Effect of selected exercise program on natural killer cytotoxic cells activity of post-mastectomy patients

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Abstract

The purpose of this present study is to define the role of cells of the innate immune system (i.e., NK cells) in infection and cancer and investigate the effect of selected exercise program on natural killer cytotoxic cells of post-mastectomy patients. Forty female patients have referred from an oncologist professor have undergone mastectomies and they have selected from the oncology surgery department, physical therapy clinic of National Cancer Institute (NCI), Cairo University. They have ranged between 40 and 60 years. They all were female patients. They all have undergone mastectomy. These patients have randomly divided into two equal groups, group A (an exercise group) \( n = 20 \) patients were received the selected exercise program and group B (a control group) \( n = 20 \) patients were received the routine postoperative physical therapy protocol of National Cancer Institute (NCI), Cairo University. All patients were assessed and pre- and post-exercise program measurements were taken by using Flow Cytometry [Dako Cytomation Corp., model Partec III] for concentrations of circulating natural-killer-cell cytotoxic activity (NKCA) using a CD56 stained with FITC (fluorescein isothiocyanate) dye. The results revealed a significant increase \((P < 0.05)\) in all measured circulating natural-killer-cell cytotoxic activity (NKCA) pretreatment and post 3 months of treatment in both exercise and control groups. But the rate of improvement in exercise group was more than that in control group which revealed the effect of the selected exercise program in circulating natural-killer-cell cytotoxic activity (NKCA). It could be concluded that, early moderate exercise has a beneficial effect on the function of in vitro NK cells in post-mastectomy patients rather than the routine postoperative physical therapy protocol.
Physical exercise has various special effects on the human body, including their immune system. After strenuous exercise, human body passes through a period of weakened immune resistance. During this period, human body is hypothetically more susceptible to URT infections; however, in case of moderate exercise seems to have a beneficial effect on the immune function, which could protect against URT infections. Exercise has effects on both the cellular and the humoral immune system. Doping products only have a modest effect on the immune system, although erythropoietin may, in rare cases, except glucocorticoids, could cause severe side-effects (Jeurnissen et al., 2003). Breast carcinoma constitutes 33% of all female cancer at NCI and 50% in private series. In western countries, the median age is one decade younger than the corresponding age. In Egyptian patients, 60.5% of patients are premenopausal (age 50 years and younger). The female to male ratio is 44.1. Breast cancer in Egyptian patients is biologically more aggressive disease than that encountered in the west. This is explained partly by the late presentation of patients at an advanced stage and the predominance of premenopausal patients (Mokhtar, 1991). Patients undergoing modified radical mastectomies frequently experience problems with ipsilateral lymphedema and shoulder dysfunction. In a recent physical therapy study achieved better shoulder ROM (range of motion) and less difficulty with functional assessment items. Another study revealed better ROM in patients receiving physiotherapy initiated 1 day postop, compared with other groups with initiation 4 and/or 10 days postop (El-Bolkainy, 1998). Professionals who work with large numbers of cancer patients believe that exercise increases their strength, endurance, well-being, and functional levels. Many of NIH research protocols for cancer patients include exercise training programs during the application of systems medical or surgical treatment this side of rehabilitation of cancer patients you from training programs.

Additionally, modern studies have shown that physical activity may enhance life quality and mood of cancer patients during and after treatment, so consistent physical activity help increasing performance status of breast cancer patients. Moreover, it has also been shown to reduce fatigue and psychological distress in patients treated with radiotherapy and after high dose chemotherapy with peripheral blood stem cell transplantation. And so, exercise could play an important role as a complementary therapy for cancer patients during and after treatment. However, designing specific exercise programs needs more information for different groups of patients with oncological diseases (Dimeo, 2000).

Research about the impact of physical activity on immune function is still at its very beginning. However, it is considered as the most active are as of research in sports medicine (Dimeo, 2000). However, cancer patients may suffer from specific medical problems, as chemotherapy could cause damage to the bone marrow; and consequently, decreases of blood oxygen transport capacity due to anemia. Agents like cyclophosphamide, and irradiation, can result in damage of myocardium and consequently, weakening the cardiac output. Administration of immunosuppressive agents could lead to myopathy. Additionally, reduced protein intake, and lessened absorption after GIT surgery, may lead to a catabolic state. Finally, an increase in the cytokines concentrations results in muscular waning. All previous factors have an effect on patient’s physical performance condition and hence designing an exercise programs should carefully considered (Dimeo, 2000).

