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Effect of Aerobic Exercise Program on Immunosensencence in Young Elderly.

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ABSTRACT

This study was to determine the effect of exercise training on the immune system mainly natural killer number, activity and macrophages activity (IL-6) in young elderly people. Compare between the response of immune system to aerobic exercise program between active and sedentary elderly people.60 elderly subjects participated in this study. The subjects divided randomly in to two equal groups, control group and study group and each group consisted of fifteen male and fifteen female. The age of persons in the present study was between 60 to 75 years old. Study group had the opportunity to participate in the exercise program for 1hour/day, 3 times/week for three months, while the control group were sedentary. The results of this study revealed that moderate intensity exercise training program, 60-85% of maximum heart rate, for elderly subjects produced a significant change in NK cells numbers and activity and IL-6 level in comparison with the control group. In conclusion: the exercise program is effective and beneficial for NK cells percentage, activity, and also macrophages activity in the elderly subjects.
Keywords: Exercise, natural killer cells, macrophages, elderly.

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INTRODUCTION

Aging is defined as the progressive accumulation of damage over time, leading to disturbed function on the cellular, tissue and organ level and eventually to disease and death. Aging is a complex, multifactorial process where genetic, endogenous and environmental factors play a role [1].

During the latter half of life, an individual is more prone to problems with the various functions of the body, and to a number of chronic or fatal diseases. The cardiovascular, digestive, excretory, nervous, reproductive, and urinary systems are particularly affected. The most common diseases of aging include Alzheimer's, arthritis, cancer, diabetes, depression, and heart diseases [2].

Immunosenescence refers to age-related changes that occur in the immune system and result in a decrease in immune functioning, but there is considerable variation in the effectiveness of the immune system in older adults[3].

The major components of immune system are: the gums, spleen, lymphatic system, bone marrow, white blood cells, antibody, hormones, and complement system [4].

Natural killer (NK) cells are a subset of lymphocytes composing 5% to 20% of peripheral blood mononuclear cells (PBMCs) in humans. Natural killer cells participate in the innate immune response and play an important role in the defense against viral infections as well as in tumor surveillance and are also involved in shaping adaptive immune responses through their production of cytokines. Recently, studies have shown that NK cells share features with B and T cells of the adaptive immune system, as mouse NK cells demonstrate immune memory after viral infection [5].

Macrophages are another class of lymphocytes belonging to the innate immune system that serve four important roles. They (1) present antigen to memory (but not naïve) cells, produce both (2) cytokines and reactive nitrogen and oxygen species, and (3) clean up cellular debris. Similar to DCs, macrophages also link innate and adaptive immunity. Some of the earlier work using macrophages from rodents tended to suggest that certain functions (ability to produce oxygen radicals in response to bacterial challenge) did not decline with age. Obtaining pure macrophages from humans is logistically difficult, and researchers instead typically collect peripheral blood mononuclear cells (PBMCs) containing the immature progenitors of macrophages, the monocytes. Overall, immunosenescence is associated with a general decline in macrophage function [6], possibly due to impaired ability of macrophages to respond to activation or due to a decline in activation signals from other cells. The antigen-presenting capacities of peripheral blood monocytes from older humans appears to be compromised due to alterations in major histocompatibility complex class II (MHC class II) gene expression, and the activities of infection-response proteins, such as heat shock proteins, may also be altered. In one human study that did obtain macrophages directly from the lungs, investigators found a decrease in accessory function of these cells [7].

Regular, systemic, appropriate exercise is one of the best anti-aging agents known. Research documents its positive influence on the older population. Physical fitness maintained by a consistent exercise regimen can substantially reduce the behavioral impact of many age related changes that limit mobility, reduce independence, and affect the enjoyment of life in older age [8].

There is increasing evidence that the black box which is referred to as “biologic aging” is composed of genetic factors and many types of environmental exposures. Some of the most potentially modifiable elements of this syndrome are those attributable to disuse or insufficient exposure to certain kinds or intensities of physical stressors during the course of life span[9].

