The Effect of Aerobic Exercise Training on Cancer Markers and Quality of Life Women with Breast Cancer Patients: A Randomized Controlled Trial

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Abstract

Background

Exercise interventions in order to improve disease-related symptoms and improve quality of life in cancer patients are an approach that has received a lot of attention in recent years. The aim of our study is to investigate the effect of aerobic exercise on cancer recovery and to determine the change of cancer markers before and after treatment.

Methods

70 women between 18–65 years were included in this study during chemotherapy. They were part of two groups; aerobic exercise (Group I) and control (Group II) groups. Their demographic features, quality of life and some cancer markers were evaluated. Assessments were done pre-chemotherapy and post-chemotherapy. In aerobic exercise group third a week aerobic exercises on submaximal level applied. A 12-week exercise program was planned, conducted under the supervision of a physiotherapist.

Results

As a result of this study, the quality of life in the aerobic exercise group was significantly higher in breast cancer patients receiving chemotherapy treatment (p < 0.05). The three most commonly used cancer markers were measured in the blood of women with breast cancer pre and post treatment. In the pre-treatment period, the mean serum levels of CEA, CEA 15 – 3, and CEA 19 – 9 were similar in Group I and Group II (p > 0.05). In terms of post-treatment evaluation results, the women in Group I had a greater decrease in CEA, CEA 15 – 3, and CEA 19.9 values than the women in Group II (p < 0.05).

Conclusion

Aerobic exercise has a positive effect on physical function, role function, cognitive state and emotional state, which are subtitles of quality of life. It has been determined that the decrease of cancer markers in blood serum is greater with aerobic exercise.

1. Introduction

Breast cancer is the most frequently diagnosed cancer in women and ranks second among cancer-related death causes in women [1]. Due to its rising prevalence and insufficient treatment outcomes, breast cancer remains a significant medical, social, and economic issue.

Surgery, chemotherapy, radiation, and hormone therapy are also used to treat breast cancer, both alone or in combination. Cancer treatment has a number of harmful adverse effects that lower the patient's quality
of life [2]. Adverse effects such as lymphedema [3], peripheral neuropathy [4], sedentary lifestyle [5], decreased aerobic fitness and muscle strength, fatigue [6], weight gain and changes in body structure, decrease in bone mineral density [7], inmatuar high inflammatory profile [8], immunosuppression [9], changes in body image perception[10], anxiety and depression [11] have all been reported in the literature. In cancer patients, immobility is a leading cause of disease progression [12]. These side effects that develop depending on the treatment cause a decrease in the quality of life of the patients. Regular exercise applied to breast cancer patients becomes a part of the treatment because of its positive effects on minimizing the side effects of treatment and increasing the quality of life of survivors [13].

Cancer markers; These are serum hormone levels obtained from laboratory results that tend to increase specific to the type of cancer and guide the determination of the presence and size of the tumor. We can also call cancer markers cancer blood tests. Cancer markers are substances produced by cancer cells or produced in response to cancer. Sometimes they increase in benign diseases. In fact, most cancer markers are also produced in small amounts in healthy cells. However, cancer-specific production is much higher, so they are used in diagnosis and follow-up of cancer. Normal value of these determinants; It is 0.2–1000µg / L for CEA, 1.00-300 kU / L for CEA 15 – 3 and 0.600–1000 kU / L for CEA 19 – 9 [14]. Comparison of pre-treatment and post-treatment values provides information about the effectiveness of the treatment [15].

Contributions of aerobic exercise to fatigue, functional capacity, cognitive status, depression and protection of the musculoskeletal system in breast cancer are known [16]. However, studies that examine the relationship between cancer markers and oncological rehabilitation and in which an individual exercise training is given in detail are not included in the literature. Based on this, we aimed to:

1. Investigate the effects of individual exercise training on cancer markers,
2. Assess the effect of aerobic exercise on quality of life in breast cancer patients in this study.

2. Materials And Methods

2.1. Study Design. This study included 90 people who had been diagnosed with stage II breast cancer and were analyzed using a simple randomized procedure, the lottery method. Twenty women opted out of treatment early due to metastasis and treatment-related adverse effects. Aerobic exercise and walking individuals (Group I, n = 40) and control group individuals (Group II, n = 30) were divided into two groups. The flow chart of participants was shown on the Figure I.

