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Impact of Moderate Interval Training on Selected Hormonal and Proinflammatory Biomarkers in Elderly Men

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Abstract: Elderly suffer from many complaints, which usually are accompanied with changes in both endocrine and immune systems. This study was designed to evaluate the effect of interval training of moderate intensity on serum cortisol and serum interleukin-6 (IL-6) in elderly men. Thirty elderly men were divided randomly into two equal groups in number, Study group: Their mean age (65.66±3.37) years and BMI (24.08±0.51) kg/m^2. Each subject in the study group performed interval training of moderate intensity calculated as 60% - 75% of their individualized maximum heart rate. The training program was applied on electronic treadmill for 40 minutes, 3 times per week for 10 weeks. Control group had their mean age (63.66±2.16) years and BMI (23.86±0.64) kg/m^2. Subjects in the control group did not participate in any form of regular exercise programs. Serum IL-6 and serum cortisol levels were measured for each subject pre and post the study. The results showed that serum IL-6 and serum cortisol levels were significantly decreased by 17.65% and 20.82% respectively in the study group compared to control group. In conclusion, interval aerobic exercise with moderate intensity can be an effective tool to decrease serum IL-6 and cortisol levels and reduce the risk of disability among elderly.

Key words: Interval exercise · IL-6 · Cortisol · Elderly

INTRODUCTION

Low-grade systemic inflammation characterizes ageing, so, inflammatory markers are significant predictors of mortality in elderly. This pro-inflammatory status of the elderly underlies biological mechanisms responsible for the decline of physical function and age-related diseases such as atherosclerosis and Alzheimer's disease which are initiated or worsened by the systemic inflammation [1].

The elderly are more susceptible to infection and immunosenescence that contributes to increase the possibility to cancer and autoimmune disease [2]. Pro-inflammatory cytokines are seen in higher concentrations in elderly compared to middle-aged or younger adults, which may have direct effects on skeletal muscle that lead to loss of myofibers and disruption of contractile function [3].

Cellular production of cytokines and circulating cytokines are, on average, 2–4 fold higher in older persons, Thus IL-6, can be coined as "cytokine for gerontologists [4]. Interleukin-6 plays multifunctional and pleiotropic roles in immune hematopoiesis, regulation, inflammation and oncogenesis [5].

Interleukin-6 differs from other cytokines in exerting its major effects at sites distant from its origin (endocrine cytokine). Inappropriate production of IL-6 is thought to have a role in the development of many age-related conditions including atherosclerosis [6].

Cortisol is basically a glucocorticoid secreted into human serum or saliva from the adrenal cortex and has a major role in the immune function, metabolism and the responses regulation of physiological stress [7].

By advancing age, there is an evidence that free radical damage may be responsible for changes in the genetic control of IL-6 regulation, which results in increasing levels of IL-6 even in the absence of an inflammatory stimulus [8].

It was reported that there is a gradual decrease in the adaptive capacity or recovery from stress throughout the aging process, A reduction in resilience to stress is

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associated with alterations in the immune system which make older people (60 years old and over) more vulnerable to the onset of diseases [9]. This consequently enhances the effects of aging on the immune system (immunosenescence) [10].

Previous studies [11, 12] reported that, reduction in the ability to respond to stress with aging can be explained, in part, by the abnormalities in hypothalamic–pituitary–adrenal (HPA) axis function which resulted in the release of cortisol in large amounts. Moreover, resistance to glucocorticoids (GCs) can occur as a result of the loss of regulation in the HPA axis, reduced GC receptor expression and feedback mechanism creating a vicious cycle that results in elevated levels of circulating cortisol.

Cortisol is commonly referred to as the "stress hormone" as it mobilizes energy sources and affects cellular metabolism to be used in the stressful situations by stimulating gluconeogenesis, lipolysis, proteolysis and glycogenolysis [13].

Regular aerobic exercise can help to control the inflammation state associated with aging [14]. All forms of aerobic exercise produce pro-inflammatory proteins depending on both the duration and intensity of exercise which can create a chemical balance between deterioration and growth within the muscles [15]. Exercise is a non-invasive, easy and low-cost intervention for many chronic diseases, as well as aging [16].

