



The Effects of a Six-Week Aerobic Exercise on Serum Levels of Klotho, IL-10, IL-1, and Oxidative Stress in Sedentary Young Women

Mahnaz Haji Abedin Rangraz^{1*}, Shahla Hojjat¹

Abstract

Objectives: Insufficient physical activity is considered one of the leading causes of premature death worldwide. This study, therefore, aimed to investigate the effects of six weeks of moderate-intensity aerobic exercise on serum levels of Klotho, interleukin 10 (IL-10), IL-1, and oxidative stress in young women with a sedentary lifestyle.

Materials and Methods: The present study was a semi-experimental study with a control group. Out of all volunteers, 20 young women eligible to participate in the study were selected and divided into the two groups (n=10) of experimental (i.e., six weeks of moderate-intensity aerobic exercise) and control (i.e., no exercise). Members of the experimental group performed an aerobic exercise program including running on a treadmill with an intensity of 55%-70% of their maximum heart rates (220-age). The running plan started with 50% of their maximum heart rates and reached 70% at the end of the six-week exercise program (three sessions per week). Paired t-test and independent t-test were conducted to examine intra-group and inter-group differences. All statistical procedures were performed using the SPSS version 26 statistical package ($P \leq 0.05$).

Results: At the beginning of the study, no significant difference was observed between the groups in terms of the markers. Six-week aerobic training increased Klotho (mean: 540, lower: 141.5, upper: 938.4) and IL-10 (mean: 0.43, lower: -1.56, upper: -0.47) in experimental group in comparison to control group ($P=0.001$). Six-week aerobic training decreased IL-1 (mean: 0.78, lower: -1.16, upper: -0.39) and H₂O₂ (mean: 0.41, lower: -0.96, upper: 0.12) in experimental group in comparison to control group ($P=0.001$).

Conclusions: In sum, six-week moderate-intensity aerobic exercise program increased Klotho and IL-10 levels and decreased IL-1 and oxidative stress levels in young women with a sedentary lifestyle. According to these results, the decrease in oxidative stress and IL-1 levels due to exercise caused an increase in Klotho, and an increase in Klotho level, in turn, increased IL-10.

Keywords: Aerobic exercise, Oxidative stress, Inflammation

Introduction

Insufficient physical activity is considered one of the leading causes of premature death worldwide and, by estimates, it accounts for at least 3.2 million deaths per year (1). In the last two decades, physical activity has decreased in all age groups as a result of some factors (2). More than 80% of the world's adult populations is not physically active enough, and most people suffer from obesity due to lack of physical activity (1). According to international reports, Iran is among the countries whose populations are not engaged in sufficient physical activities. In 2019, the prevalence of physical inactivity in Iran's total population was reported 54% (females: 61.9%; males: 45.3%) (3).

Studies have shown that physical inactivity increases oxidative stress. Oxidative stress is a condition in which the body's antioxidants are not able to optimally reduce free radicals. Mitochondria are the main site of reactive oxygen species or free radicals production (4). When inactive, mitochondria lose their efficiency, and free radicals spread rapidly (5). Various factors, including

antioxidant proteins, are effective in regulating oxidative stress. Klotho is a protein expressed in the kidneys, heart, and some other tissues, which is present in the bloodstream. Klotho protein can reduce free radicals; however, the circulating level of this protein (enzyme) is affected by the amount of exercise, age, and different diseases, meaning that physical inactivity and increasing age reduce its expression and, thus, increase oxidative stress (6). Considering Klotho's anti-inflammatory effects (7), increased inflammation also occurs as a result of decreased Klotho levels.

In this regard, it has been reported that physical inactivity is associated with persistent low-grade systemic inflammation. In general, a sedentary lifestyle is an independent risk factor for many chronic diseases, including those associated with persistent systemic inflammation. Such relationships result in higher rates of morbidity as well as in lower life quality and life expectancy (8). Physical inactivity leads to chronic inflammation, which results from the accumulation of visceral fat and is usually accompanied by fatigue and muscle atrophy.



