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THE PSYCHOLOGICAL AND PHYSICAL BENEFITS OF THE SUPERVISED INDIVIDUAL EXERCISE PROGRAM DURING RADIOTHERAPY IN BREAST CANCER PATIENTS: A RANDOMIZED STUDY

MEME KANSERİ HASTALARINDA RADYOTERAPİ SIRASINDA DENETİMLİ BİREYSEL EGZERSİZ PROGRAMININ PSİKOLOJİK VE FİZİKSEL FAYDALARI: RANDOMİZE BİR ÇALIŞMA

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Öz

Amaç
Meme kanserindenkurtulan hastalarda uzun dönem tedavi yan etkileri yaşam kalitesi üzerinde olumsuz etkilere yol açmaktadır. Egzersizin, bu hastaların fiziksel ve psikolojik durumları üzerindeki olumlu etkisi bilinmektedir. Bu çalışmada, meme kanseri tanısıyla radyoterapi alan hastalarda tedavi sırasında egzersizin fiziksel ve psikolojik duruma etkisini araştırmayı amaçladık.

Gereç ve Yöntem
Çalışma, randomize kontrollü olarak rehabilitasyon polikliniğinde yapıldı. Adjuvan radyoterapi için sevk edilen histolojik olarak kanıtlanmış evre I - III meme kanseri hastaları, denetimli bir aerobik ve güçlendirme egzersiz programı veya egzersiz eğitimi olmaksızın standart tıbbi bakım olmak üzere iki gruba randomize edildi. Birincil sonuç parametreleri Rosenberg Benlik Saygısı Ölçeği (RSES), Kısa Form-36 (SF_36) Yaşam Kalitesi, Başa Çıkma Stratejileri Anketi (COPE Envanteri), Yorgunluk Şiddeti Ölçeği (FSS), Beck Depresyon Envanteri (BDI), Beck Anksiyete Envanteri (BAI) olarak belirlendi. Bu parametreler 6 haftalık egzersiz antrenmanından 1 hafta önce ve 1 hafta sonra değerlendirildi.

Bulgular
Tekrarlanan ölçüm analizinde egzersiz grubunda BAI ve FSS skorları azalmış, genel sağlık (GH) ve enerji/yorgunluk (E) skorları egzersiz grubunda artmış (p=0.045, Cohen d=0.757 BAI için, p= 0.02, Cohen d=0.863, p=0.010, Cohen d =1.02 GH için, p=0.032, Cohen d=0.801 E için) olarak bulundu. Kontrol grubunda probleme dayalı başa çıkma puanının ise azaldığı saptandı (p=0.049, Cohen d=0.641). BDI ve RSES puanlarında anlamlı fark bulunmadı (p>0.05).

Sonuç
Sonuç olarak, adjuvan radyoterapi sırasında denetimli egzersiz eğitiminin anksiyete, yorgunluk, enerji, genel sağlık algılarını iyileştirdiği ve etkili baş etme stratejilerinin kullanılmasında azalmayı önlediği görüldü.

Anahtar Kelimeler: Başa çıkma, Çalışma hızı, Denetimli egzersiz, Maksimal oksijen uptake, Meme radyoterapisi, Yorgunluk

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Abstract

Objective
Treatment side effects lead to a negative impact on the quality of life in breast cancer survivors. Exercise is reported to improve the physical and psychological status of these patients. We aimed to investigate the effect of exercise during radiotherapy on physical and psychological status in breast cancer patients.

Material and Method
A randomized controlled study was set in outpatient rehabilitation clinic. Histologically proven stage I-III breast cancer patients referred for adjuvant radiotherapy were randomly assigned to a supervised aerobic and strengthening exercise program or usual medical care without exercise training. The primary outcome parameters were Rosenberg Self Esteem Scale (RSES), Short Form-36 (SF_36) Quality of life, Coping Strategies Questionnaire (COPE Inventory), Fatigue Severity Scale (FSS), Beck Depression Inventory (BDI), Beck Anxiety Inventory (BAI). End points were assessed 1 week prior to and 1 week following 6 weeks of exercise training.

Results
In the repeated measured analysis, BAI and FSS scores decreased, general health (GH) and energy/ fatigue (E) scores of SF-36 increased in the exercise group (p=0.045, Cohen d=0.757 for BAI, p=0.02, Cohen d=0.863, p=0.010, Cohen d =1.02 for GH, p=0.032, Cohen d=0.801 for E), while the use of problem-based coping score decreased in the control group (p=0.049, Cohen d=0.641). No significant differences were found in scores for BDI and RSES (p>0.05).

