The Frequency and Determinants of Metabolic Syndrome in Operated Patients with Stage I-III Breast Cancer

Furkan SARICI[1], Veli SUNAR[2], Sercan AKSOY[2]

[1] Istinye University, Faculty of Medicine, Department of Medical Oncology, Istanbul
[2] Hacettepe University, Cancer Istitute, Department of Medical Oncology, Ankara, TURKEY

ABSTRACT

Metabolic syndrome is a clinical condition with a combination of multiple cardiac risk factors including obesity, insulin resistance, hypertriglyceridemia, low HDL, and hypertension. There is serious evidence that metabolic syndrome increases the risk of breast cancer. In this study, we aimed to define the frequency and determinants of metabolic syndrome in operated patients with stage I-III breast cancer. Operated patients with stage I-III breast cancer who admitted to our clinic between April 2009 and April 2018 were examined cross-sectionally. Metabolic syndrome was defined according to NCEP criteria. Metabolic syndrome criteria, demographic data, tumor size, grade, lymph node, estrogen-progesterone, HER2 status, and chemotherapy / endocrine treatment histories were obtained from patients and hospital records. 700 patients with a median age of 50.6 were analyzed. Tamoxifen was given to 194 patients and aromatase inhibitors were given to 240 patients. Any hormonal therapy was not given to 266 patients (new diagnosis and/or triple-negative patients). Metabolic syndrome was observed in 43.1% of patients according to NCEP criteria. Metabolic syndrome was found to be more frequent in the group receiving aromatase inhibitor than the group receiving tamoxifen (53.4% vs. 24.7%, p< 0.001). The frequency of metabolic syndrome was 48.2% in the group not receiving any hormonal treatment. Metabolic syndrome was more common in the postmenopausal patient group than the premenopausal group (49.0% vs. 26.1% p< 0.001). The incidence of metabolic syndrome was lower in patients with HER2 positive and a history of oral contraceptive use. (33.9% vs. 44.0% HER2, p= 0.11 and 37.7% vs. 40.8% oral contraceptive use history, p= 0.25). 75.1% of the patients had received adjuvant chemotherapy. There was no difference in the frequency of metabolic syndrome between the groups receiving and not receiving adjuvant chemotherapy. There was no statistically significant correlation between the presence of metabolic syndrome and estrogen/progesterone receptor status, tumor size, lymph node, stage, grade, hormone replacement therapy, chemotherapy, and smoking history. 43.1% of operated patients with stage I-III breast cancer had metabolic syndrome. Metabolic syndrome was more common in patients receiving adjuvant aromatase inhibitors, whereas less common in patients using oral contraceptives and having HER2 positive. These findings suggest that aromatase inhibitors may contribute to the development of the metabolic syndrome. Prospective studies are needed to explain this relationship.

Keywords: Breast Cancer, Metabolic Syndrome, Aromatase Inhibitors

ÖZET

Opere Evre I-Iii Meme Kanseri Hastalarında Metabolik Sendrom Sıklığı ve Belirleyicileri

Metabolik sendrom obezite, insulin rezistansı, hipertrigliseridemi, düşük HDL ve hipetansiyondan oluşan multiple kardiyak risk faktorlerinin birlikteliğinden oluşan bir durumdur. Metabolik sendromun meme kanseri riskini artırdığı yönünde ciddi bulgular vardır. Bu çalışmada opere evre I-III meme kanserli hastalarda metabolik sendrom sıklığı ve belirleyicileri tanımlamayı amaçlandı. Kliniğimize Nisan 2009-Nisan 2018 tarihleri arasında başvuran opere evre I-III meme kanserli hastalar kesitsel olarak olarak incelenmiştir. Hastalarda metabolik sendrom tanımı NCEP kriterlerine göre yapılmıştır. Metabolik sendrom kriterleri, demografik veriler, tümör boyutu, grade, lenf nodu, östrogen, progesteron, HER2 durumu ve kemoterapi/endokrin tedavi hikayeleri hastalardan ve hastane kayıtlarından öğrenilmiştir. Ortanca yaşı 50.6 olan 700 hasta analiz edildi. 194 hasta tamoksifen, 240 hasta aromataz inhibitörü alıyordu. Geri kalan 266 hasta hormonal tedavi almıyor idi (yeni tanı ve/veya triple negatif hastalar). NCEP kriterlerine göre hastaların %43.1'inin metabolik sendromu vardı.