Key Messages

- ▶ Physical inactivity is associated with an increase in inflammatory markers (IL-1) and oxidative stress and a decrease in anti-inflammatory markers (Klotho and IL-10).
- ▶ But, moderate-intensity aerobic exercise program increased Klotho and IL-10 levels and decreased IL-1 and oxidative stress levels in young women with a sedentary lifestyle.

However, the association between chronic systemic inflammation and physical inactivity is independent of the obesity condition (8).

Interleukin 1 (IL-1) is the main regulator of inflammation via controlling a variety of innate immune processes. IL-1 has a wide range of biological functions, including the functions as a leukocytic pyrogen, a fever mediator, and a leukocytic endogenous mediator; it also induces several components of the acute-phase response and lymphocyte activating factor. However, the main functions of this cytokine are faster differentiation and production of white blood cells, causing inflammation and releasing acute-phase protein. IL-1 α and IL-1 β are the most famous members of this family (9,10). IL-1 β is produced as a 269-AA precursor protein, activated in inflammations by caspase-1 – also known as IL-1 β -converting enzyme (ICE) – and processed to the C-terminal 153 AA as mature IL-1 β (11). The IL-1 β precursor is also processed by other serine proteases. Neutrophils derived from caspase-1-deficient mice release mature IL-1 β processed by elastase in response to lipopolysaccharide stimulation (12). The neutrophil proteases (e.g., elastase, chymases, granzyme A, cathepsin G, and proteinase-3) biologically separate the IL-1 β precursor in a secreted form (13).

Together with inflammatory cytokines, there are also anti-inflammatory cytokines, including IL-10. The IL-10 involvement has been demonstrated in many disease states, both in animal models and in humans with mutations in the IL-10/IL-10R axis (14). IL-10 signals through a receptor set consisting of two IL-10 receptor-1 and two IL-10 receptor-2 proteins (6). Accordingly, the functional receptor consists of four IL-10 receptor molecules. IL-10 binding induces STAT3 signaling through the phosphorylation of the cytoplasmic tails of IL-10 receptor 1+IL-10 receptor 2 by JAK1 and Tyk2 respectively (15). IL-10 reduces the expression of Th1 cytokines, MHC class ii antigens, and costimulatory molecules in macrophages; it also increases B cell survival and antibody production. IL-10 can block NF-kappa B activity and is involved in the regulation of the JAK-STAT signaling pathway (15). Some studies have shown that IL-10 can reduce IL-1 production (16). However, the results of some studies show that inactivity increases IL-10 (17). Other studies have shown that IL-10 decreases oxidative stress (18), and that the increased oxidative stress increases IL-1 (19).

Considering the adverse effects of physical inactivity on proteins and factors affecting the immune system,

exercise has been offered as the major recommendation. Some studies have confirmed the increase of antioxidants after aerobic exercise (4). But the effects of exercise on Klotho and inflammation in sedentary women have not been accurately detected. The present study, therefore, aimed to examine the effects of six weeks of moderate-intensity aerobic exercise on serum levels of Klotho, IL-10, IL-1, and oxidative stress in young women with a sedentary lifestyle.

Materials and Methods

The present study was a semi-experimental study with a control group. The study's statistical population consisted of physically inactive young women working at the Ministry of Health departments. After the call for participation, volunteers were first introduced to the research process; then, their physiological characteristics, including height, weight (using the SECA height and weight scale made in Germany), body mass index (BMI), systolic and diastolic blood pressure, heart rate (using OMRON digital sphygmomanometer), and VO₂max level (via graded exercise testing) were measured. Volunteers with an age range of 22-30 years and a body mass index of 20-24 kg/m² were included in the study. Those performing regular sports activities, afflicted with chronic diseases or movement problems, taking blood pressure/fat lowering drugs or other medications, and consuming antioxidants and nutritional supplements were excluded from the study.