Conclusion
In conclusion, supervised comined exercise training during adjuvant radiotherapy improved anxiety, fatigue, energy, general health perceptions and prevented decreasing in using effective coping strategies.

Keywords: Breast cancer radiotherapy, Fatigue, Coping, Maximal oxygen uptake, Supervised exercise, Work rate

Introduction

More than a million annual breast cancer diagnosis is recorded worldwide. It is also confirmed in World Health Organization's (WHO) recent reports (1). Whole treatment process, commonly initiated with mastectomy followed by adjuvant therapies, such as hormone therapy, chemotherapy and radiotherapy, cause many early and late side effects and consequential deterioration in quality of life (QoL) (2). While breast cancer (BC) survival rate increases, physical, social and psychological problems related to cancer and treatments also increase. Fatigue is the most common complaint among these consequential QoL issues (3).

Illness perception is another important concept in QoL which defines patients' feelings, emotions and cognitions, in terms of symptoms they have and their disease generally (4). And the consequential issues related to disease itself and treatment is associated with illness perception and sense of well-being in breast cancer patients. Social support is suggested to improve their sense of well-being (5). For the very reason, effect of exercise on physical and psychological status in women with breast cancer has been a frequent concern of investigation so far (6, 7)

Improving effect of exercise on QoL during adjuvant radiotherapy has been proven in a meta-analysis (8). Therefore WHO also recommended physical exercise (9) for breast cancer patients to support well-being. However, these patients frequently has decreased physical activity (10).

Exercise during adjuvant treatment for breast cancer is reported to be a supportive self care intervention that reduces fatigue, improves physical fitness, QoL and cognitive function (11). Additional improving effect on cardiorespiratory and general physical fitness in breast cancer patients and survivors is detected by Mc Neely et al (12). In terms of social and psycological well being, exercise intervention is also found beneficial with regard to anxiety, depression, and individual body image (13). However; evidence evaluating the alterations on anxiety, depression, high self-efficacy and QoL, with a combined supervised exercise program and the relationship between patients' demographic characteristics and psychological parameters is scarce.

In consideration of the above-mentioned studies, we assumed that, an exercise program would provide a detectable improvement in QoL, fatigue, physical fitness, self-esteem and coping strategies.

We aimed to test this foresight via evaluating the effects of a 6-week supervised individualized prescriptive aerobic and resistance exercise program on self-esteem, coping style, fatigue, quality of life, cardiovascular fitness, and psychological status applied during radiotherapy in breast cancer patients. We hypothesized that this 6 weeks of concomitant intervention significantly reduces anxiety, improves general health perceptions, and physical fitness, coping strategies and positively changes coping style with an objective increase in VO2 and work rate levels.

Material and Method

Study Design

This randomized controlled study was designed using Strobe Statement. The intervention group attended exercise-based rehabilitation (Exercise group), control group received usual medical care. All procedures in this study were approved by the Scientific Research Ethics Committee of Medical Faculty of University (protocol code, 2017/168) and were performed in terms of the ethical standards of the institutional research committee in alliance with the 1964 Helsinki declaration and its later amendments. All patients were informed about the procedures and signed a related printed informed consent. Subjects were also informed that the data was confidential and informed that they should feel free to leave the study at any time without any change in their treatment or usual medical care. End points were assessed 1 week prior to (baseline) and 1 week following 6 weeks exercise training (postintervention).

Participants

Twenty five breast carcinoma patients who were referred for adjuvany radiotherapy after chemotherapy between November 2017 and June 2018 in our university hospital were enrolled in this study. As they declined to complete the intervention, 5 patients were excluded from the group.

Inclusion criteria were: sedentary females between 26-60 years old histologically proven breast carcinoma of stage I – III. Patients who has a medical history of uncontrolled cardiac or hypertensive diseases, pulmonary disease, orthopedic disabilities limiting optimal exercise, peripheral vascular disease, uncontrolled systemic disease, major psychiatric disease were excluded.

Recruitment

Participants were recruited from the Department of Radiation Oncology. Recruitment is mainly through the doctors' recommendations. Patients interested in this trial were evaluated by physicians. Patients who meet the inclusion criteria and want to participate, were asked to sign the informed consent and then were included in the trial for randomization. The envelopes were kept by a study administrator who did not directly participate in the exercise program and outcome measures (EEO) and the group numbers were subsequently disclosed.

After completing the baseline questionnaires and maximal cardiopulmonary test (CPET), participants are randomized to exercise group and control group over a period of 6 weeks with a 1:1 ratio by SPSS 16.0 will be used for randomization. Randomization diagram after simple randomization we used is plotted as a CONSORT 2010 diagram in Figure 1.

