Impact of aerobic training combined with diet protocol on the immune system in breast cancer patients receiving adjuvant chemotherapy

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Abstract

Background: Chemotherapy drugs treat cancer by destroying the body's rapidly proliferating cells; as a result, they do not only affect the cancer cells but also have a variety of negative side effects on non-target tissues, including marked effects on the immune system that make it difficult for the body to fight infection. **Objectives:** The major cause of the current academic work is to investigate the possible outcomes of aerobic training combined with diet protocol on the immune system in breast cancer cases receiving adjuvant chemotherapy. **Design:** An open-label randomized control study. **Setting:** Outpatient setting. **Participants:** 60 female breast cancer cases were randomly sub-categorized into three groups and given adjuvant chemotherapy. Group (A) performed aerobic exercise and adhered to a special diet protocol; Group (B) only followed the diet plan; and Group (C) only performed aerobic exercise. **Intervention:** The duration of each treatment intervention was 12 weeks, with each group receiving two sessions each week. **Outcome measures:** Before and after the 12-week intervention, total lymphocyte count (TLC), neutrophil to lymphocyte ratio (NLR), and platelet to lymphocyte ratio (PLR) measurements were made. **Results:** After 12 weeks of intervention, the percentage of change in TLC, NLR, and PLT in the aerobic training and diet protocol group was 34.74%, 40.79%, and 30.69%, respectively. In the diet protocol group, it was

5.59%, 6.64%, and 5.22%, and in the aerobic training group, it was 28.16%, 22.54%, and 18.17%. A marked variation in all immunological indicators was found between the groups, favoring the aerobic training and nutrition plan ($p < 0.001$). **Conclusion:** Both aerobic exercise and a diet plan may be beneficial therapeutic strategies for boosting the immune system, but a combination of aerobic exercise and a diet plan has been demonstrated to be more effective at boosting immunological markers than either aerobic exercise alone or diet alone.

Keywords: Aerobic training, diet protocol, immune system, adjuvant chemotherapy, and breast cancer.

Introduction

After lung cancer, breast cancer is thought to affect more women globally than any other type of cancer; every year, 30% of new female cases are diagnosed with breast cancer. Every year, 190 out of every 100,000 women die [Wang et al., 2022].

Typically, endocrine therapy, biologics, radiation, and/or cytotoxic chemotherapy are given in addition to surgically removing the tumor. In 30% of instances, chemotherapy is part of the recommended treatment plan [Verma et al., 2016].

Chemotherapy affects a large number of healthy cells in the blood, bone marrow, mouth, digestive system, nose, nails, vagina, and hair in addition to fast-dividing cancer cells. Evidence suggests that chemotherapy, which causes a reduction in lymphocytes, neutrophils, and platelets and lowers a patient's immune system's capacity to mount a successful response to infection, is the prominent cause of immune system deterioration in cancer patients. According to Verma et al. (2016), these side effects begin during the course of treatment and can linger for up to 3 months following the final chemotherapy cycle.

Exercise increases life expectancy and improves the life of cancer cases who have finished their treatment, according to ample evidence (QoL). A growing body of research indicates that exercise during treatment can help lessen the side effects of chemotherapy, with reports of fatigue reductions of up to 30% and a decrease in chemotherapy-induced peripheral neuropathy. Exercise has also been linked to a reduction in the frequency of dose adjustments and the amount of time patients miss from work while receiving chemotherapy. Preclinical research published more recently [Cave et al., 2018] suggests that exercise may increase the cytotoxic effects of chemotherapy.

Additionally, the World Cancer Research Foundation (WCRF), the American Institute for Cancer Research (AICR), and the American Cancer Society (ACS) recommended the importance of adopting a healthy dietary scheme full of important nutrition elements. This dietary plan would reduce the risk of breast cancer, recurrence, and mortality ratios [Sanft et al., 2021].

Purpose of the study

The study's major cause is to determine what impact do aerobic exercise and a nutrition plan had on the immune system of breast cancer cases having chemotherapy.