Of all volunteers, 20 young women eligible to participate in the study were selected. The selected participants signed the informed consent form and became familiar with the research stages, such as the duration of the exercise plan and the non-consumption of drugs affecting the research variables. Finally, the selected participants were divided into the two groups (n=10) of experimental (i.e., six weeks of moderate-intensity aerobic exercise) and control (i.e., no exercise). In the initial stage, venous blood samples were taken from the participants in both groups 12 hours after fasting. Then, each group initiated its specified program. Members of the experimental group participated in an aerobic exercise program that included running on a treadmill with an intensity of 55%-70% of their maximum heart rates (220-age). Running commenced with 50% of their maximum heart rates and reached 70% at the end of the six-week exercise program (three sessions per week, 45 minutes). Members of the control group were prohibited from participating in all sorts of sports activities. After examining the effects of moderate-intensity aerobic exercise on the study's variables, the participants' venous blood samples were retaken and their biological indices were remeasured.

Measurement of Maximal Oxygen Consumption (VO₂max)

In the present study, the GXT exercise protocol was used

for determining VO₂max. Participants were asked to walk on a treadmill set at a minimum percent incline for three minutes. Increasing the exercise duration (20 minutes), the incline percentage and speed of the activity were also increased, reaching to five percent incline and speed of 7.5 miles (12 km/h) (4).

*VO₂max calculation formula: (heart rate * 0.1453) - (speed per hour/mile * 4.47) + (weight in kg * 0.193)-54.07*

The IL-1 β level was determined by using the ELISA test and a BioVendor Company-made laboratory kit; IL-10 level was determined using a commercial kit made in Germany, and serum α -klotho level was determined using the ELISA test and a Demeditec Diagnostics made kit. An autoanalyzer was used to measure hydrogen peroxide.

In this study, the Kolmogorov-Smirnov test was performed to examine the normality of data distribution. Paired *t* test and independent *t* test were conducted to examine the intra-group and inter-group differences. All statistical procedures were carried out using the SPSS-26 statistical package ($P \leq 0.05$).

Results

The results of physiological characteristics are presented in Table 1. Paired *t* test showed that weight and body mass index did not change significantly in the experimental and control groups. But the Vo₂max levels in the experimental group were significantly higher than those found in the pretest ($P = 0.01$; Table 1).

Klotho

Six-week aerobic training increased Klotho in post-test compared to pre-test ($P = 0.001$). In the post-test phase, moreover, the experimental group had more klotho compared to the control group ($P = 0.001$) (Figure 1 and Tables 1 and 2).

H₂O₂

H₂O₂ decreased in experimental group after six-week aerobic training in comparison to basal ($P = 0.001$). (Figure 2). In the post-test phase, moreover, the experimental group had less H₂O₂ than the control group ($P = 0.001$) (Figure 2 and Tables 1 and 2).

IL-1

Six-week aerobic training decreased IL-1 in in post-test compared to pre-test ($P = 0.001$). In the post-test phase, moreover, the experimental group had less IL-1 than the control group ($P = 0.001$) (Figure 3 and Tables 1 and 2).

IL-10

Six-week aerobic training increased IL-10 in post-test compared to pre-test ($P = 0.001$). In the post-test phase, moreover, the experimental group had more IL-10 than the control group ($P = 0.001$) (Figure 4, Tables 1 and 2).