All patients were referred to the physiatrist for the maximal cardiopulmonary test (CPET) (FS) to prescribe exercise intensity. Another impartial physiatrist (ZT), who was blinded about the group of patients, evaluated the outcome parameters of the test performed before and after the program.

Radiotherapy

External beam radiation (EBRT) was given with two tangential fields using field in field (FiF) technique, 5 days per week for 5 - 6 weeks. In case of breast conserving surgery, whole breast was given 50 Gy in 25 fractions with an additional 10 Gy boost in 5 fractions to surgical bed. After mastectomy (MRM), chest wall was treated to 50 Gy in 25 fractions. Axillary region and supraclaviculary fossa received 50 Gy in 25 fractions if any metastatic lymph nodes was detected pathologically regardless of primary surgery. Haemoglobin (Hb) values obtained before radiotherapy and at the end of 6th week of intervention were recorded.

Interventions

Exercise program

In order to obtain maximal heart for prescribing intensity of aerobic exercise individually, patients underwent maximal exercise testing (MET) with ramping bicycle protocol before exercise intervention. EG underwent a structured, individual, supervised exercise training program for a period of 6 weeks in outpatient cardiopulmonary rehabilitation unit. Exercise program was applied by a physiatrist (FS). CR program consisted of aerobic exercise on treadmill at 50% to 85% of maximal heart rate based on the results of a cardiopulmonary exercise test which is performed at baseline for 3 sessions per week plus usual care. The exercise program consisted of 5 min

warm up period followed by graded aerobic training and 5 min cool down period with a total duration of 40 minutes. Heart rate (HR) and blood pressure were monitored throughout the training. Any adjustment in the intensity of exercise was allowed in the following sessions according to patients' adaptation. Exercise intensity was monitored and work rate was automatically adjusted to maintain target HR. The supervised exercise program was terminated if there were signs of exercise intolerance, bradycardia, chest pain, fatigue rated 6 of 10 on the perceived exertion Borg (PEB) scale, a drop in systolic blood pressure > 15 mm Hg compared with baseline, an excessive rise in systolic blood pressure defined as > 200 mm Hg, a rise in diastolic blood pressure during exercise > 110 mm Hg or electrocardiographic signs of cardiac ischemia or ventricular arrhythmias. Patients were informed about PEB scale scoring before first training session individually.

Strengthening exercise sessions following aerobic exercises were comprised of machine-based resistance exercise including chest press, leg press and upper extremity pulley system (deltoid, biceps, and triceps). One repetition maxima (RM) was defined for each resistance exercise, and the intensities were adjusted as 60-80% of 1 RM. The resistance exercise program was prescribed one to three sets for 8-12 repetitions. Weight is adjusted in three consecutive sessions, and after completion of three sets of 12 repetitions it is increased by 5%.

Control patients are not aware of study participation and will receive usual care.

Outcomes

All participants completed a self-administered questionnaire that included demographic background and health history with the questions regarding age, gender, body mass index, marital status, education status, family support status, comorbidities such as hypertension (HT), diabetes mellitus (DM), hyperlipidemia (HL), cerebrovascular disorder (CVD), peripheral vascular disorders (PVD), cardiopulmonary problems, chronic renal insufficiency (CRI), and any surgical histories.

The primary outcome parameters were Rosenberg Self-Esteem Scale (RSES), Short Form-36 (SF-36) Quality of life, Coping Strategies Questionnaire (COPE Inventory), Fatique Severity Scale (FSS), Beck Depression Inventory (BDI), Beck Anxiety Inventory (BAI). The outcomes were assessed within 1 week prior to and 1 week following 6 weeks exercise training.

Rosenberg Self-Esteem Scale (RSES)

RSES was developed by Rosenberg (14). This scale consists of 10 items, with three choices on the Likert point scale (1 = completely agree; 2 = neither agree nor disagree; 3 = completely disagree). The first factor of the test comprises six items related to positive self-esteem; the second factor consists of four items that refer to negative self-esteem and lower total score denotes higher self-esteem. The validity and reliability studies of the RSES in Turkey were performed by Cuhadaroglu et al. (15) who reported test-retest reliability coefficients of 0.71 during a 4-week period.

