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Eight weeks of high intensity interval training improve the expression of interleukin-17 and interleukin-18 genes in the heart tissue of cadmium-poisoned rats

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Abstract.

Introduction: lL-17 and IL-18 are pro-inflammatory cytokines. The aim of present study is to evaluate the effect of endurance training on IL-17 and IL-18 in heart tissue of rats which have been poisoned by cadmium.

Material & Methods: Twenty Wistar rats were randomly divided into four groups: 1) control, 2) sham, 3) cadmium and 4) high intensity interval training (HIIT training) with cadmium. HIIT training was performed 8 weeks and 3 days a week (80 to 110% of their VO_{2max}). Cadmium groups received

2mg/kg cadmium intraperitoneally everyday. At the end of protocol, the rats were sacrificed and their heart tissues were prepared to measure gene expression of IL-17 and IL-18. The data was analyzed by independent sample t-test and one-way ANOVA ($P \leq 0.05$).

Results: The HIIT training led to significantly reducing IL-17 and IL-18 gene expression in heart issue of rats ($P = 0.001$).

Conclusion: The 8 weeks of HIIT training will improve the levels of pro-inflammatory cytokines in rats which have been poisoned by cadmium.

Key words: Cadmium, HIIT training, IL-17, IL-18

1. Introduction

Nowadays, environmental pollution is one of the problems of human health in industrialized and developed countries. Extensive studies have shown that exposure to airborne contamination and inhalation of heavy metals in the air and the consumption of food contaminated with these substances is associated with an increase in inflammation in the cardiovascular system, resulting in cardiovascular disease and even death (1,2). In addition, through the production of free radicals, and thus an increase in inflammation, the toxic effects of these heavy metals may impair the function of various organs in the body, including the cardiovascular system (1,3). In fact, one of the factors that increase inflammation and the prevalence of cardiovascular disease is the presence of cadmium in air and soil (4). Actually, an evidence suggests that exposure to cadmium is associated with an increased risk of cardiovascular disease, including high blood pressure and heart tissue damage (5). Products containing cadmium, such as batteries, electronic devises, jewelry and toys, as well as fertilizers containing cadmium through soil and food, threaten people's lives (6,7). According to available research, cadmium levels are high in people with inflammatory cardiovascular disease (8). Cadmium causes an increase in the level of pre-inflammatory cytokines such as interleukins, which causes the development of atherogenic plaques in coronary arteries (9). Recent

research has shown that inflammation plays a key role in coronary artery disease (CAD). In addition, inflammation is related to the two inflammatory factors of IL-17 and IL-18 in the heart tissue. Interleukin 18 (IL-18), a pro-inflammatory cytokine, is a member of the family of interleukin-1 cytokines, which is originally described as an interferon-gamma-inducing factor (9). Also, in most cardiovascular patients, the level of IL-18 is high, indicating a direct relationship with cardiovascular disease (10). Another inflammatory cytokines that play a major role in cardiovascular disease is IL-17. IL-17 is a pro-inflammatory cytokine derived from CD4, but play a role in the spread of inflammatory diseases in the tissue (11). Considering the harmful effects of cadmium on the cardiovascular system, and the increasing probability in exposure to air pollution on the one hand, and the impact of adopting an inappropriate life style, including the lack of systematic physical activity (12) on the other hand, researchers have investigated different strategies to neutralize the harmful effects of cadmium on inflammation of the cardiovascular system. It has been suggested that regular physical activity plays an important role in the improvement of inflammation from cadmium (13, 14, 18-20). Physical activity is a well-known and applied method for reducing inflammation and risk of cardiovascular disease (23). Blair et al. have reported that regular physical activity has an inverse relationship with blood level of inflammatory markers and eliminates chronic inflammation (18). In addition, Dorneles et al (2016), in the study of obese and lean men, concluded that HIIT exercises reduced IL-8 and increased IL-6 and IL-18 without altering IL-17 (24). It has also been shown that after regular HIIT activities IL-18 concentrations were lower than that of non-athletes (25). Numerous studies have confirmed the fact that severe interval exercises increase the levels of pre-inflammatory cytokines such as IL-6, IL-17 and IL-18 in athlete's body, and on the other hand, regular intensive endurance exercises with mean severity modifies these cytokines in various tissues, including the cardiovascular system (26-28). Also, Daryanoosh et al. (2013) concluded that high intensity interval exercises reduce inflammatory cytokines such as interleukin 6 and alpha necrosis factor (30). No studies have been found to investigate the effects of HIIT exercises on levels of IL-17 and IL-18 in conditions exposed to cadmium

poisoning, and considering the harmful effects of cadmium. So, the purpose of this study was to investigate the effect of HIIT exercises on the inflammation in the heart tissue of cadmium-poisoned rats.