2.2. Ethical Approval. Ethical permission was obtained from Non-Interventional Clinical Research Ethics Committee (17.12.2019 and 2019 – 121). The study was carried out by Declaration of Helsinki. Individuals were informed about the study and informed consent was signed. Written and oral information were given to all patients before evaluation.

2.3. Participants. The study involved 70 volunteer women between the ages of 18 and 65 who were admitted to the Gaziantep University Oncology Training and Research Hospital outpatient clinics with
Stage II breast cancer and were permitted to exercise by the cardiology service. 

The criteria included in the study; (1) to be in the age range of 18–65, (2) breast cancer stage II diagnosis, (3) to have a chemotherapy protocol determined. Patients who underwent having cancer-related breast surgery, continuing complications as a result of a previous orthopedic problem, having a diagnosis of depression for the last 6 months, having been diagnosed with cancer before, having a physical disability, chronic disease or metastasis accompanying the cancer history, having lymphedema, being pregnant or getting a substantial risk of being pregnant excluded from the study.

2.4. Evaluation Methods. To assess the efficacy of the recovery program for women in groups I and II, the evaluations were replicated two times. Evaluations were applied to both groups in the same way by the same physiotherapist. Following the diagnosis of breast cancer, two evaluations were made, one week before starting chemotherapy and at the end of chemotherapy and exercise training.

Demographic features, quality of life were evaluated in participants.

The participants' quality of life was assessed using the European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC QOL-C30). General functions (physical, role, cognitive, emotional, and social), symptoms (fatigue, pain, nausea, and vomiting), and worldwide life assessments, as well as six cases, are included on the scale (dyspnea, sleep disorder, loss of appetite, constipation, diarrhea, and financial problems). It consists of 30 questions in total.

During the period of chemotherapy treatment of the individuals, routine blood values and general conditions were recorded once every three weeks and one day before the treatment. In this regard, blood values such as hemoglobin level, platelet count and serum levels of CEA, CEA 15 – 3, CEA 19 – 9 cancer markers were recorded. Blood was also not taken for the cancer marker data used in this study.

2.5. Treatment Protocol. The treatment was based on a hospital protocol that included four cycles of cure in three weeks, with medications and dosages planned individually. During chemotherapy, both patients were given 30–40 minutes of exercise at 50–60% of their maximum heart rate.

In Group I, aerobics treatments were applied twice a week and submaximal walking was done once a week. 12-week exercise program was devised. On a 12-week-designed form, the participants were asked to mark their exercise and chemotherapy days, which were checked weekly. In Group II; Only cancer markers were recorded in the control group.

Rehabilitation Program

Group I: Aerobic Exercise Group

Warming up and breathing exercises were performed in the first 5-minutes of the exercise. There were 14 different aerobic exercises to choose from. These exercises include the following: Supine position (reciprocal hip flexion, straight leg raise, bridging exercise), side-lying position (hip abduction), prone
position (trunk extension), sitting (bilateral shoulder elevation, bilateral shoulder circumduction, scapular adduction), upright position (shoulder flexion, shoulder abduction, hip and knee flexion to 90°, half squat). A 5-minutes period of strengthening and relaxation was added at the end of each exercise. Exercises training program was done first 4 weeks 10–15 times, 5–8. weeks 15–20 times, 9–12. weeks were 20–30 times. Exercises were allowed according to the patient's tolerance. Evaluation and treatment were performed by the same physiotherapist.

2.6. Statistical Analysis. The sample size required for our study was determined by the G * Power (G * Power Ver. 3.0.10, Franz Faul, Universität Kiel, Germany) package program. In the power analysis, the number of individuals for each group was determined as 21 with $\alpha = 0.05$ and $\beta = 0.20$. It was planned to reach 70 women by increasing the number of individuals by 10%.

The data obtained as a result of the evaluations were analyzed using the SPSS 21.0 program. The compliance of the variables to normal distribution was examined by visual (histogram and probability graphs) and analytical methods (Shapiro-Wilks test). Measurable data were given as arithmetic mean ± standard deviation, frequency distributions were expressed as n (%). The results of the variables are presented as arithmetic mean standard deviation (X ± SD). All numerical evaluation results of the two groups were compared using the Mann Whitney U test. Chi-Square Test was used for comparing categorical data between groups. The level of significance was set at $p < 0.05$.