COPE Inventory

It is a multidimensional coping scale consisting of 60 questions and 15 scales to assess the different ways in which people respond to stress (16). It allows to evaluate a problem-focused coping, emotion-focused coping and non-functional coping strategies, including positive reinterpretation and growth (COPE 1), mental disengagement (COPE 2), focus on and venting of emotions (COPE 3), use of instrumental social support (COPE 4), active coping (COPE 5), denial (COPE 6), religious coping (COPE 7), humor (COPE 8), behavioral disengagement (COPE 9), restraint (COPE 10), use of emotional social support (COPE 11), substance use (COPE 12), acceptance (COPE 13), suppression of competing activities (COPE 14), planning (COPE 15). COPE 4, COPE 5, COPE 10, COPE 14 and COPE 15 were categorized as problem-focused coping (effective coping strategy); COPE 1, COPE 7, COPE 8, COPE 11 and COPE 13 were categorized as emotion-focused coping; COPE 2, COPE 3, COPE 6, COPE 9 and COPE 12 were categorized as non-functional coping strategies.

Fatigue Severity Scale

Fatigue was assessed using FSS which is one of the self-assessment questionnaires developed to assess fatigue in breast cancer patients (17). It has 9 items allowing to investigate physical, affective and cognitive aspects of fatigue. Higher final scores indicate worse fatigue.

All the abovementioned tests were administered prior to and following training program.

Statistical Analysis

For sample size estimation, an a priori statistical power was conducted in G*Power software, version 3.1.9.4 (ANOVA: Repeated measures, within-between interaction). An estimated effect size of 0.5, a statistical power 1–β of 95% and an alpha of 5% (. The minimum sample size required for the study was

16 participants. Considering a dropout rate of 25%, we recruited a total of 20 participants (18).

The Statistical Package for the Social Sciences (SPSS), version 22.0 for Windows, was used for data analysis. To examine the differences between EG and CG in nominal variables, the chi-square test was used. For numerical variables, we used the independent sample t-test and Mann - Whitney U test according to showing normal distribution or not. For correlation analyses, we used Pearson correlation test. Differences within group and between groups in mean changes for outcome variables at baseline and post-intervention were analyzed using repeated measures ANOVA test and analyses of covariance (ANCOVA). Effect size with-in group (Cohen's d) was calculated by dividing the mean difference between baseline and 6th week by standard deviation of difference for both groups. Cohen's d =0.2 was considered as 'small' effect size, 0.5 represents a 'medium' effect size and 0.8 a 'large' effect size.

Results

Twenty of 25 patients completed study (Table 1). Five patients declined to participate before randomization. The flow chart of the study was demostrated in figure 1.

Table 1 Demographic data of participants

		EG n=10	CG n=10	P value
Age		42.10±9.06,	48.90±8.29	0.097
BMI (kg/m²)		27.83 ±2.45	30.55±5.22	0.160
Hb (g/dl) baseline		12.35±0.75	12.06±1.78	0.642
Education	Primary School	4	3	0,565
	High School	0	1	
	University	6	6	
Menopausal status	Primary	8	4	0.090
	Secondary	2	4	
	No	0	2	
Marital Status	Single	0	0	0,500
	Married	9	8	
	Divorced	1	2	
Primary Surgery	MRM	1	1	0.763
	BCS	9	9	
Axillary Intervention	AD	5	4	0.500
	SLND	5	6	
T Stage	T1	4	1	0.057
	T2	5	7	
	T3	0	2	
	T4	1	0	
N Stage	N0	6	6	0.818
	N1	2	2	
	N2	2	2	
	N3	0	1	

MRM, modified radical mastectomy, BCS, breast conservation surgery,
AD, axillary dissection, SLND sentinel lymph nodes dissection

Table 2 The mean ±standard deviation, analyses of the repeated measures between groups and within groups and effect size within groups