Beneficial adaptations to exercise once thought restricted to genetically endow master athletes now are seen to occur just as predictably in frail elders with chronic diseases, opening the door to vastly improved physical function and associated health benefits. Knowledge of the benefits of physical activity, however well substantiated, may be necessary, but it is not sufficient to change either physician-prescribing habits or the likelihood of adoption and long-term adherence to exercise on the part of patients. Ultimately, the penetration of exercise prescription to optimize aging into the most inactive cohorts in the community, who have the most

to gain from increases in levels of physical activity and fitness, will depend on a combination of clear evidence-based guidelines coupled with health professional training and behavioral programs tailored to age- specific barriers and motivational factors [9].

SUBJECTS AND METHODS

Subjects:

Sixty elderly subjects (30 males- 30 females) participated in this study. They were assigned into two groups equal in number and gender: .Group A, Exercise group included thirty subjects of matched gender. Group B, Control group included thirty subjects of matched gender.The age of persons in the present study was between 60 to 75 years old.

Study group had the opportunity to participate in the exercise program for 1hour/day, 3 times/week for three months, which is walking on treadmill, while the control group were sedentery.

All subjects participated in this study were aberatly healthy young old age. Subjects who reported chronic health problems (e.g., malignancy), severe inflammation and infection, autoimmune diseases or any immune system disorders were excluded from this study. All persons underwent careful physical examination. All subjects signed an informed consent.

Ethical consideration:

The whole procedure was explained for every patient and written consent was obtained from every patient to insure complete satisfaction. The protocol accepted from the protocol commette of faculty of physical therapy, cairo university.

Procedures

Procedures of evaluation

Immunological studied

Blood stamples

The blood sample was obtained by intravenous puncture (usually in wrist or arm).The skin over the vein is cleaned with the antiseptic and then collected with small sterile needle attached to disposable syringe.

Preparation of mononuclear cells

Of the heparinized peripheral venous blood. 3ml was mixed with an equal volume of phosphate-buffered saline (PBS. PH 7.4), layered over 4 ml of Ficoll-paque gradient and centrifuged at 400 g for 30min at room temperature. The mononuclear cell layer was collected and wished twice, firstly wish 10 ml of PBS and secondly with 10 ml of PRMI [Roswell Park Memorial Institute (medium)] -1640 containing 10% foetal calf serum (FCS), then re-suspended in (FCS)-RPMI-1640.

Determination of Natural killer sub-set (CD16+CD56+) usingflow cytometery:

Sample containing 1×10^6 mononuclear cells in (FCS)-RPMI-1640 were treated with 10 µl of selected monoclonal antibodies conjugated with fluorescein-isothiocyanate (FITC) or phycoerythrin (PE) in the following double staining combinations: Anti-CD16 (FITC)/ anti-CD56 (PE). After a 40 min incubation on ice in the dark, the cells were washed twice with PBS+ and re-suspended in 1 ml of cold 0.5% paraformaldehyde-PBS+, and analyzed using a FACScan flow cytometery. 10,000 cells were scanned per sample, and the findings were expressed as the percentage of cells yielding a specific fluorescence in a gated lymphocyte region.

Determination of Natural killer activity usingflow cytometery:

The natural Killer (NK)-cell activity was measured using K562 (human chronic myelogenous leukaemia cells) target cells in a calacein-release assay. Briefly, K562 cells were adjusted to 1×10^6. ml $^{-1}$ in (FCS)-RPMI-1640, in a test tube and Calcein-AM was added to final concentration of 25 µmol.1 $^{-1}$ (100× dilution of a 2.5 mmo1.1 $^{-1}$ stock solution in dimethylsulphoxide). The cells were incubated for 30 min at 37°C in a water-bath, then washed twice with PBS. Then 100µl of the labelled target cell solution [containing 1×10^5 cells in (FCS)-RPMI-1640] were added to a standard 96 well microtiter plate. Mononuclear cells are effectors from each subject were pipetted into each well at desired effector: target ratios in a final volume of 200 µl. The plate is incubated for 4 h at 37°C in a humidified atmosphere containing 5% CO_2. After this incubation, the plate was centrifuged at 200 g for 5 min. The fluorescence activity was measured in 100µl aliquots using an automated scanner. The percentage specific lysis was calculated using the following equation: (*F* experimental release minus *F* spontaneous release)/ (*F* total lysis minus *F* spontaneous release) × 100. Where *F* represented the supernatant fluorescence. Total lysis referred to the fluorescence activity (*F)* obtained after adding Triton X-100 (final concentration 1%).

