Effect of Aerobic Exercise and Natural Extract on TNF (α) in Women with Metabolic Syndrome

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Abstract

Background and Purpose: Aerobic training and natural extract (green tea) for women with metabolic syndrome improves the level of Tumor Necrosis Factor (α), exercise capacity, restores endothelial function and skeletal muscle changes. The effects of three months aerobic exercise training and natural extract on inflammatory cytokines (tumor necrosis factor (α)) in women with metabolic syndrome were studied.

Patients and Methods: Sixty women diagnosed as metabolic syndrome patients as a result of some metabolic and cardiovascular diseases with age of 40-50 years were included in the present study. Their Body Mass Index (BMI) (30-39.9 kg/m²). They were randomly divided into three equal groups, Group (A) who participated in a program of aerobic exercise in the form of treadmill walking (4 times per a week) for 30min and drank 5 cups of the water extract of the green tea leaves daily, Group (B) who participated only in the same program of aerobic exercise as Group (A), and Group (C) who drank the same green tea extract in the same manner as Group (A) but without application of any aerobic exercise at all. The study was conducted from May 2015 till August 2015, at PT Department of El-Monira Hospital in Cairo.

The biochemical changes in inflammatory markers [tumor necrosis factor (α)] were measured at the beginning of the study and after twelve weeks.

Results: Showed that a program of aerobic exercise training and water extract of green tea had highly significant effect to decrease TNF (α) in Group (A) as this group had significant reduction by (42%) while Group (B) showed reduction by (20.45%) and in Group (C) by (21.88%).

Conclusion: It was concluded that a program of aerobic training combined with green tea had the most statistically significant reduction in TNF (α) in metabolic syndrome women.

Key Words: Aerobic exercise – Natural extract – TNf (α) – Metabolic syndrome.

Introduction

THE metabolic syndrome refers to a constellation of clinical factors associated with an increased risk of diabetes and coronary artery disease. These factors include abdominal obesity, hypertension, dyslipidemia, impaired glucose metabolism, prothrombotic state. Also called the dysmetabolic syndrome, syndrome X or insulin resistance syndrome [1].

Systemic inflammation is linked to numerous chronic health conditions, including cancer. Pro-inflammatory factors, such as C-reactive protein, serum amyloid A, interleukin-6, and tumour necrosis factor-alpha plus the anti-inflammatory factors as adiponectin, interleukin-4, interleukin-10 and transforming growth factor-beta-1 (TGF-beta-1), are now being investigated as markers of disease risk and prognosis. Physical activity may reduce systemic inflammation alone or in combination with body weight or composition [2].

Inflammatory activation with increased serum cytokine levels has been described by several authors as an important factor in the progression of the syndrome of Chronic Heart Failure (CHF). IL-6 is a "myokine", a cytokine produced from muscle, and is elevated in response to muscle contraction. It is significantly elevated with exercise, and precedes the appearance of other cytokines in the circulation. During exercise, it is thought to act in a hormone-like manner to mobilize extracellular substrates and/or augment substrate delivery [3].

Exercise training has been documented to improve the inflammatory profile and (TNF-α) by inhibition of cytokine-chemokine production, reg-
ulation of monocyte activation and adhesion, inhibition of inflammatory cell-growth signals and growth factor production, reduction of soluble apoptosis signaling molecules [4].

Green tea treatment also was found to reduce adipose tissue mass (21% decrease) and hepatic lipids (13% decrease). Immunological analysis showed that 1% green tea extract treatment decreased hepatic expression of the inflammatory marker, tumor necrosis factor (TNF-α), in the liver and adipose tissue [5].

Purpose of the study:

To determine the response of tumor necrosis factor (TNF-α) to aerobic training and natural extract on women with metabolic syndrome.