Aromataz inhibitörü alan grupta tamoksifen alan gruba göre metabolik sendrom daha sık bulundu (%53.4 vs. %24.7, p< 0.001). Herhangi bir hormonal tedavi almayan grupta ise MS sıklığı %48.2 idi. Postmenapozal hasta grubunda premenapozal olan gruba göre metabolik sendrom daha sıktı (%49.0 vs. %26.1 p< 0.001). HER2 pozitif tümörlü ve oral kontraseptif kullanma öyküsü olan hasta gruplarında metabolik sendrom sıklığı daha düşük bulundu (%33.9 vs. %44.0 HER2, p= 0.11 ve %37.7 vs. %40.8 oral kontraseptif kullanım öyküsü, p= 0.25). Hastaların %75.1'i adjuvan kemoterapi almıştı. Adjuvan kemoterapi alan ile almayan grup arasında metabolik sendrom sıklığı açısından fark yoktu. Metabolik sendrom varlığı ile östrogen/progesteron reseptör durumu, tümor boyutu, lenf nodu, evre, grade, hormon replasman tedavisi, kemoterapi ve sigara içme öyküsü arasında istatistiksel anlamlı bir korelasyon saptanmadı. Opere evre I-III meme kanserli hastaların %43.1'inin metabolik sendromu vardı. Adjuvan aromataz inhibitorü kullanan hasta grubunda daha sık metabolik sendrom saptanırken, oral kontraseptif ve HER2 poziitif hasta grubunda daha az metabolik sendrom tespit edildi. Bu bulgularla aromataz inhibitörlerinin metabolik sendrom gelişimi sürecine bir katkısı olabileceği anlaşılmaktadır. Bu ilişkiyi açıklayacak prospektif çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Meme Kanseri, Metabolik Sendrom, Aromataz İnhibitörleri

INTRODUCTION

Breast cancer is the most common malignancy in women and is the most common cause of cancer-related deaths in women after lung cancer.[1] Metabolic syndrome is a condition characterized by a combination of a group of metabolic disorders which are risk factors for diabetes, coronary artery diseases, peripheral vascular diseases, and cerebrovascular events.[2] In recent years, with the spread of obesity especially in industrialized countries, the incidence of breast cancer and metabolic syndrome has increased rapidly.[3] Due to the rapid increase in incidence, there is a need to identify and control the modifiable risks of breast cancer.[4] Metabolic syndrome is thought to be associated with increased risk in many cancers, including breast cancer.[5] Compared to women with benign breast tumors and healthy control groups; The prevalence of type 2 diabetes, dyslipidemia, and hypertension are higher in women with breast cancer.[6] Many hormonal, metabolic and inflammatory mechanisms are known to play a role in the development and progression of breast cancer.[7] As a result of increased visceral fat and the development of insulin resistance, increased insulin biosynthesis together with increased extraglandular estrogen production, decreased sex hormone-binding globulin, and consequently an increase in bioactive plasma free estradiol levels have a mitogenic effect on breast epithelial cells.[8] Especially in postmenopausal women, an increase in the frequency of metabolic syndrome is considered as one of the factors leading to an increase in the incidence of breast cancer.[9] In the Women's Health Initiative (WHI) study, 5000 women aged 50-80 years were followed for 8 years, it was observed that the risk of developing breast cancer in patients with metabolic syndrome doubled in the 3 to 5 years before the diagnosis of breast cancer. In addition, an occult breast tumor was detected in 40% of postmenopausal women followed up, which was thought to be triggered by hormones.[10] There are studies advocating that metabolic syndrome can be evaluated not only a prognostic factor but also a risk factor for breast cancer.[7] Especially obesity and high plasma glucose levels are associated with an increase in postmenopausal breast cancer mortality, and the incidence of central obesity and metabolic syndrome is increased in patients with postmenopausal breast cancer. It is thought that metabolic syndrome might be associated with more aggressive tumor biology.[11] Many growth factors and elevated plasma levels of sex hormones due to central obesity and insulin resistance syndrome are held responsible for tumorigenesis. These factors, together with an increase in the risk of breast cancer, are thought to increase the risk of recurrence of the disease and worsen the prognosis.[12] It is stated that lifestyle changes that prevent the development of the metabolic syndrome and the treatment of metabolic syndrome components may be effective in reducing the risk of breast cancer.[5]

