High intensity interval training and L-Arginine supplementation decrease interleukin-6 levels in adult trained males

L'entraînement par intervalles à haute intensité et la supplémentation en L-Arginine diminue les taux d'interleukine 6 chez des hommes adultes entrainés

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Abstract

Objective: To evaluate the effect of six weeks of high intensity interval training (HIIT) and L-Arginine supplementation on interleukin-6 (IL-6) levels and body composition in Iranian adult trained males.

Methods: This experimental study was performed as an intervention with a pretest-posttest design in three experimental groups and one control group. Forty-eight young males from Qazvin province (Iran) were selected voluntarily based on convenience sampling. Participants were randomly divided into four groups (12 participants in each group): "HIIT"; "L-Arginine supplementation"; "HIIT + L-Arginine supplementation", and "HIIT + placebo". At 7 a.m., when the level of inflammation was at its lowest, a blood sample was taken from the participants, and body mass index (BMI), body fat percentage (BFP), and lean body mass (LBM) were determined. IL-6 analysis was performed using STATE FAX device and ELISA method. Training sessions were conducted for six consecutive weeks, three sessions a week. Analysis of covariance and Bonferroni post hoc test were used to analyze the data.

Results: i) There were no significant differences between groups in BMI, BFP, or LBM. ii) There was a significant difference in IL-6 levels between the groups ($p < 0.05$), so that the inflammatory levels in the "HIIT + L-Arginine supplementation" and "HIIT + placebo" groups were lesser than the "HIIT" (0.002 and <0.001, respectively) and "L-Arginine supplementation" (<0.001and <0.001, respectively) groups. HIIT "seems" to reduce the level of inflammation.

Conclusion: HIIT had no significant effect on body composition indices. Plasma IL-6 levels decreased after six weeks of HIIT and L-Arginine supplementation. The level of IL-6 in the "HIIT + L-Arginine supplementation" and "HIIT + placebo" groups were lower than the control group (i.e.; "HIIT") and supplement control group (i.e.; "L-Arginine supplementation").

Key words : Body Composition; C-Reactive Protein; Exercise; Inflammation

Résumé

Objectif: Évaluer l'effet de six semaines d'entraînement par intervalles à haute intensité (EIHI) et de supplémentation en L-Arginine sur les taux d'interleukine-6 (IL-6) et la composition corporelle chez des hommes iraniens adultes entraînés.

Méthodes: Cette étude expérimentale était réalisée en tant qu'intervention avec une conception pré-test/post-test dans trois groupes expérimentaux et un groupe témoin. Quarante-huit jeunes hommes de la province de Qazvin (Iran) étaient sélectionnés volontairement sur la base d'un échantillonnage de commodité. Les participants étaient répartis au hasard en quatre groupes (12 participants dans chaque groupe): «EIHI»; «Supplémentation en L-Arginine»; «EIHI + Supplémentation L-Arginine» et «EIHI + placebo». À 7 heures du matin, lorsque le taux d'inflammation était à son plus bas, un échantillon de sang était prélevé, et l'indice de masse corporelle (IMC), le pourcentage de masse graisse (%MG), et la masse maigre (MM) étaient déterminés. L'analyse de l'IL-6 a été effectuée à l'aide du dispositif STATE FAX et de la méthode ELISA. Les sessions d'entraînement étaient menées pendant six semaines consécutives, trois sessions par semaine. L'analyse de covariance et le test post hoc de Bonferroni étaient utilisés pour analyser les données.

Résultats: i) Il n'y avait pas de différences significatives entre les groupes en termes d'IMC, de %MG ou de MM. ii) Il y avait une différence significative dans les taux d'IL-6 entre les groupes ($p < 0,05$), de sorte que les niveaux inflammatoires dans les groupes «EIHI + Supplémentation en L-Arginine» et «EIHI + placebo» étaient inférieurs au «EIHI» (0,002 et <0,001, respectivement) et «Supplémentation en L-Arginine» (<0,001 et <0,001, respectivement). L'EIHI «semble» réduire le niveau d'inflammation.

