

Acute Aerobic Exercise Decreased Tumor Necrosis Factor Alpha (TNF- α) Levels in Obese Adolescent Females

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Abstract

Introduction – Systematically, obesity was associated with low-grade inflammation indicated by abnormal adiponectin secretion, thereby activating inflammatory signaling pathways that could impact chronic inflammation and increased the risk for causing cancer cells. The exercise was an effective and efficient strategy in maintaining pro and anti-inflammatory homeostasis. Exercise performed regularly could increase adiponectin levels as anti-inflammatory markers and decreased pro-inflammatory cytokines, such as Tumor Necrosis Factor- α (TNF- α).

Objective – This study aimed to prove the effect of acute aerobic exercise in the decrease of TNF- α levels on obese adolescent females.

Material and Methods – A total of 14 obese adolescent females were participated in this study and were randomly divided into two groups, namely CG ($n=7$, control group), AEG ($n=7$, acute aerobic exercise group). ELISA was used to measure TNF- α levels in all samples. Statistical analysis was performed using the Paired Samples T-Test and Independent Samples T-Test.

Results – The results of the Paired Samples T-Test on CG showed that there was no significant difference between the mean of TNF- α levels in pre-exercise and 10 min post-exercise ($p>0.05$). However, AEG showed a significant difference between the mean of TNF- α levels in pre-exercise and 10 min post-exercise ($p<0.05$). The results of the Independent Samples T-Test showed that there was no significant difference between the mean levels of TNF- α pre-exercise in CG and AEG ($p>0.05$), while the mean TNF- α level of 10 min post-exercise among CG and AEG showed a significant difference ($p<0.05$).

Conclusion – Our data showed that TNF- α levels were decreased by 10 min post-acute aerobic exercise. Therefore, acute aerobic exercise could be used as a method to decrease the level of inflammation in obese adolescent females.

Keywords: Acute aerobic exercise, TNF- α levels, obese adolescent females

Introduction

Obesity was a world health problem that must be noticed¹, because obesity increased the risk of various

chronic diseases such as type 2 diabetes (T2D), hypertension, and cardiovascular disease (CVD)²⁻³, and several types of cancer⁴. Obesity was also associated with bad impact on health quality including metabolic complications which involved many cytokines and hormones¹. One of the cytokines that played a role in obesity was Tumor Necrosis Factor alpha (TNF- α)⁵. TNF- α was a pro-inflammatory cytokine that found increased in obese condition⁶⁻⁷. Research conducted by

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Dahlman *et al.*⁸ reported that there was a correlation between TNF- α polymorphism and obesity-related phenotypes. The increased TNF- α could cause hyperlipidemia and insulin resistance, especially in the presence of single nucleotide polymorphisms (SNP) on the promoter (-308 G/A and -238 G/A)⁹. In addition, TNF- α was also an insulin receptor antagonist, so that increased TNF- α production could interfere with the signaling of insulin and inhibited glucose absorption¹⁰, which could lead to insulin resistance¹¹.

Systematically, obesity was associated with low-grade inflammation indicated by abnormal secretion of adiponectin, so that could activate inflammatory signaling pathways¹² which could impact chronic inflammation¹³ and increased the risk for causing cancer cells¹⁴. That was proved by an increase in inflammatory markers, such as TNF- α in obese individuals compared to normal and lean individuals⁵⁻⁶. The high level of TNF- α was the characteristic of many malignant cancers, including breast cancer, and was often associated with cancer cell aggressiveness and poor prognosis¹⁵. Therefore, a specific strategy was needed to prevent the increase of inflammation in obese individuals through non-pharmacological therapy based on exercise. The exercise was an effective and efficient strategy in maintaining pro and anti-inflammatory homeostasis in the body¹⁶. Exercise performed regularly could increase adiponectin levels as a marker of anti-inflammatory¹⁷⁻¹⁸ and decreased pro-inflammatory cytokines, such as TNF- α ¹⁹, so that exercise could be used as a strategy in maintaining the balance of inflammation level. However, several previous studies reported controversial results. Such as research conducted by Dos Santos *et al.*²⁰ reported that moderate-intensity continuous exercise (55% VO_{2max}) did not significantly change TNF- α levels in obese adolescents aged 15-18 years. Study conducted by Gerosa-Neto *et al.*²¹ found a decrease in TNF- α levels in obese subjects who were exercised with 70% HR_{max} intensity for 16 weeks and increased in 90% HR_{max} intensity. Meanwhile, research conducted by Mokhtarzade *et al.*²² also reported that aerobic interval exercise significantly decreased TNF- α levels. Research

conducted by Salamat *et al.*⁵ reported that there were no significant decrease in TNF- α level after endurance, resistance and concurrent (endurance-resistance) exercises.