MATERIALS AND METHODS

Between April 2009 and April 2018, operated patients with stage I-III breast cancer who applied to our Medical Oncology Department were evaluated cross-sectionally. Metabolic syndrome was defined

Table 1. Demographic Characteristics of Patients

Features	n= 700 (%)
Median age	50.6
Age range	20-84
Menopausal status at the time of diagnosis	
Premenopausal	356 (50.8)
Perimenopausal	42 (6.8)
Postmenopausal	296 (42.2)
Currently menopausal status	
Premenopausal	103 (14.7)
Perimenopausal	35 (5.0)
Postmenopausal	562 (80.2)
History of oral contraceptive use	
No	620 (88.5)
Yes	80 (11.5)
History of hormone replacement therapy	
No	656 (93.7)
Yes	44 (6.3)
Smoking history	
No	512 (73.1)
Quit Smoking	131 (18.7)
Still Smoking	57 (8.1)
Comorbidities	
Type 2 diabetes	72 (10.2)
Hypertension	177 (25.2)
Hyperlipidemia	96 (13.7)
Other	47 (6.7)

Table 2. Clinical and Pathological Characteristics of Patients

Features	
Stage	
I	144(20.6)
II	358 (51.1)
III	198 (28.2)
Grade	
I	91 (13.0)
II	382 (54.6)
III	227 (32.4)
Hormone receptor status	
ER or PR (+), HER2 (-)	373 (53.2)
ER and PR (-), HER2 (+)	52 (7.4)
ER or PR (+), HER2 (+)	198 (28.2)
ER (-) and PR (-), HER2 (-)	77 (11.0)
HER2 receptor status	
Positive	245 (35.0)
Negative	455 (65.0)
Lymph node	
Positive	362 (51.7)
Negative	338 (48.3)
Treatment	
Adjuvant chemotherapy	576 (75.1)
Adjuvant endocrine therapy	434 (62.0)
Mean Antropometric Measurements	
Length (cm)	161.0
Body weight (kg)	73.4
Waist circumference (cm)	90.8
Hip circumference (cm)	107.3
Waist / Hip ratio	0.84

according to NCEP ATP III (National Cholesterol Education Program Adult Treatment Panel III) criteria. The data about demographics, metabolic syndrome criteria, tumor size, tumor grading, staging, estrogen, progesterone receptor status, HER2 / neu status, and chemotherapy or endocrine treatments were obtained from patients, patient files and hospital records. NCEP ATP III criteria are; abdominal obesity (waist circumference > 102 cm in men, > 88 cm in women), hypertriglyceridemia (TG ≥ 150 mg / dl), low HDL - cholesterol (< 40 mg / dl in men, <50 mg / dl in women), hypertension (Blood pressure ≥ 130/85 mmHg), and hyperglycemia (APG≥ 110 mg / dl). The patients who met at least three of the criteria are accepted as metabolic syndrome. Metastatic patients were excluded from the study at the time of diagnosis or at the time of metabolic syndrome evaluation. SPSS 18.0 program was used to analyze the data. It was a retrospective, cross-sectional, a treatment-free study. The approval of the Hacettepe University Senate Ethics Committee was obtained before the study (Decision No: 431.10-728).

