active or chronic infectious disease, thyroid conditions, liver diseases, chronic kidney failure, secondary malignancy, those had cerebral stroke or transient ischemic attack, and pregnant women were not included in the study. None of the participants in the present study were using drug medications including vitamins or antioxidant drugs.

The research protocol received approval from the SBU Bozyaka Training and Research Hospital Ethics Committee and all the patients were informed before the research.

Blood samples were obtained from all individuals after fasting. After centrifugation of the blood samples, aliquots of serum were stored at -80°C until the analysis.

Ischemia modified albumin analysis

IMA levels were measured using Bar Or et al. [14] method which is based on the colorimetric detection of the color complex formed by dithiothreitol (DTT) and cobalt that does not bind to albumin. Albumin corrected IMA (A-IMA) levels of all samples were given in absorbance unit (ABSU) with the following formula: A-IMA=IMAx (albumin/albumin median of the group) [15].

Total oxidant status analysis

TOS levels were studied in Beckman Coulter's Olympus AU 680 autoanalyzer (Brea, CA, USA) using a TOS kit (Relassay®, Gaziantep, Türkiye). This automatic colorimetric measurement method developed by Erel et al. [9] was performed. Ferrous iron is oxidized to ferric iron and forms a colored compound. The color intensity in a sample corresponds to the total oxidant molecules present in the sample. Calibration was performed using hydrogen peroxide, and the TOS results are expressed as μmol H_2O_2 Eq/L [9].

Total antioxidant status analysis

TAS levels were also studied in Olympus 680 autoanalyzer using a commercially available TAS kit (Relassay®, Gaziantep, Türkiye). This method was also developed by Erel et al. [9] and is based on antioxidants that cause fading of dark blue green 2,2'-azinobis- 3-ethylbenzothiazoline-6-sulfonic acid. This color change is measured at 660 nm spectrophotometrically and the results are given in mmolTrolox/L.

Oxidative stress index

TAS results were calculated as μmol/L and OSI was determined according to the following formula:

OSI=TOS (μmol H2O2Eq/L)/TAS [μmol Troloks/L)x100

Statistical analysis

For statistical analysis, SPSS 21 statistics program was used. The normality of the variables was analysed by Kolmogorov-Smirnov test. The parameters having normal or abnormal distribution were examined with Student's t test and Mann-Whitney U test, respectively. Mean and standard deviation (SD) values were specified for normally distributed parameters. Median and 25^{th}-75^{th} percentile values were specified for abnormally distributed parameters. Chi-square test was used for categorical data.

The relation between parameters was investigated with Pearson and Spearman correlation analysis according to normal or abnormal distribution, respectively. Cut-off value was determined for the IMA, TOS, and OSI values by the Receiver operating characteristic (ROC) graph. *P* value <0.05 was accepted as a significance level.

Results

The age of the patients and controls were between 15-84 and 29-61 years, respectively. The age of the control and patient group were 47.5±5.6 and 50.9±9.5, respectively. The age between the groups did not exhibit a statistically significant difference (p>0.05).

When the cases in the breast cancer group were questioned about the presence of cancer in their family history, it was observed that the answer was positive in 26.4% (n=28) of the patients. There was a statistically significant distinction between the patient group and the control group concerning family history. The breast cancer group demonstrated a higher utilization of oral contraceptives (OC) (p=0.001) and hormone replacement therapy (HRT) (p=0.041), with a statistically significant difference between the groups. However, no statistically significant differences were observed between the patient and control groups regarding birth and breastfeeding or smoking (p>0.05). Table 1 provides a summary of the demographic information for both the control and patient groups.