Based on those exposures, this study aimed to prove the effect of acute aerobic exercise on decreasing TNF- α levels in obese adolescent females. We hypothesize that acute aerobic exercise could decrease TNF- α levels in obese adolescent females.

Materials and Methods

Study design

This study was true experiment with the pretest-posttest control group design. The total subjects were 14 obese adolescent females, aged 20-23 years, body mass index 27.5-35 kg/m², normal blood pressure, normal resting heart rate, fasting blood glucose <100 mg/dL, hemoglobin 13-17 g/dL and randomly divided into two groups, namely CG ($n=7$, control group), AEG ($n=7$, acute aerobic exercise group). All subjects received information verbally and written about this research. Subjects filled out and signed informed agreements before participating in the study. All procedures in this study have approved by the Health Research Ethics Commission of the Faculty of Medicine, Universitas Brawijaya Malang by number 26/EC/KEPK-S1/02/2020.

Exercise protocol

The intervention was given at the Malang City Health Office Fitness Center. The intervention of aerobic exercise was performed by running on a treadmill with an intensity of 60-70% HR_{max} for 40 minutes with details of 5 minutes for warming-up (50-60% HR_{max}), 30 minutes of the core performed continuously (60-70% HR_{max}) and 5 minutes for cooling down (50-60% HR_{max})²³⁻²⁵. The intervention was performed at 07.00-09.00 A.M. using a treadmill (Pulsar 4.0 HP Cosmos Sports & Medical, Nussdorf-Traunstein, Germany). The heart rates were monitored during exercise using a polar heart rate monitor (Polar H10 Heart Rate Sensor, Inc., USA). The research environment had a room temperature of 26 \pm 1 °C and a humidity level of 50-70%²⁶⁻²⁷.

Anthropometric measurements and physical fitness

Measurement of body height used stadiometer (SECA, Chino, CA, USA). Measurement of body weight used electronic scale (Tech 05®, China). Body mass index (BMI) was measured by calculating body weight (kg) divided by body height in meter quadrat (m^2)⁴. Blood pressure was measured using an OMRON automated device (OMRON, HEM-7130 L Model, Omron Co., Osaka, Japan). *Maximum measurement of oxygen volume* (VO_{2max}) used Astrand 6-minute cycle test method using Monark 828 E tools Version 1010 ergo cycle (Monark, Vansbro, Sweden).

Blood collection and analysis

The blood sample was taken 3 ml from cubital veins. At the time of blood taking, the subject was in a sleeping position. Blood was taken two times, before exercise and 10 minutes after exercise. The blood was centrifuged for 15 minutes at a speed of 3000 rpm. Measurement of TNF- α levels used Enzyme-Linked Immunosorbent Assay (ELISA) kit (Catalog No. E-EL-H0109; Elabscience, Inc., China) by standard curve range 7.81–500 pg/mL and sensitivity 4.69 pg/mL. Blood was

taken to check FBG and Hb levels performed on the capillaries located at the tip of the middle finger. FBG was measured in mg/dL using an Accu-Chek Performa (Roche, Mannheim, Germany), while Hb was measured in g/dL by Easy Touch GCHb (Easy Touch, Hsinchu, Taiwan).

Statistical Analysis

Data were analyzed using Statistical Package for the Social Sciences (SPSS) for Windows, version 17 (SPSS Inc., Chicago, IL, USA). The normality of data was tested using Shapiro-Wilk. To compare the results, we used Paired Samples T-Test and Independent Samples T-Test. All data were presented as mean \pm standard error of the mean (SEM), and $p < 0.05$ was considered significant.

Results

The basic profiles of the samples, including age, body height, body weight, body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), resting heart rate (RHR), maximal oxygen volume (VO_{2max}), hemoglobin (Hb), fasting blood glucose (FBG), were displayed in Table 1.

Table 1. Characteristics of research subjects.

| Variable | CG (n=7) | AEG (n=7) | Independent Samples T-Test p-values |
|--------------------------------------|-------------------|-------------------|--|
| | Mean \pm SEM | Mean \pm SEM | |
| Age (years) | 20.43 \pm 0.57 | 20.71 \pm 0.52 | 0.718 |
| Body weight (kg) | 1.58 \pm 0.02 | 1.59 \pm 0.02 | 0.746 |
| Body height (m) | 75.21 \pm 2.32 | 74.26 \pm 2.86 | 0.800 |
| Body mass index (kg/m ²) | 29.94 \pm 0.56 | 29.30 \pm 0.46 | 0.395 |
| Systolic blood pressure (mmHg) | 115.14 \pm 1.81 | 115.00 \pm 1.69 | 0.955 |
| Diastolic blood pressure (mmHg) | 75.14 \pm 1.26 | 76.43 \pm 1.51 | 0.526 |
| Resting heart rate (bpm) | 71.00 \pm 2.34 | 72.00 \pm 2.00 | 0.751 |
| Maximal oxygen volume (mL/kg/min) | 26.66 \pm 0.49 | 27.94 \pm 0.66 | 0.148 |
| Hemoglobin (g/dL) | 16.09 \pm 0.67 | 15.21 \pm 0.38 | 0.286 |
| Fasting blood glucose (mg/dL) | 92.71 \pm 1.89 | 88.43 \pm 2.06 | 0.151 |