RESULTS

Demographic, clinical and pathological characteristics of the patients are summarized in Tables 1 and 2. In our study, 700 patients were evaluated retrospectively and cross-sectionally. The median age was 50.6 years (range; 20-84 years). 14.7% of the patients were premenopausal, 5.0% were perimenopausal and 80.2% were postmenopausal. 10.2% of patients had type 2 diabetes, 25.2% had hypertension, and 13.7% had hyperlipidemia. While 73.1% of the patients had no history of

Table 3. Distribution of metabolic syndrome according to endocrine treatments

Treatment	Metabolic syndrome (%)
All patients	43.1
Patients receiving Tamoxifen	24.7
Patients receiving Aromatase inhibitors	53.4
Not receiving endocrine treatment	48.2

smoking, 18.7% of patients quitted smoking, and 8.1% continued to smoke. Only 11.5% of patients had a history of oral contraceptives and 6.3% had a history of hormone replacement therapy (Table 1). Antropometric measurements of the patients are shown in Table 2.

According to NCEP ATP III criteria, 43.1% of patients had metabolic syndrome. Tamoxifen was given to 194 patients and aromatase inhibitors were given to 240 patients. Any hormonal therapy was not given to 266 patients (new diagnosis and/or triple-negative patients) (Table 4). The metabolic syndrome was more frequent in the group receiving aromatase inhibitor than the group receiving tamoxifen (53.4% vs. 24.7%, p< 0.001). The incidence of metabolic syndrome was 48.2% in the group non-receiving hormonal treatment (Table 3).

Metabolic syndrome was more common in the postmenopausal group than in the premenopausal group (46.6% vs. 26.1%, p< 0.001). Metabolic syndrome was found in 17.6% of patients between 20-40 years, 42.7% of patients between 40-60 years and 57.3% of patients above 60 years of age. It was found that the frequency of metabolic syndrome increased with age (p< 0.001).

The incidence of metabolic syndrome was found to be lower in patients with HER2 positive (33.9% vs. 44.7%, p= 0.11). The incidence of metabolic syndrome was lower in patients with a history of oral contraceptive use (37.7% vs. 40.8%, p= 0.25) (Table 4).

While waist circumference was higher than 88 cm in 57.7% of all patients included in the study, it was found to be higher than 88 cm in 83.4% of patients with metabolic syndrome. Waist circumference was higher than 88 cm in 43.5% of patients receiving tamoxifen, 67.1% of patients receiving aromatase inhibitor and 54.6% of those not receiving any hormonal treatment (Table 5). Waist circumference was significantly lower in tamoxifen group (p< 0.001).

Table 4. Factors associated with metabolic syndrome

	Metabolic Syndrome		
	No	**Yes**	**P value**
Age	46.2	54.1	< 0.001
Hormonotherapy			
No	51.8%	48.2%	< 0.001
Tamoxifen	75.3%	24.7%	
Aromatase inhibitors	46.6%	53.4%	
HER2 status			
Negative	55.3%	44.7%	
Positive	66.1%	33.9%	0.11
Oral contraceptive history			
Yes	62.3%	37.7%	0.25
No	59.2%	40.8%	
Adjuvant chemotherapy involving taxane			
No	64.2%	35.8%	
Paclitaxel	55.1%	44.9%	0.065
Docetaxel	54.6%	46.4%	

Table 5. Distribution of metabolic syndrome parameters in patients and the relationship between metabolic syndrome parameters and endocrine treatments

	All Patients	Patients with MS	Tmx (%)	AI (%)	None (%)	P value
WC > 88	57.7	83.4	43.5	67.1	54.6	< 0.001
TG ≥ 150	52.4	79.7	43.5	55.6	53.2	0.025
HDL < 50	44.0	66.8	38.3	45.2	46.4	0.012
APG ≥ 110	27.2	58.0	15.6	35.4	28.5	< 0.001
BP ≥ 130/85	30.0	55.4	17.8	45.1	24.5	< 0.001

AI= Aromatase inhibitor; APG= Fasting plasma glucose; BW= Waist circumference; HDL= High-density lipoprotein; BP= Blood pressure; MS= Metabolic syndrome; TG= Triglyceride, Tmx= Tamoxifen

44% of all patients had lower HDL-cholesterol levels than 50 mg /dl. This rate was 66.8% in patients with metabolic syndrome. HDL-cholesterol levels were higher than 50 mg/dl in 38.3% of patients receiving tamoxifen, 45.2% of patients receiving aromatase inhibitors and 46.4% of those who did not receive endocrine therapy, and there were no significant differences between them (p= 0.012).