The results of the comparison of serum albumin, IMA, TAS, TOS and OSI levels between groups are presented in Table 2. Despite the patient group having a lower serum albumin level, the difference was not statistically significant. Therefore A-IMA levels were not different from IMA levels. The mean level of IMA was 0.559±0.128 in the patient group and was statistically higher than the control group (p<0.001). When the mean TAS values in the patient and control groups were compared; it was seen that TAS was lower in breast cancer patients than healthy women, but the difference was not statistically significant (p>0.05). Mean

values of TOS; 3.78±4.13 μmol H_2O_2 Eq/L in the control group and 2.37±1.45 μmol H2O2 Eq/L in the patient group. TOS demonstrated a statistically significant increase in breast cancer patients compared to healthy women (*p*=0.005). OSI was found to be higher in breast cancer patients than in healthy women. These results exhibited statistically significant (*p*=0.004).

Table 1. Demographic characteristics of the groups

Characteristics	Breast cancer (n=106)	Control (n=30)	*p*
Age (years)	50.92±9.45	47.53±5.63	0.064
BMI (kg/m²)	28.9±5.9	24.3±3.4	<0.001
Menopausal Status			
Premenopause	30 (28.3)	22 (73.3)	<0.001
Postmenopause	76 (71.7)	8 (26.7)	
Family History			
Positive	28 (26.4)	0 (0)	0.002
Negative	78 (73.6)	30 (100)	
Birth			
Positive	94 (88.7)	23 (76.7)	0.132
Negative	12 (11.3)	7 (23.3)	
Breast Feeding			
Positive	85 (80.2)	23 (76.7)	0.674
Negative	21 (19.8)	7 (23.3)	
OC			
Positive	38 (35.8)	0 (0)	0.001
Negative	68 (64.2)	30 (100)	
HRT			
Positive	15 (14.2)	0 (0)	0.041
Negative	91 (85.8)	30 (100)	
Smoking			
Positive	28 (26.4)	6 (20)	0.474
Negative	78 (73.6)	24 (80)	

Data are presented as the (mean±SD) or n (%)
OC, oral contraceptives; HRT, hormone replacement therapy, SD, standard deviation

Table 2. Serum albumin, IMA, TAS, TOS and OSI levels

	Breast cancer (n=106)	Control (n=30)	*p*
Albumin (g/dL)	4.16±0.32	4.22±0.21	0.315
IMA (ABSU)	0.559±0.128	0.466±0.164	0.001
TAS (mmolTroloks/L)	1.23±0.20	1.26±0.15	0.485
TOS (μmol H_2O_2 Eq/L)	2.65 (1.9-4.09)	1.96 (1.65-2.59)	0.005
OSI	0.211 (0.157-0.308)	0.154 (0.129-0.225)	0.004

Data are presented as the (mean±SD) or median (25^{th}-75^{th} percentile)
SD, standard deviation

IMA, TOS and OSI levels were also evaluated with ROC curve analysis. Cut-off values, sensitivity and specificity, for the parameters are demonstrated in Table 3. The cut-off value for IMA was >0.51 ABSU (Figure 1). The cut-off value for TOS was >2.14 μmol H2O2 Equivalent/L (Figure 2). The OSI cut-off value was >0.174 (Figure 3).

Eighty-nine of breast cancer patients were diagnosed with invasive ductal carcinoma. The others were 11 lobular, 3 mucinous, 1 medullary, 1 papillary, and 1 metaplastic carcinoma. Histopathologic findings of breast cancer patients were evaluated (Table 4). Among our patients, patients with Stage 1 and Stage 2 tumors constituted 84.9% of all breast cancer patients. TNM Classifications of patients were as follows; Stage IA: 36 (34%), Stage IB: 3 (2.83%), Stage IIA: 26 (24.5%), StageIIB: 25 (23.6%), Stage IIIA: 6 (5.7%), Stage IIIB: 2 (1.9%), Stage IIIC: 8 (7.5%). No significant correlation was found between tumor stage and tumor size and IMA, TAS, TOS and OSI values of the patients. The difference between estrogen and progesterone receptor positivity, proliferative change, necrosis, elastosis, calcinosis, lymph node positivity, c-erbB2 and oxidative stress parameters were not statistically significant (p>0.05).