Liner Regression Between Markers

A significant relationship was observed between klotho with IL-10 ($P = 0.001$) and IL-1 ($P = 0.021$) as well as oxidative stress (0.04). There was also a significant relationship between IL-10 with IL-1 ($P = 0.009$) and

Table 1. Paired *T* Test Result for Physiological, Inflammation, and ROS Markers

Markers	Group	Pre-test	Post-test	<i>P</i> (Intra-group)	Mean	95% CI of the Difference	
						Lower	Upper
SBP (mm Hg)	Experimental	124.12±2	121.1±4	0.99	-3.02	-5.483	1.82
	Control	125.16±2	125.19±2	0.99	0.03	-5.387	3.81
DBP (mm Hg)	Experimental	75.12±8	75.1±2	0.2	0.06	-4.63	1.823
	Control	74.3±2	77.09±3	0.82	2.7	-0.42068	3.85
Weight (kg)	Experimental	55.09±6	55.04±3	0.2	-0.05	-3.284	4.09
	Control	58±2.6	58.1±1.9	0.82	0.1	-10.78	2.82
BMI (kg/m ²)	Experimental	22.21±1.99	21.7±1.67	0.32	-0.51	-3.107	1.09
	Control	22.07±2.08	22.04±1.67	0.71	-0.03	-2.75488	0.730
VO ₂ max (ml/kg/min)	Experimental	47.34±1.17	50.02±2.16	0.01	2.68	2.20221	6.34
	Control	46.44±3.19	46.28±4.88	0.86	-0.16	-0.17281	0.044
Klotho (pg/mL)	Experimental	933.333±294.39	1433.33±314.11	0.001	540.00	141.5	938.49
	Control	966.66±150.55	1000±209.76	0.99	-20.00	204.16	164.16
H ₂ O ₂ (μm)	Experimental	2±0.8	1.77±0.3	0.001	-0.418	-0.96103	0.12503
	Control	1.99±0.4	2.02±0.39	0.87	0.016	0.00489	0.02711
IL-1 (ng/mL)	Experimental	2.2±0.2549	1.42±0.1923	0.001	-0.780	-1.16	-0.393
	Control	2.3±0.2236	2.3±0.2549	0.99	0.000	-0.263	0.26340
IL-10 (pg/mL)	Experimental	1.7±0.29	2.72±0.21	0.001	-1.020	-1.56	-0.475
	Control	1.76±0.288	1.78±0.22	0.64	0.020	-0.24919	0.28919

Table 2. Independent *T* Test Result for Physiological, Inflammation, and ROS Markers

Markers		Mean	95% CI of the Difference	
			Lower	Upper
SBP (mm Hg)	Pre-test	-1.01	-3.4	1.4
	Post-test	-2.05	-5.5	1.45
DBP (mm Hg)	Pre-test	1.12	-2.3	4.6
	Post-test	-1.99	-3.03	-0.96
Weight (kg)	Pre-test	-3.36	-8.8	2.16
	Post-test	1.02	-1.4	3.35
BMI (kg/m ²)	Pre-test	0.435	-2.8	1.34
	Post-test	0.294	-2.2	0.77
VO ₂ max (mL/kg/min)	Pre-test	0.56	-0.9	2.02
	Post-test	4.89	3.63	6.16
Klotho (pg/mL)	Pre-test	0.0	-335.75	335.75
	Post-test	560	217.96	902.03
H ₂ O ₂ (μm)	Pre-test	0.2	0.25	0.66
	Post-test	0.22	-0.24	-0.2
IL-1 (ng/mL)	Pre-test	-1	-0.44	0.24
	Post-test	-0.88	-1.2	0.55
IL-10 (pg/mL)	Pre-test	-0.4	-0.46	0.38
	Post-test	-10.8	-1.4	-0.75

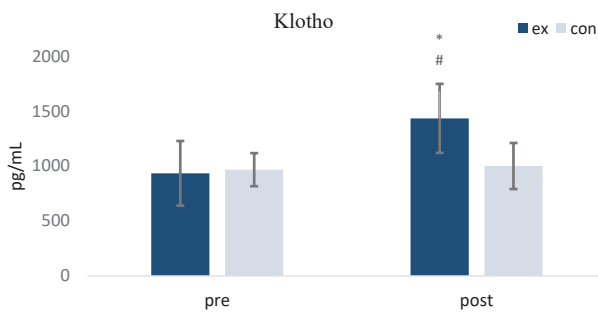


Figure 1. Klotho Levels in Experimental and Control Groups. By dependent and independent *t*-test. * Compared to the pre-test. # Compared with the control group in the post-test.

oxidative stress ($P=0.031$). The relationship between IL-1 and oxidative stress was also significant ($P=0.008$; Table 3).