Determenation of IL-6 using ELISA:

Peripheral venous blood samples were collected into serum separation tubes. Sera were obtained after a 20-min centrifugation, aliquoted and stored at −80°C until analysis. Serum neopterin was measured using a commercially available competitive enzyme-linked immunosorbent assay (ELISA). This immunoassay has a sensitivity of 0.8 nM and an interassay coefficient of variance of 5.29%. Serum IL-6 was measured using an ultra-sensitive sandwich-based ELISA human cytokine kit, which has a sensitivity of 0.05 pg/l and an interassay coefficient of variance of 3.92% for serum IL-6 measurement.

Procedures for training:

Each session of exercise contained the following categories.

Warm-up exercise:

It consisted of 15 minutes of continuous, low-intensity movement for healthy older adult to warm up before aerobic conditioning. Activities that gradually elevate patient heart rate to lower limit of their target exercise heart rates range produced the desired increase in internal temperature[10].

Conditioning phase (Walking on the treadmill):

Aerobic exercise walking on treadmill**.** Subjects walking on the treadmill for 30-40 minutes/ Session. The intensity recommended for aerobic exercise is 60-85% of maximum heart rate calculated by Karvonen method [11].

$$T \text{ (target HR)} = (\text{HRmax} – \text{HRrest}) \times (\text{present intensity}) + \text{HRrest}$$

Cool-down phase:

The aim of this phase was to discourage patients from leaving session before it ends. The cool-down was basically the warm-up in reverse, but with more static flexibility exercise and relaxation activities. Subjects Used low-intensity, continuous movement for 5 to 10 minutes to allow the body to adjust from exertion to rest

Statistical analysis

Statistical analysis was conducted using SPSS for windows, version 18 (SPSS, Inc., Chicago, IL).2×2 mixed design MANOVA was used to compare the tested variables of interest at different tested groups and measuring periods. With the initial alpha level set at 0.05.

RESULTS

The age of persons in the present study was between 60 to 75 years old with mean of (63.96±2.94), and with body mass indx range is 18.5 – 24.9(study group(23.44±1.08), control group (23.24±1.19) (Table 1).

Table (1): Physical characteristics of patients in both groups

Items	Study group	Control group	Comparison		
	Mean ± SD	Mean ± SD	t-value	P-value	S
Age (yrs)	63.96±2.94	63.96±2.94	0.00	1.00	**NS**
Height (m)	1.67±0.04	1.66±0.05	-0.699	0.487	**NS**
Body mass (Kg)	65.5±4.52	64.36±4.52	-0.97	0.336	**NS**
BMI (kg/m^2)	23.44±1.08	23.24±1.19	-0.667	0.507	**NS**

***SD: standard deviation, P: probability, S: significance, NS: non-significant.**

CD16+CD56+

Within groups:

As presented in table (2) and illustrated in figure (1), within group's comparison the mean ± SD values of CD16+CD56+ in the "pre" and "post" tests were **20.11±1.15 and 24.85±1.01**respectively in the study group. Multiple pairwise comparison tests (Post hoc tests) revealed that there was significant increase of CD16+CD56+ at post treatment in compare to pretreatment (P-value =0.0001*).Additionally, the mean ± SD values of CD16+CD56+ in the "pre" and "post" tests were **20.47±1.47 and 20.69±1.34** respectively in the control group. Multiple pairwise comparison tests (Post hoc tests) revealed that there was no significant difference of CD16+CD56+at post treatment in compare to pretreatment (P-value =0.255).

