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Prevention and Rehabilitation

Effect of aerobic exercise on immunoglobulins and anemia after chemotherapy in breast cancer patients

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1. Introduction

Intense and extended treatments are common with patients diagnosed with breast cancer and even though the possibility of surviving cancer is reasonably high, it usually requires an exhaustive medical intervention (Courneya et al., 2003).

Women surviving breast cancer may exhibit some physiological and psychosocial deficits related to the quality, intensity, or lengthiness of the treatment applied. Most of the time, such outcomes might negatively influence different aspects of wellbeing, health-related quality of life (HRQoL), and eventually, prognosis. Exercise through various physical activity protocols has been claimed to enhance prognosis while potentially alleviating the adverse effects of interventions and treatments applied (Lahart et al., 2018).

At the end of the 20th century, more focus was placed on the immunological response as a potential pathophysiological detriment during the breast cancer disease process (Coussens et al., 1999), and consequently more attention was drawn to the beneficial use of immunological factors in breast cancer prognosis (Singh et al., 2006). A strong relationship was found between disease stage, tumor load, and levels of serum immunoglobulin (IgA) in breast cancer patients. Such correlation has been explained by potential disturbance in cell–mediated immunity (Singh et al., 1991). An increase in complement activity levels was also correlated with breast cancer and was found to increase with the advancement of the disease stage (Jurianz et al., 1999). This is suggested to be due to the presence of an intrinsic cellular complement resistance mechanism (Hakulinen and Meri, 1998).

Surgery, radiotherapy, medications (hormone therapy), and chemotherapy are widely used interventions in treating breast cancer. Survivors from breast cancer are commonly victims of secondary complications either physically, functionally, emotionally, or spiritually. All these complications negatively impact social wellbeing, and consequently the person's quality of life (Cheema and Gaul, 2006).

Chemotherapy is a medical intervention aiming to eradicate malignant cells originating from the primary tumor. It is administered either alone, or in addition to radiation therapy before surgical intervention; in these cases it is designated neoadjuvant chemotherapy; or after surgical intervention it is designated adjuvant chemotherapy. Several factors determine the type of chemotherapy intervention including the tumor type, size and location, in addition to the patient's medical condition (Schiller et al., 2002). Nausea, vomiting, loss of appetite, and fatigue are commonly encountered in patients treated with chemotherapy. Additionally, it has been found that chemotherapy is highly associated with many side effects; particularly loss of muscle mass and strength, and consequently, a significant reduction in quality of life scores (Ferreira et al., 2008). More recently, chemotherapy has also been claimed to lead to a drastic decrease in immune cells (Schmidt et al., 2018b).

Furthermore, anemia is an additional common complication of chemotherapy that contributes to decreased functional capacity, increased fatigue, and marked reduction in quality of life scores (QOL) for cancer survivors (Vadhan-Raj et al., 2017).

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Physical activity and exercise are essential factors for good health, enhancing the natural ability to overcome psychological, social, and economic problems (McArthur et al., 2014). Capacity for physical activity varies among individuals; a quality directly related to the activity of the internal organs. One important adaptation associated with exercise is blood circulation and its transferring components of oxygen (Suzuki and Joo, 2006). Physical activity has also been claimed to enhance anti-cancer immune response in breast cancer survivors (Bianco et al., 2017). Additionally, exercise has been found to increase the potential of the body to target tumor growth through regulation of immune and inflammatory functions, this is why exercise has been recommended as anticancer treatment to be incorporated into standard oncological therapy (Hojman, 2017).

Based on the above points, this study aims to explore the effect of a specific protocol on IgA, in addition to hemoglobin (Hb) in patients receiving chemotherapy for breast cancer.

2. Methods

2.1. Participants and recruitment procedure

Thirty women diagnosed with Stage 1 breast cancer participated in this study with an age range of 40–50 years. Recruitment was done through the outpatient clinic at the Faculty of Physical Therapy - Cairo University. Inclusion criteria consisted of women diagnosed with breast cancer treated only by chemotherapy. Exclusion criteria consisted of any participant being subjected to any other treatment than chemotherapy or unable or not agreeing to participate in the designed exercise program.

Prior to the start of the study, the study protocol was granted the ethical approval from the Research Ethical Committee of Faculty of Physical Therapy - Cairo University.

All women agreed to participate through a signed informed consent declaring their understanding of the study details. Afterwards they were randomly assigned into two equal groups. The first group, designated group A, consisted of fifteen patients undergoing chemotherapy in addition to supervised aerobic exercise for 5 months, 3 sessions per week (Lahart et al., 2018). Group B was composed of fifteen patients only receiving chemotherapy, and thus serving as the control group.