Interval training is based on a very simple concept: go fast then go slow. Repeat. Within this simple formula lays a tremendous number of possible variations and strategies that can be employed to take full advantage of the power available. Interval training can be performed on almost any cardiovascular machine (including the stair machine, treadmill, stationary bike, etc.) as well as almost any type of cardiovascular exercise (such as swimming, cycling, running, etc.) [17].

A criterion which separates interval exercise from continuous exercise is the repetitious performance of brief excursions of energy associated with anaerobic metabolism, followed by equal or greater periods of recovery [18].

Interval exercise has been the basis for athletic training routines for many years. It is a well known exercise protocol which helps strengthen and improve the one's cardiovascular system. Moreover, Interval exercise helps with general fitness, weight loss and the reduction of heart diseases [19].

It was found that, the body's energy production system is utilized and both aerobic and anaerobic energy sources are activated during interval training. Energy from these two sources is then distributed efficiently throughout the body for the duration of the workout period [20]. This study was carried out to evaluate the effect of moderate interval training on serum interleukin-6 and serum cortisol levels in elderly men.

MATERIALS AND METHODS

Subjects: Thirty elderly men were involved in this study. Their age ranged from 60 to 70 years old. They were selected randomly from different geriatrics nursing homes in Cairo, Egypt. The practical part of the current study was performed in The Outpatient Clinic of Faculty of Physical Therapy, Cairo University, Egypt.

Inclusion Criteria:

- Normal BMI (ranged from 18.5 to 24.9 kg/m^2).
- None of them was practicing any regular exercise activities.
- Their IL-6 level ranged from 7 to 14 Pg/ml.
- Their cortisol level ranged from 6 to 30 ug/dl.

Exclusive Criteria:

- Deficits in perception or cognition.
- Unstable metabolic disorders
- Severe orthopedic disorders that interfere with the aerobic exercise program.
- Advanced neuromuscular and neurological disorders.
- Evidence of any other systemic or malignant diseases or major immune-based disease.

Subjects were divided into two groups; study group: (n=15) performed supervised interval aerobic training with moderate intensity for 10 weeks (3sessions\week). Control group: (n=15), did not participate on exercises.

Material:

Evaluation Equipment:

- Standard weight and height scale (floor type, RGT-200, made in China) was used to measure body weight and height of each subject to calculate body mass index for each subject.

- Disposable plastic syringes were used for drawing venous blood samples and Polypropylene tubes with EDTA for keeping blood samples.
- Centrifuge which was used for separating blood serum.
- ELISA reader (Stat fax -2100) for estimation of serum IL-6 and serum cortisol levels.

Therapeutic Equipment: Electronic treadmill (Enraf Nonius, EN –TRED, made in Germany), was used in the interval aerobic training program of the subjects in the study group.

Methods:

Before Starting the Study, the Following Were Performed:

- The procedures and the study protocol were explained in details for each subject before the initial assessment.
- Explain signs and symptoms that when occurred, the patient must stop exercise or decrease the intensity in case of: chest pain, dizziness, headache, confusion, cold or clammy skin, sever fatigue and noticeable change in heart rate or increase of blood pressure.
- A written informed consent was signed by each patient before participation in the study as an agreement to be included in the present study.
- Before starting the exercise program, a complete medical history was taken and physical examination was done by a physician for all subjects.
- The patients were instructed not to have heavy meal for at least two hours before the exercise training.
- Each subject of both groups passed through the following steps of measurements by the physician and the physical therapist. The parameters were recorded at the beginning and the end of the total study period (10 weeks).

Measurement of Body Weight and Height: The weight and height of each subject were measured using weight and height scale and then BMI for each subject was calculated to select just normal weight subjects (BMI 18.5-24.9 Kg/m^2) using the following formula: BMI= weight (Kg) / $[height (m)]^2$ [21].

Laboratory Investigations: The laboratory investigations were done before and after the completion of the study (10weeks) for subjects of both groups.A three milliliter-sample of venous blood was drawn from the antecubital vein from all subjects to be assayed for measurement of serum interleukin-6 and cortisol levels before and after the study period (10 weeks).

- Blood samples were collected in serum separator tubes and immediately sent to the laboratory for centrifuge. Sera were stored at -70°C for later cytokine analysis by enzyme linked immunosorbent assay using commercially available kits.
- Cortisol was measured as a physiological index of the neuroendocrine response to stress. A radioimmunoassay procedure using commercially available kits was used to determine plasma cortisol levels. The laboratory investigations of cortisol were done at 9 am for all subjects of both groups without fasting.