Patients and Methods

Sixty untrained obese women with metabolic syndrome who were encouraged to follow their habitual life style throughout the study period. They were selected randomly and referred by the physician from the clinic of Internal Medicine in El-Monira Hospital and they were operated in the Department of Physical Therapy at El-Monira Hospital one of the Egyptian Health Ministry Hospitals in Cairo. Their weight and height allowed them to be considered obese according to Body Mass Index (BMI) equation, between (30-39.9kg/m²), the study was performed from May 2015 till August 2015. The sixty women metabolic syndrome patients were randomly divided into three groups; each group consisted of twenty patients. The first received a program of aerobic exercise and drank green tea in specific manner (Group A) and the second group (Group B) that performed the same aerobic exercise program as (Group A), the third group drank only green tea without participation in any exercise at all (Group C). All groups was under their medical treatment prescribed by the physician all patients were diagnosed as having metabolic syndrome. Their inclusion criteria was as follow: Age from 40-50 years, body mass index from (30 to 39.9kg/m²), the onset of the disease was more than 5 years, and received the same necessary required drugs. Any patient had hepatic disease, severe life limiting illness (cancer, renal failure), other endocrinal disorders, orthopedic limitation, severe hyper tension, chronic pulmonary disease was excluded from the study.

Instrumentation:

A treadmill was used for warming up exercise (tunturi original treadmill W1 electronics), sphygmomanometer and stethoscope for measuring blood pressure before, during and after training sessions, weight and height scale: (Healthy scale 160kg) to evaluate the height, weight and BMI.

\[
\text{BMI} = \frac{\text{Weight (Kg)}}{\text{Height (m²)}}
\]

Kits and tubes of blood sample.

Procedure:

A- Evaluation session:

After selection of the patients an informed consent was taken from all patients who accepted to participate in the study. Before starting the study all patients were informed about the nature, benefits and procedure of the study, the sample was randomly divided into three equal groups equal in number, 20 for each group; Group A received a program of aerobic exercise training and drank 5 cups of green tea per day, Group B performed a program of aerobic exercise only (as Group A), Group C women in this group drank green tea only in the same manner as the Group (A).

Plasma or serum samples were obtained by venipuncture (arterial cannula used in Larsen's study) and stored on ice. Concentration of tumor necrosis factor (TNF-α) was measured by commercially available enzyme-linked immunosorbent assays (ELISAs) [7].

B- Aerobic training: (Program for Group A & B):

All women in the (Group A), and Group (B) attended the program of aerobic exercises for 12 weeks according to the following parameters:

- Mode of exercise was regular aerobic exercise for large group of muscles (legs and arms) in form of walking used treadmill.

- Intensity of exercise was ranged from 60 to 70% of Target Heart Rate (THR) and the THR=60 to 75% maximum heart rate (MHR=220-age) [8].

- Duration: The first five to ten minutes of each session was dedicated to warming up exercise on a treadmill and the same for the cooling down phase. There was a thirty minute of aerobic exercise.

- Frequency: Four times per week for three months.

- Treadmill training recommendations for patients with metabolic syndrome were described by Warm up and cool down duration from 5-10 minutes, active phase 30 minutes, the duration of session was 40-50min., the mode was aerobic exercises training in form of walking.
Blood pressure was measured before, during and after session.

C- Regimen of natural extract drink for Group (A) & (C):
Each women of the Group (A) and those of the Group (C) drank 5 cups of green tea every day for 3 months without sugar and with the following procedure taking in consideration that extraction of the dried leaves with water through heating with a temperature exceeding 45ºC may result in hydrolysis of the bioactive constituents included in the water extract as follow:
- Use 2 grams (one tea spoon) of tea/cup (each cup bears about 150ml of water).
- Fill a kettle with cold water and bring to a boil.
- After unplugging the kettle allow it to stand for up to fifteen minutes.
- Pour the heated water over the tea and allow it to steep for up to 10 minutes.

After 12 weeks program, another blood sample was taken and tumor necrosis factor (α) was measured and then the pre and post samples for the three groups were compared.