Parameter	Group	Mean±SD		p[1] value	Within-Group Effect size	p[2] value	h[2]
		Baseline	Postintervention				
BAI	EG	16.70±13.09	11.50 ±8.98	0.040	0.757	**0.009**	0.320
	CG	9.50±7.29	13.20±8.35	0.110	0.559		
BDI	EG	10.10±6.26	7.70±6.34	0.206	0.431	0.756	0.006
	CG	13.80±3.76	10.60±8.22	0.113	0.554		
RSES	EG	1.30±0,62	0.89±0,52	0.065	0.665	0.352	0.048
	CG	0.75±0.33	0.56±0.26	0.235	0.402		
FSS	EG	4.90±0.98	3.07±1.79	**0.023**	0.863	**0.045**	0.205
	CG	4.63±1.86	4.76±1.43	0.832	0.069		
COPE							
COPE 4	EG	12.40±3.06	12.40±3.02	1.00	0.000	0.255	0.071
	CG	13.50±3.17	12.00±3.36	0.129	0.528		
COPE 5	EG	13.00±2.10	13.50±1.58	0.475	0.235	0.177	0.099
	CG	14.50±1.71	13.60±2.59	0.253	0.386		
COPE 10	EG	10.00±1.94	9.40±2.41	0.483	0.231	0.372	0.045
	CG	10.90±1.37	9.40±2.06	**0.022**	0.877		
COPE 14	EG	11.10±3.03	10.40±1.71	0.650	0.229	0.458	0.031
	CG	11.70±2.31	10.10±3.14	**0.045**	0.737		
COPE 15	EG	13.40±2.11	13.80±1.22	0.494	0.225	**0.049**	0.198
	CG	13.90±1.96	12.60±3.02	**0.044**	0.711		
Problem-focused coping strategies	EG	59.90±9.45	59.40±5.08	0.878	0.057	0.212	0.085
	CG	63.20±4.41	57.70±11.03	**0.049**	0.641		
COPE 1	EG	14.50±2.36	14.60±1.17	0.879	0.049	0.198	0.090
	CG	15.00±1.41	13.30±4.24	0.185	0.454		
COPE 7	EG	15.20±1.22	16.10±3.34	0.356	0.307	0.180	0.098
	CG	15.00±0.96	14.60±3.16	0.343	0.316		
COPE 8	EG	9.20±3.35	9.00±2.44	0.849	0.062	1.000	0.000
	CG	8.30±2.26	8.10±2.18	0.693	0.129		
COPE 11	EG	12.40±3.53	11.70±3.30	0.398	0.282	0.943	0.000
	CG	12.60±2.67	11.80±3.01	0.494	0.225		
COPE 13	EG	9.60±3.06	10.40±2.83	0.494	0.225	0.224	0.081
	CG	10.80±2.44	9.60±3.43	0.312	0.337		
Emotion-focused coping strategies	EG	61.20±8.67	61.20±7.03	0.674	0.137	0.179	0.098
	CG	62.50±5.89	57.60±12.65	0.260	0.430		

Table 2 The mean ±standard deviation, analyses of the repeated measures between groups and within groups and effect size within groups

Parameter	Group	Mean±SD		p[1] value	Within-Group Effect size	p[2] value	h[2]
		Baseline	Postintervention				
COPE 2	EG	9.40±2.98	9.80± 2.39	0.749	0.104	0.332	0.052
	CG	10.10±2.30	9.20±3.39	0.095	0.592		
COPE 3	EG	12.60±2.88	11.90± 2.68	0.132	0.526	0.476	0.029
	CG	11.60±2.67	10.10±4.17	0.173	0.468		
COPE 6	EG	8.10±3.44	6.50±3.20	0.288	0.357	0.238	0.076
	CG	7.60±3.13	7.90±3.34	0.656	0.145		
COPE 9	EG	7.50±2.63	5.20±1.98	**0.030**	0.812	0.030	0.238
	CG	6.30±2.00	6.40±2.27	0.840	0.065		
COPE 12	EG	4.10±0.31	4.00 ±0.00	0.343	0.062	0.222	0.082
	CG	4.00±0.00	4.30±0.94	0.317	-0.316		
Non-functional coping strategies	EG	41.60±10.37	38.40±8.11	0.377	0.294	0.820	0.003
	CG	40.20±6.57	37.90±8.74	0.245	0.393		
SF-36							
Physical Functioning (PF)	EG	62.50±26.48	79.50 ±16.90	0.082	-0.618	0.434	0.034
	CG	46.00±30.53	52.50±0.28	0.525	-0.209		
Role Limitations due to Physical Health (RP)	EG	42.50±45.72	52.50 ±39.87	0.583	-0.180	0.494	0.026
	CG	37.50±32.95	30.00±0.40	0.685	0.132		
Role Limitations due to Emotional Problems (RE)	EG	46.66±47.66	63.33 ±36.69	0.212	-0.424	0.032	0.231
	CG	76.67±41.72	49.99±45.13	0.087	0.607		
Energy/Fatigue (E)	EG	56.50±15.64	72.00 ±18.28	**0.032**	-0.801	0.221	0.082
	CG	44.00±20.52	49.50±17.70	0.297	-0.350		
Emotional Well-Being (EW)	EG	58.00±21.84	65.20 ±19.69	0.244	-0.394	0.277	0.065
	CG	72.80±20.29	72.40±16.91	0.913	0.035		
Social Functioning (SF)	EG	62.70±22.97	71.25 ±19.58	0.434	-0.258	0.566	0.319
	CG	56.25±31.86	65.00±23.42	0.177	-0.382		
Pain (P)	EG	64.00±26.19	71.25 ±25.14	0.369	-0.298	0.375	0.044
	CG	68.75±27.72	67.50±23.12	0.820	0.074		
General Health (GH)	EG	55.00±24.49	69.50 ±24.20	**0.010**	**-1.02**	0.004	0.377
	CG	61.50±15.46	59.00±11.49	0.343	0.316		
Health Change (HC)	EG	25.00±23.57	35.00±26.87	0.157	0.474	0.118	0.130
	CG	40.00±29.34	35.0±024.15	0.414	0.253		