2. **Material & methods**

Forty female patients, referred by an oncologist professor have undergone mastectomies and they have selected from the oncology surgery department, physical therapy clinic of National Cancer Institute (NCI), Cairo University. These patients have selected based on certain criteria: Their ages ranged between 40 and 60 years and have randomly divided into two equal groups group A (an exercise group) ($n = 20$) patients have received the selected exercise program and group B (a control group) ($n = 20$) patients. However, patients had taken anticancer & immune-suppression therapy. Or suffering from Cachectic & Fatigue and depression patients have excluded from the selection.

2.1. **Equipment & evaluation tool**

Flow Cytometry (Dako Cytomation Corp., model Partec III) had used to evaluate the number of NKCA cells in pre- and post-exercise program measurements. These have done through staining the circulating natural-killer-cell cytotoxic activity (NKCA) using a CD56 stained with FITC (fluorescein isothiocyanate) dye. Blood samples had obtained from the right cephalic vein in each group while patients in sitting position on postoperative day (POD) 1 and 90 of both exercise group (A) and control group (B) on morning.

2.2. **Therapeutic procedure**

The procedures of this protocol achieved as summarized in the following Table 1; however a full exercise figures have provided as in Supplement-I;

2.3. **Statistical tools & data analysis**

In this study, the mean, standard deviation, standard error, Linear Regression and ANOVA were calculated for concentrations of circulating NK cells on postoperative day (POD) 1 and 90 of both exercise group (A) and control group (B), also the differences of mean between group (A) & group (B), normalization, Linear Regression and ANOVA have calculated for correlation between NKCA of both exercise group (A) and control group (B) and age, residence, marital status, offspring, family history, exercise duration, different hormonal/anti-hormonal drugs used as medication postoperatively like tamoxifen, cataflam, and chlorpheniramine.
### Table 1 – The procedures protocol.

<table>
<thead>
<tr>
<th>1st week</th>
<th>Selected exercise therapy protocol</th>
<th>Duration and frequency of the exercise program</th>
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</thead>
<tbody>
<tr>
<td>1st month 1st day</td>
<td>Lateral costal and diaphragmatic breathing exercise, bronchial drainage and coughing if there are secretions (Kigin, 1981). Gentle passive and active assisted shoulder exercises for: flexion: for about 40°. Abduction: for about 40°. Internal and external rotation: to tolerance (Na et al., 1999). Gentle active hand and elbow range of motion exercises (Harris, 1996).</td>
<td>The duration and frequency of first package of exercises are 30 min twice a day (Wingate et al., 1989).</td>
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<tr>
<td>2nd day</td>
<td>Same as above. Hand and forearm isometric exercises (Markowski et al., 1981) squeeze a foam ball (Binehart-Ayres, 1998).</td>
<td>The duration and frequency of first package of exercises are 30 min twice a day (Wingate et al., 1989).</td>
</tr>
<tr>
<td>3rd day</td>
<td>Same as in 1st and 2nd day. Progressive shoulder active free exerciser as following: flexion: 45°; abduction: 45°; internal and external rotation to tolerance (Harris, 1996).</td>
<td></td>
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<tr>
<td>4th–6th day</td>
<td>Same above exercise. Progressive active free motion of shoulder as following: flexion: 45°–90°; abduction: 45°; internal and external rotation: to tolerance (Harris, 1996). After removal of drain: proprioceptors neuromuscular facilitation (P.N.F.).</td>
<td></td>
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<tr>
<td>7th day</td>
<td>Same as above. Progressive active free motion of shoulder as following: flexion: to tolerance; abduction: to tolerance; internal and external rotation: to tolerance (Harris, 1996).</td>
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<tr>
<td>2nd week</td>
<td>Same as above. After removal of sutures shoulder mobilizing exercises by assistive devices (Wingate et al., 1989; Na et al., 1999).</td>
<td></td>
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<tr>
<td>3rd and 4th week</td>
<td>Continue with above exercise. Home exercises as following: Keeping her arms straight. Lift them both forward and up as high as she can go. Keeping her arm straight and the palms of her hand facing forward, lift both arms out to the side and up as high as she can comfortably go. Reach her hand to low back and then slide the hand as high up back as possible. Reach hand behind neck and slide it down back as far as possible. While the patient in standing facing a wall her toes approximately one foot from the wall. Ask her to place the palm of affected arm against the wall. Then walk her fingers up the wall until she have climbed as far as she can and feel a stretch hold to a count of 5 then slowly climb down. Rest repeat. Standing side ways: ask patient to place her palm of affected aim against the wall. And work hand up the wall as far as she can hold for count of 5 and then slowly climb down. Rest. Repeat (Cooley and Erikson, 1999). 3 Sessions per week each of 30 min in addition to instruction of home exercises as following each exercise is done 10 times for 2 times a day (Cooley and Erikson, 1999).</td>
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<tr>
<td>2nd month</td>
<td>Active assisted and free exercises for shoulder using pulley system and shoulder wheel.</td>
<td>Continuous all above home exercises till the end of second month (Wingate et al., 1989; Na et al., 1999; Brennan et al., 1996). 5 Session per week each of 30 min in addition to instruction of home exercises as following each exercise is done 10 times for 2 times a day (Na et al., 2000; Cooley and Erikson, 1999).</td>
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<tr>
<td>3rd month</td>
<td>All above shoulder exercises Exercises consisted of supervised aerobic activity using arm and bicycle ergometers.</td>
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</table>
3. Results