While serum triglyceride level was found to be 150 mg/dl or more in 52.4% of the patients, this rate was 79.7% of the group with metabolic syndrome. High triglyceride levels were 43.5% in the tamoxifen group, 55.6% in the aromatase inhibitor group and 53.2% in the non-endocrine treatment group. There was no statistically significant difference (0.025). Fasting plasma glucose level was 110 mg/dl and above in 27.2% of the patients. Fasting plasma glucose criterion was achieved in 58.0% of patients with metabolic syndrome. This rate was 15.6% in patients receiving tamoxifen, 35.4% in patients receiving aromatase inhibitor and 28.5% in patients not receiving endocrine therapy, and the difference was found to be statistically significant (p< 0.001) (Table 4).

Systolic blood pressure was 130/85 mmHg and above in 30.0% of all patients included the study and 55.4% of patients with metabolic syndrome. 17.8% of those receiving tamoxifen, 45.1% of those receiving aromatase inhibitors, and 24.5% of those who did not receive endocrine treatment met the high blood pressure criteria. Blood pressure was significantly lower in the tamoxifen group compared to the aromatase inhibitor group (p< 0.001) (Table 5). 75.1% of the patients had received adjuvant chemotherapy. There was no difference in the frequency of metabolic syndrome between the group receiving adjuvant chemotherapy and group non-receiving adjuvant chemotherapy. While the incidence of metabolic syndrome was 35.8% in patients without taxane-containing chemotherapy protocol, this rate increased to 44.9% in patients receiving paclitaxel and 46.4% in patients receiving docetaxel (p= 0.065) (Table 4). There was no statistically significant correlation between the presence of metabolic syndrome and estrogen/progesterone receptor status, tumor size, lymph node, stage, grade, hormone replacement therapy, chemotherapy, and smoking history.

DISCUSSION

Metabolic syndrome is common in both premenopausal and postmenopausal women, which is a complex and heterogeneous metabolic problem and its frequency has been increased day by day.[5,13,14] According to studies, the prevalence of metabolic syndrome in our country s found to be around 40% in women. The incidence of metabolic syndrome in women is 39.6% in METSAR study and 40% in TEKHARF study.[15,16] In recent years, the frequency of metabolic syndrome in patients with cancer has attracted attention. It is important to know that metabolic syndrome, especially together with visceral obesity, is increased in patients with colon, endometrium, kidney, liver, esophagus, and breast cancer.[3,13] In recent years, the incidence of type 2 diabetes, metabolic syndrome, and breast cancer has increased significantly, especially in industrialized countries.[3,12,17] Breast cancer has be-