2. Material & Methods

Animals

The present study was approved by the Ethic Committee on Animal Use of Larestan branch, Islamic Azad University, Larestan, Iran. Twenty adult male Wistar rats weighing 184.9 ± 15.6 g (at the beginning of the study) were used in this experiment. The animals were kept in accordance with the Guideto the Care and Use of Experimental Animals (1993).

Rats were submitted to seven days of acclimatization in polypropylene boxes (dimensions 41 cm × 34 cm × 17.5 cm), containing wood shavings (for absorbing urine and water). Five rats were placed in each box. Throughout the experimental period, rats were housed under controlled temperature (20°C ± 2°C), humidity (45% ± 15%) and lighting conditions (7:00 a.m. to 19:00 p.m.) with food and water made available *ad libitum*. Animals were randomly divided into four groups (n=5 in each group): control, sham, cadmium and HIIT training with cadmium group. For 8 weeks, the rats of cadmium and HIIT training with cadmium groups received 2 mg/kg cadmium per day (29). It should be noted that sham group rats received peritoneal cadmium solvent in the entire study period.

Treadmill exercise protocol

High intensity interval exercise protocol consisted of three parts, including warming up (5 minutes), exercise including 2-minute (2 × 2) interval phases (with an active 2 minute recovery interval between each set) and cool-down (5 minutes). First, the rats warmed up to the treadmill with a maximum intensity of 50 to 60% of VO_{2max} for 5 minutes. The interval exercises included a combination of high intensity and low intensity interval phases. High intensity interval phases included 2 minutes exercises with maximum intensity of 80% VO_{2max} in the first week, maximum intensity of 90% VO_{2max} in the second week, maximum

intensity of 100% VO_{2max} in the third week and maximum intensity of 110% VO_{2max} from the beginning of the fourth week until the end of the training, and low intensity interval phases (Recovery Interval) included 2 minutes with a maximum intensity of 50% VO_{2max}. After performing the last high intensity interval phases, the rats performed cooling with a maximum intensity of 50 to 60% VO_{2max} for 5 minutes (figure 1). Initially, the standard test of Bedford et al. (1979) was used to determine the maximum oxygen consumption (32). This test included 10 three-minute stages. The speed at the first stage was 0.3 km / h and in the next steps, 0.3 km / h was added to the treadmill speed, while at all the steps the slope was zero. At each stage of the test, when the animal was no longer able to continue, the velocity at that stage was considered to be the equivalent of the speed of the animal at the maximum oxygen consumption.

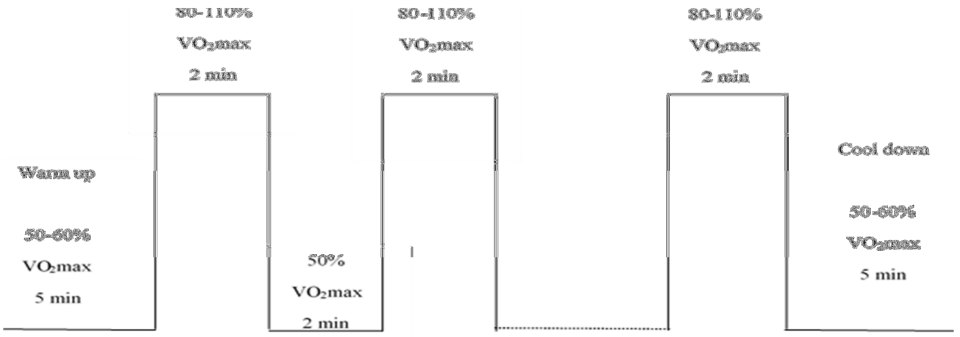

Figure 1. HIIT program

At the end of the study period, 48 hours after the last training session, the rats were anesthetized by ketamine and xylazine and then their heart tissues were removed to measure the research variables.