This study involved 40 female patients who had undergone mastectomy. They have selected from the National Cancer Institute, Cairo University in the period between October 2007 and Jan 2008. These patients have divided into two equal groups as follow: group A (an exercise group): twenty patients (20 females) have given 3 months of the selected exercise program as mentioned previously in details. Group B (control group): twenty patients (20 females) have given 3 months of usual postoperative regimen. The data related to the patients’ age, sex, preoperative procedure and postoperative management had been considered in this study, while the data concerning the patient postoperative physical status had been measured before the study (pre) and after three months (post), the data regarding to blood samples analysis had been measured before the study (pre) and after three months (post), and a control group. The results presented according to the following: results of an exercise group (group A), results of a control group (group B) and comparative analysis between both groups and their correlation to age, residence, marital status, offspring, family history, exercise duration and different anti-hormonal drugs used as medication post-operatively like tamoxifen, cataflam and chlorpheniramine. The complete data have provided in the provided Supplement-II.

4. Discussion

The obtained results of exercise and control groups revealed that there was a considerable significant difference in case of exercise group and to some extent a significance in the control group, and this in harmony with that detected by Pedersen and Ullum (1994), who demonstrated that natural killer (NK) cells are highly influenced by physical exercise. The probable main mechanisms behind exercise-induced changes in NK cell function are cytokines, hyperthermia, and stress hormones, including catecholamine, growth hormone, cortisol, and beta-endorphins. Also, such finding coincides with that obtained by Albright and Albright (1985), who found that the decline in NK activity during aging is a reflection of loss of competence to lyse targets rather than a major decline in the actual numbers of NK cells. The results of residence in this study were statistically significant revealed that patients with a good overall lifestyle showed significantly higher NK cell (P < 0.05) activities than those with poor overall lifestyles (Morimoto et al., 2001). The results of marital status in this study were statistically non-significant. These data are parallel to that achieved by Arranz et al. (2009), who found that animals isolated during old age showed functional and cognitive decline, with increased neophobia and anxiety as well as learning and memory deficits. In addition, NK activity of thymic cells is reduced by isolation. Both solitude and social isolation impair immunological involution and mental during this period, despite normal social life during previous stages of life.

The results of offspring in this study were statistically non-significant. Such findings coincide with that obtained by Morimoto et al. (2001), who found that subjects who complained of unstable mental status had significantly lower NK cell activity than those who reported stable mental status. When subjects were divided into four groups by mental health status and lifestyle, subjects who had poor or moderate lifestyle and reported unstable mental status showed the lowest NK cell activity and subjects who had good lifestyle and reported stable mental status showed the highest NK cell activity among four groups. Also Reiche et al. (2004) found that depending on the type and intensity of the stressor and on the animal species, strain, sex, or age. In general, both depression and stressors are associated with the decreased natural-killer-cell and cytotoxic T-cell activities that affect processes such as immune surveillance of tumors, and with the events that modulate development and accumulation of somatic mutations and genomic instability. The results of correlation between family history and NKCA were non-significant. These data were non-parallel to that achieved by Lee (2005), who reported that family history of cancer contributes to increased cancer risk in individuals especially with the possibility of persons with reductions in systemic natural cytotoxic activity.