Conclusion: L'EIHI n'a eu aucun effet significatif sur les indices de la composition corporelle. Les taux d'IL-6 ont diminué après six semaines d'EIHI et de supplémentation en L-Arginine. La concentration d'IL-6 dans les groupes «EIHI + Supplémentation en L-Arginine» et «EIHI + placebo» était inférieur à celle du groupe témoin (cad «EIHI») et du groupe témoin supplémenté (cad «Supplémentation en L-Arginine»).

Mots clés : Composition corporelle; Exercise; Inflammation; Protéine C-réactive

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INTRODUCTION

Increased inflammatory factors in the body can be the prelude to many diseases including atherosclerosis, type 2 diabetes mellitus, insulin resistance, obesity, depression and disability in humans (1). Studies have reported that the production of large amounts of cytokines such as interleukin-6 (IL-6) is involved in the development of metabolic syndrome and diabetes mellitus (2, 3). IL-6 is an important cytokine that is secreted by white blood cells and adipose tissue, and is involved in inflammatory and immune responses (4). IL-6 has pro-inflammatory and anti-inflammatory roles and with increasing body fat percentage (BFP) and obesity, its secretion from adipose tissue increases (5). A great deal of research has indicated a positive relationship between body composition components such as body mass index (BMI), BFP and level of inflammatory cytokines, such as IL-6 (6-8). Therefore, it can be stated that body composition indicators are related to inflammatory markers (6-8). People are increasingly turning to sports that produce better results in less time in terms of body composition and fitness as well as health (9-11). In this regard, high intensity interval training (HIIT) is considered as a productivity strategy in less time to improve metabolic health (12). The effects of exercise on inflammatory markers and cytokines is very important in improving metabolic processes (13, 14). The expression of cytokines following exercise is highly dependent on the intensity, duration, volume of exercise, and training period (15, 16). Studies have highlighted that the anti-inflammatory effects of exercise can be due to an increase in IL-6 immediately after exercise, which leads to a decrease in tumor necrosis factor alpha (TNFα) and insulin resistance (15, 17). It "seems" that the metabolic effects of IL-6 appear is associated with endogenous glucose production during muscular activity (15). Therefore, due to the HIIT, glucose depletion may cause significant changes in IL-6 (18). On the other hand, using supplement besides the exercise intervention is another factor considered by health professionals and researchers (9, 19, 20). In this regard, L-Arginine is a supplement used for health purposes (9, 19, 20). L-Arginine is an important factor in several physiological and biochemical processes (21, 22). Recently, scientists studied L-Arginine effect on inflammatory mediators such as C-reactive protein and TNFα and IL-6 (23). Results indicated that L-Arginine might not be able to reduce selected inflammatory mediators, but for making a firm decision more studies are needed to be conducted with longer intervention duration, separately on male and female and with different doses of L-Arginine (23). It seems that reducing the levels of inflammatory cytokines such as IL-6 and TNFα has an effective role in decreeing blood pressure in people with high blood pressure, and the use of L-Arginine can have a synergistic effect in reducing systolic blood pressure with exercise (23).

To the best of the authors' knowledge, a few studies considered long-term effects of HIIT on inflammatory factors and reported conflicting results. First, Dimitriou et al. (24) did not observe a change in plasma IL-6 levels in the elderly after 10 weeks of combined aerobic and resistance training. Second, combining 12 weeks of moderate-intensity aerobic, strength, balance, and flexibility training resulted in a 32% reduction in C-reactive protein, and a 16% reduction in IL-6 in the elderly (1). Third, Stewart et al. (25) did not observe significant changes in resting IL-6 and TNFα levels in healthy elderly after 12 weeks of combined aerobic and resistance training. Fourth, in patients with arterial hypertension, both short-term (*i.e.;* two weeks) and long-term (*i.e.;* eight weeks) HIIT protocols induced significant decreases of IL-6 (26). Fourth, Ahmadizad et al. (27) have compared the effects of six weeks of intense and moderate intensity training on inflammatory factors and reported no significant changes in IL-6 plasmatic levels, and a decrease in BFP. Fifth, performing 10 weeks of HIIT and continuous moderate-intensity training in overweight females with type 2 diabetes mellitus did not cause any significant change in myokines despite significant weight loss (28). On the other hand, nutritional factors and exercise protocols are considered by researchers to reduce anti-inflammatory cytokines (29). For instance, Nascimento et al. (30) reported that IL-6 levels was decreased after exercise. However, in a study including young males, Hiratsa et al. (31) have reported that the use of 5-grams of L-Arginine acutely, as well as 13 days of exercise by cycling at 75% of the reserve heart rate, had no effect on ammonia levels. In addition, it was found that caraway supplementation decreased inflammatory markers significantly (32).