Materials and methods

An open-label, parallel-group, randomized control trial was used for the investigation. The study was carried out between June 2022 and December 2022 at the Physical Therapy Outpatient Clinic at Police Academy Hospitals, with participants recruited from the oncology unit. The study was authorized by the faculty of physical therapy's ethics committee (P.T.REC/012/003747). The Clinical Trial Registry received a prospective registration for the trial (NCT05605808).

To determine who was qualified to take part in the trial, all patients with breast cancer who had also chemotherapy protocol were evaluated. Women who fit the inclusion requirements for the trial—being between the ages of 30 and 60, having breast cancer, receiving adjuvant chemotherapy, and finishing at least one session—were the only ones allowed to enrol in the study.

If a participant has one of the following medical complications, they were disqualified: heart diseases, uncontrolled hypertension, thyroid disease, lymphatic complications, diabetes mellitus, mental illness, musculoskeletal or neurological issues that prevent them from engaging in aerobic exercise, and patients who failed to adhere to the diet protocol for at least 60% of the prescribed days. Patients who refused to engage in the trial or sign the written consent form were also not allowed to participate.

The G*power software 3.1.9 (G power program version 3.1, Heinrich-Heine-University, Düsseldorf, Germany) was adopted to determine the sample size for this investigation using a one-tailed test. The previous research [Imayama et al., 2012; Kim et al., 2015] provided the effect size for the sample size calculation. With three independent groups being compared for three outcomes of major variables, the sample size was calculated adopting F tests (MANOVA: Special effects and interactions), Type I error () = 0.05, power (1- error probability) = 0.90 (to avoid type II error), Pillai V = 0.3505999, and effect size f2

(V) = 0.2125621. Upon this investigation, a minimum sample size of 45 patients was necessary (15 cases in each category as a minimum).

To engage in the study, sixty cases had to sign a written consent form after being given extensive information about its nature, goals, and advantages. Cases were divided into three equal groups by random allocation: an aerobic training and diet protocol group (group A, study group), a diet protocol group (group B), and a group that only engaged in active comparison (group C). The names of the groups were written on cards and placed inside sealed envelopes. Based on the chosen card, cases were placed in the appropriate group. After the first week of the randomization process, the start dates for the treatment were decided upon.

Study design

Interventions

Diet therapy:

All cases in groups A and B were instructed to follow a specific diet protocol rich in vitamin D, fibers, and multiple nuts and seeds such as almond, walnut, pistachio, sunflower seeds, flax seeds, and sesame seed to improve the immune system for 12 weeks [De, 2020].

Aerobic training:

Participants in groups A and C performed aerobic exercises by having a walking practice on a treadmill, for 30 minutes, two sessions per week for 12 weeks. The intensity was around 60-85% of each patient's maximum heart rate. The maximal heart rate predicted by age was computed using (220-age). Each exercise session consisted of three phases; a five-minute warming-up phase in form of stretching exercises and walking on the treadmill at the slowest speed, a 20-minute conditioning phase in form of walking on the treadmill at 60% of the participant's maximum heart rate in the first two weeks then progressed gradually to reach the 85% of maximum heart rate by the 12th weeks", and five-minutes cool down phase that was constant as warming up phase. During the training, the patient's blood pressure, heart rate, and breathing pattern were frequently monitored [Par et al., 2021].

Participants were asked to walk continuously at a low intensity for 20 minutes throughout their chemotherapy session week as a safety measure to account for the likelihood of an adverse reaction to chemotherapy [Thomas et al., 2020].

Both before and after the treatment, the outcome measures were evaluated. Before and after our intervention of 12 weeks, blood samples from each patient in each group were taken while they were sitting, after a six-hour fast from food and liquids, to evaluate their immunological markers (TLC, NLR, and PLR).

