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Effects of Adjuvant Chemotherapy on Insulin Resistance in Patients with Early Breast Cancer

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What is known on this subject?

In the literature, a few studies have investigated the correlation between insulin resistance and cancer development. The presence of insulin resistance increases the risk of breast cancer. Also, there are studies showing interactions between insulin resistance and chemotherapy.

What this study adds?

This study confirmed that early breast cancer patients had a higher rate of insulin resistance. There was a statistically insignificant rise in fasting blood glucose levels throughout and after the chemotherapy procedure, which is probably due to the steroid impact. Homeostatic model assessment for insulin resistance score's mean values dropped.

ABSTRACT

Objective: To assess the effect of adjuvant chemotherapy on insulin resistance in patients with early breast cancer.

Material and Methods: Twenty-three non-diabetic patients were included. Patients were prospectively evaluated before, during, and after chemotherapy. Demographic, anthropometric, histopathological features, and treatment data were recorded. Blood samples were taken to evaluate fasting blood glucose, fasting insulin levels, and HbA1c. Homeostatic model assessment for insulin resistance (HOMA-IR) score measured using fasting blood glucose and fasting insulin levels.

Results: Overall, pre- and post-chemotherapy mean weights were comparable (70.17 kg vs. 71.43). Prechemotherapy mean HOMA-IR was 4.99 and significantly higher than the control group of the healthy population (p=0.008). The mean values of the HOMA-IR score before, during, and after chemotherapy were 4.99, 3.47, and 3.13, respectively. Although the mean HOMA-IR decreased after chemotherapy, these decreases were not statistically significant (p=0.089). The mean fasting glucose levels before, during, and after chemotherapy were 95.5, 101.9, and 94.1 mg/dL, respectively. Before, during, and after chemotherapy, the mean fasting insulin levels were 21.43, 13.32, and 13.28 µIU/mL, respectively.

Conclusion: In the study, we observed a higher rate of insulin resistance in patients with breast cancer. The mean values of the HOMA-IR score decreased during and after chemotherapy.

Keywords: Breast cancer, chemotherapy, HOMA-IR, insulin resistance

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Introduction

Breast cancer is the most common malignancy in females and the second most common cause of death from cancer (1). Palpable mass, axillary node, skin changes (erythema, thickening, or dimpling) are the most common symptoms of breast cancer. There are many risk factors for breast cancer, including reproductive factors (menarche age, menopause age, number of pregnancies, lactation), genetic factors (BRCA 1-2 mutations), and obesity (2). Breast cancer is treated in a multidisciplinary manner by surgical oncology, medical oncology, and radiation oncology.

Insulin resistance is decreased physiologic effects of insulin with normal serum concentration. Insulin resistance may be caused by many risk factors such as obesity, medications (glucocorticoids, contraceptives), insulin antibodies, and genetic defects in insulin-signaling pathways (3). It is measured using the euglycemic clamp technique and homeostatic model assessment for insulin resistance (HOMA-IR) score. Insulin resistance can be seen in 15.5%-46.5% of the general population (4). A few research has examined the correlation between insulin resistance and the development of cancer in the literature. The risk of breast, endometrial, colon, prostate, esophageal, liver, and kidney cancers increases with the presence of insulin resistance (5). Breast cancer risk is increased by approximately 10%-20% in patients with type 2 diabetes (6). Also, women with a familial history of breast cancer have a significantly higher frequency of insulin resistance (7).

There is essential evidence demonstrating the interactions between insulin resistance and chemotherapy. The insulin-like growth factor (IGF) is important for cell proliferation, differentiation, and growth. The IGF pathway is involved in the development of breast cancer (8,9). By suppressing apoptosis, IGF-1 prolonged cell survival in human breast cancer cells treated with methotrexate, 5-fluorouracil, and tamoxifen (10). Also, a study found that phosphatidylinositol-3 (PI-3) kinase was necessary for IGF-I rescue of doxorubicin-induced apoptosis, but both PI-3 kinase and MAP-kinase were required for IGF-I rescue of paclitaxel-induced apoptosis (11). A multi-center study showed that breast cancer patients with insulin resistance had a poor prognosis (12). Another study also showed that low-quality and high amounts of upper visceral fat tissue were related to insulin resistance and prognosis in patients with breast cancer (13). It has also been stated that hyperinsulinemia conditions due to transient hyperglycemia may reduce the effectiveness of chemotherapy (14). Only a few studies have evaluated interactions between insulin resistance and chemotherapy using measurement methods, including the HOMA-IR score. This study's goal was to assess the effect of adjuvant chemotherapy on insulin resistance in patients with early breast cancer.