Given the importance of HIIT on various systems of the body, especially the immune system of athletes, as well as the possible effects of arginine supplementation, the main purpose of this experimental study was to investigate the effects of six weeks of L-Arginine supplementation and HIIT on IL-6 levels in Iranian adult trained males.

METHODS

Study design

The research design was pretest/posttest three experimental (***i.e.;*** "L-Arginine supplementation" group; "HIIT + L-Arginine supplementation" group, and "HIIT + placebo" group) and control group (***i.e.;*** no intervention including exercise or supplementation). Local ethical committee of Imam Khomeini International University approved the research design (reference number: 17628). The research was performed from April 2021 to September 2021 in sport physiology lab of Imam Khomeini International University. Participants were asked to sign the written consent form before the study. During each study step, all recommended preventive measures to fight against coronavirus disease 2019 transmission were applied.

Participants

The study participants were young males living in Qazvin province (Iran). Participants were selected by convenience sampling through Social media, and during their presence in

sports complexes of Qazvin. Only healthy participants were included (***i.e.;*** no chronic conditions such as cardiovascular diseases, arterial hypertension, kidney disease, liver disease, osteoporosis, and diabetes mellitus). Exclusion criteria included absence in any of the three test sessions, and any injury occurred within the experiment. Participants were asked to avoid consuming any supplementation such as L-Arginine and other vitamins or minerals prior to the study, mainly 24 hours before blood sampling. Figure 1 describes the study flowchart/protocol.

