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Original Article

Effects of adjuvant therapy on body composition measurements in women with early breast cancer

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Abstract

Aim: This study aimed to determine the effects of adjuvant therapy on body mass index (BMI) and body fat (BF) measurements in women with early-stage breast cancer (ESBC).

Material and Methods: We prospectively evaluated BMI and BF measurements including trunk fat mass kilograms (kg), trunk fat mass (%) and total body fat (%) on a bioelectric impedance analyzer in 29 women with stages I-III breast cancer. All of the patients received anthracycline-based adjuvant chemotherapy (ACT). Six patients were hormone receptor (HR)-negative. Twenty-three patients were HR-positive and received adjuvant endocrine therapy (AET) following ACT. Eleven HR-positive postmenopausal patients were treated with an aromatase inhibitor (AI), and the remaining twelve HR-positive premenopausal patients were treated with tamoxifen (TMX). A total of 3 measurements were performed in the beginning of chemotherapy, at 6th, and 12th months.

Results: Although the BMI was significantly increased, there was no significant change in the BF during chemotherapy in patients receiving only ACT. Both BMI and BF measurements were significantly increased in premenopausal patients receiving TMX after ACT. However, no significant change was observed in BMI and BF measurements in postmenopausal patients receiving AI after ACT.

Conclusions: ACT increased both BMI and BF measurements in patients with HR-positive premenopausal ESBC. Treatment with TMX or AI after ACT did not enhance the changes due to chemotherapy on body composition. Therefore, especially patients with HR-positive premenopausal ESBC should be careful not to gain weight during ACT.

Keywords: Early breast cancer; adjuvant therapy; body mass index; body fat measurements.

INTRODUCTION

Patients with early-stage breast cancer (ESBC) are operated for the local disease. In addition, if necessary, radiation therapy (RT) is applied to patients in order to ensure complete local control. Moreover, adjuvant systemic therapy including adjuvant chemotherapy (ACT), anti-human epidermal growth factor 2 (anti-HER2) therapy, and adjuvant endocrine treatment (AET) is administered to patients who required. The decision of systemic treatment is given considering several features such as tumor size, grade, number of involved lymph nodes, the status of estrogen receptor (ER) and progesterone receptor (PR), and expression of HER2 receptor.

The body composition changes occur in women receiving adjuvant systemic therapy for ESBC during or after therapy. Most of these patients have increased body weight, body mass index (BMI) and fat mass. Many studies have shown that this effect is closely related to the type of treatment and is associated with poor prognosis (1). It has been demonstrated that over 5% weight gain during the treatment process is significantly worse disease-free survival (DFS) and overall survival (OS) in patients with breast cancer receiving anthracycline-based ACT (2).

In this study, we prospectively evaluated whether adjuvant systemic therapy affects the body mass index (BMI) and body fat (BF) measurements in patients with ESBC.

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MATERIALS and METHODS

Study Patients

We prospectively evaluated body compositions in patients with ESBC receiving ACT between July 2016 and May 2017 at the Medical Oncology Department of Necmettin Erbakan University Hospital. This study was approved by the Ethics Committee of Necmettin Erbakan University, and written consent was obtained from all patients participating in the study.

All woman patients with operated breast cancer between July 2016 and May 2017 and who will receive ACT are enrolled in the study. Patients who have metastatic disease or will not receive ACT were excluded. Body composition measurements, including the BMI, trunk fat mass kilograms (kg), trunk fat mass (%), and total BF (%) were performed a total three times at the beginning of chemotherapy (visit 1), sixth month (visit 2), and 12th month (visit 3). All of the measurements were performed after ≥ 8 hours of fasting.

A total of 29 women were included in the study. The data of age, menopausal status, primary tumor location, type of surgery, type of ACT, and prognostic markers such as tumor stage, histological grade, ER, PR and HER2 status were recorded.

Measurements

The Multi-Frequency Bioelectric Impedance Analysis (MF-BIA) by using the TANITA MC-180 Body Composition Analyzer (TANITA, MC-180) was used to measure body compositions. Participants were asked to stand on the Body Composition Analyzer with bare feet, remove all the accessories, and make sure there was no metal in the body. Body compositions were measured by the prediction equations of the manufacturer within the Analyzer.

Statistical Analyses

Descriptive analyses were performed to examine distributions, means and standard deviations of all continuous variables. Friedman (nonparametric K-related samples test) test was used to compare measurements because there were three different repeated body measurements. For those with significant significance in the Friedman test, the Wilcoxon signed rank test was performed to determine which groups were among these differences. Statistical analysis was performed by using SPSS version 22.0 (SPSS Inc., Chicago, IL, USA). A p-value <0.05 was required for statistical significance.