Statistical analysis:
Descriptive statistics and MANOVA-test were conducted for comparison of subject characteristics between groups. MANOVA-test was conducted for comparison of pre and post treatment mean values of TNFα between the three groups. Paired t-test was conducted for comparison between pre and post treatment mean values of TNF (α) in each group. The level of significance for all statistical tests was set at \( p < 0.05 \). All statistical measures were performed through the Statistical Package for Social Studies (SPSS) version 19 for windows.

Results

Subject characteristics:
Table (1) showed the mean ± SD and BMI of Group A, B, and C. There was no significant difference between the three groups in the mean age and BMI (\( p > 0.05 \)), at the starting of the study.

Between group comparison:
There was no significant difference in TNFα between groups pre-treatment (\( p > 0.05 \)) (Table 2).

Post treatment, there was a significant decrease in TNFα of Group A compared with Group B (\( p = 0.0001 \)) with the favour for Group A. Also there was a significant decrease in TNFα of Group C compared with that of Group B (\( p = 0.0001 \)) with the favour for Group C. However There was no significant difference in TNFα between Group A and C (\( p = 0.68 \)) (Table 3).

Within group comparison:
Statistical analysis of TNFα values in each groups showed significant reduction after the study.

There was a significant decrease in TNFα post treatment compared with pre treatment in group A (\( p = 0.0001 \)), the percent of decrease in TNFα was 42%. Also, there was a significant decrease in TNFα post treatment compared with pre treatment in Group B (\( p = 0.0001 \)), the percent of decrease in TNFα was 20.45%. In Group C, there was a significant decrease in TNFα post treatment compared with pre treatment (\( p = 0.0001 \)), the percent of decrease in TNFα was 39.69% (Table 4).

![Pre and post treatment mean values of TNF α of Group A, B, and C.](image)

Table (1): Descriptive statistics and MAANOVA test for the mean age and BMI of Group A, B, and C.

<table>
<thead>
<tr>
<th>Group</th>
<th>X ± SD</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A</td>
<td>45.1±2.77</td>
<td>0.76*</td>
</tr>
<tr>
<td>Group B</td>
<td>44.75±3.16</td>
<td></td>
</tr>
<tr>
<td>Group C</td>
<td>45.45±2.99</td>
<td></td>
</tr>
</tbody>
</table>

\( \times \) : Mean.
\( \text{SD} \) : Standard Deviation.
\( p \)-value : Level of Significance.
\( \ast \) : Non-Significant.

Table (2): Comparison of TNFα pre treatment between Group A, B, and C.

<table>
<thead>
<tr>
<th>Group</th>
<th>X ± SD</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A</td>
<td>15±0.58</td>
<td>0.62*</td>
</tr>
<tr>
<td>Group B</td>
<td>15.11±0.5</td>
<td></td>
</tr>
<tr>
<td>Group C</td>
<td>14.94±0.57</td>
<td></td>
</tr>
</tbody>
</table>

\( \times \) : Mean.
\( \text{SD} \) : Standard Deviation.
\( p \)-value : Level of Significance.
\( \ast \) : Non-Significant.
The purpose of the present study was designed to determine the response of tumor necrosis factor (α) to aerobic training and natural extract on women with metabolic syndrome. Sixty women metabolic syndrome patients were randomly divided into three equal groups; each group consisted of twenty patients. The first received a program of aerobic exercise and drank green tea in specific manner (Group A) and the second group (Group B) that performed the same program as (Group A), the third group drank only green tea without participation in any exercise (Group C).

The results showed that program of aerobic exercise and green tea had an effect on tumor necrosis factor (α) to an extent statistically significant by (42%; \( p>0.05 \), 20.45%; \( p>0.05 \), 39.69%; \( p>0.05 \)) in Group (A), (B), (C) respectively, but the effect was highly significant in the Group (A) followed by Group (B), which means that aerobic exercise when combined with drinking green tea had a highly significant effect than using green tea only.