2.2. Treatment procedures

Group A participants, undertaking prescribed chemotherapy sessions (one dose every 21 days), were informed about treatment procedures, in addition to the possible effects associated with exercise. Before starting the treatment, they were asked to wear comfortable clothes during the exercise sessions. Aerobic exercises implemented sued a treadmill, cycle ergometer, or elliptical machine according to patient preference, three times per week. The first six weeks, exercises were performed at 60% of the VO2max, maximal oxygen consumption. During weeks 7–12, this progressed to 70% and reached 80% after week 12. VO2 max was calculated using heart rate conversion formula VO2 max = 15 x (HRmax/HRrest), where HRmax was considered as HR max = 220-age. For the first three weeks, the exercise session duration was set at 15 min, and increased by 5 min every 3 weeks, reaching 45 min in the 18th week (Pollock et al., 1998). Group B only received chemotherapy. Calculation of VO2 max was recalculated each three weeks to assure relevant suitable exercise tolerance.

2.3. Evaluation procedures

For both groups, serum blood analyses were performed through phlebotomy before and after the five-month study. Serum analysis included Immunoglobulins A (IgA) and hemoglobin (Hb).

2.4. Data analysis

Data analysis was performed using Statistical Package for Social science (SPSS) V2 software. Before the final analysis, data were screened for presence of extreme scores, homogeneity of variance, and normality assumption. Evidence of linear relationships existed between all dependent variables, as shown in the scatterplot, and no sign of multicollinearity was demonstrated by Pearson correlation ($|r| < 0.9$). Inspection of a boxplot and Mahalanobi's distance revealed, respectively, neither univariate nor multivariate outliers in the data. Immunoglobulins IgA and Hemoglobin (Hb) revealed normal distribution, as confirmed by the Shapiro-Wilk test ($p > .05$). Additionally, Levene's test ($p > .05$) confirmed the homogeneity of variances for all dependent variables. Two-way mixed MANOVA was utilized for the comparison of the measured variables at different measuring time intervals and tested groups. Alpha level was set at 0.05.

3. Results

Independent *t*-test showed no statistically significant differences ($p > .05$) in age, body mass, height and BMI mean values when comparing both tested groups (Table 1).

Data was analyzed using Mixed MANOVA. Results showed significant between subject effect [$F = 223.859$; $p = .0001$], within subject effect [$F = 317.098$; $p = .0001$], and treatment time effect [$F = 382.471$; $p = .0001$]. Table (2) consists of both descriptive statistics and post hoc pairwise comparison tests for the all measured parameters.

These tests showed that the increase was significant ($p < .05$) in immunoglobulins IgA and Hemoglobin (Hb) after treatment compared with the pretreatment in group A only. Regarding the between subject effects, comparisons also demonstrated a significant increase ($p < .05$) in immunoglobulin IgA and Hemoglobin (Hb) in group A in comparison to group B.

4. Discussion

This study revealed that five months of supervised aerobic exercise did enhance immune response and reversed anemia secondary to chemotherapy in breast cancer survivors undergoing chemotherapy.

Aerobic exercise has been defined as a type of physical activity that aims mainly to improve cardiovascular and respiratory fitness (Kenney et al., 2015). It has further been claimed to protect and even boost the immune response. Many studies have proven that regular aerobic exercise (even brisk walking) can significantly

Table 1
Demographic characteristics of patients in both groups.

Characteristics	Group A (n = 15)	Group B (n = 15)	*t-value*	*P*-value
Age (years)	45 ± 3.25	45.06 ± 2.98	−0.058	0.954
Body weight (Kg)	78.1 ± 5.7	78.2 ± 8.35	0.245	0.81
Height (cm)	166.5 ± 8.38	165.28 ± 6.3	0.349	0.73
BMI (kg/m^2)	28.19 ± 1.3	28.5 ± 1.6	−0.47	0.6

*Significant ($p < .05$).

Table 2
Multiple pairwise comparison tests for IgA and Hb for groups A and B at different measuring instances.

Variable measured	Group A		Group B	
	Pre	Post	Pre	Post
Immunoglobulins IgA	230.69 ± 7.33	255.74 ± 11.27	230.76 ± 7.31	225.38 ± 12.26
Hemoglobin (Hb)	101.9 ± 0.72	125.86 ± 4.12	101.2 ± 1.33	100.72 ± 1.67
Within groups (Pre Vs. post) p-value	Immunoglobulins IgA		Hemoglobin (Hb)	
Group A	.0001*		.0001*	
Group B	.112		.553	
Between groups (group A Vs. group B)	Immunoglobulins IgA		Hemoglobin (Hb)	
Pre treatment	.98		.089	
Post treatment	.0001*		.0001*	

*Significant ($p < .05$).

enhance many defense mechanisms especially the antibody and the natural killer (T cell) response (Siedlik et al., 2017). Others discussed the possible role of aerobic exercise in the reduction of the effects associated with breast cancer and anticancer medical intervention (Adraskela et al., 2017).