RESULTS

Patients' characteristics

The median age was 52.28 years (37-71 years), and 51.7% were postmenopausal at the time of diagnosis. The rates of patients with the primary tumor site in the right breast and left breast were 44.8% and 55.2%, respectively. Neoadjuvant chemotherapy was not applied to any patient because of the preference of surgeons. All of the patients were operated for the local disease before ACT. More than half of the women have been performed modified radical mastectomy surgery (69%). The rates of patients with stage-1, stage-2, and stage-3 were 20.7%, 44.8%, 34.5%, respectively. Regarding histologic grade, 3 patients were grade 1 (10.3%), 22 patients were grade 2 (75.9%) and 4 patients were grade 3 (13.8%). The rates of patients with ER-positive, PR-positive, and HER-positive were 75.9%, 55.2%, and 17.2%, respectively. The demographic and clinical parameters of patients are shown in Table 1.

Table 1. Demographic and disease characteristics of patients

Characteristic	Total (N =29)
Mean Age at Diagnosis, Years	52.28
Age Range, Years	37-71
Primary Tumor Location	
Right	13 (44.8%)
Left	16 (55.2%)
Cancer Stage	
I	6 (20.7%)
II	13 (44.8%)
III	10 (65.5%)
Menopausal status	
Premenopausal	14 (48.3%)
Postmenopausal	15 (51.7%)
Radiation Therapy	
No	9 (31%)
Yes	20 (69%)
Hormone Therapy	
None	6 (20.7%)
Tamoxifen	12 (41.4%)
Aromatase inhibitor	11 (37.9%)
HER2 Receptor	
Negative	24 (82.8%)
Positive	5 (17.2%)
Estrogen Receptor	
Negative	7 (24.1%)
Positive	22 (75.9%)
Progesterone receptor	
Negative	13 (44.8%)
Positive	16 (55.2%)
Chemotherapy	
Anthracycline based CT	15 (51.8%)
Anthracycline based CT+taxan	9 (31%)
Anthracycline based CT+ taxan+trastuzumab	5 (17.2)
Histological grade	
Grade 1	3 (10.3%)
Grade 2	22 (75.9%)
Grade 3	4 (13.8)
Surgery Type	
Mastectomy	20 (69%)
Lumpectomy	9 (31%)

CT: Chemotherapy
HER2: Human epidermal growth factor receptor 2

Treatments

All of 29 patients received anthracycline-based ACT. 9 (31%) of the patients received taxane along with anthracycline. Also, 5 (17.2%) of the patients received adjuvant trastuzumab along with taxane plus anthracycline-based ACT. Six patients received only ACT because the hormone receptor (HR) was negative. 69% of patients were treated with RT in addition to ACT. Twenty-three (79.3%) patients who were HR-positive received AET following ACT. Patients were treated with either tamoxifen (TMX) or an aromatase inhibitor (AI) according to their menopausal status. Eleven (37.9%) postmenopausal patients were treated with an AI, 12 (41.4%) premenopausal patients were treated with TMX.

Body composition measurements during adjuvant therapy

We compared the changes in body composition measurements at visit 1, visit 2, and visit 3 in patients who received only ACT, who received TMX after ACT and who received AI after ACT (Table 2).

There was an increase in all body composition measurements from visit 1 to visit 3 in patients who received only ACT. This increase was significant only in BMI (27.2±2.1, 29±2.8, 29.5±3.2, p: 0.009) (Table 2). BMI measurements showed a significant increase between visit 1 and visit 2 (27.2±2.1 vs. 29±2.8, p:0.028), and between visit 1 and visit 3 (27.2±2.1 vs. 29.5±3.2, p: 0.028), but did not showed a significant increase between visit 2 and visit 3 (29±2.8 vs. 29.5±3.2, p: 0.463) (Table 3).