Measurement of mRNA expression by RT-PCR

For molecular analysis at the gene expression level, first, extraction of RNA from the heart tissue was carried out according to the manufacturer's protocol (Sina Gene, Iran), and then, using the light absorption property at 260 nm wave length, with the following equation, the concentration and purity of the sample RNA was quantitatively obtained.

$$C\ (\mu g/\mu l) = A260\times\ \varepsilon\times\ d/1000$$

After extracting RNA with high purity and high concentration, all of the study samples were taken cDNA synthesis steps according to the manufacturer's protocol, and then synthesized cDNA was used for reverse transcription reaction. At first, designed primers for genes were studied, and then genes expression was evaluated using q-RT PCR quantitative method. The sequence of primers used in the study includes:

IL-17 (f)	CCGTTCCACTTCACCCTG
IL-17 (r)	GTCCAACTTCCCCTCAGC
IL-18 (f)	ATGTCTACCCTCTCCTGT
IL-18 (r)	TTCCATTTTGTTGTGTCCTG

Statistical analysis

Data analyses were performed using SPSS software for windows. Results were expressed as the mean ± SD, one-way ANOVA ($P\leq0.05$), Kolmogorov-smirnov tests and distributions of all variables were assessed for normality.

3. Results

Table 1 shows the weight of rats in different groups

Table 1. Weight of Rats in the Four Groups

Group	First Week	Last Week
Control	184.80 ± 7.69	201.00 ± 15.03
Sham	180.00 ± 20.94	199.40 ± 40.69
Cadmium	149.80 ± 20.42	157.80 ± 22.85
Cadmium and HIIT	115.80 ± 4.26	118.00 ± 4.63

The expression levels of IL-17 and IL-18 in the four groups of the study are presented in Table 2.

Table 2: Expression Level of IL-17 and IL-18 in the Four Groups

Group Variable	IL-17 (Mean ± SD)	IL- 18 (Mean ± SD)
Control	0.0144 ± 0.0041	0.0053 ± 0.0003

Group Variable	IL-17 (Mean ± SD)	IL- 18 (Mean ± SD)
Sham	0.0152 ± 0.0068	0.0047 ± 0.0007
Cadmium Consumption	0.8128 ± 0.1561	0.9134 ± 0.4506
HIIT + cadmium	0.022 ± 0.022	0.011 ± 0.002

The results of the one-way ANOVA presented in Table 3 show that eight weeks of HIIT had a significant effect on IL-17 expression (P = 0.028 and F = 8.4449 with effect size of 0.301) and IL-18 (P = 0.002 and F = 14.168 with effect size of 0.470) of cadmium-poisoned rats.

Table 3: the Effect of HIIT on the expression of IL-17 and IL-18 in Cadmium-Poisoned Rats

Variable	Statistics Factor	F	Significance Level	Effect Size
IL-17	HIIT	8.449	0.028	0.301
IL-18	HIIT	14.168	0.002	0.470

The results of tukey post hoc test illustrated which eight weeks of cadmium consumption led in increasing the expression of IL-17 and IL-18 of cadmium-poisoned rats. In addition, the results showed that HIIT training could change the expression of IL-17 and IL-18 in cadmium-poisoned rats.

Table 4. The results of tukey post-hoc so as to compare the meaning of IL-17 between groups

Levels of comparisons		sig
placebo	Cadmium	0.0001
	Control	0.03
	HIIT Training	0.001
cadmium	Control	0.0001
	HIIT Training	0.0001
control	HIIT Training	0.01

Table 5. The results of tukey post-hoc so as to compare the meaning of IL-18 between groups

Levels of comparisons		sig
placebo	Cadmium	0.002

Levels of comparisons		sig
	Control	0.01
	HIIT Training	0.02
cadmium	Control	0.002
	HIIT Training	0.002
control	HIIT Training	0.03

4. Discussion

The findings of the present study indicated that exercise decreases IL-17 and IL-18 significantly in the heart tissue of cadmium-poisoned rats. In fact, the serious problem of cadmium is the induction of inflammatory reactions in various organs of the human and the animal body. Changes in the synthesis of nitric oxide and free radicals, which play an important role in the development of inflammation in various tissues, including the heart, are the possible mechanisms of inflammatory activity of cadmium in various tissues. Based on available research, in patients with inflammatory cardiovascular diseases and arterial cramps, cadmium levels are high (24). Therefore, cadmium increases the level of inflammatory cytokines such as interleukins, which causes the development of atherosclerotic plaques in coronary arteries (25). In fact, cellular mechanisms that cadmium causes damaging the endothelium include the release of pro-inflammatory mediators such as the alpha-necrosis factor, and interleukins 17 and 18, and the antitrombolitic elements of vascular endothelial cell culture (26). For this purpose, the present study found that HIIT exercises lead to a significant reduction of IL-17 and IL-18 in cadmium-infected rats. But some study findings are not consistent with the results of present study. For example, Dorneles et al. (2016), in their study on obese and lean men, concluded that HIIT exercises reduced IL-8 and increased IL-6 and IL-18 without altering IL-17 (15). Robeson Ansley et al. (2007) showed that performing intensive interval exercises can suppress the intrinsic immune system and increase the incidence of pro-inflammatory cytokines such as interleukin 6, 17 and 18 (27). Tofighee et al., (2014) after a semi-experimental study, stated that severe exercise had no significant effect on IL-17 levels compared to pre-exercise, which was due to short periods of exercise (28). Therefore,