3. Results

As a result of our study, the results of the relationship between cancer markers serum levels and exercise and the effects of aerobic exercise on the quality of life of individuals who received chemotherapy were investigated. The findings obtained from Group I aerobic exercise group ($n = 40$) and Group II control group ($n = 30$) are given below.

The age range of the participants was 18–65 and the mean age was $49.53 \pm 9.12$. The age, BMI, affected extremity of women in Group I and Group II are given in Table I. The groups were similar in terms of descriptive data ($p > 0.05$).

Table I. Demographic Profile of Participants
### Table II. Comparison of quality of life between groups

|                        | Group I (n=40) | Group II (n=30) | z    | p*  |
|------------------------|----------------|-----------------|------|-----|
| **Age (year)**         | 49.35 ±10.17   | 49.78±8.83      | 0.308| 0.75|
| **Body Mass Index (kg/m²)** | 28.49 ±3.39   | 27.23±4.87      | -0.505| 0.13|
| **Affected Extremity** |                |                 |      |     |
| Right                  | 14 (60%)       | 15 (66%)        | 0.760|     |
| Left                   | 9 ( % 40)      | 8 ( % 34)       |      |     |

p* =0.05; Mann Whitney U Test, p**=Chi-square test

### Examination of Quality of Life

General well-being, physical function, role function, cognitive status, emotional and social status subtitles were evaluated and similar values were found in both groups in the pre-treatment period (p > 0.05). The improvement in physical function, role function, cognitive status and emotional status of the groups after treatment was higher in women in Group I (p < 0.05). It was observed that general well-being and social status results increased similarly in all women (p > 0.05).

In the comparison of the quality of life results of the individuals before and after the treatment, it was seen that the results of all subtitles in both groups increased significantly after the treatment.
Group I (n=45)  

| Function              | X ±SD       | X±SD       | Z       | P       |
|-----------------------|-------------|------------|---------|---------|
| Pre-treatment         |             |            |         |         |
| General Function      | 62.31±15.25 | 63.76±19.39| -0.391  | 0.696   |
| Physical Function     | 63.75±15.43 | 62.83±12.38| -1.159  | 0.124   |
| Role Function         | 74.52±11.92 | 76.10±13.12| -1.676  | 0.094   |
| Cognitive Function    | 63.36±16.41 | 62.34±15.16| -1.378  | 0.168   |
| Emotional Status      | 58.32±12.37 | 59.23±13.21| -0.890  | 0.373   |
| Social Status         | 63.15±25.20 | 61.32±10.98| -0.766  | 0.502   |
| Post-treatment        |             |            |         |         |
| General Function      | 66.46±15.41 | 63.74±14.23| -1.676  | 0.094   |
| Physical Function     | 65.24±16.02 | 60.86±16.31| -3.159  | 0.001   |
| Role Function         | 75.89±15.23 | 71.34±13.24| -2.961  | 0.003   |
| Cognitive Function    | 66.33±16.42 | 59.25±15.14| -3.002  | 0.001   |
| Emotional Status      | 63.22±16.21 | 60.32±12.21| -1.901  | 0.057   |
| Social Status         | 66.67±18.34 | 65.22±14.65| -1.956  | 0.045   |

* p=0.05; Mann Whitney U Test.

**Cancer Markers Laboratory Results**

Serum levels of the 3 most commonly used cancer markers in women with breast cancer were examined pre and post treatment. Mean serum levels of CEA, CEA 15 – 3 and CEA 19 – 9 were similar in Group I and Group II in the pre-treatment period (p > 0.05). In terms of post-treatment evaluation results, the decrease in CEA, CEA 15 – 3 and CEA 19.9 values of the women in Group I was more evident than the women in Group II (p < 0.05).

CEA value post treatment decreased 49.33% in group I and 26.94% in group II in blood serum. CEA 15 – 3 value post treatment decreased 55.14% in group I and 36.73% in group II in blood serum. CEA 19 – 9 value post treatment decreased 50.78% in group I and 33.39% in group II in blood serum.