When we evaluated the premenopausal patients receiving TMX after ACT, all of their body composition measurements were significantly increased from visit 1 to visit 3 [p: 0.035 for BMI, p: 0.017 for trunk fat mass kg, p: 0.009 for trunk fat mass (%), p: 0.011 for total body fat (%)] (Table 2). The increase in BMI, trunk fat mass kg, and trunk fat mass (%) was significant between visit 1 and visit 2, and significant between visit 1 and visit 3, but was not significant between visit 2 and visit 3. The increase in total BF (%) was significant between visit 1 and visit 3 (28.3±4.3 vs. 32.1±1.6, p: 0.019), but was not significant between visit 1 and visit 2 (28.3±4.3 vs. 31.1±2.6, p: 0.062), and not significant between visit 2 and visit 3 (31.1±2.6 vs

Table 2. The relationship between changes on body composition measurements and adjuvant therapy

Adjuvant Therapy		BMI (kg/m2 (Mean± Std Deviation)	Mean Rank	p	Trunk fat mass kg (Mean±Std. Deviation)	Mean Rank	p	Trunk fat mass (%) (Mean± Std Deviation)	Mean Rank	p	Total body fat % (Mean± Std Deviation)	Mean Rank	p
	Visit 1	27.2±2.1	1		8.1±1.7	1.5		22.2±3	1.83		29,1±1.4	1.67	
Only CT (n=6)	Visit 2	29±2.8	2.33	0.009	8.7±2.9	2.17	0.311	22.4±5.7	2	0.846	30.2±4.1	2	0.412
	Visit 3	29.5±3.2	2.67		9.2±1.8	2.33		23.9±3.6	2.17		31.3±2.9	2.33	
	Visit 1	28.9±5.2	1.46		8.2±2	1.42		20±4.5	1.33		28.3±4.3	1.38	
Tamoxifen after CT (n=12)	Visit 2	30.2±5.1	2.04	0.035	9.7±1.8	2	0.017	23.3±3.8	2.13	0.009	31.1±2.6	2.04	0.011
	Visit 3	30.6±4.6	2.5		10.4±1.5	2.58		24.5±3.2	2.54		32.1±1.6	2.58	
	Visit 1	29.7±6.2	1.95		10.1±3.7	2.27		25.3±6	2.27		32.3±6.3	2.09	
AI after CT (n=11)	Visit 2	29.5±6.1	1.91	0.85	8.9±3.8	1.55	0.178	22.6±8	1.55	0.178	30.4±8	1.55	0.148
	Visit 3	30.1±6.5	2.14		10.2±4.2	2.18		25±7	2.18		32.5±7	2.36	

CT: Chemotherapy BMI: Body mass index AI: Aromatase inhibitor

Table 3. The changes on BMI between visits in patients receiving only chemotherapy

	BMI (kg/m2) (Mean± Std Deviation)	p
Visit 1	27.2±2.1	0.028
Visit 2	29±2.8	
Visit 1	27.2±2.1	0.028
Visit 3	29.5±3.2	
Visit 2	29±2.8	0.463
Visit 3	29.5±3.2	

BMI: Body mass index

32.1±1.6, p: 0.195) (Table 4).

All of the baseline body composition measurements were higher in postmenopausal patients receiving AI after ACT compared to the other two groups. These values decreased during ACT and then exceeded the baseline values again. However, these changes were not significant (p: 0.85 for BMI, p: 0.178 for trunk fat mass kg, p: 0.178 for trunk fat mass (%), p: 0.148 for total body fat (%) (Table 2).

Table 4. The changes on body composition measurements between visits in patients receiving tamoxifen after chemotherapy

	BMI (kg/m2 (Mean± Std Deviation)	p	Trunk fat mass kg (Mean±Std Deviation)	p	Trunk fat mass (%) (Mean±Std Deviation)	p	Total body fat % (Mean± Std Deviation)	p
Visit 1	28.9±5.2	0.045	8.2±2	0.034	20±4.5	0.045	28.3±4.3	0.062
Visit 2	30.2±5.1		9.7±1.8		23.3±3.8		31.1±2.6	
Visit 1	28.9±5.2	0.009	8.2±2	0.017	20±4.5	0.026	28.3±4.3	0.019
Visit 3	30.6±4.6		10.4±1.5		24.5±3.2		32.1±1.6	
Visit 2	30.2±5.1	0.158	9.7±1.8	0.170	23.3±3.8	0.308	31.1±2.6	0.195
Visit 3	30.6±4.6		10.4±1.5		24.5±3.2		32.1±1.6	

BMI: Body mass index

DISCUSSION

In this prospective study, we found that BMI was significantly increased during and after ACT in women with HR-negative ESBC. Besides, we found that BF measurements along with BMI increased significantly during and after treatment in women with HR-positive premenopausal ESBC, but did not increase significantly during and after treatment in women with HR-positive postmenopausal ESBC. This change was associated only with ACT, but not with TMX or AI. Because the changes in the measurements were not significant between the 2nd visit which was beginning of AET and the 3rd visit.