Table 3. The receiver operating characteristic (ROC) curve and diagnostic scan values

	Cut-off	Sensitivity %	Specifity %	AUC	*p*
IMA (ABSU)	>0.51	67	76.7	0.737	<0.001
TOS (μmol H_2O_2 Eq/L)	>2.14	64.2	66.7	0.667	0.005
OSI	>0.174	67.9	66.7	0.672	0.004

AUC = area under the curve

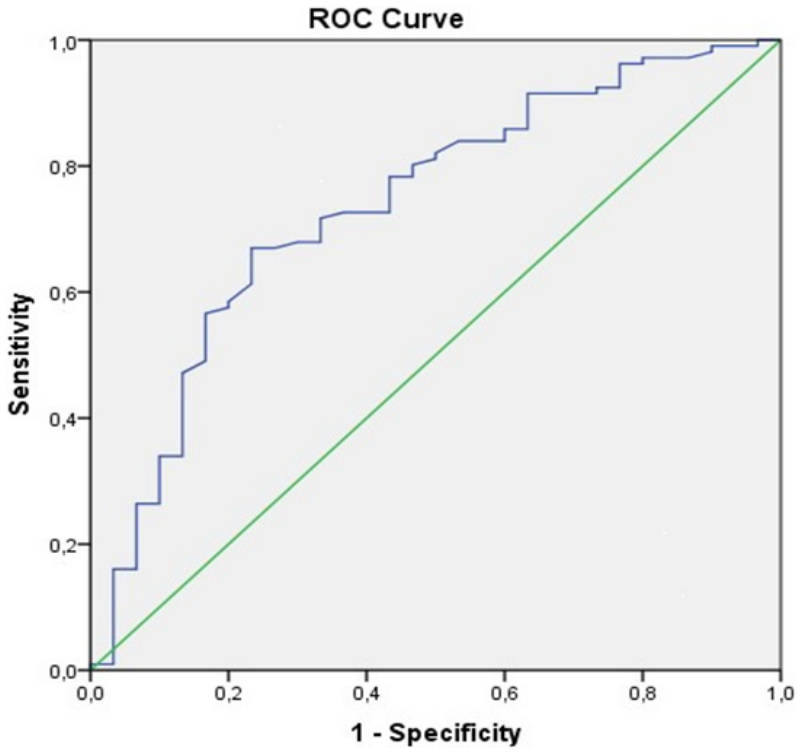

Figure 1. Receiver operating characteristic (ROC) curve analyses of IMA value

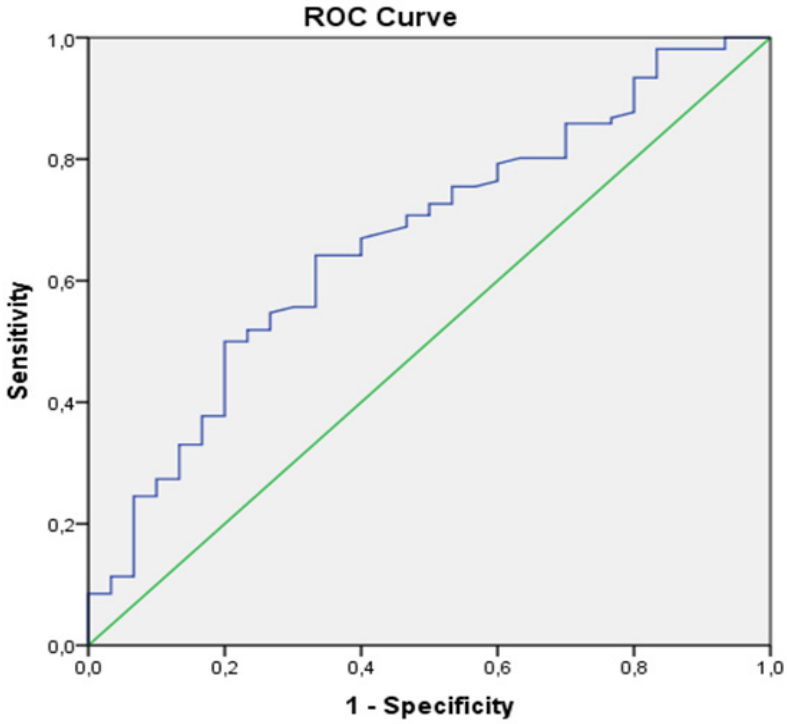

Figure 2. Receiver operating characteristic (ROC) curve analyses of TOS value

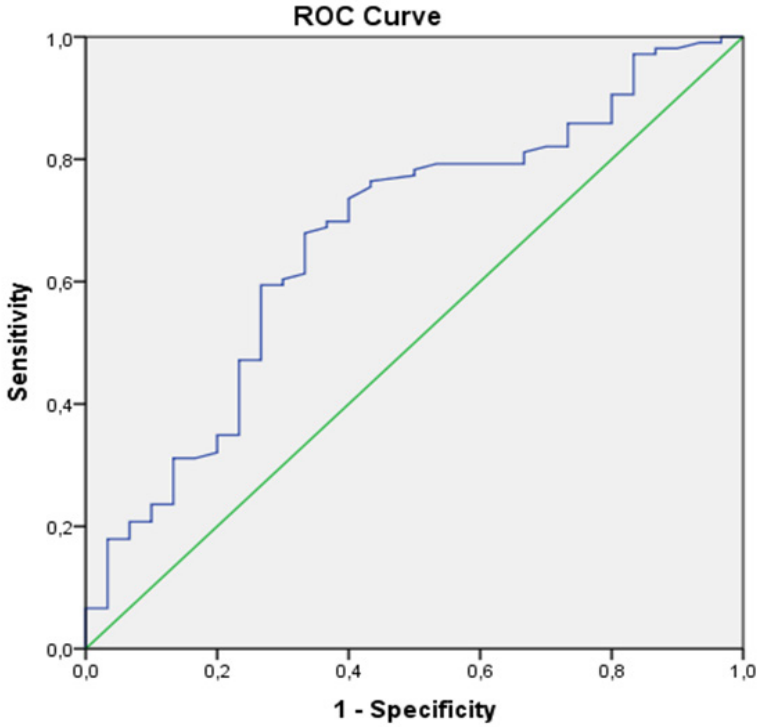

Figure 3. Receiver operating characteristic (ROC) curve analyses of OSI value

Table 4. Histopathologic findings of patients

Characteristics	n (%)
Tumor size	
≤2cm	40 (37.7)
>2cm	66 (62.3)
Lymph Node	
Positive	43 (42.5)
Negative	63 (57.5)
Metastatic Lymph Node	
1-3	32 (30.2)
4-7	4 (3.8)
>7	7 (6.6)
Stage	
1	39 (36.8)
2	51 (48.1)
3	16 (15.1)
Histologic Grade	
1	19 (18.6)
2	62 (60.8)
3	21 (20.6)
Estrogen Receptor	
Positive	85 (80.2)
Negative	21 (19.8)
Progesterone Receptor	
Positive	77 (72.6)
Negative	29 (27.4)
c-erbB2	
Positive	45 (33.1)
Negative	61 (45.9)
e-kaderin	
Positive	83 (78.3)
Negative	23 (21.7)
Proliferative Change	
Positive	60 (56.6)
Negative	46 (43.4)
Necrosis	
Positive	23 (21.7)
Negative	83 (78.3)
Elastosis	
Positive	58 (54.7)
Negative	48 (45.3)
Calcinosis	
Positive	34 (32.1)
Negative	72 (67.9)

Data are presented as the n (%)

Discussion

Breast cancer is one of the most common cancers [1]. Although there are great advances in treatment, the etiology of breast cancer has not been adequately clarified yet [16]. Although some markers have been identified that can guide the treatment or follow-up and predict the prognosis of breast cancer patients, studies are continuing in finding a suitable marker in the diagnosis of breast cancer.