come an important health problem for women in the USA and all around the world.[4] It is the most common cancer in women in the USA and it is the second most common cancer-related death.[1] Therefore, there is a need to identify the modifiable risks of breast cancer and to take preventive measures.[4] Many genetic, reproductive, and lifestyle factors have an impact on the development of breast cancer.[10] Many studies have shown that; various hormonal, metabolic and inflammatory factors affect the development and progression of breast cancer.[7,14] One of the most important of these factors is the metabolic syndrome prevalence of which is increasing rapidly all over the world. An increase in the prevalence of metabolic syndrome and an increase in the incidence of breast cancer are parallel.[18,19] Compared with patients with benign breast tumors and healthy control groups, it was found that the prevalence of type 2 diabetes, hypertension, and dyslipidemia was higher in women with breast cancer.[6] In our study, the incidence of metabolic syndrome was found to be 46.3% in newly diagnosed breast cancer patients who did not receive treatment and in hormone receptor-negative patients without any endocrine treatment. This rate is above the prevalence of metabolic syndrome in our country. The incidence of breast cancer is significantly increased, especially in postmenopausal women affected by the metabolic syndrome.[9,15,20] However, an increase in the incidence of obesity and metabolic syndrome in young breast cancer cases before the age of 40 is also noteworthy.[21] In our study, the prevalence of metabolic syndrome was 46.6% in postmenopausal patients. This rate was 26.1% in premenopausal patients. There was a significant increase in the frequency of metabolic syndrome with menopause. In our study, while the prevalence of metabolic syndrome was 17.6% in 26 patients aged between 20-40 years, it increased to 42.7% between the ages of 40-60 and 57.3% above the age of 60 years. While some of the patients were in natural menopause, some of them had menopause due to chemotherapy. The frequency of metabolic syndrome was significantly increased in postmenopausal patients regardless of the cause of menopause. This relationship is thought to be due to insulin resistance and hyperinsulinemia, which play the most critical role in the pathogenesis of metabolic syndrome.[3,22] Western lifestyle, reduced physical activity, a diet rich in fat, refined carbohydrate, and animal proteins cause an increase in visceral fat with or without obesity. As a result, insulin resistance leads to an increase in plasma levels of many growth factors and sex hormones that contribute to the development of breast cancer.[12]

According to the results of our study, the incidence of metabolic syndrome in non-metastatic breast cancer patients is quite high as in the general population. With the spread of the western lifestyle in our country, an increase in the incidence of metabolic syndrome can be expected to cause an increase in the incidence of breast cancer.

Studies are showing that metabolic syndrome has increased breast cancer-related mortality especially in women older than 60 years as well as increasing the risk of breast cancer.[15] In addition, the presence of metabolic syndrome in breast cancer patients in remission has been shown to increase the risk of disease recurrence.[12] In conclusion, metabolic syndrome is thought to be a prognostic factor in addition to being a risk factor for breast cancer.[7] In our study, although there was no statistically significant relationship between metabolic syndrome and disease stage, grade, and lymph node involvement, it was noted that the incidence of metabolic syndrome was increased in stage III patients when compared to stage I and stage II patients (47.1% vs. 37.6%), ($p= 0.078$). This relationship could be expected to be statistically significant in a study involving stage IV patients.

It is known that estrogen facilitates the formation and development of breast tumors. This effect increases by adding progestin.[10] Decreased sex hormone-binding globulin accompanying with estrogen aromatization occurring in fat tissues results in an increase in the plasma level of free estradiol and has a mitogenic effect on breast epithelial cells.[4,8] Epidemiological data suggest that hormone replacement therapies are associated with an increased risk of breast cancer. Other conditions that increase estrogen exposure such as early menarche, late menopause, and late first birth also cause a relative increase in the risk of breast cancer.[10]

Reducing progestin exposure with low-dose estrogen reduces the risk of breast cancer.[8,10] Relatively low doses of estrogen-containing hormone

replacement therapies may improve insulin resistance and reduce the increased risk of breast cancer in obese patients. However, this positive effect of low-dose estrogen is antagonized by progestin.[10] In our study, no statistically significant difference was found in terms of the frequency of metabolic syndrome in patients receiving hormone replacement therapy. However, in our study, only 44 patients (6.3%) had a history of hormone replacement therapy. Therefore, it could be thought that a significant relationship could not be detected because of the small number of patients. Although there was no statistically significant relationship between oral contraceptive use and the frequency of metabolic syndrome in our study, it was found that the frequency of metabolic syndrome was lower in patients using oral contraceptives compared to non-users (37.7% vs. 40.8%, p= 0.25). In our study, 80 patients (11.5%) used oral contraceptives. An inadequate number of patients may be effective in the absence of a statistically significant relationship.