Discussion

This study was conducted to examine the effects of six weeks of moderate-intensity aerobic exercise on serum levels of Klotho, IL-10, IL-1, and oxidative stress in young women with a sedentary lifestyle. According to our study results, six weeks of aerobic exercise increased Klotho and IL-10 levels and decreased IL-1 and oxidative stress levels in the experimental group. Moreover, members of the experimental group had higher levels of Klotho and IL-10 but lower levels of IL-1 and oxidative stress compared to those in the control group. These findings were consistent with the results from the study by McLeay et al, since

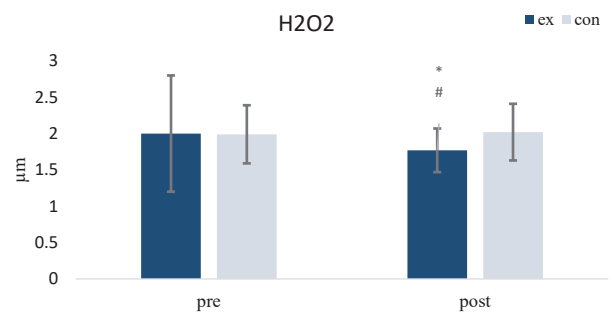


Figure 2. H₂O₂ Levels in Experimental and Control Groups. By dependent and independent *t*-test. * Compared to the pre-test. # Compared with the control group in the post-test.

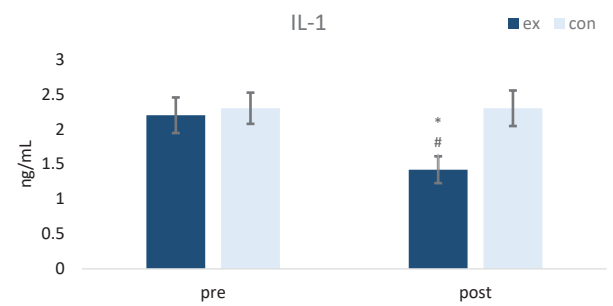


Figure 3. IL-1 Levels in Experimental and Control Groups. By dependent and independent *t*-test. * Compared to the pre-test. # Compared with the control group in the post-test.

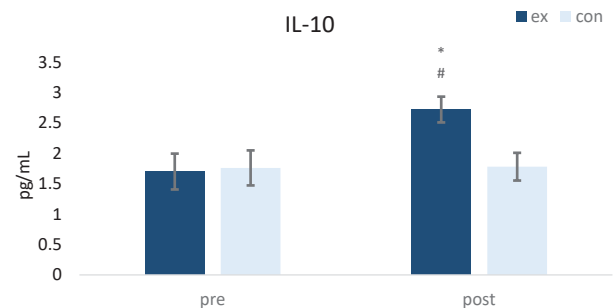


Figure 4. IL-10 Levels in Experimental and Control Groups. By dependent and independent *t*-test. * Compared to the pre-test. # Compared with the control group in the post-test.

they reported a significant decrease in oxidative stress indices as a result of exercise (20). Bouzid et al reported that exercise reduced oxidative stress caused by aging (21). Reduction of hydrogen peroxide due to aerobic exercise can be attributed to the increased activity and expression of antioxidant enzymes. On the other hand, non-enzymatic antioxidants, such as vitamins E and C, reduce free radicals by directly reacting with free radicals and supporting antioxidant enzymes (4). Various studies have shown that long-term activity leads to increased activity and gene expression of antioxidant enzymes and non-enzymatic antioxidants (4). The role of Klotho in reducing

Table 3. Liner Regression Between Markers

Markers	ROS	IL-10	IL-1
Klotho	0.04	0.001	0.021
IL-10	0.031	-	0.009
IL-1	0.008	-	-

oxidative stress is also important. In this regard, Baghaiee et al showed that eight weeks of aerobic exercise increased Klotho and oxidative stress levels in middle-aged rats (6). In the present study, a significant relationship was observed between oxidative stress and Klotho.