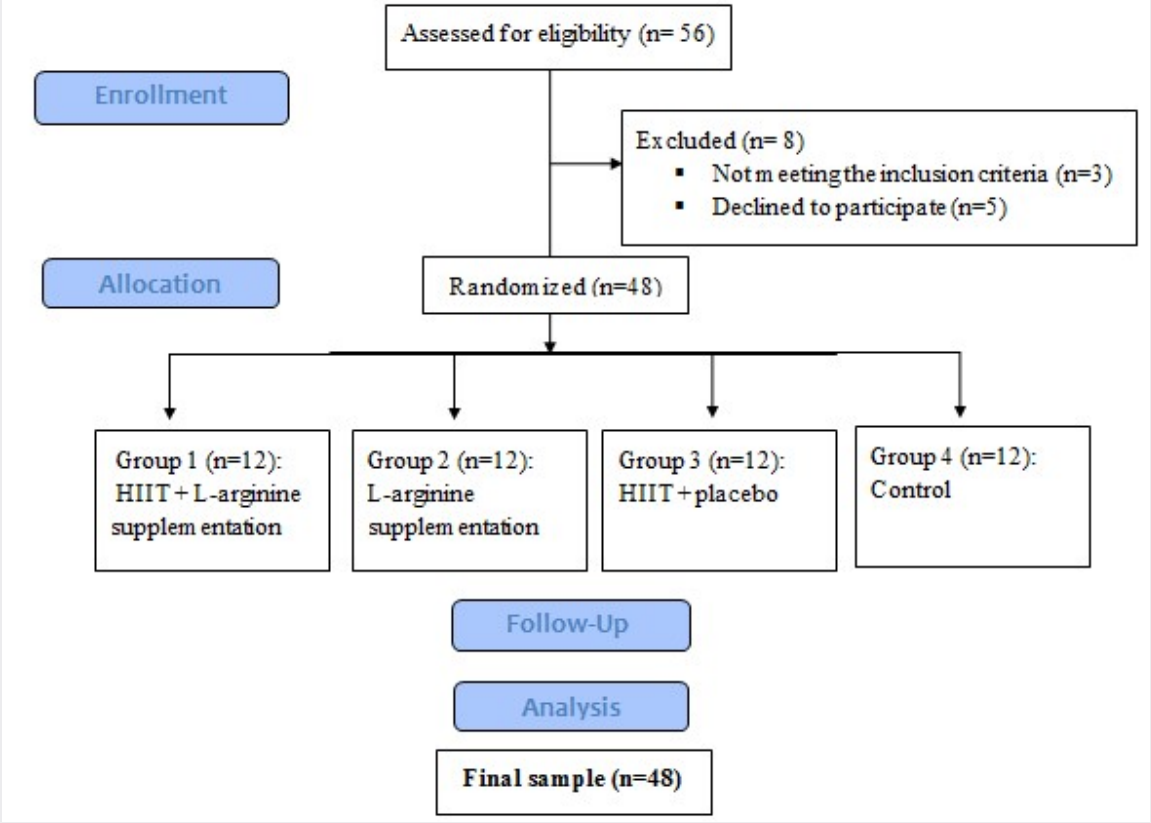

Figure 1. Study flowchart.
HIIT: high intensity interval training.

Collected data and applied protocols

Height (m) of the participants was measured (Seca weight, model 220, Germany). Weight (kg), BMI (kg/m^2), lean body mass (kg), fat free mass (kg), and BFP (%) were measured by a body composition analyzer (ZEUS 9.9 PLUSE, Korea).

A fasting venous blood sample was taken (a 5 ml syringe marked AVA and poured into a 6 ml tube without anticoagulation) from the participants when the level of inflammation was at its lowest (*i.e.;* at 7 a.m) (33). After 2-3 minutes at room temperature, the serum was separated from blood samples by centrifugation at 4000 revolutions per minute for seven minutes and stored at -18 °C. Serums were removed from the freezer and gradually melted at room temperature. Enzyme-linked immunosorbent assay method (ELISA IL-6 kits, Diagnostics GmbH Demeditec Company, Germany) were used was used with STATE FAX for measuring IL-6.

Training sessions were performed for six weeks (three sessions/week) including 5-10 minutes of warm-up, and then the main exercise, which included 20-60 minutes of high-intensity, non-resting exercise over six weeks as shown in Box 1 (34). Exercises were done in such a way that the training time was added every week, so that from the first week, which was 22.5 minutes, to the 6th week, it reached 45 minutes (Box 1). The number of movements of each session was performed consecutively without rest between training sets (Box 1). Exercises protocol included running, rope jump, squats, push up, pull-up, crunch, curl crunch, side planks, lunges, side crunch. The Karvonen-formula was used to determine the intensity of exercise based on resting heart rate (35). The participants' heart rate was monitored during the protocol by a POLAR pulse meter (FT2 model; Finland).

Exercise protocol was provided for "HIIT + L-Arginine supplementation" and "HIIT + placebo" groups according to Box 1. The "supplementation" group did not have any exercise or physical activity. Participants in the "L-Arginine supplementation"; "HIIT + L-Arginine supplementation" took 6.4 grams of L-Arginine supplement daily. The supplementation used in this study was a powder from the British company (Balk), which was consumed in 2.3-gram capsules in two meals after breakfast and after lunch (36). Starch powder capsules were given to "HIIT + placebo" as a placebo. All participants were retested after 18 exercise sessions.

Box 1. The exercise method.