**Table III.** Difference of cancer markers
|                | Group-I |                  | Group-II |                  |   |   |
|----------------|---------|------------------|----------|------------------|---|---|
|                | pre-treatment | post-treatment | d       | pre-treatment | post-treatment | d  | Z  |
| CEA (ng/mL)   | 5.25±2.65 | 2.66±1.53 | 2.59    | 4.90±2.49 | 3.58±1.76 | 1.32 | -3.040  |
| CA 15-3 (U/mL)| 33.97±15.45 | 15.24±7.44 | 18.73   | 32.56±17.88 | 20.60±15.50 | 11.96 | -4.198  |
| CA 19-9 (U/mL)| 36.11±14.12 | 17.77±9.30 | 18.34   | 35.70±15.70 | 23.78±16.93 | 11.92 | -4.198  |

4. Discussion

The purpose of this study was to see how aerobic exercise affected the quality of life and cancer markers of women with breast cancer. The participants in this study were given aerobic exercises to do for 12 weeks while undergoing chemotherapy.

The literature has shown that disease and treatment processes have negative effects on the quality of life of women with breast cancer [17].

It was observed that there was no significant difference in the quality of life before treatment in group-I and group-II individuals. On the other hand, improvement of physical function, role function, cognitive function and social status, which is the subtitle of quality of life, was observed in group-I patients who received 12-week aerobic exercise therapy after treatment.

The effects of exercise on quality of life in breast cancer patients receiving chemotherapy were predicted to be associated with depression at the beginning of treatment [18].

In a systematic review by Zhang et al. in which they examined the effect of exercise on quality of life in patients with breast cancer, twenty-two of 25 studies reported that aerobic exercise had a significant effect on quality of life in breast cancer patients compared to the control group [19].

In accordance with the literature, according to the results of our study, it was observed that the quality of life of individuals who participated in the regular aerobic exercise program during the chemotherapy process was higher.

In a study by Porika et al. on cancer markers CEA15.3 and CEA values had sensitivities and specificities of 35.3 % and 18.3 %, respectively, and 95.6 % and 62.7 %. Cancer markers need to be measured at all stages of breast cancer, including metastasis prediction, treatment, diagnosis, and screening [20]. In the early levels, of breast cancer 10% of patients have high blood levels, and in the advanced levels of breast cancer about 70% of patients have high blood levels. Following successful management, CA 15 – 3 levels usually decrease [21]. In individuals assumed to have localized disease, high levels of CA 15.3 (e.g. 150 U/ml) and/or CEA (e.g. 120 ng/ml) signal the possibility of undetected metastatic disease [22].
It is known that cancer markers show significant changes depending on the chemotherapy treatment process. However, no study explaining the relationship between cancer markers and exercise was found in the literature. In our study, in which the effects of the aerobic exercise training were done by physiotherapist during chemotherapy on cancer markers were also examined, a decrease was found in the serum values of the CEA, CEA 15 – 3 and CEA 19 – 9. In this respect, we believe that our study will make an innovation and contribution to the literature.

The reason why the cancer marker values between the groups were significantly different after treatment compared to the pre-treatment values, also comes to mind that there may be psychosocial effects. Considering the positive effects of exercise on motivation and general health, detailed studies are needed to better understand the effect of cancer marker values between groups on the difference between pre-treatment and post-treatment values.

Contributing to the improvement of cancer markers with aerobic exercise in line with the results of our study within the scope of oncological rehabilitation is gratifying for physiotherapists. We hope that our study will guide health professionals working in the field of oncological rehabilitation.

Current management for breast cancer includes targeted therapies, hormonal therapy, radiation therapy, and surgery. We hope that in the future, exercise will be included in the treatment as a supplement to these current treatment strategies.

There were some limitations to this study. Our study's limitations include an insufficient multidisciplinary study in oncological rehabilitation, the lack of an oncological rehabilitation unit in the hospital where we conducted our research, and the lack of a study examining the effect of exercise on cancer markers.

5. Declarations

Funding: The authors did not receive support from any organization for the submitted work.

Conflicts of interest/Competing interests: The authors declare that they have no conflict of interest

Availability of data and material: Available.

Code availability: N/A

Authors’ contributions: All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by DK, NF, RCY, TD, YY. The first draft of the manuscript was written by DK, NF, RCY, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Ethics approval: Ethical permission was obtained from Non-Interventional Clinical Research Ethics Committee (17.12.2019 and 2019-121). The study was carried out by Declaration of Helsinki.
Consent to participate: Informed consent was obtained from all individual participants between the age 18-65 years old included in the study

Consent for publication: N/A

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Figure 1

CONSORT diagram. Patient flow
Figure 2

Difference of cancer markers with diagram