Statistical analysis

The subject characteristics of the study categories were compared while adopting the ANOVA test. The Shapiro-Wilk test was adopted to determine both the normal distribution of the study's data. The homogeneity was examined utilizing Levene's test. To compare TLC, NLR, and PLR between groups, MANOVA was adopted. Tukey's test post hoc analyses were run for consecutive multiple comparisons. Pre- and post-treatment measures were compared using a paired t-test. The statistical tests had a significance threshold of $p < 0.05$. The statistical program for social studies (SPSS) version 25 for Windows was adopted for the statistical analysis (IBM SPSS, Chicago, IL, USA).

Results

Figure 1 highlights the cases' flow chart, and Table 1 lists the cases' fundamental data, showing that there was no appreciable change in the mean age of the patients ($p > 0.05$).

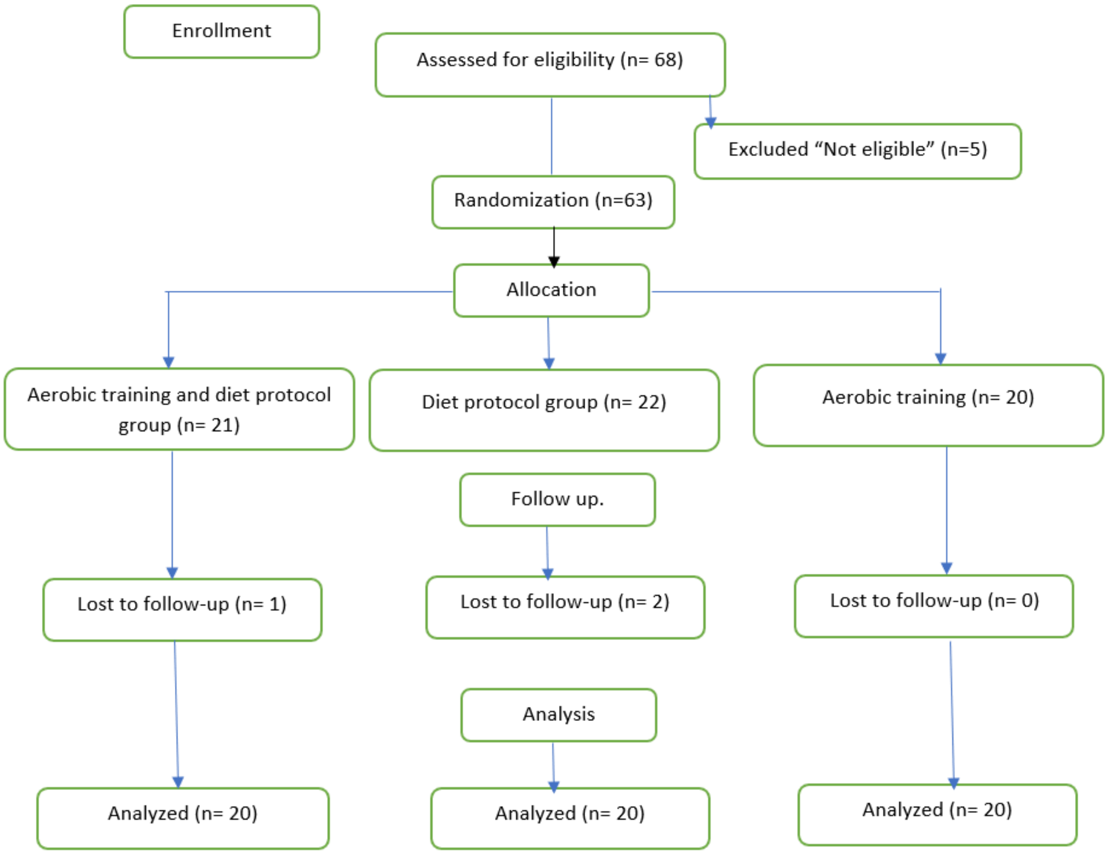

Figure (1): Flow diagram showing the progress of subjects at each stage of the clinical trial.

Table 1. Basic characteristics of participants.