Table (2): Mean ±SD and p values of CD16+CD56+ pre and post-test at both groups.

CD16+CD56+	Pre test	Post test	MD	% of change	p- value
	Mean± SD	Mean± SD			
Study group	20.11±1.15	24.85±1.01	-4.733	23.5%	0.0001*
Control group	20.47±1.47	20.69±1.34	-0.221	1.07%	0.255
MD	-0.355	4.157			
p- value	0.31	0.0001*			

*Significant level is set at alpha level <0.05

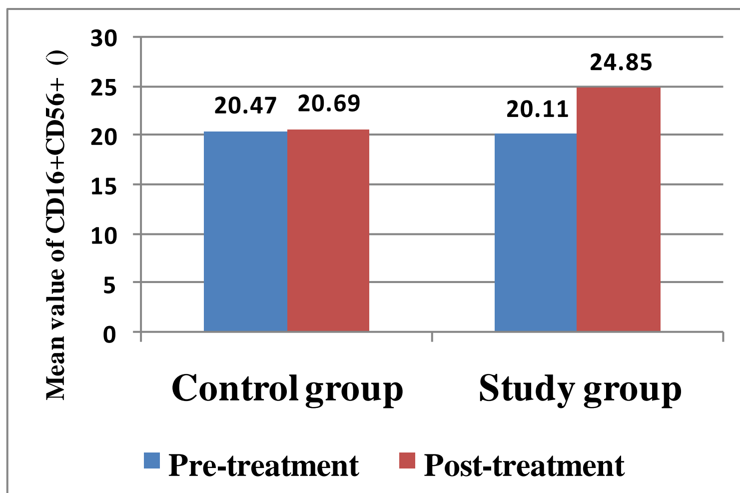

Figure (1): Mean values of CD16+CD56+ between both groups at different measuring periods.

NK lytic

Within groups:

As presented in table (3) and illustrated in figure (2), within group's comparison the mean ± SD values of NK lytic in the "pre" and "post" tests were **29.44±1.15 and 29.67±1.14**respectively in the study group. Multiple pairwise comparison tests (Post hoc tests) revealed that there was significant increase of NK lytic at post treatment in compare to pretreatment (P-value =0.0001*).Additionally, the mean ± SD values of NK lytic in the "pre" and "post" tests were **28.83±1.32 and 28.83±1.36** respectively in the control group. Multiple pairwise comparison tests (Post hoc tests) revealed that there was no significant difference of NK lytic post treatment in compare to pretreatment (P-value =0.976).

Table (3): Mean ±SD and p values of NK lytic pre and post-test at both groups.

NK lytic	Pre test	Post test	MD	% of change	p- value
	Mean± SD	Mean± SD			
Study group	29.44±1.15	29.67±1.14	-0.221	0.75%	0.0001*
Control group	28.83±1.32	28.83±1.36	0.00	0%	0.976
MD	0.613	0.836			
p- value	0.065	0.014*			

*Significant level is set at alpha level <0.