Training Program: Each subject in the study group performed a supervised interval training of moderate intensity, 3 times per week for 10 weeks on electronic treadmill. Subjects had a preparatory session to get familiarized with treadmill walking and exercise limiting symptoms (e.g. chest pain, breathlessness, fatigue and leg cramp). The intensity of exercise has been determined as a training heart rate (THR) based on the subject's maximum heart rate (HR max) and resting heart rate (HR rest) calculated according to Karvonen formula: THR=HRrest + (HRmax –HRrest), TF where TF=training fraction, the moderate training was from 60 to 75% [22]. Each subject started the session by 5minutes warming-up in the form of walking slowly on the treadmill (30-40% of the Hrmax), then, the active phase (30 minutes) in which the subjects increased their activity to achieve the chosen higher HR (i.e. 75%) for 5 minutes and then decreased their activity to achieve the lower chosen HR (i.e. 60%) for 5minutes, alternating between low and high HR for the length of the activity [23], then the exercise session was ended by cooling down in form of slow walking on the treadmill (30-40% of the Hrmax). During exercise, heart rate was monitored on treadmill screen and after cooling down, the subjects were seated and monitored for heart rate using pulse meter until reaching the resting heart rate level. All exercise sessions were under the supervision of the physical therapist and subjects were monitored for any signs of fainting or fatigue and the patient was allowed to stop the session whenever he wanted.

Statistical Procedures: The data obtained were analyzed using SPSS (version 17 for windows; statistical package, 2008). Descriptive statistics were presented in terms of mean and standard deviation for age, height, weight and BMI. Dependent and independent t-tests were used to determine the differences in mean values of IL-6 and cortisol levels between the two groups and within each group. Significance was set at $p < 0.05$.

RESULTS

Subjects Descriptive Data in Both Groups: Table (1) show the statistical analysis of age, height, weight and body mass index (BMI) of study and control groups, there was no significant difference between the two groups, p-value > 0.05.

Results of Serum Interleukin-6 and Cortisol Levels: In comparison of the changes between both groups as shown in table (2), The results revealed that the mean concentration of serum IL-6 in the study group pre and post training was 11.33±1.11 and 9.33±1.45 respectively, thus the serum IL-6 concentration decreased after 10 weeks of interval training in study group (p= 0.001) compared to control group. Also, statistical analysis of the mean concentration of serum cortisol in study group pre and post training showed significance difference as the serum cortisol level decreased from 15.08±4.22 to 9.33±1.45 (p=0.03) compared to control group.

DISCUSSION

This study was conducted to determine the impact of moderate interval training on serum IL-6 and serum cortisol levels among elderly men. After 10 weeks of training, there was a significant decrease in serum interleukin-6 and cortisol levels with a percentage of improvement (decrease) of 17.65% and 20.82% respectively in the study group compared to control group. Indeed, several studies have examined, using continuous training load, the effect of physical exercise on proinflammatory and hormonal biomarkers in elderly. For this, we chosed to evaluate the interval training's contribution to the health benefits of exercise in elderly.

It was found that serum interleukin-6 and serum cortisol levels can act as predictors of future disability among elderly [24]. Interval exercise has received a large amount of attention for its ability to elicit both performance and health benefits.

Unlike continuous aerobic exercise in which the intensity levels are maintained at a steady state, interval exercise uses repetitive alternating periods of high intensity activity and low intensity recovery. Interval training offers an increase in aerobic fitness, but its anaerobic excursions may resulted in added benefits [25].

Intensity and duration of exercise are important determinants of the physiologic adaptations that occur in response to training [26]. Compared with the same total amount of work performed continuously, interval exercise imposes maximal loads on both peripheral muscles and

Table 1: Descriptive data of subjects of both groups

	Study group	Control group			
Variable	Mean± SD	Mean± SD	t-value	p-value	Significance
Age (year)	65.66±3.37	63.66±2.16	1.93	0.06	NS
Weight (kg)	69.80±2.71	68.80±5.69	0.54	0.57	NS
Height (cm)	170.93±2.86	170.60±3.56	0.28	0.78	NS
BMI(kg/cm^2)	24.08±0.51	23.86±0.64	1.04	0.30	NS

SD: Standard Deviation, P- value: Probability Level, NS: Non-Significant

Table 2: Comparison of serum IL-6 and cortisol level between study and control groups pre and post study.