	Group A	Group B	Group C	p-value
	mean ± SD	mean ± SD	mean ± SD	
Age (years)	42.9 ± 7.1	42.2 ± 6.72	43.2 ± 7.4	0.91

SD, standard deviation; p-value, level of significance

Within the group comparison, A marked increase in TLC and another clear decrease was noticed in NLR and PLR in the three groups' post-treatment values in comparison to the pre-treatment values ($p < 0.001$). The percent of change of TLC, NLR, and PLR in group A was 34.74, 40.79 and 30.69% respectively, and in the group, B was 5.59, 6.64 and 5.22% respectively. While in group C the percentage of change was 28.16, 22.54 and 18.17% as highlighted in (Table 2).

Between-group comparison, A crystal-clear increase was marked in TLC of group A in comparison to group B and group C post-treatment ($p < 0.05$). Also, an increase in TLC of group C is marked in comparison to group B post-treatment ($p < 0.05$). Also, a noticeable decrease in NLR and PLR of group A in comparison to the other two categories post-treatment ($p < 0.05$) was observed. A clear decrease was noticed in NLR and PLR of group C in comparison to group B post-treatment ($p < 0.05$), Table 2.

Table 2. ***Mean TLC, NLR, and PLR pre- and post-treatment of groups A, B, and C:***

	Group A	Group B	Group C	p-value		
	mean ± SD	mean ± SD	mean ± SD	A vs B	A vs C	B vs C
TLC (103 /ul)						
Pre-treatment	1.90 ± 0.48	1.79 ± 0.43	1.74 ± 0.42	0.73	0.51	0.93
Post-treatment	2.56 ± 0.37	1.89 ± 0.44	2.23 ± 0.41	0.001	0.03	0.03

MD (% of change)	-0.66 (34.74%)	-0.1 (5.59%)	-0.49 (28.16%)			
t- value	-0.54	-3.55	-10.97			
	p = 0.001	***p = 0.002***	***p = 0.001***			
NLR						
Pre-treatment	2.28 ± 0.37	2.11 ± 0.41	2.13 ± 0.52	0.42	0.53	0.98
Post-treatment	1.35 ± 0.27	1.97 ± 0.43	1.65 ± 0.37	0.001	0.02	0.02
MD (% of change)	0.93 (40.79%)	0.14 (6.64%)	0.48 (22.54%)			
t- value	11.35	3.73	9.57			
	p = 0.001	***p = 0.001***	***p = 0.001***			
PLR						
Pre-treatment	139.86 ± 31.71	146.29 ± 23.09	144.61 ± 32.16	0.76	0.86	0.98
Post-treatment	96.94 ± 26.21	138.66 ± 24.39	118.33 ± 24	0.001	0.02	0.03
MD (% of change)	42.92 (30.69%)	7.63 (5.22%)	26.28 (18.17%)			
t- value	11.11	5.59	5.89			
	p = 0.001	***p = 0.001***	***p = 0.001***			

SD, Standard deviation; MD, Mean difference; p-value, Level of significance

Discussion

The combined aerobic and diet protocol groups exhibited a crystal-clear increase in the outcome measures compared to the other two groups post-treatment, and the current study indicated statistical improvements in immunological markers in all three groups ($p < 0.001$).

Chemotherapy is also linked to a variety of harmful side effects on tissues that are not the target, including considerable immune system consequences. The most severe hematological toxicity, neutropenia, is frequently seen as being linked to infections that may necessitate lowering chemotherapy doses and/or treatment delays that may jeopardize outcomes. There is general agreement that chemotherapy lowers the number of circulating lymphocytes in people with breast cancer, whether during the medication process or up to three months following the final cycle of chemotherapy. It is also well-recognized that treatment for many other tumors can cause lymphopenia [Grossman et al., 2015; Verma et al., 2016].

No study has specifically addressed supplementing traditional physical therapy for breast cancer patients receiving chemotherapy with aerobic training and a diet protocol to improve their immune response, as the majority of previous studies concentrated on either aerobic training or diet protocol alone. The current trial's findings are in line with those of other studies that focused on the impact of either aerobic exercise (Agha-Alinejad et al., 2022; Chastin et al., 2021; Nobari et al., 2022) or an immune-targeted diet protocol (Iddir et al., 2020; Lockyer, 2020; Wypych et al., 2017).