Tamoxifen which is a non-steroidal selective estrogen receptor regulator (SERM) used in the adjuvant treatment of breast cancer acts by blocking the effects of estrogen on selected target organs in both premenopausal and postmenopausal patients.[23] While tamoxifen inhibits breast epithelial cell proliferation and tumorigenesis with its anti-estrogenic effect on breast tissue, it reduces the risk of cardiovascular disease with its estrogenic effect on lipid profile.[16,24] In our study, it was found that the frequency of metabolic syndrome was decreased significantly in patients receiving tamoxifen. On the other hand, the frequency of metabolic syndrome was significantly increased in patients using aromatase inhibitors acting as non-selective anti-estrogenic agents compared to tamoxifen users. When the lipid profiles of the patients were examined, triglyceride elevation was seen in 43.5% of the patients receiving tamoxifen, 55.6% of the patients receiving aromatase inhibitors, Low HDL-cholesterol levels were seen in 38.3% of the patients receiving tamoxifen and 45.2% of those receiving aromatase inhibitor. On the other hand, waist circumference criterion, which is an indicator of abdominal obesity, was found in 43.5% of patients receiving tamoxifen, and in 67.1% of patients receiving aromatase inhibitor. Other metabolic markers were also more positive in patients receiving tamoxifen. The decrease in the incidence of metabolic syndrome in breast cancer patients receiving tamoxifen could be expected to manifest itself as a decrease in cardiovascular risk in the postmenopausal period. Obesity causes increased estrogen exposure due to peripheral estrogen aromatization and increased insulin resistance due to increased visceral adipose tissue, it also contributes to the development of breast cancer by decreasing adiponectin production and an increase in leptin production in adipose tissue.[4] Changes in plasma leptin and adiponectin levels increase the risk of developing breast cancer through many endocrine and paracrine mechanisms. It also appears to be associated with a rapid course of disease with high metastatic potential and poor prognosis. In 2 in vitro studies, it was shown that tumor cell division and small vessel angiogenesis were increased by leptin over activation and adiponectin inhibition.[8] Adiponectin is an adipocytokine, which has an anti-inflammatory effect. Inadequate adiponectin released from adipose tissue has been shown to play a role in the pathogenesis of obesity-related diseases, metabolic syndrome, systemic insulin resistance, and cardiovascular diseases.[25] Recently, a decrease in plasma levels of adiponectin is thought to be effective in the pathogenesis of carcinogenesis. The decrease in adiponectin levels increases insulin resistance and peripheral estrogen aromatization by various endocrine and paracrine mechanisms and contributes to tumorigenesis. In addition, the decrease in adiponectin levels is thought to have a direct effect on tumor development.[4] Adiponectin has been shown to increase the expression of the tumor suppressor gene, LKB1, which inhibits adhesion, migration, and invasion of breast cancer cells. It is cited that the invasion and migration of cancer cells can be stopped or slowed by the use of adiponectin analogs in the treatment of breast cancer.[25]

Leptin is known as an obesity hormone. Increased insulin activity with hyperinsulinemia increases leptin secretion. High plasma leptin levels are thought to trigger the development of breast cancer.[26] According to the results of our study, abdominal obesity was seen in the majority of breast cancer patients. Further studies are needed to ex-

plain the relationship between breast cancer development and increased plasma leptin-decreased plasma adiponectin levels as a result of abdominal obesity.

In our study, abdominal obesity was more common in patients with metabolic syndrome. While abdominal obesity was 83.1% in patients with metabolic syndrome, this rate was 56.5% in all patients. Increased prevalence of breast cancer may be expected due to the increased prevalence of obesity in the future.

Glucose metabolism has a complex mechanism controlled by many regulatory metabolic pathways. In case of abnormalities in glucose metabolism, the impairments of cell growth and regulation are seen. A strong association of changes in glucose metabolism with cancer development has been shown in many cohort studies. The risk of malignancy begins to increase in the early period of abnormalities in glucose metabolism. Generally, there is a linear relationship between cancer risk and elevated plasma insulin levels in diabetes or metabolic syndrome.[27] In particular, the relationship between type 2 diabetes and colorectal cancers, pancreatic cancer, and breast cancer is very important and noteworthy.[3,8] However, the relationship between type 2 diabetes mellitus and breast cancer has not been fully elucidated. Because both diseases have common risk factors such as obesity, sedentary life, saturated fats and excessive consumption of refined carbohydrates and this situation leads to the complexity of the relationship between the two diseases.[27,28]