Variables		Study group	Control group	t. value	P. Value	Significant level
Interleukin-6 (pg/ml)	Pre	11.33±1.11	11.27±1.16	0.16	0.87	NS
	Post	9.33±1.45	11.42±1.22	-4.27	0.001	S
Cortisol level (ug/dl)	Pre	15.08±4.22	14.68±2.45	0.32	0.75	NS
	Post	11.9±4.53	14.85±2.84	-2.91	0.03	S

SD: Standard Deviation, P- value: Probability Level, NS: Non-Significant, S: Significant, Pre: at base line measurement, Post: after 10 weeks of study

oxygen-transporting organs without significant engagement of anaerobic processes and accumulation of lactic acid (less glycogen is used and the lactate concentration in the muscle is much lower) [27].

It was found that, the reduction in serum cortisol levels was associated with the reduction in levels of serum IL-6 in older adults. So, cortisol may have an indirect role among elderly through its association with interleukin-6 which act as a pro-inflammatory marker [28].

The results of the current study is supported by Brown [29] in which cortisol level was investigated in 20 older adults after 8 weeks of exercise training and it was found that the cortisol level decreased in study group but the level increased in the controls.

These results are consistent with the findings of Ronsen *et al.*[30] who study the effect of different exercise modalities on serum cortisol in 40 older adults in which subjects were divided randomly to three groups: group(A) control; group(B); performed aerobic exercise of moderate-intensity; group(C) performed resisted exercise. Serum cortisol levels were measured before and after 10 weeks. The results revealed that, the serum cortisol levels decreased in the two exercising groups, but the reduction was significant especially in group (c), compared to control group.

Also, Papanicolaou *et al.* [31] reported that, the level of serum cortisol can be changed by changing the type of exercise as it was found that its values were significantly lower than controls in rowers (-22%)and swimmers (-50%). So, a regular program of exercise training is desired to achieve a significant decrease in serum cortisol level

This study is also supported by Corazza *et al.* [32] who observed that chronic exercise may have a positive influence on serum cortisol level in older people, causing a decrease in concentration, which may help prevent comorbidities and acting as a nonpharmacological treatment.

The results of the current study agree with Helge *et al.* [33] who found that interleukin-6 was decreased by -15% among elderly women who performed moderate-intensity aerobic exercise (60% - 75% of maximal HR) and increased by 5% in subjects who did not perform any type of exercise. The reduction in IL-6 may support the importance of exercise in adjust the pro-inflammatory cytokines.

It was found also that sixteen weeks of aerobic exercise training lead to improvements of pro-inflammatory cytokines measurements as noted by IL-6 reduction [34]. Also, aerobic training program was found to decrease IL-6 levels significantly compared to control group in older women [35].

Mazzeo *et al.* [36] demonstrated that physical activity has been shown to decrease stress-induced immunosuppression and enhance immune regulation through increasing the production of immune components and decreasing the production of cytokines, especially IL-6 and TNFá, in older adults.

Tracey [37] reported that exercise training might reduce systemic inflammation in the elderly by the "cholinergic anti-inflammatory pathway," in which stimulation of the parasympathetic nervous system, via the efferent vagus nerve, inhibits pro-inflammatory cytokine production and protects against systemic inflammation.

Research work done by Yung *et al.* [38] may explain the concept that physical fitness promotes cardiovascular health, including improved endothelial function and possibly reduced proinflammatory cytokines responses to stressors. This study examined the effects of fitness on leukocyte-endothelial adhesion in response to an acute exercise challenge. The findings indicate that immune cells that demarginate in response to exercise have reduced ability to adhere in individuals, who are physically fit, an effect apparently independent of ICAM-1 binding. The findings provide evidence of how physical fitness might protect individuals from proinflammatory cytokines responses to exercise.

However, other studies had not found any changes in IL-6 basal levels after training [39, 40], It can be attributed to the differences between the studied groups, exercise duration, exercise period, intensity and mode.

CONCLUSIONS

It can be concluded that moderate interval training program could be used as a good alternative treatment modalitiy to the constant-load exercise training to modulate the serum cortisol and serum interleukin-6 levels among elderly. Hence, reduce the risk of future disability in older adults.

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