Material and Methods

Patients and Study Design

Between October 2011 and September 2012, early-stage breast cancer patients were evaluated prospectively at Ankara University Medical Oncology Outpatients Clinics. The Ankara University Faculty of Medicine Ethics Committee (number 38-824) allowed this research, which was carried out in accordance with the Helsinki Declaration and good clinical procedure. Informed consent was obtained from all patients after the study procedures were explained. Patients without diabetes and did not use drugs that affect insulin metabolism were included in the study. The presence of diabetes mellitus (DM) in patients was determined using the standardized HbA1c method. Clinical data, pathological features (tumor type, tumor size, lymph node, grade, lymphovascular invasion, Ki67% levels), estrogen receptor (ER), progesterone receptor (PR), HER2/neu receptor status, and treatment approach (surgery type, radiotherapy, chemotherapy, and endocrine therapy) of the patients were recorded. Also, a history of family breast cancer and diabetes was noted. Immunohistochemistry was used in the examination of ER and PR status. Immunohistochemistry (score 3+) and *in situ* hybridization also used to detect HER2 overexpression. Tumor staging was done according to the 7th edition of the American Joint Committee on Cancer-TNM.

Patients were prospectively evaluated before, during (after 2-3 cycles of chemotherapy), and after chemotherapy (at least one month after the last chemotherapy cycle). Blood samples were taken from the patients with at least 8 h of fasting in the morning before chemotherapy to assess fasting insulin levels, fasting blood glucose, and HbA1c. Fasting blood glucose levels were evaluated using spectrophotometric method, fasting insulin levels were assessed by radioimmunoassay method, and HgA1c levels were assessed by high-performance liquid chromatography) method without waiting. Normal values for fasting blood glucose were accepted as 74-100 mg/dL, normal values for fasting insulin levels were 4-16 µIU/mL, and normal values for HbA1c were accepted as 4.4%-6% according to the laboratory's device validation of our institution. The height and weight of the patients were recorded in all visits. The formula for calculating the body mass index (BMI) is BMI: kg/m^2, where kg is a person's body weight in kilograms and m^2 is their length in meters squared. BMI is evaluated with World

Health Organization classification. With the model: Fasting glucose (nmol/L) x fasting insulin (μ/L)/22.5, the HOMA-IR score was computed using fasting insulin levels and fasting blood glucose. The diagnosis of insulin resistance was achieved with a HOMA-IR score >2.24, which is the mean level of the historical control group of a healthy population (15).

Statistical Analysis

Statistical analysis was performed using the SPSS version 20. Continuous variables are shown as median (minimum-maximum) values, whereas categorical variables are shown as numbers and percentages. A one-sample and paired-sample t-test used to detect statistical differences. Statistical significance was considered a p value from less than 0.05.

Results

The research enlisted the participation of twenty-three patients. Patients' median age was 45 years (range: 31-78). Sixteen (69.6%) patients were diagnosed as premenopausal, and the remaining were postmenopausal. The most common pathology was invasive ductal carcinoma (16; 69.6%). Twenty patients (87%) had ER and PR positive breast cancer, and five (21.7%) patients showed HER2 positivity. The mean BMI was 27.66 kg/m^2. While six (26.1%) patients had obesity (BMI >30 kg/m^2), 11 (47.8%) patients were overweight (BMI: 25-30 kg/m^2). Table 1 presents the clinic and pathological features of the patients.