Furthermore, the present study's results indicated that six weeks of aerobic exercise increased serum Klotho level in inactive young women. This finding was consistent with the findings from the studies by Baghaiee et al (6), Amaro-Gahete et al (22), and Ji et al (23). Semba et al reported a strong negative relationship between S-Klotho and the risk of cardiovascular diseases as well as the risk of all-cause mortality (24). Other studies have demonstrated that patients with coronary artery disease have lower plasma S-Klotho concentration and decreased expression of the α -Klotho gene in the walls of their arteries (25). The increase of angiotensin-2 and oxidative stress have been determined as causes of Klotho decrease (6). In the present study, oxidative stress was significantly reduced due to aerobic exercise. Therefore, the reduction of oxidative stress due to exercise may have been suggested as a Klotho-increasing mechanism. On the other hand, Zhao et al reported that IL-1 had the potential to inhibit Klotho; thus, exercise may have increased Klotho by lowering IL-1 (26).

In the current study, IL-1 levels decreased as a result of aerobic exercise. Moreover, a significant relationship was detected between Klotho and IL-1 levels after a six-week aerobic exercise program. Butts et al and Shi et al found similar results and determined that the increased ASC methylation (27,28) and decreased oxidative stress due to exercise may have been the contributory factors responsible for IL-1 reduction. In the present study, a significant relationship was observed between IL-1 and oxidative stress. The failure to examine methylation of ASC was one of the limitations of our study. On the other hand, IL-10 affects IL-1. Hence, IL-10 changes triggered by exercise are among the mechanisms that affect IL-1 levels.

In this study, IL-10 levels significantly increased as a result of aerobic exercise in young women with a sedentary lifestyle. Eizadi et al reported similar results in this regard (29). One of the mechanisms involved in IL-10 increase is the increase of IL-6 due to exercise. It has been shown that physical activity increases muscle metabolism and leads to an increase in IL-6 levels in both muscle and blood. Increased IL-6 increases IL-10 secretion in macrophages. By negatively regulating NF-kappa B activity, the exercise increases IL-10 secretion by monocytes and T cells via

Th2 (30). The failure to examine the NF-kappa B and Th2 was another limitation of our study. IL-10 is also affected by Klotho changes (31). It has been determined that a decrease in Klotho levels reduces the levels of IL-10. Klotho level was significantly increased in the present study, and a significant relationship was observed between Klotho and IL-10. Therefore, the observed increase in Klotho level due to aerobic exercise may have been one of the factors contributing to the IL-10 increase.

Conclusions

In sum, it was found that a six-week moderate-intensity aerobic exercise program increased Klotho and IL-10 levels as well as decreased IL-1 and oxidative stress levels in young women with a sedentary lifestyle. It was also detected that the decrease in oxidative stress and IL-1 levels due to exercise resulted in an increase in Klotho, and an increase in Klotho level, in turn, increased IL-10.

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Authors' Contribution

Investigation: Mahrnaz Haji Abedin Rangraz and Shahla Hojjat.
Methodology: Mahrnaz Haji Abedin Rangraz and Shahla Hojjat.
Supervision: Mahrnaz Haji Abedin Rangraz.
Writing – original draft: Shahla Hojjat Rangraz.
Writing – review & editing: Mahrnaz Haji Abedin Rangraz.

Conflict of Interests

The authors have no conflict of interests to declare.

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