BAI: Beck Anxiety Inventory, BDI:Beck Depression Inventory, RSES: Rosenberg Self Esteem Scale, FSS: Fatigue Severity Scale COPE: Coping Strategies Questionnaire

P[1] value for repeated measures ANOVA test comparing changes in EG from baseline to post-intervention and in Cg from baseline to post-intervention P[2] value for repeated measures ANOVA test comparing changes between the exercise and control group from baseline to post-interv

The mean ages of EG and CG were 42.10 ±9.06 and 48.90±8.29 years respectively (p=0.097). None of the patients received anthracycline chemotherapy during the exercise program. The mean BMI was 27.83±2.45 in EG and 30.55±5.22 in CG (p=0.160). There was no statistically significant difference between groups regarding education level, marital and menopausal status. All patients were living with their family having family support. None of the patients needed special care.

The mean±standard deviation (SD) values of the baseline and post-intervention RSES, BDI, BAI, FSS scores are shown in table 2. A repeated evaluation of ANOVA with a Greenhouse-Geisser correction revealed statistically significant difference in mean BAI scores between time points (F=8.454, p=0.009). In the EG, BAI score decreased significantly after intervention (p<0.05) where the different was not statistically significant (p>0.05) in the control patients. RSES scores were not significantly different in group x time interactions (F=4.410, p=0.352). There was a significant correlation between baseline BAI and RSES (r=0.592, p=0.006). In covariance analysis, no significant interaction was found over RSES change related with intervention and baseline BAI (p=0.691, η2=0.010).

FSS score decreased from 4.90 to 3.07 in the EG after intervention, however no statistically significant change was recorded in the control group. In the analyses of variances for repeated measures, FSS scores differed significantly between time points (F=9.624 p=0.045). The effect size of exercise on FSS was larger in EG (Cohen d=0.863). As confounding variables, age and baseline Hb were analyzed and no statistically significant interactions was found (p=0.757 for Hb, p=0.497 for age).

Problem-based coping strategies were found to impaired in the CG, especially in terms of COPE 10, COPE 14 and COPE 15. Figure 2 demonstrated the changes between time points in problem-focused coping strategies (effective-active coping). On the other hand, emotional-focused coping strategies were not statistically significant. Patients in the EG had a significant decline in COPE 9 score. A repeated measures ANOVA with a Greenhouse-Geisser correction determined that all above mentioned COPE subscales scores revealed a statistically significant difference between time points in the CG group. The results of repeated measures ANOVA test for COPE subscales with comparison in exercise and control groups from baseline to post-intervention were demonstrated in table 2. While the supervised EG showed large effect size within group on COPE 9 (Cohen d=0.812), the CG showed large effect size on COPE 10 (Cohen d=0.877), medium effect size on COPE 14 (Cohen d=0.737) and COPE 15 (Cohen d=0.711). We found statistically significant interaction between changes in COPE 15, 10, 14 and changes in BAI (F=10.765, p=0.004 for COPE 10, F=7,888, p=0.012 for COPE 14 and F=10.756 p=0.004 for COPE 15).

However, the repeated measures analysis of variance with E (F=1.609, p=0.221) as the dependent variable did not show any significant group x time interaction, large effect size was observed within exercise group (Cohen d=0.801). GH subscores revealed statistically