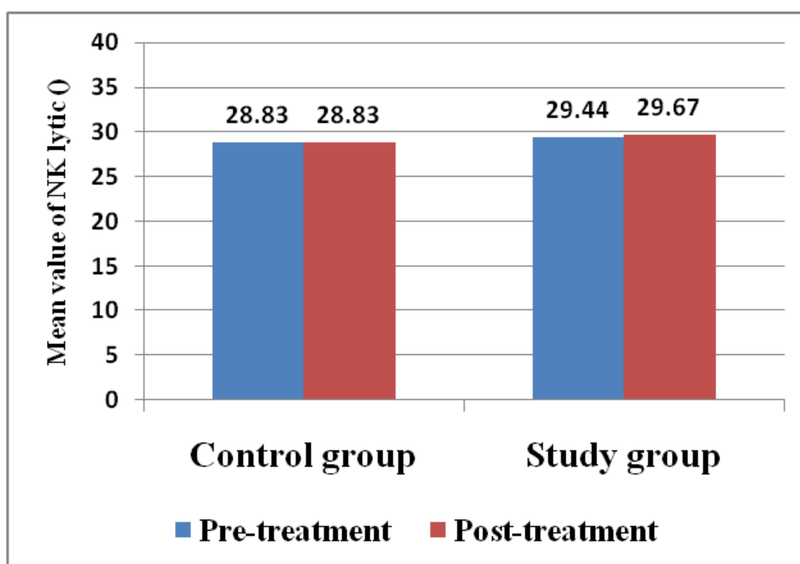

Figure (2): Mean values of NK lytic between both groups at different measuring periods.

IL-6

Within groups:

As presented in table (4) and illustrated in figure (3), within group's comparison the mean ± SD values of IL-6 in the "pre" and "post" tests were **5.01±0.47 and 2.89±0.42**respectively in the study group. Multiple pairwise comparison tests (Post hoc tests) revealed that there was significant reduction of IL-6 at post treatment in compare to pretreatment (P-value =0.0001*).

Additionally, the mean ± SD values of IL-6 in the "pre" and "post" tests were **4.85±0.58 and 4.9±0.58** respectively in the control group. Multiple pairwise comparison tests (Post hoc tests) revealed that there was no significant difference of IL-6 at post treatment in compare to pre-treatment (P-value =0.461).

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Table (4): Mean ±SD and p values of IL-6 pre and post-test at both groups.

IL-6	Pre test	Post test	MD	% of change	p- value
	Mean± SD	Mean± SD			
Study group	5.01±0.47	2.89±0.42	2.117	42.25%	0.0001*
Control group	4.85±0.58	4.9±0.58	-0.046	0.94%	0.461
MD	0.153	-2.01			
p- value	0.277	0.0001*			

*Significant level is set at alpha level <0.05

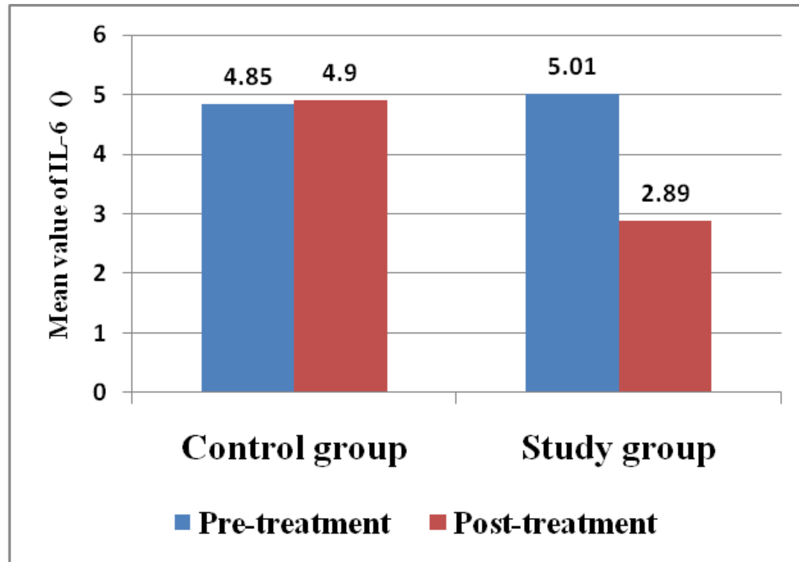

Figure (3): Mean values of IL-6 between both groups at different measuring periods.

DISCUSSION

Immunoscencence seems to occur mainly in lymphocyte components of the immunocompetent cells [12]. Selection of Natural Killer cells in this study was due to their important role in immune system, that NK cells are known as frontline responders capable of rapidly mediating a response upon encountering transformed or infected cells. Recent findings indicate that NK cells, in addition to acting as innate effectors, can also regulate adaptive immune responses, as well as long-term antiviral T cell responses, and their role in modulating immune pathology and disease[13].