Week N°	Sets N°	Time (seconds)	N° of full rounds	Duration (minutes)
1st	At least 5	45	3	22.5
2nd	At least 6	45	3	27
3rd	At least 5	45	4	30
4th	At least 6	45	4	36
5th	At least 5	45	5	37.5
6th	At least 6	45	5	45

Sample size and statistical analysis

Estimating sample size was calculated based on G*Power version (3.1.9.2). α error and power were fixed at 0.05 and 0.70, respectively. The needed sample was 48 participants. Quantitative data were presented as mean ± standard deviation. Analysis of covariance (ANCOVA) and Bonferroni post hoc test were used to analyze the data. Significant level was set at p≤0.05.

RESULTS

Among the initial samples, and after applying the inclusion and exclusion criteria, 48 participants were included (Figure 1).

Table 1 exposes the plasmatic concentration' of IL-6 and anthropometric data of each group.

Table 1. Plasma concentration of interleukin-6 and body composition in the four groups (n=12 each group).

Variables	Source	"HIIT + Placebo"	"HIIT + L-Arginine"	"L-Arginine"	"Control"
Interleukin-6 (pg/mL)	Pretest	7.75±0.42	5.46±1.49	6.46±0.37	6.12±0.56
	Posttest	2.85±0.32	3.10±0.36	5.67±0.45	6.26±0.51
Body mass index (kg/m²)	Pretest	25.77±3.27	26.86±3.04	26.97±3.09	25.30±4.08
	Posttest	26.30±3.17	26.42±3.06	29.10±6.55	25.92±4.04
Body fat percentage (%)	Pretest	22.30±4.35	24.15±3.51	24.22±3.61	21.63±4.95
	Posttest	22.93±4.06	23.56±3.52	26.77±8.38	22.38±4.80
Fat free mass (kg)	Pretest	60.59±6.06	67.08±8.68	67.11±8.81	66.38±7.55
	Posttest	61.49±6.68	64.57±9.71	70.49±10.37	68.39±9.11

Data were mean±standard deviation. **HIIT:** High Intensity Interval Training.

Table 2 exposes the results of ANCOVA for four test groups for IL-6 and body composition. Figure 2 exposes the Bonferroni test results to compare the means of IL-6 levels and body composition in four test groups. According to the findings of Table 2, there is a significant difference between the groups in the level of IL-6 ($p < 0.05$). Figure 2A showed that the level of inflammation in the "HIIT + L-Arginine supplementation" and "HIIT + placebo" was lower than the "L-Arginine supplementation" ($p<0.05$). It seems that HIIT reduces the level of inflammation.

Table 2. Results of analysis of covariance for four test groups for interleukin-6 (IL-6) and body composition.

Variables	Source	Total sum of squares	Degrees of freedom	Mean square	Distribution	P-value	Eta coefficient
Interleukin-6 (pg/mL)	Pretest	942.87	1	942.87	2.38	<0.001	0.36
	Groups	253.04	3	84.35	1.14	0.001	0.66
	Error	1707.92	43	39.71	-	-	-
Body mass index (kg/m²)	Pretest	253.71	1	253.71	2.38	<0.001	0.30
	Groups	48.63	3	16.21	2.15	0.364	0.07
	Error	639.45	43	14.87	-	-	-
Body fat percentage (%)	Pretest	467.62	1	467.62	21.29	<0.001	0.33
	Groups	70.71	3	23.57	1.07	0.371	0.07
	Error	944.59	43	21.97	-	-	-
Fat free mass (kg)	Pretest	857.02	1	857.02	11.99	0.001	0.22
	Groups	315.03	3	105.01	1.47	0.236	0.09
	Error	3073.28	43	71.47	-	-	-