Exercise at a moderate intensity has a marked direct or indirect impact on lymphocytes, modifying the effectiveness of immune system activity. Aerobic exercise directly has an impact on the immune system by enhancing T-cell proliferation, improving the function of neutrophils, macrophages, and monocytes, regulating circulatory levels of pro-inflammatory cytokines, reducing pro-inflammatory cells responsible for the onset of autoimmune diseases, raising IgA and IgG levels, regulating C- reactive protein levels, and lowering age-related changes in immune function. While improving the glycaemic, insulin, and lipidic metabolisms, reducing anxiety and depression, increasing physical activity and cardiopulmonary conditioning, reducing oxidative stress, and improving these metabolisms all have an indirect impact on the immune system [Da Silveira et al., 2021; Mohamed et al., 2021; Nobrai et al., 2022].

Diet therapy also affects the immune system in two different ways. The diet components have an impact on the direct effects because fibres, which are not digested and absorbed by the host and act as nutrients for the microbiota, regulate the function of innate immune cells to participate in the immune system, such as macrophages, neutrophils, and dendritic cells. A diet rich in seeds and nuts produces boosts immunity. Furthermore, innate and adaptive immune responses can be modified by vitamin D.

Proper diet components improve cholesterol and glucose metabolism while inhibiting inflammatory signals. Although a healthy diet indirectly affects the immune system by improving the overall health status of the body by promoting the growth and maintenance of muscle and body organs like skin and hair [Calder, 2020; Kim, 2018; Yao et al., 2022].

In group B, the improvement is only attributable to the diet protocol's impact on the immune system, but in group C, the improvement is solely attributable to aerobic exercise's impact on the immune system, which is more effective than the diet protocol alone. While the combination of the immune system's benefit from aerobic exercise and the food protocol provided the largest improvement in group A. Both led to a multifaceted improvement in the immune system in breast cancer cases receiving chemotherapy medication protocol.

The current academic work has specific limitations. On one level, this study encompassed a small sample size. To give considerably better statistical data analysis, a larger sample size is therefore needed. On another level, none of the groups have provided a long-term follow-up. Therefore, a spectrum of academic work is crucial to trace the long-term effects of aerobic exercise coupled with a diet protocol targeting the immune system.

Taking the current study's results into consideration, it is possible to conclude that while both aerobic exercise and a diet plan can help breast cancer patients receiving adjuvant chemotherapy by enhancing their immune systems, the combination of aerobic exercise and a diet plan is superior in terms of raising immune markers.

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Conflict of interest

No conflict of interest concerning this academic work is declared.

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References

Agha-Alinejad H, Ahmadi Hekmatikar AH, Ruhee RT, Shamsi MM, Rahmati M, Khoramipour K, and Suzuki K. A Guide to different intensities of exercise, vaccination, and sports nutrition in the course of preparing elite athletes for the management of upper respiratory infections during the covid-19 pandemic: A narrative review. *International Journal of Environmental Research and Public Health* 2022; 19(3): 1888.

Calder P C. Nutrition, immunity, and COVID-19. *BMJ Nutrition, Prevention & Health* 2020; *3*(1): 74.

Cave J, Paschalis A, Huang C Y, West M, Copson E, Jack S, and Grocott M P W. A systematic review of the safety and efficacy of aerobic exercise during cytotoxic chemotherapy treatment. *Supportive Care in Cance*r 2018; 26(10): 3337-3351.

Chastin SF, Abaraogu U, Bourgois JG, Dall PM, Darnborough J, Duncan E, and Hamer M. Effects of regular physical activity on the immune system, vaccination and risk of community-acquired infectious disease in the general population: systematic review and meta-analysis. *Sports Medicine* 2021; 51: 1673-1686.

Da Silveira M P, da Silva Fagundes KK, Bizuti MR, Starck É, Rossi RC, and de Resende E, Silva DT. Physical exercise as a tool to help the immune system against COVID-19: an integrative review of the current literature. *Clinical and experimental medicine* 2021; 21(1): 15-28.