Seventeen (74%) of the patients had undergone modified radical mastectomy. Fourteen (60.9%) patients received radiotherapy with a median 50 Gy in 25-28 fractions. The patients received different chemotherapy regimens, including anthracyclines, taxane, cyclophosphamide, and carboplatin. Also, the patients received dexamethasone 16 mg for premedication before taxane treatment. Table 2 presents the treatment approach of the patients

Insulin resistance was detected in 15 (65.3%) patients. Prechemotherapy mean HOMA-IR was 4.99 and significantly higher than the control group of the healthy population (p=0.008). The mean values of the HOMA-IR score before, during, and after chemotherapy were 4.99, 3.47, and 3.13, respectively. Although the mean HOMA-IR decreased after chemotherapy, this result was not statistically significant (p=0.089). The mean fasting glucose levels before, during, and after chemotherapy were 95.5, 101.9, and 94.1 mg/dL, respectively. The mean levels of fasting insulin before, during, and after chemotherapy were 21.43, 13.32, and 13.28 μIU/mL, respectively (Table 3). Overall, pre- and post-chemotherapy mean weights were similar (70.17 kg vs. 71.43).

Table 1. Clinicopathological characteristics of the patients

	Number of patients (n=23)	(%)
Median age, at diagnosis		
45 (range: 31-78)		
Family history		
Breast cancer	1	4.3
Diabetes	7	30.4
No	15	65.3
Body mass index kg/m^2		
<25	6	26.1
25-30	11	47.8
≥30	6	26.1
Menstruation status		
Premenopausal	16	69.6
Postmenopausal	7	30.4
HOMA-IR score, at diagnosis		
2.5<	15	65.3
2.5>	8	34.7
Histological type		
Invaziv ductal carcinoma	16	69.6
Mixed type	4	17.5
Tubular carcinoma	1	4.3
Micropapillary carcinoma	1	4.3
Invasive lobular carcinoma	1	4.3
pT status		
T1 (≤2 cm)	7	30.5
T2 (2-5 cm)	14	60.9
T3 (>5 cm)	2	8.6
pN status		
N0	7	30.4
N1 (1-3)	6	26.1
N2 (4-9)	7	30.4
N3 (≥10)	3	13.1
ER status		
Positive	20	87
Negative	3	13
PR status		
Positive	20	87
Negative	3	13
HER2 overexpression		
Positive	5	21.7
Negative	18	78.3

HOMA-IR: Homeostatic model assessment for insulin resistance, ER: Estrogen receptor, PR: Progesterone receptor

Discussion

In this study, compared with a healthy population, we observed a higher frequency of insulin resistance in early breast cancer patients. While insulin levels and HOMA-IR

Table 2. Treatment approaches of the patients

	Number of patients (n=23)	%
Breast surgery		
Lumpectomy + SNB[1]	3	13
Lumpectomy + AD	3	13
Modified radical mastectomy	17	74
Adjuvant radiotherapy		
Yes	14	60.9
No	9	30.1
Chemotherapy regimens		
3 FEC + 3 T	2	8.7
4 AC	6	26.1
4 AC + 4 T	10	43.5
3 AC + 3 T	2	8.7
6 TCb	3	13
Trastuzumab therapy		
Yes	5	21.7
No	18	78.3
Endocrine therapy		
Tamoxifen	18	78.4
Aromatase inhibitors	2	8.6
No endocrine therapy	3	13

SNB: Sentinel node biopsy, AD: Axillary dissections, MRM: Modified radical mastectomy, FEC: Fluorouracil + epirubicin + cyclophosphamide, CA: Adriamycin + cyclophosphamide, T: Trastuzumab, TCb: Docetaxel + carboplatin, T: Docetaxel

Table 3. The mean values of insulin resistance parameters before, during, and after chemotherapy

	n	Mean	SD	p value
Body weight-1 (kg)	23	70.17	11.82	0.126
Body weight-3		71.43	11.94	
FBG-1 (mg/dL)	23	95.5	10.88	0.073
FBG-2		101.9	18.73	
FBG-1	21	95.4	11.35	0.614
FBG-3		94.1	9.89	
Insulin levels-1 (µIU/mL)	23	21.43	20.78	0.075
Insulin levels-2		13.32	7.68	
Insulin levels-1	21	21.23	21.61	0.09
Insulin levels-3		13.28	7.44	
HbA1c-1 (%)	23	5.38	0.36	0.054
HbA1c-2		5.51	0.42	
HbA1c-1	21	5.40	0.32	0.162
HbA1c-3		5.30	0.30	
HOMA-IR-1	23	4.99	4.54	0.134
HOMA-IR-2		3.47	2.52	
HOMA-IR-1	21	4.92	4.70	0.089
HOMA-IR-3		3.13	1.90	
HOMA-IR-1*	23	4.99	4.54	0.008