The duration of exercise effect on NKCA revealed a considerable significance difference. Such finding coincides with that obtained by Na et al. (2000), as in his study, a moderate exercise training for 2 weeks induced significant increase in NKCA. A possible explanation is that the level of NKCA was very low because subjects had just undergone surgery that could lower NKCA and surgery itself might have been stressful to them. Therefore, the sensitivity to exercise-induced immunologic change could be increased. However, there are arguments that exercise induces immunologic change. Nieman et al. (1993) reported that the NKCA of an exercise group who performed a moderate intensity exercise program three times a week for 8 weeks did not show significant increase compared with that of a control group. They suggested that a possible explanation for this finding was that the exercise duration was too short to lead to changes in NKCA.

Tamoxifen acts as an antagonist of the estrogen receptor in breast tissue through its active metabolite, hydroxytamoxifen. Tamoxifen acts like a broken key inside the lock thus preventing estrogen from binding to its receptor. Hence breast cancer cell growth is blocked. In this study the correlation between NKCA and tamoxifen revealed a considerable significance different. Such finding coincides with that obtained by Berry et al. (1987), who found that in post-menopausal patients with breast cancer received tamoxifen, showed a significant increase in NK activity.

Diclofenac salt (cataflam) is a non-steroidal anti-inflammatory agent possessing both analgesic and antipyretic properties. Diclofenac sodium inhibits prostaglandin synthesis through interfering with the action of prostaglandin synthetase. The correlation between the NKCA and cataflam
revealed a significance difference. Such finding coincides with that obtained by Medsafe (2012), the ability of natural killer (NK) cells to lyse tumor cells was increased following i.p. injection of diclofenac into mice. The correlation between NKCA and chlorpheniramine revealed that a considerable significant difference, such finding coincides with that obtained by Asea et al. (1996), who concluded that histaminergic mechanisms may be involved in the regulation of NK cell function in vivo.

5. Summary & conclusions

The main aim of this study was to evaluate the therapeutic efficacy of selected exercise program on natural killer cytotoxic activity (NKCA) of post-mastectomy patients. Forty female patients who had undergone mastectomies selected from in patient clinic of the National Cancer Institute (NCI), Cairo University in the period between October 2007 and Jan 2008 were evaluated. These patients were divided into two equal groups as follow: Twenty post mastectomies patients (20 females) received 3 months of the selected exercise program as mentioned previously in details. Twenty patients (20 females) received 3 months of the usual postoperative regimen. The data related to the patients’ age, sex, preoperative procedure and postoperative management had been considered in this study, while the data concerning the patient postoperative physical status had been measured before the study (pre) and after three months (post), the data regarding to blood sample analysis had been measured before the study (pre) and after three months (post), and a control group.

The statistical analysis of the mean differences of Pre-NK (%) and of Post-NK of an exercise group (group A) revealed very significant differences \( P < 0.05 \) after 3 months of treatment with the selected exercise program for group A and before treatment with the selected exercise program. The statistical analysis of the mean differences of Pre-NK (%) and of Post-NK of a control group (group B) revealed significant differences \( P < 0.002 \) after 3 months of treatment with the usual postoperative regimen for (group B) and before treatment with the usual postoperative regimen. The statistical analysis of the mean differences of group (A) & group (B), normalization, also Linear Regression and ANOVA and Correlation Between NKCA of both Exercise group (A) and Control group (B) revealed very significant differences \( P < 0.01 \) after 3 months of treatment with the selected exercise program for exercise group (group A) and treatment with the usual postoperative regimen for control group (group B).

The correlation between NKCA and some parameters including, marital status, offspring, and family history was statistically non-significant. However, in case of residence, exercise duration, chlorpheniramine, catarfam and tamoxifen revealed a significant difference.

From the obtained results of this study, it can be concluded that, moderate exercise training for 3 months induced significant increase in NKCA. A possible explanation is that the level of NKCA was very low because subjects had just undergone surgery that could lower NKCA and surgery itself might have been stressful to them. Therefore, the sensitivity to exercise-induced immunologic change could be increased.

This study suggests that initial modest exercise has a favorable effect on the function of in vitro NK cells in post-mastectomy patients.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.bjbas.2013.03.003.

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