Based on Table 1, the results of the Independent Samples T-Test showed that there was no significant difference in the mean data of the research subject's

characteristics between CG and AEG ($p>0.05$). The analysis results of TNF- α levels between pre-exercise and 10 minutes post-exercise could be seen in Figure 1.

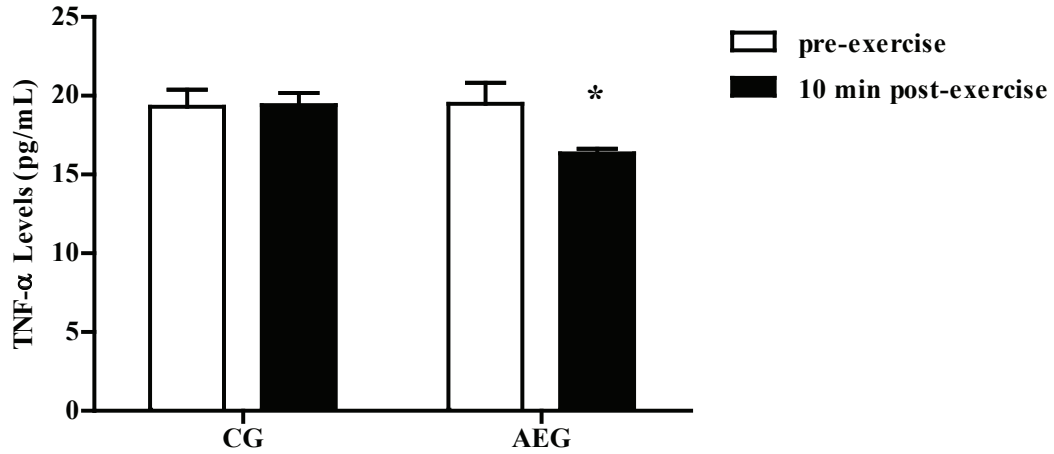


Figure 1. TNF- α level pre-exercise vs. 10 min post-exercise. CG: Control group; AEG: Acute aerobic exercise group. Data were presented as mean \pm SEM. p -values was obtained using Paired Samples T-Test to compare 10 min post-exercise and pre-exercise TNF- α level.

Based on Figure 1, the results of Paired Samples T-Test on CG showed that there was no significant difference between the mean TNF- α levels in pre-exercise and 10 min post-exercise (19.30 \pm 1.10 vs. 19.41 \pm 0.77 pg/mL, (p -values=0.940)). However, the results of AEG showed a significant difference between the mean of TNF- α levels in pre-exercise dan 10 min post-exercise (19.50 \pm 1.31 vs. 16.35 \pm 0.29 pg/mL, (p -values=0.038)). The analysis results about the mean TNF- α levels in pre-exercise (CG*AEG) dan 10 min post-exercise (CG*AEG) could be seen in Figure 2.

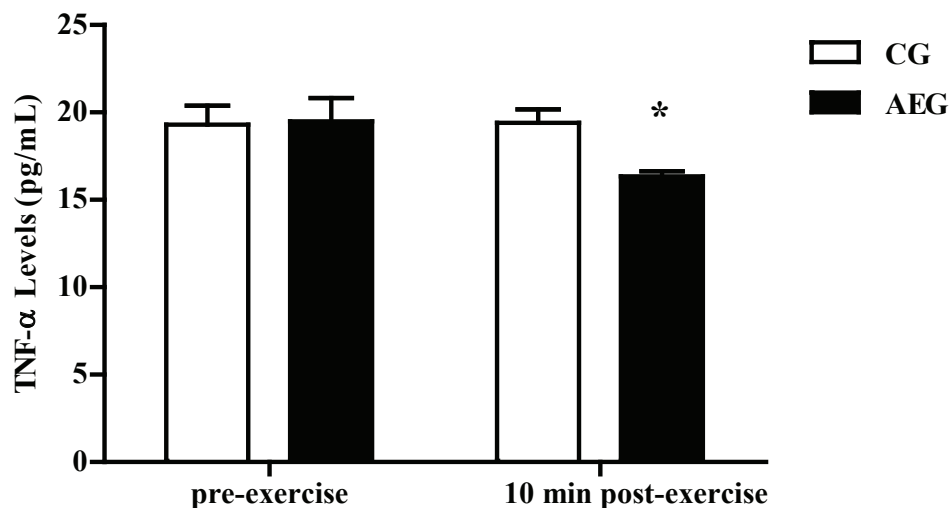


Figure 2. TNF- α level CG vs. AEG. CG: Control group; AEG: Acute aerobic exercise group. Data were presented as mean \pm SEM. p -values was obtained using Independent Samples T-Test to compare AEG and CG TNF- α level.