Several possible mechanisms can explain why aerobic exercise training reduced chronic inflammation. First, long-term exercise may protect against chronic systemic low grade inflammation via IL6 independent pathways, IL-6 may partly contribute to the anti-inflammatory activities (e.g., decreased production of TNF-α), because TNF-α stimulates the production of IL-6. In return, IL-6 inhibits the transcription of TNF-α and stimulates the production of anti-inflammatory cytokines and the shedding of TNF receptors that bind TNF-α with high affinity. Second, resisted exercise training can protect against chronic systemic low-grade inflammation through improve blood pressure, insulin resistance, and muscle mass [9].

Inflammatory markers that included (TNF-α) were recorded in the three groups at two intervals; the starting of the experiment (pre) and at the end of the twelve weeks (post program).

The result of the present study was supported by Kishiko et al. [10], who approved that aerobic exercise training-combined with drinking water extract of green tea leaves was associated with slightly reduction of TNF-α. Twenty-one elderly women (mean age ± SD, 85.0±4.5 years) participated in 12 weeks of moderate intensity aerobic exercise training combined with green tea drinking Muscle thickness and circulating levels of interleukin-6 (IL-6) and TNF-α. Were measured before and after the program. The program induced significant reductions in TNF-α.

In agreement with present study results of Suleen et al. [11], who approved that aerobic exercise and green tea drinking had been shown to slightly lower levels of interleukin-6 and TNF-α. The effect of 12 weeks of moderate-intensity aerobic exercise was examined on TNF-α. Compared to no exercise in overweight and obese individuals. TNF-α levels were significantly decreased at week 12 compared to baseline in the other control group. Therefore, aerobic exercise training when combined with green tea drinking may be physiologically relevant in decreasing the risk of developing metabolic syndrome.

A randomized, controlled trial was done by Josef [12] who documented the effects of aerobic exercise training on inflammatory markers (TNF-α) in patients with metabolic syndrome, inflammatory mediators such as tumor necrosis factor-alpha, interleukin-6, and nitric oxide can produce effects that mimic features of heart failure, including (but not limited to) progressive left-ventricular dysfunction, pulmonary edema, left-ventricular remodeling, and cardiomyopathy. This study performed on 50 patients with age ranged from 40 to 60 years old these patients asked to perform 12 weeks of moderate intensity aerobic training. Tumor necrosis factor (TNF)-α, IL-6 were measured before and after finishing the exercise program, the result was reduction in (TNF)-α by 18%, CRP by 23% but IL-6 was not statistically significantly decreased. However, there are several randomized trials which

<table>
<thead>
<tr>
<th>Group A</th>
<th>Group B</th>
<th>Group C</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>( X±SD )</td>
<td>( X±SD )</td>
<td>( X±SD )</td>
<td>A vs B</td>
</tr>
<tr>
<td>TNFα (pg/ml)</td>
<td>8.7±0.22</td>
<td>12.02±1.5</td>
<td>9.01±1.38</td>
</tr>
</tbody>
</table>

\( \times \) : Mean. \( p\)-value : Level of Significance.

<table>
<thead>
<tr>
<th>( X±SD )</th>
<th>( X±SD )</th>
<th>MD</th>
<th>% of change</th>
<th>( p)-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A</td>
<td>15±0.58</td>
<td>8.7±0.22</td>
<td>6.3</td>
<td>42</td>
</tr>
<tr>
<td>Group B</td>
<td>15.11±0.5</td>
<td>12.02±1.5</td>
<td>3.09</td>
<td>20.45</td>
</tr>
<tr>
<td>Group C</td>
<td>14.94±0.57</td>
<td>9.01±1.38</td>
<td>5.93</td>
<td>39.69</td>
</tr>
</tbody>
</table>

\( \times \) : Mean. \( R\)-value : Level of significance.

Discussion

Table (3): Comparison of TNFα post treatment between Group A, B, and C.