In our patients who received only ACT, BF measurements along with BMI was increased but the increase in BF measurements was not statistically significant. The patient's BMI is based on the patient's weight and height and is calculated using the following formula: BMI = body weight (kg) / height (m^2). Weight is body weight and refers to the sum of the total body water, muscle mass, minerals and BF weight. A significant increase in BMI without significant increase in BF measurements can be explained by the increase in other parameters that make up the weight.

Weight gain is typical among women diagnosed with ESBC. In a population-based cohort study of 5014 women with stage 0–III ESBC, it has been demonstrated that higher disease stage, younger age, lower BMI at diagnosis, and receiving CT or RT during the first six months after cancer diagnosis were associated with weight gain (3). Body composition changes including an increase in adipose tissue percentage along with a decrease in lean body mass are also observed in addition to weight gain in women with ESBC who received ACT (4-6). Although the underlying mechanism for weight gain is not entirely known, weight gain is associated with side effects such as treatment-related weakness, taste and odor change, and decreased physical activity. The decreased physical activity during ACT is also consistent with the increase in total fat mass, especially in the trunk and leg regions (7,8). It has been revealed that energy expenditure at rest was reduced in women receiving ACT, however, energy intake did not decrease in this period and caused an increase in BF (9). In addition, another study showed that weight gain was not associated with the type of ACT **(anthracycline vs. non-anthracycline)** or treatment duration (shorter or longer) (10). Also, studies are suggesting that menopausal status is predictive on weight gain in addition to ACT in women with ESBC, but the results are contradictory. Premenopausal status was found associated with weight gain in a study, whereas postmenopausal status was found associated with weight gain in another study (3,11). In a prospective study of 50 postmenopausal women with ESBC receiving ACT, it was shown that 20% of women gained weight during ACT, but no significant increase in their fat mass during ACT was detected. However, in these women with weight gain, an increase in fat mass was observed, especially in the abdominal region, six months after ACT (12). Besides, Pedersen et al. demonstrated that weight gains related to increased body fat were observed mainly in premenopausal women receiving ACT, but no change in weight and fat mass was observed in postmenopausal women receiving AI (13). In our study, we found a significant increase in BMI and BF measurements in HR-positive premenopausal women receiving ACT, but no significant change was observed in HR-positive postmenopausal women receiving ACT.

Weight gain is higher among women receiving ACT or ACT+AET. Despite the increase in trunk fat mass in women receiving TMX following ACT, this increase was not observed in women receiving AI following ACT and women receiving only ACT without AET (14). The impact of AET alone on weight gain is unclear. Many studies showed that TMX and AI did not lead to a significant

change in weight (10,15,16). Saquib et al. evaluated the association between weight gain and treatment of breast cancer in WHEL study and demonstrated that both anthracycline-based and non-anthracycline based ACT were significantly associated with weight gain, but that TMX was not associated with weight gain, and that TMX did not modify the impact of ACT on weight gain (10). As in the WHEL study, we found that ACT was significantly associated with the increase in BMI and that TMX and AI did not enhance the impact of ACT on body composition.

The weight changes during ACT are essential because they may have potentially adverse effects on prognosis and survival (17). Higher BMI was associated with a higher risk of breast cancer-specific mortality in pre- or post-diagnosis among women ≥65 years of age at diagnosis (18). The gain in BF percentage six months after surgery in women with postmenopausal breast cancer was associated with distant metastasis but was not related to survival (19). In a cohort analysis of 3,993 women with ESBC who gained weight after diagnosis, each 5 kg weight gain was associated with an increase in all-cause mortality, breast cancer-specific mortality, and cardiovascular disease mortality (20). In a pooled analysis of LACE, WHEL, NHS and SBCSS studies involving 12915 BC patients, it was shown that weight gain after treatment increased all-cause mortality but did not increase breast cancer-specific mortality (21). In our study, we did not perform a survival analysis because the survival results of patients were not yet mature.

In conclusion, we demonstrated that ACT caused an increase in BMI in women with ESBC who were HR-positive premenopausal and HR-negative. In particular, HR-positive premenopausal women are potentially at risk for changes in BMI and BF measurements during ACT. According to our results, TMX and AI have no impact on BMI and BF measurements. Although our study is a prospective study, the major limitation of this study is the small number of patients. Further studies with a large number of patients and longer follow-up periods should be designed to understand the impact of BMI and body composition changes during the ACT on the prognosis of breast cancer.

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