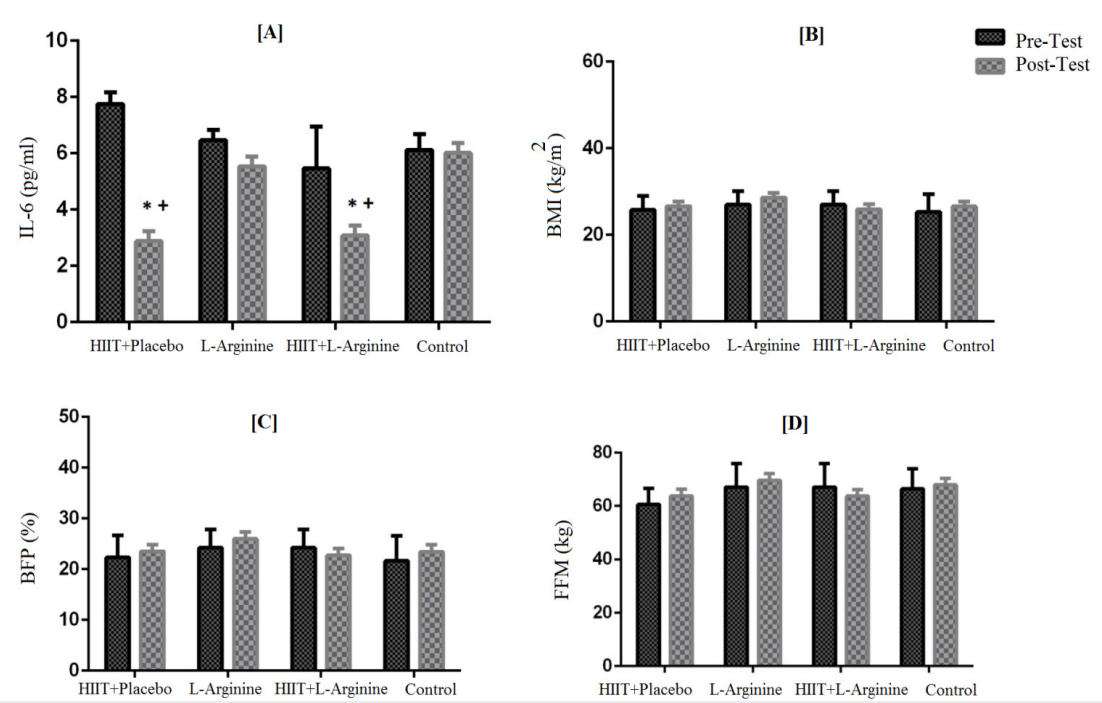

Figure 2. Bonferroni test results to compare the means of interleukin-6 (IL-6) levels and body composition in four test groups.

[A] Interleukin-6 (IL-6), [B] Body mass index (BMI), [C] Body fat percent (BFP), [D] Fat free mass (FFM).

HIIT: High intensity interval training. Significant difference with the control group ($p<0.05$). $^{+}$ Significant difference with the supplement group ($p<0.05$).

Table 3 exposes the adjusted body composition status for the four test groups. There were no significant differences between groups in body composition indices (Table 2, Figures 2B, 2C, 2D).

Table 3. Adjusted body composition for four test groups (n=12 for each group).

Data	Source	"HIIT + Placebo"	"HIIT + L-Arginine"	"L-Arginine"	"Control"
Body mass index (kg/m^2)	Pretest	25.76±3.27	26.97±3.09	26.91±3.59	25.95±4.02
	Posttest	25.99±3.48	26.42±3.06	27.02±3.89	26.02±4.11
Body fat percentage (%)	Pretest	23.89±4.54	24.12±3.61	24.21±3.61	23.65±3.62
	Posttest	36.1±3.23	23.55±3.51	25.01±3.21	23.1±3.23
Fat free mass (kg)	Pretest	65.62±7.52	66.35±8.31	66.98±7.53	65.98±7.49
	Posttest	66.01±7.36	67.03±7.86	66.08±8.30	66.12±7.99

Data were mean±standard deviation. **IIT:** High intensity interval training.