In this study, a relative age-related decline of natural killer cells percentage and lytic activity in both groups before the beginning of study period. These results agreed with other studies [14] [15] showed that there was a decrease in NK cell numbers in old individuals and this associated with an increased incidence of infectious diseases in the elderly humans. Thus, low NK cell number and activity is associated with development of infections and death due to infection. Furthermore, elderly people with low numbers of NK cells were reported to have three times mortality risk in the first 2 years of follow-up than those with high NK cell numbers. Low NK cell activity is also associated with medical disorders such as atherosclerosis in the elderly and higher NK cell numbers and NK cytolytic activity were associated with better retained ability to maintain an autoimmune life style.

The decreased proliferation and production of NK cells in the elderly can be associated to the telomere shortening observed in the elderly. Thus it has been shown that NK lymphocytes show age-related loss telomeres together with an age-associated reduction of telomerase activity that was evident in individuals over 80 years in particular in the oldest individuals and in those with increased NK cell number [16].

Significant increase in the percentage and/or absolute number of CD16+ CD56+ NK cells was reported by studies that have investigated the effect of age on NK cell frequency [17] [18] [19].

For the level of interleukin-6, the results of present study before the beginning of the study period revealed that there was an increase in interleukin-6 levels in the elderly subjects. These results agree with a study applied on healthy, nonobese women (n = 208, 44.5 ± 0.70 years, 22.4 ± 0.17 kg/m2) were categorized into four age groups (22–31, 32–41, 42–51, and 52–63 years; cross-sectional study). Cytokine levels in serum and those produced from peripheral blood mononuclear cell (PBMC) were measured. The oldest group had the highest circulating levels of IL-6 [20].

Also another study reviewed from 30 selected studies dealing with immune system and aging. The concept of immunosenescence reflects changes in both cellular and serological immune responses throughout the process of generating specific response to foreign antigens. This may be related with a higher incidence of infectious and chronic diseases. After menopause, there is an increase in pro-inflammatory serum markers as IL6, an increase in response of the immune blood cells to these cytokines, a decrease in CD4 T and B lymphocytes and a decrease in the cytotoxic activity of NK cells. Additionally, IL-6 is a key factor in bone resorption and also seems to be associated with other diseases more common after menopause such as diabetes, atherosclerosis and cardiovascular disease [21].

Substantial evidence is accumulating of the relationship between exercise and immunity, and it is believed that regular participation in moderate exercise enhances the immunological capacity of the elderly, which otherwise would decline with age [12]. In this study, we investigated whether the elderly exercisers, who were not elite athletes but who regularly enjoyed moderate exercise such as walking on treadmill, had higher immunological capacities than age-matched non-exercising controls.

In the natural killer cells, the intensity of exercise influences both the number and the activity in the study group, compared to that of the age and sex matched control subjects. Also recent studies have demonstrated that the percentage and activity of NK cells elevated in elderly exercisers [22] [23]

In contrast, a single bout of exercise for at least 1 h causes cell decrease and a decline of the function; thus, the capacity to lyse tumor target cells is inhibited [24].

The response to chronic stress of an intensive exercise, in athletes compared with non-athletes, leads to increased NK cell activity (NKCA). In the old adults, a single bout of moderate exercise does not have influence on NKCA. A training program gives beneficial effects on resting NKCA, followed by increase control of both viral infections and of malignant cell formation [24].

Regular physical exercises with moderate intensity can help to reduce pro-inflammatory cytokines levels and also help to normalize this inflammatory response, as Interleukin- 6 (IL-6) [25] [26]. Additionally, exercise training has an effect on endothelial cells to reduce leukocyte adhesion and cytokine production systemically, and its effect on the immune system to lower the number of pro-inflammatory cells and reduce pro-inflammatory cytokine production per cell [27].

CONCLUSIONS

In conclusion, the exercise program is effective and beneficial for natural killer cells percentage, activity, and also macrophages activity in the elderly subjects.

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