Based on Figure 2, the results of the Independent Samples T-Test showed that there was no significant difference between the mean of TNF- α levels in pre-exercise of CG and AEG (19.30 ± 1.10 vs. 19.50 ± 1.31 pg/mL, (p-values=0.909). Meanwhile, the mean between TNF- α level in 10 min post-exercise of CG and AEG showed a significant difference (19.41 ± 0.77 vs. 16.35 ± 0.29 pg/mL, (p-values=0.003).

Discussion

Based on the results of the study, it showed that the acute aerobic exercise which was performed for 40 minutes/exercise session significantly decreased TNF- α levels. These results were in line with the results of research conducted by Jahromi *et al.*¹⁹ reported that resistance exercise significantly decreased pro-inflammatory cytokines, such as TNF- α . Likewise, exercise with an intensity of 70% VO_{2max} significantly decreased TNF- α levels²⁸. However, these results were opposite with the research conducted by Bernecker *et al.*²⁹ which reported that heavy-intensity exercises exactly increased pro-inflammatory markers while circulating, such as TNF- α . These different results might be due to the differences in the intensity of the exercises performed. In our research, exercise was performed in moderate-intensity (60-70% HR_{max}) meanwhile the previous studies used heavy-intensity. Exercise with an intensity of 70% VO_{2max} could significantly decrease TNF- α ²¹. Based on a review article conducted by Gonzalez-Gil *et al.*¹⁶ also reported that moderate-intensity exercise could increase the anti-inflammatory environment, so that could decrease systemic inflammation indicated by the decreased pro-inflammatory cytokines such as TNF- α and the increase of adiponectin as anti-inflammatory markers. Moderate-intensity exercise could be an effective strategy in maintaining the anti-inflammatory environment¹⁶, because moderate-intensity exercise could decrease pro-inflammatory cytokines such as TNF- α ³⁰ and increased the level of adiponectin as the anti-inflammatory marker³¹, so the moderate-intensity exercise could be used to maintain the balance of inflammatory level.

Exercise played a role in regulating the level of systemic inflammation because exercise could increase muscle contraction so that it could suppress pro-inflammatory activity through the release of myokines and cytokines³⁰. The increase of muscle contraction regularly could produce and released cytokines to the circulation and other body areas, including the immune system³⁰. Interleukin-6 (IL-6) was a cytokine produced and released by binding the skeletal muscle fibers to affect the other organs³². The production and the release of IL-6 was believed that had a correlation with the decrease of TNF- α level induced by exercise, so it could activate the anti-inflammatory response, which was affected by the increase of interleukin-10 (IL-10), interleukin-1 receptor antagonist (IL-1RA), and the level of tumor necrosis factor- soluble receptor (sTNFr), so that caused pro-inflammatory cytokines, such as TNF- α decreased³³⁻³⁶. When inflammation occurred in the human body, IL-6 could limit the gene expression which coded pro-inflammatory cytokines, such as TNF- α , Interleukin 1 beta (IL1 β), Nitric Oxide Synthase 2 (NOS2), and activated terminal c-Jun N kinase (JNK), so that could add the responsiveness of macrophages on interleukin-4 (IL-4) to decrease the inflammation level³⁷. Besides, exercise could also increase adiponectin levels¹⁷⁻¹⁸. When adiponectin levels increased and binded to adiponectin receptor 1 (ADIPOR1) or adiponectin receptor 2 (ADIPOR2) there would be activation of AMP-activated protein kinase (AMPK) and peroxisome proliferator-activated receptor alpha (PPAR α)¹⁶, caused a decrease in liver gluconeogenesis and lipogenesis, and increased glucose uptake in skeletal muscle (SKM) and white adipose tissue (WAT). This directly suppressed the secretion of TNF- α and monocyte chemoattractant protein-1 (MCP-1), and also increased interleukin 10 (IL-10) and macrophage polarization (M2)^{16,28-29}.

Conclusion

Based on the results, it could be concluded that acute aerobic performed for 40 minutes/session exercise significantly decreased TNF- α level compared with the control group. Acute aerobic exercise could be one of the effective non-pharmacological methods to decrease

inflammation level indicated by the decrease of pro-inflammatory cytokines, such as TNF- α .

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