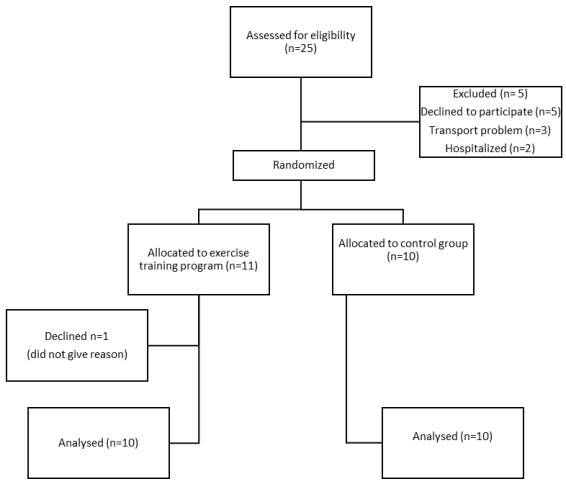

Figure 1
CONSORT diagram of the study

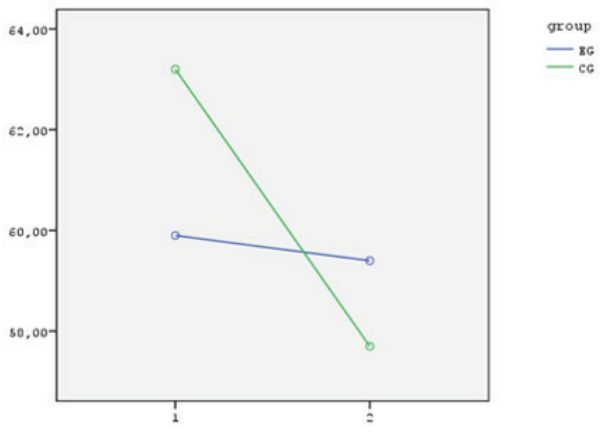

Figure 2
The changes between time points in problem-focused coping strategies

significant group x time interactions and large effect size in EG (Cohen d=1.02). Energy/Fatigue and general health subscales were also significantly improved with exercise intervention (p=0.032 and p=0.01 respectively). The mean +SD values of the SF 36 subscales and analysis of the groups were demonstrated in table 2.

Discussion

In our study, we found that 6 weeks supervised moderate-intensity, individually adjusted aerobic and resistance exercise program during radiotherapy reduces anxiety, fatigue, increases energy, general health perceptions, and physical fitness levels. While patients were supported with exercise program, they reduce to use behavioral disengagement. Over time, patients who did not participate in exercise training reduced to use of effective coping strategies such as restraint, suppression of competing activities and planning.

Fatigue, which can be attributed to physical deconditioning, with a consequent decrease in QOL (19), is reported as one of the most common and often long lasting complaint among breast cancer survivors (20). Therefore, these results showing the improving effect are important. Approximately 77% of patients suffers from fatigue during treatment (21). Previously, it was thought that fatigue was increased by activity so patients were recommended to stay inactive (22). Physical activity became a promising strategy for prevention and treatment of fatigue in the consequence of increasing evidence reporting the effectiveness of exercise (6,7,23). Contrarily, a Cochrane review (2) investigating the effects of exercise in women receiving adjuvant therapy for breast cancer concluded that exercise did not significantly improve fatigue but this manuscript is criticized in terms of studies analyzed within.

Our study will provide a contribution to current literature regarding the points such as supervised application of the exercise during radiotherapy, type of intervention, individualization of prescription, and combining aerobic-resistance type of exercises. There are plenty of articles reported about the effects of exercise on fatigue during radiotherapy to date (24-32). Most of these articles investigated the effect of aerobic exercise. The effect of supervised, combined aerobic-resistance exercise was evaluated in four of these trials (25-27,29). Positive effect of 4-week home-based exercise on fatigue was reported by one of them (25), while other three studies reported the positive effect of supervised exercise (26-29). Recently Lipsett et al. (8) reviewed the effect of exercise on fatigue during radiotherapy and concluded that supervised exercise was more effective than home based exercise. And the authors suggested combined aerobic-resistance exercise as a promising therapy for regulation of fatigue during radiotherapy. In our study accordingly; we found that combined aerobic-resistance improved energy/fatigue ratio. Considering that anemia is a strong determinant of fatigue (22), we also evaluated the effect of hemoglobin values on change in fatigue, but no statistically specific interaction was found. This result can be attributed to normal (> 12 g/dl) Hb levels in our whole study sample.

Depression is an undesirable outcome in breast cancer survivors both during and after treatment, with prevalence ranging between 1.5 - 46% and antidepressant and anxiolytic effects of aerobic exercise in this patient population is reported (32,33). According to the results of subanalysis in the very studies, moderate aerobic exercise interventions with an optimal duration of ≥135min for up to 12 weeks were significantly more beneficial than resistance training, aerobic training and yoga training. Similarly, we performed a 6 week training program with ≥135min duration. A Cochrane review reported by Furmaniak et al (11) concluded that exercise had little or no effect on depression. On the contrary, in our study, exercise showed a moderate improving effect on depression, however; we were unable to prove a significant superiority of exercise to usual care.