A cohort study done on a large number of women surviving breast cancer concluded that moderate-to high-level aerobic exercise lowered the risk of death associated with breast cancer (West-Wright et al., 2009).

Many benefits of exercise on the immune system have been identified, including an increase in the circulation of the major two humoral cells responsible for innate immunity, neutrophils and natural killer cells (Gillum et al., 2011). Additionally, macrophages were also found to be positively affected through moderate exercise (Murphy et al., 2004). Other recent findings suggested that exercise produced alterations in many biomarkers (Greenham et al., 2018).

On the other hand, current results are inconsistent with others that have stated that 12 weeks of resistance or endurance training were insufficient in suppressing cellular immunity (Schmidt et al., 2018b). This may be explained by the fact that, either the inclusion of strength training or the 12-week duration of intervention was not sufficient to induce significant changes as observed in the current study, where the exercise intensity was initiated at 60% of maximum oxygen consumption and was increased gradually until it reached 80%. The timing also was gradually increased from 15 to 45 min throughout the 5-month study period. Another possible explanation might be that, if the aim is to boost immunity, exercise must be implemented more than twice per week to achieve significant results. Such conclusion might need further studies to be elucidated.

In another study, thirty minutes of moderate, intermittent, aerobic exercise had a similar effect on breast cancer survivors compared to a group of physically comparable women with no breast cancer history; the effect was assessed at the level of the natural killer cells (Evans et al., 2015). Such reporting is more compatible with the present study's findings, even though there is a difference in the study design and the subjects' recruitment; particularly the point that the exercise intervention took place twice a week.

Although many authors have not offered clear explanations for the positive effect of exercise in breast cancer survivors, it is postulated that physical activity may modulate tumor behavior and consequently, it triggers protective innate immune mechanisms that might fight tumor cells (Goh et al., 2012).

Furthermore, the aerobic exercise program implemented in this study led to improvement in the hemoglobin levels in chemotherapy treated breast cancer patients. This observation is compatible with other studies stating that sixteen weeks of high-intensity interval and resistance exercises produced significant improvements in many outcomes measured, including increased muscle strength, cardiac and respiratory fitness, and elevations in the pressure-pain threshold and hemoglobin levels (Mijwel et al., 2018a). The possible explanation for these observations may be the protective effect of exercise on skeletal muscles' structural and metabolic characteristics from side effects triggered by chemotherapy (Mijwel et al., 2018b). Additionally, it was reported that moderate exercise could reduce chemotherapy-induced anemia among women surviving breast cancer (Dolan et al., 2010; Mohamady et al., 2017). This may be explained by the humoral and physiological adaptations associated with exercise which might have led to an increase in the number of red blood cells, consequently raising the hemoglobin plasma concentration. The combined effect of the aerobic exercise regimen on both IgA and hemoglobin can be explained by the presence of humoral effects associated with such observed improvement (Walsh et al., 2011).

A more recent study stressed the identification of broad 'fatigue' associated with cancer survivors (Schmidt et al., 2018a). Additionally, it has been stated that deconditioning might account for the development and persistence of cancer-related fatigue following chemotherapy (Neil et al., 2013). Overall, it can be concluded that the applied aerobic exercise regimen may have reversed the deconditioning that might have occurred secondary to the breast cancer condition, or to the physical inactivity associated with either the patient's condition or the administered chemotherapy treatment.

4.1. Limitations

This study had its limitations including: the reduced participant enrollment number, the previous level of activity of each participant, and the potential enrolment of participant in physical activities outside the plan of exercise implemented, which was difficult to be controlled. Additionally, informing the participants about the potential effect of exercise, before starting the supervised exercise program, might have had an uncontrollable placebo effect on the outcomes.

5. Conclusion

It is concluded that supervised aerobic exercise has significant positive effects on immunoglobulin IgA and hemoglobin (Hb) in breast cancer patients undergoing chemotherapy as evidenced by serum blood analysis. Aerobic exercise can be considered a safe and effective modality for reversing a potential drop in immunity and serum hemoglobin associated with chemotherapy-treated breast cancer patients.

5.1. Clinical relevance

- When dealing with chemotherapy-treated breast cancer survivors, supervised aerobic exercise has a boosting effect on immunity, particularly on immunoglobulin A.
- When dealing with chemotherapy-treated breast cancer survivors, supervised aerobic exercise program can reverse anemia associated with chemotherapy.

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Declaration of competing interest

The authors have declared that no competing interests exist.

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