Table (4): Comparison of TNF (α) between pre and post treatment in each group.
unanimously documented that patients with metabolic syndrome opposed to acute bouts of exercise does not only lead to a reduction of cytokines (interleukin-6, TNF-α) and oxidative stress, but that patients dramatically benefit by the increase in maximal oxygen consumption, exercise capacity, quality of life, reduction in hospitalization, morbidity, and mortality.

Similarly, Hilde et al. [13], defined the effects of aerobic treadmill exercise on inflammatory markers (interleukin-6) in patients with metabolic syndrome compared with healthy controls, to determine whether exercise elicits an abnormal inflammatory response in those patients for 3 months of mild to moderate intensity exercise. Circulating levels of Serum Amyloid A (SAA), tumor necrosis factor (TNF)-α and IL-6 were measured before and after the exercise training. 60 persons with mean age 45 years were included in this study. These patients were diagnosed as metabolic syndrome. The result was decreased in (TNF)-α by 14%, decreased Serum Amyloid A (SAA) by 17% and no significantly changed in IL-6. Chronic inflammatory diseases strike millions of people all over the world, and exercise is often prescribed for these patients to improve overall fitness and quality of life. Evidence was found that chronic aerobic exercise training programs can lower systemic inflammation in patients with chronic metabolic syndrome compared to healthy matched controls.

It also come in support with the results of the study by Aldujaili et al. [14] that was published in 2009 which concluded that short term consumption of commercial green tea decrease TNF-α and also reduces systolic and diastolic BP, fasting total cholesterol, % body fat and body weight, suggesting a role for green tea in decreasing established potential cardiovascular risk factors. Participants (n=12; 9 females and 3 males) were asked to drink 4 cups of green tea for 14 days then the final evaluation was applied and provided these results: Mean systolic BP was reduced significantly by 7.1 mmHg (p<0.0001), mean diastolic BP reduced by 7.8mmHg over 14 days (p<0.0001), mean fasting total cholesterol was reduced significantly by 0.556 mmol/l (p<0.008), BMI by 0.34kg/m² (p<0.001), body weight by 0.96kg (p<0.001) and body fat by 2.36% (p<0.005).

Similarly, Miguel et al., [15], examined the effect of aerobic exercises training in heart failure on TNF-α, IL-6 and IL-10. A program of resisted exercise training with moderate intensity applied to thirty patients for three months. Circulating levels of tumor necrosis factor (TNF)-α, IL-6 and IL-10 were measured before and after the exercise training. The exercise training-induced cardiovascular benefits of physical exercises performed at intensities ranging from mild to moderate. (TNF)-α was significantly decreased.

The results showed by Stephan et al., which came in contrast with results of the current study [16], who assessed the effects of aerobic exercise training in the skeletal muscle of patients with metabolic syndrome; twenty male patients with metabolic syndrome; mean age 54±2 years were randomized to a training group (n=10) or a control group (n=10). At baseline and after six months. Serum Tumor Necrosis Factor (TNF)-alpha, Interleukin (IL)-6, and IL-1 beta levels were measured. Serum levels of IL-6, and IL-1-beta remained unaffected by training, TNF-alpha increased significantly by 2%.

On the other hand, Balducci et al. [17], investigated the effect of different exercise modalities on high sensitivity-C Reactive Protein (CRP) and other inflammatory markers (IL-1, IL-4, IL-6, IL-10, (TNF)-α) in patients with type 2 diabetes and the metabolic syndrome. Eighty-two patients were randomized into four groups: (A) Sedentary control; (B) Receiving counseling to perform low-intensity physical activity; (C) Performing prescribed and supervised high-intensity aerobic exercises. Inflammatory biomarkers were performed at baseline and every 3 months. Levels of CRP decreased in all three exercising groups, but the reduction was significant only in Groups C and D, and particularly in Group D.