DISCUSSION

The present study reported that plasma IL-6 levels decreased after six weeks of HIIT and L-Arginine supplementation. The level of IL-6 in the "exercise-supplement" and "exercise-placebo" groups were lower than the "control" and "supplement" groups. This finding is inconsistent with the research of Cullen et al. (18). The latter examined the response of IL-6 and associated cytokines to high intensity exercise, and suggested that high intensity exercise increased IL-6' level (18). Generally, IL-6 can be considered as one of the indicators that should be expected to be changed with exercise. However, according to the literature, the amount of changes during different activities will be different. Since the intensity of exercise determines the inflammatory response to exercise, considering different intensities should be considered (37). According to one study, IL-6 increases in response to a strenuous exercise session (38). On the other hand, the theory states that the main source of IL-6 production is skeletal muscle and is also dependent on muscle mass involved in exercise (39). In this regard, increasing the amount of IL-6 in resistance training

has also been confirmed (38). On the other hand, one study which evaluated the effect of both aerobic interval training (for six weeks) and taking tamoxifen on IL-6 and IL-10 tumor levels in mice with breast cancer, concluded that IL-6 level decreased by high intensity exercise (40-43). The result also showed that high intensity exercise had no significant effect on body composition variables such as BFP, lean body mass, and BMI (43). Consistent with our study, do Nascimento et al. (30) reported that L-Arginine supplementation attenuates the cytokine increase after acute resistance exercise, in particular peak IL-6 levels decrease and exercise induced decreases in IL-10 levels are attenuated. However, contrary to our findings, Martina et al. (44), reported no change of inflammatory markers following L-Arginine supplementation. In another study including obese subjects (45), it was highlighted that moderate intensity training had no significant effect on inflammatory profile of proinflammatory cytokines TNFα and IL-6. Researchers believe that exercise plays a role in controlling and modulating inflammation through three major mechanisms such as reducing visceral fat, increasing the production of anti-inflammatory cytokines, and reducing inflammatory cytokines (3). Weight loss by physical activity is one of the mechanisms that reduces inflammation (6). Weight loss can decrease cytokines in adipose tissue-derived (17). It can be stated that training participants with a positive effect on weight loss would reduce the levels of inflammatory cytokines (18). Monzillo et al. (40) investigated the effect of weight loss in response to a lifestyle modification program on blood levels of inflammatory cytokines in obese people with insulin resistance. The authors suggested that a significant changing in body weight improved the insulin sensitivity index and decreased IL-6 (40). Although many studies have shown that high intensity exercise can reduce weight, subcutaneous fat percentage, and visceral fat, the reported reductions were s not been significant (41-43). One of the most important reasons for these contradictions is influential variables that are not easily controllable. Nutrition can be one of these variables that was not completely controlled in the present study. Therefore, it can be one of the possible effective reasons for those obtained results. Generally, exercise training such as HIIT would increase appetite and food intake (46). Some studies reported that interval exercise also causes significant changes in muscle metabolism by increasing the capillary network, vasodilation, and increasing the amount of mitochondrial enzymes; that leads to increasing fat oxidation (47, 48). They stated that high intensity exercise increases beta-hydroxy acyl-dehydrogenase and fat oxidation capacity (47, 48). High intensity exercise reduces the BFP, BMI, weight and waist/hip ratio, which is contradictory to the results of the present study (47, 48). The reason for the difference in findings may be related to the individual differences among participants (49). One study reported a significant decrease in weight, BFP and BMI of participants (49). In the above cited study, despite a negative energy balance due to the participants' involvement in the 12-week exercise program, the body composition did not change (49). The researchers stated that one of the possible reasons was the participants' incorrect report of their energy intake during the exercise program (49). In addition, the increase of appetite and compensation of energy consumption due to activity was announced as another significant change in the participants' BFP (50). The conflict results would be attributed to individual differences of participants (*i.e.;* sex, level of fitness and health situation), HIIT training program (*i.e.*; intensity of exercise, time of exercise, number of cycles, and rest time), and the duration of training. One of the limitations of the present study is the small number of participants and the short duration of the training protocol, which should be considered by researchers in future research.

Generally, it was concluded that groups with L-Arginine supplementation and HIIT exercise, had significant decline in IL-6 and combination of HIIT training and L-Arginine reverses inflammation process through suppression of IL-6. Therefore, L-Arginine and HIIT training supplementation could prevent elevation of inflammation and oxidative stress markers.

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