It is known that hyperinsulinemia due to insulin resistance causes proliferation abnormalities in tissues. This effect is due to insulin because insulin causes an increase in cell proliferation in DNA synthesis and insulin-like growth factor-1 (IGF-1) receptors.[6] Various case-control and cohort studies have shown that high serum IGF-1 levels are associated with breast cancer risk.[28,29] It is thought that low plasma IGF-1 levels may reduce the risk of breast cancer in patients with type 2 diabetes.[28] For this purpose, pharmacological agents that reduce IGF-1 concentration have been studied in several studies.[28,29] Antibodies specific for IGF-1 receptors have been planned to be used in the treatment of breast cancer.[29,30]

It has been shown that breast cancer mortality increases in proportion to an increase in plasma glucose levels.[31,32] In some studies, it has been shown that an increase in plasma glucose levels is associated with advanced-stage disease in breast cancer patients with type 2 diabetes.[8] In a study, it was shown that mortality due to breast cancer in women over 60 years increased in those with metabolic syndrome and plasma glucose level was the component with the strongest association with this increase.[32] In our study, although stage III disease was seen more frequently in patients with diabetes, this increase was not found to be statistically significant. This may be due to the fact that metastatic patients were not included in our study. Improving hyperinsulinemia is vital with the aim of reducing the risk of breast cancer in healthy women, preventing the progression of the disease stage for patients with early-stage breast cancer in order to improve prognosis and should be one of the treatment targets.[10] For this purpose, metabolic syndrome should be tried to be prevented, lifestyle changes and medical treatments of patients with metabolic syndrome should be regulated.[10]

Disorders of lipid metabolism are associated with increased risk of breast cancer, especially in postmenopausal women.[33] Low serum HDL-cholesterol level, which is one of the components of metabolic syndrome, increases the risk of postmenopausal breast cancer.[18,34,35] In women with low HDL-cholesterol levels than the general population, the increased risk is more pronounced in the case of concomitant obesity.[33] Elevated triglyceride, another component of the metabolic syndrome, is also associated with an increased risk of breast cancer .[9,31] HDL-cholesterol was below 50 mg/dl in 44% of all breast cancer patients included in our study. This rate increased to 46.6% in newly diagnosed patients who had not yet received treatment. HDL-cholesterol was below 50 mg/dl In 66.8% of patients with metabolic syndrome. In our study, serum triglyceride levels were found to be 150 mg/dl and above in 52.4% of all patients and 79.7% of patients with metabolic syndrome. Dyslipidemia was found to be the second most common metabolic disorder after abdominal obesity.

In our study, no significant difference was found in the frequency of metabolic syndrome between patients receiving and non-receiving chemotherapy. Although there was no statistically significant relationship between the type of chemotherapy and the frequency of metabolic syndrome, it was noteworthy that the frequency of metabolic syndrome was increased in patients receiving chemotherapy protocols including taxane. While the incidence of metabolic syndrome was 35.8% in patients not-receiving a taxane-containing chemotherapy protocol, this rate increased to 44.9% in patients receiving paclitaxel and 46.4% in patients receiving docetaxel (p= 0.065). Although the median age and median bodyweight of the patients receiving taxane were lower, the incidence of metabolic syndrome was increased. Prospective studies are needed to explain this relationship.

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Correspondence:
Dr. Furkan SARICI
Medical Park Trabzon Hastanesi
Devlet Sahil Yolu Caddesi
61700 Yıldızlı, Akçaabat
TRABZON / TURKEY

e-mail: saimfurkan@gmail.com
Tel: (+90-555) 560 80 24

ORCIDs:
Furkan SARICI: *0000-0001-9662-3760*
Veli SUNAR: *0000-0003-4672-4621*
Sercan AKSOY: *0000-0003-4984-1049*