On the contrary, Niebauer et al. [18], determined the effect of aerobic exercise training combined with watery extract of green tea in metabolic syndrome patients on inflammatory cytokines and markers of endothelial damage. Measured tumor necrosis factor α (TNF-α), its soluble TNF-receptors 1 and 2, interleukin 6 (IL-6), in 18 patients with CHF and 9 age-matched controls in a randomized cross-over study of 8 weeks of exercise training. At baseline, patients had significantly elevated levels of TNF-α and TNF-R2; after a program of aerobic exercises there was significant reduction in TNF-α, TNF-R 1 and 2 and IL-6 levels in the training group.

In contrast, Conraads et al. [19], who assessed the relation between aerobic training with green tea regular drinking according to specific program
and TNF-alpha and IL-6 levels in patients with metabolic syndrome. Blood sampling for measurement of plasma concentrations (ELISA) of inter-leukin-6, tumor necrosis factor-alpha, soluble TNF receptor-1 (sTNFR1) and 2 (sTNFR2) as well as cardiopulmonary exercise testing were performed at baseline and after 4 months. Training induced no significant decrease in sTNFR1, sTNFR2 concentrations and TNF-a level were no significantly altered. Cytokine concentrations remained unchanged in an untrained age-and sex-matched control group due to the small sample of the study.

Conclusion:
A program consisted of aerobic exercise training and green tea showed significant reduction in TNF-a in the three groups, but this reduction was highly significant in patients who drank green tea with the aerobic exercise (Group A) when compared with patient of Group (B) and Group (C). This combination between aerobic exercise and green tea can greatly lower the risk for metabolic syndrome, coronary heart disease, and risk of immune disease.

References


الملخص العربي

هدف البحث هو دراسة تأثير التمرينات الهوائية على معدل التعرض السرطاني لدى السيدات المصابات بمتلازمة الأيض.

أجري البحث على ستون مريضة من مستشفى المنيره العام بالقاهرة حيث تراقبت أعمارهم ما بين أربعين وخمسون عاماً والثاني بعدها من مترشمه الأيض. وقد تمت هذه الدراسة على مدار اثني عشر أسبوع لقياس نسبة دخل الانتحابات التي تشكل (معامل التعرض السرطاني الفا). ثم تقسيم المريضات إلى ثلاث مجموعات كل مجموعة تكونت من عشر مريضة. المجموعة الأولى التي تلقى برنامج التمرينات الهوائية (240 دقيقة) وتتأهل كميات معينة من المستخلص المائي للشاي الأخضر. بينما المجموعة الثانية (ب) أدين نفس البرنامج الذي أثرت المجموعة (أ) من التمارين الهوائية فقط. كما قامت المجموعة الثالثة (ج) فقط بتناول نفس جرعة الشاي الأخضر الذي تناولته المجموعة (أ) دون أداء أي تمارين توفرت على الإطلاق. وقد استمر البرنامج لمدة أثاث عشر أسبوعاً (بمراعاة أربع جلسات من التمارين الهوائية أسبوعياً، خمسة أربعة من الشاي الأخضر يومياً) وقد تم قياس نسبة معدل التعرض (التنكرز) السرطاني الفا بالدم والمجموعة الثانية التي لم تلقى أي برنامج تمرينات. وقد تم تسجيل النتائج على مرتين، عند البدء وبعد مرور اثاث عشرة أسابيع.

النتائج: أظهرت النتائج وجود انخفاض في دالة إحصائية بنتسبة معدل التعرض السرطاني (الفا) في الثلاث مجموعات لكنها كان ذو دالة إحصائية عالية داخل المجموعة الأولى بقدر (4.23) ثم المجموعة الثالثة بقدر (2.69) وقد تتبع النتائج كانت لدى المجموعة الثانية والتي تحققت البرنامج من التمرينات فقط (2.40) وذلك بعد الأسبوع الثاني عشر.

الخلاصة: إضافة التمرينات الهوائية إلى شرب كميات من المستخلص المائي للشاي الأخضر يحفز تأثيرها على معدل التعرض السرطاني (الفا) في السيدات المصابات بمتلازمة الأيض.