Free radicals and antioxidant defense systems are in balance in healthy individuals. If this balance is disrupted, oxidative stress occurs and causes oxidative damage of the basic structural molecules of our body such as lipid, protein and DNA [17]. Oxidative stress caused by increased reactive oxygen species accelerates mutation and oncogenic transformation, resulting in DNA damage and may eventually lead to cancer development [18]. It was shown that oxidative stress causes cellular damage which in turn takes part in the development of breast cancer [16, 19-21]. In addition to the increase in free radicals, decrease in antioxidant activity also plays an important role in cancer formation. Endogenous and exogenous antioxidants can prevent cancer development by neutralizing or inhibiting cancer-causing free radicals [6].

When the results of our study are evaluated; IMA, TOS and OSI levels were significantly elevated in women with breast cancer compared to healthy women. Despite breast cancer patients having lower TAS values than healthy women, the difference was not statistically significant. These results support other studies indicating that increased oxidative stress formation or insufficient antioxidant capacity can cause breast cancer [16, 19, 22].

IMA is an oxidative stress marker that has been studied heavily in recent years. Bilgili et al. [23] found IMA levels significantly higher in breast cancer in comparison to other groups in their study on breast cancer, fibroadenoma and healthy women and similar to our study, no significant correlation was found between histopathological findings such as tumor size, stage, hormone receptor and IMA levels. Kosova et al. [24] also compared serum IMA levels in breast cancer patients and control group and found IMA levels to be significantly higher in the breast cancer patients. In the study conducted by Hunur et al. [25], IMA levels and their relationship with clinicopathological features in breast cancer patients were examined; IMA levels were significantly higher in the breast cancer patients compared to the healthy women, no significant relationship was found between clinicopathological factors (age, stage, smoking, comorbidity, subtype, menopausal status, body mass index and IMA. In their study conducted by Kundaktepe et al. [26] IMA values in breast cancer patients were significantly higher than in controls. IMA showed a strong positive correlation with tumor size, as well as very strong correlations with TNM stage and the presence of metastasis.

Plasma TAS levels in breast cancer group were significantly lower than control group in some studies [27-29]. They thought that the reduced antioxidant defense system played a role in breast cancer pathogenesis, causing increased ROS and lipid peroxidation products. Zowczak M. et al. [30] found that the TAS levels were low in breast cancer patients compared to the healthy controls. They thought that antioxidant consumption in plasma and the consequent oxidative stress in newly diagnosed breast cancer patients played a role in breast cancer pathogenesis. In our study, TAS levels were low in the patient group, but this difference was not statistically significant.

In the study conducted by Feng et al. [16, 22] TOS and OSI levels were significantly higher and TAS levels were significantly lower in breast cancer patients compared to the control group. These findings are consistent with our study in terms of TOS and OSI.

In conclusion, in patients diagnosed with breast cancer, IMA, TOS and OSI values were found to be significantly higher and TAS value lower than in healthy women. Disturbed oxidative stress status and IMA may contribute to the pathogenesis of breast cancer. There was no correlation of histopathologic findings with IMA, TOS and OSI levels in terms of tumor size, grade, lymph node involvements, histologic grade, c-erbB-2, estrogen and progesteron receptor positivity. We think this may be due to the low number of advanced stage patients. IMA, TOS, OSI values may be a new biomarker that can be used to differentiate patients with

breast cancer and healthy women. Further studies with larger groups are needed for these markers to be used as routine breast cancer markers.

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

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Authors' contributions to the article

G.B., O.F. constructed the main idea and hypothesis of the study. O.F., B.Z. collected data. G.B., O.F., N.U. developed the theory and arranged the material and method section, have done the evaluation of the data in the results section. Discussion section of the article written by O.F. and G.B., N.U. reviewed, corrected and approved. In addition, all authors discussed the entire study and approved the final version.