De LC. Edible seeds and nuts are in the human diet for immunity development. *Int. J. Recent Sci. Res.* 2020; 6(11), 38877-38881.

Grossman SA, Ellsworth S, Campian J, Wild AT, Herman JM, Laheru D, and Ye X. Survival in patients with severe lymphopenia following treatment with radiation and chemotherapy for newly diagnosed solid tumors. *Journal of the National Comprehensive Cancer Network* 2015; 13(10): 1225-1231.

Iddir M, Brito A, Dingeo G, Fernandez Del Campo SS, Samouda H, La Frano MR, and Bohn T. Strengthening the immune system and reducing inflammation and oxidative stress through diet and nutrition: Considerations during the COVID-19 crisis. *Nutrients* 2020; 12(6): 1562.

Imayama I, Ulrich CM, Alfano CM, Wang C, Xiao L, Wener MH, and McTiernan A. Effects of a caloric restriction weight loss diet and exercise on inflammatory biomarkers in overweight/obese postmenopausal women: a randomized controlled trial. *Cancer research* 2012; 72(9): 2314-2326.

Kim C H. 2018; Immune regulation by microbiome metabolites. *Immunology*, *154*(2), 220-229.

Kim JJ, Shin YA, and Suk MH. Effect of a 12-week walking exercise program on body composition and immune cell count in patients with breast cancer who are undergoing chemotherapy. *Journal of exercise nutrition and biochemistry* 2015; 19(3): 255.

Lockyer S. Effects of diets, foods, and nutrients on immunity: Implications for COVID- 19? *Nutrition Bulletin* 2020; 45(4): 456-473.

Mohamed AA, and Alawna M. The effect of aerobic exercise on immune biomarkers and symptoms severity and progression in patients with COVID-19: A randomized control trial. *Journal of bodywork and movement therapies* 2021; 28: 425-432.

Nobari H, Saedmocheshi S, Johnson K. Suzuki K, and Maynar-Mariño M. A brief overview of the effects of exercise and red beets on the immune system in patients with prostate cancer. *Sustainability* 2022; 14(11): 6492.

Par JH, Park KD, Kim JH, Kim YS, Kim EY, Ahn HK, and Sym SJ. Resistance and aerobic exercise intervention during chemotherapy in patients with metastatic cancer: A pilot study in South Korea. *Annals of Palliative Medicine* 2021; 10(10):10236-10243.

Sanft T, Harrigan M, Cartmel B, Ferrucci LM., Li FY, McGowan C, and Irwin ML. Effect of healthy diet and exercise on chemotherapy completion rate in women with breast cancer: The lifestyle, exercise, and nutrition early after diagnosis (LEANer) study: Study protocol for a randomized clinical trial. *Contemporary Clinical Trials* 2021; 109: 106508.

Thomas VJ, Seet-Lee C, Marthick M, Cheema BS, Boyer M, and Edwards KM. Aerobic exercise during chemotherapy infusion for cancer treatment: a novel randomized crossover safety and feasibility trial. *Supportive Care in Cancer* 2020; 28(2): 625-632.

Verma R, Foster RE., Horgan K, Mounsey K, Nixon H, Smalle N, and Carter CR. Lymphocyte depletion and repopulation after chemotherapy for primary breast cancer. *Breast Cancer Research* 2016; 18(1): 1-12.

Wang X, Ahmad I, Javeed D, Zaidi SA, Alotaibi FM, Ghoneim ME, and Eldin ET. The intelligent hybrid deep learning model for breast cancer detection. *Electronics* 2022; 11(17): 2767.

Wypych TP, Marsland BJ, and Ubags ND. The impact of diet on immunity and respiratory diseases. *Annals of the American Thoracic Society* 2017; 14(5): S339-S347.

Yao Y, Cai X, Fei W, Ye Y, Zhao M, and Zheng C. The role of short-chain fatty acids in immunity, inflammation, and metabolism. *Critical reviews in food science and nutrition* 2022; 62(1): 1-12.