another important factor in secretion of these cytokines is the duration of the exercise. Indeed, much of the research has pointed to increased cytokine, which is probably due to the intensity of exercise, which liberates pro-inflammatory cytokines and anti-inflammatory cytokines through leukocytes and skeletal muscles. However, the effect of exercise intensity on levels of IL-17 and IL-18 in some studies is considered as an important factor. For example, Duzova et al., (2009) in their study investigated the effect of two types of exercise programs of running on a roller belt (high intensity exercise: 85% of maximum oxygen consumption with slope, and light exercise: 50 to 60% of maximum oxygen consumption without slope) and found that after 8 weeks, the level of these cytokines increased in the group that used intensive exercise, but in the other group there was no significant change (29). On the other hand, results of some other studies confirm the present study findings which can be due to the duration and intensity of exercises. For instance Daryanoosh et al. (2013) concluded that intensive interval exercises reduced inflammatory cytokines such as interleukin 6 and alpha necrosis factor (30). Also, in a comprehensive study, researchers found that performing 8 weeks of regular HIIT exercises can significantly reduce levels of inflammatory cytokines such as IL-17 and IL-18 (31). In this regard, Leggate et al., (2012) in a study, showed that levels of inflammatory cytokines, including interleukins 6, 17 and 18 in those who carry out HIIT exercises were low (32). In addition, Nikseresht et al. (2014) in their study on middle-aged obese men concluded that intensive interval exercises compared with endurance exercises had better efficacy on inflammatory cytokines (33). Also, some studies have indicated that HIIT exercises protect heart tissue by modulating the bad effects of cadmium in the body (25). This means that the type of intensity and duration of aerobic exercises, which took place in the present study with a relatively long time and moderate intensity, is an important and essential factor in reducing the inflammatory cytokines caused by environmental contamination such as exposure to cadmium. Tofighee et al., (2014) after a semi-experimental study, stated that severe exercise had no significant effect on IL-17 levels compared to pre-exercise, which was due to exercises short periods (28). So another important factor in secreting these cytokines is the duration of exercise. In fact, most of the

research has pointed to the increase in this cytokine, which is probably due to the intensity of exercise, which liberates pro-inflammatory cytokines and anti-inflammatory cytokines through leukocytes and skeletal muscle (34) HIIT, however, can produce similar results to endurance training including muscle oxidative capacity and mitochondrial enzyme activity, but in addition to providing various cardiometabolic benefits HIIT is also very time-efficient. The lack of large-scale post-HIIT or post-ET inflammatory responses indicates that a regimen of two to three HIIT sessions per week may noticeably aid in improving general health and fitness such as body fat percentage, maximal oxygen uptake, and cardiovascular endurance while exerting relatively little stress on the immune system in untrained and healthy young adults (35-37). Finally, despite all controls imposed on the sex, race and weight of the animals, environmental factors (such as light, temperature and sound, etc.), the exercise program and animal feed, the lack of measurement of the rate of absorption of cadmium in the heart tissue and also, the lack of control over night activity are the limitations of this research. In spite of the above, considering the increasing use of cadmium in air and food products and its harmful effects on heart tissue health, the controlled review of affordable and safe non-prescriptive strategies, such as various physical activities, for instance, swimming exercises, endurance exercises and herbal antioxidant supplements, especially in the presence of other pollutants in animal species for longer duration, can be considered as a fundamental research for future human research.

5. Conclusion

The results of this study showed that performing HIIT exercises significantly reduces the levels of IL-17 and IL-18 which can increase inflammation due to cadmium intake. Therefore, these exercises protect the heart tissue from inflammation caused by cadmium intake.

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Conflict of interests: No conflict of interests amongst authors.

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