**Test value: 2.24, 1: Before chemotherapy, 2: During chemotherapy, 3: After chemotherapy, FBG: Fasting blood glucose, HOMA IR: Homeostatic model assessment insulin resistance, SD: Standard deviation; n: Number*

decreased after chemotherapy, BMI and fasting glucose levels were comparable. Chemotherapy is associated with clinically significant weight gain. In a study of 3,088 breast cancer patients, chemotherapy-associated statistically significant weight gain was observed (16). Body weight gain after chemotherapy usually ranges between 1 and 6 kg (17). In a study by Makari-Judson et al. (18) in which 95 patients with early-stage breast cancer were included, an average of 0.4 kg increase in body weight was detected in the 6th month after adjuvant chemotherapy, while this increase increased to an average of 0.9 kg in the 12th month. It has been stated that weight gain may be associated with the effect of dexamethasone used during chemotherapy and the deterioration of insulin resistance (18). Overall, pre- and post-chemotherapy mean weights in our study were similar (70.17 kg vs. 71.43), not statistically significant.

Prechemotherapy mean HOMA-IR was 4.99 and significantly higher than the historical control group of the healthy population (p=0.008). Insulin resistance was detected in 15 (65.3%) of patients in our study. In a published study by Capasso et al. (19), insulin resistance was found in 49% of breast cancer patients. Similarly, Lawlor et al. (20) showed that hyperinsulinemia is positively linked with breast cancer in a cross-sectional study of 3868 women aged 60-79 years. In another study by Duggan et al. (21) in which 527 patients with early-stage breast cancer were evaluated, it was shown that with an increase in HOMA-IR score, survival due to breast cancer and all-causes decreased.

We found an increase in blood glucose levels during chemotherapy among patients who received dexamethasone. Similarly, Hickish et al. (22) found that blood glucose levels increase during chemotherapy. Also, hyperglycemia may result in transient hyperinsulinemia. Transient hyperglycemia may also affect the efficacy of chemotherapy by perturbations of the tumor microenvironment (14). Conversely, we did not find that transient hyperinsulinemia was associated with hyperglycemia. Some studies found increased HOMA-IR in breast cancer patients who received chemotherapy (18,23,24) but these changes tended to return to baseline in the 12th month (18,25). A study including 128 breast cancer patients without a history of DM was found β-cell dysfunction and insulin resistance after systemic treatment (26). In another study by Chala et al. (27), a statistically significant decrease

was found in 2-hour insulin levels in OGTT tests performed before and after chemotherapy.

Study Limitations

This study had some limitations. The number of patients was small, and therefore no differentiation was made for insulin resistance change according to chemotherapy groups. The patients had naturally taken steroids for premedication before the chemotherapy session.

Conclusion

In conclusion, we observed that patients with early breast cancer had a higher rate of insulin resistance. During and after the chemotherapy protocol, there was a statistically insignificant increase in fasting blood glucose levels, which is thought to be related to the steroid effect. However, the mean values of the HOMA-IR score decreased. These decreases can be explained by chemotherapy's influence on the insulin pathway or more attention to nutritional status. Our study provides important data even though the number of patients is small due to the limited number of studies in the literature. However, further studies that included many patients needed to verify these results. There are limited studies examining insulin resistance and cancer development. Further translational studies must be conducted to elucidate the pathophysiological mechanisms leading to cancer development.

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Ethics

Ethics Committee Approval: Ankara University Faculty of Medicine Ethics Committee (number 38-824) allowed this research.

Informed Consent: Informed consent was obtained.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: İ.D., Y.Ü., H.O., Design: İ.D., Y.Ü., H.O., Data Collection or Processing: İ.D., Y.Ü., Analysis or Interpretation: İ.D., Y.Ü., H.O., Literature Search: İ.D., Y.Ü., H.O., Writing: İ.D., Y.Ü.

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