Self-esteem is defined as feeling of selfrespect and worth, but not superiority to others. It also includes expecting personal improvement (34). Self-esteem may also decline in breast cancer patients due to fatigue, physical changes resulted from mastectomy, radiotherapy and/or chemotherapy side effects such as scarring, hair loss and obesity. Results of studies about the effect of physical activity on self-esteem are contradictory and the underlying mechanism is not fully known while the evidence in this respect is scarce. Musanti et al (35) studied the effects of exercise modalities on physical and global self-esteem in breast cancer survivors. While either aerobic or resistance exercise program had a positive effect on the sub-scores of physical self-esteem on an individual basis, both physical and global self-esteem efficacy were not shown in the combined aerobic and resistance exercise program. Another study also reported improvement in self-esteem but no benefit in cancer-specific QOL in breast cancer patients with aerobic or resistance exercise (36). A systematic quantitative review reported by Speck et al (37) suggested that physical activity shows significant improvement in

weighted mean effect size during treatment on self-esteem (0.25, p=0.02). On the contrary, Segar et al (38) were not able to report any inluence of mild to moderate aerobic exercise on self-esteem in breast cancer survivors. In accordance with this, a recent Cochrane review, concluded that physical exercise during adjuvant treatment for breast cancer had no improvement on self-esteem (11). Similarly, in our study, we also found that exercise did not have a positive effect on self-esteem which can be attributed to higher baseline levels of self-esteem in EG.

SF-36 is another widely utilized test for quality of life. Gierset et al compared the level of general health related quality of life (HRQOL) after one week exercise programme in cancer survivors. They could not report any statistically significant difference in any of the 8 SF-36 scales (39). In another study evaluating the effect of lymphedema on HRQOL in breast cancer survivors. The authors reported that SF-36 scores of women with lymphedema was significantly lower except the mental summary scale, mental health subscale, and role limitations emotional subscale. Which is statistically significant for all scales after age adjustment (40). In the results of ALPHA trial, participants of the exercise group reported much better or somewhat better than a year ago which was significantly higher compared to the reports of control group (41). In our study we found significant improvement in role limitations due to emotional problems (p: 0.032) and general health (0,01) subscales of SF-36.

Breast cancer survivors are exposed to stress during the disease process and tries to cope both behaviorally and cognitively (42). Coping is most commonly divided into active (or problem-oriented), passive (or emotion-oriented) and ineffective strategies. Lan et al (43) suggested that improving illness perceptions may lead to more positive coping styles and better functional exercise adherence. We hypothesized that exercise has positive effect on coping style in breast cancer survivor based on the information that exercise increases the illness perception, improve the psychological status. We have obtained results confirming our hypothesis. And to our knowledge, this is the first study to evaluate the effects of exercise on coping strategies in breast cancer patients. Exercise program increased the use of problem-based active coping strategies. On the contrary, it increased the use of ineffective strategy and reduced the use of emotional based strategies in patients who did did not have exercise intervention. In previous studies examining the relationship between anxiety and coping attitudes it was determined that individuals with anxiety symptoms or disorders are not able to use coping attitudes effectively (44). Therefore, it is assumed that there is a relationship between dysfunctional coping attitudes and certain anxiety symptoms (44). Confirming this, in our study, we observed that improving anxiety level with exercise contributes to the effect on coping strategies. Non-functional coping strategies such as behavioral disengagement was reduced in patients who underwent exercise intervention. In control group, problem focused coping strategies such as restraint, suppression of competing activities and planning decreased over time.

Study Limitations

For sure the most distinct limitation of our study is small sample size. This is due to slow accrual of patients while a long exercise program should be accepted. Another challenge is the evaluation of psychological tests such as coping, self esteem due to patient generated subjective nature of these scales. However we tried to mitigate this effect with complicated statistical analysis.

Conclusion

In conclusion, supervised aerobic and resistance exercise has positive effects on coping style, anxiety, fatigue, energy, general health perceptions, and physical fitness levels during radiotherapy. Therefore we suggest a physician consult for exercise to alleviate both radiotherapy induced and disease related side effects although our results needs confirmation with studies on larger sample size.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Ethical Approval

Scientific Research Ethics Committee of Medical Faculty of University was approved the study (protocol code, 2017/168) and study was conducted in line with the principles of the "Helsinki Declaration".

Consent to Participate and Publish

All patients were informed about the procedures and signed a related printed informed consent to participate the study and publish the data. Subjects were also informed that the data was confidential and informed that they should feel free to leave the study at any time without any change in their treatment or usual medical care.

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Availability of Data and Materials
Data are available on request due to privacy or other restrictions.

Authors Contributions
EEO: Conceptualization, Investigation, Methodology, Project administration, Supervision, Writing
FS: Formal analysis, Methodology, Resources
ZT: Investigation, Resources, Validation

Editorial
Although EEO, one of the authors of the article, is editorial board member of the journal, she has not taken part in any stage of the publication processes of this article.

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