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The Interactive Effects of Continuous and Interval Training with Crocin Consumption on the Levels of Interleukin-17 and Interleukin-18 in the Soleus Muscle of Rats with Type II Diabetes

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ABSTRACT

Introduction: Muscle inflammation and atrophy are among the main complications of diabetes, which lead to motor disability in the patients. Studies have shown that physical exercise with various intensities and use of herbal medicines could positively affect diabetes. The present study aimed to evaluate the interactive effects of continuous and interval training with crocin consumption on the levels of interleukin-17 (IL-17) and interleukin-18 (IL-18) in the soleus muscle of rates with type II diabetes.
Methods: This experimental study was conducted on 49 adult diabetic rats, which were randomly assigned to seven groups, including: high-intensity interval training (HIIT), low-intensity continuous training (LICT), HIIT with crocin consumption, LICT with crocin consumption, crocin consumption, sham, and control. The HIIT and LICT groups received training for eight weeks using a rodent treadmill. The crocin consumption groups were intraperitoneally administered with crocin (25 mg/kg) daily for eight weeks. The gene expression levels of IL-17 and IL-18 were measured using real-time polymerase chain reaction (RT-PCR).
Results: HIIT increased IL-17 and IL-18 in the soleus muscle tissue of the diabetic rates ($P \leq 0.05$), while LICT had no significant effects on the levels of IL-17 and IL-18 ($P \geq 0.05$). On the other hand, crocin consumption decreased the expression of IL-18 and increased the expression of IL-17 in the soleus muscle tissue ($P \leq 0.05$), and the interactive effects of LICT and crocin consumption were considered significant in increasing IL-17 and IL-18 ($P \leq 0.05$).
Conclusion: According to the results, HIIT may exert inflammatory effects on the muscle tissue of rats with type II diabetes. However, the interactive effects of LICT and crocin were significant on increasing IL-17 and IL-18 in the soleus muscle tissue of diabetic rats.

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Introduction

In recent decades, the prevalence of type II diabetes has increased drastically in humans [1]. Muscle atrophy is an uncontrolled diabetes marker, which leads to increased proteolysis and inability of the damaged skeletal muscles to regenerate through protein synthesis [2]. In addition, the metabolic disorders induced by diabetes reduce the physical ability to respond to physiological stresses, such as increased oxidative stress and inflammation. In general, insulin resistance and deficient energy production in muscle tissues play a pivotal role in the pathology of diabetes [1, 3]. Several studies have confirmed the association of diabetes and increased inflammation markers [2]. For instance, increased fat mass may cause an upsurge in insulin resistance in various tissues (e.g., muscles and liver) by increasing chronic inflammation [3].

According to the literature, physical exercise plays a key role in the management and control of diabetes. Furthermore, physical exercise could have potential effects on weight loss and the improvement of type II diabetes [4], thereby leading to changes in inflammatory and pro-inflammatory cytokines, such as interleukin-17 (IL-17) and interleukin-18 (IL-18) as the key predictors of diabetes [5]. Numerous studies have been focused on the effects of physical exercise on inflammation markers in diabetic patients, proposing conflicting results. For instance, researchers have reported that one

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session of moderate-intensity resistance training could reduce IL-18 and increase IL-6 in physically inactive, obese men [6]. Moreover, 12 weeks of high-intensity interval training has been reported to increase IL-17 levels and improve glycemic indices in obese men, while no significant changes have been denoted in IL-10 levels [7]. In another study in this regard, four weeks of no training followed by four weeks of combined training could increase the levels of IL-17 in obese men [8].

In addition to the substantial effects of regular physical exercise on the health of patients with type II diabetes, researchers believe that proper diet and use of herbal medicines, along with physical activity, could accelerate the treatment process of type II diabetes [9]. Crocin is a compound found in saffron with potent antioxidant and anti-inflammatory properties. By reducing free radicals and oxidative stress, crocin could stimulate homeostasis [10, 11]. On the other hand, some studies have examined the health benefits of saffron and its components along with physical exercise. For instance, resistance training combined with saffron supplementation has been reported to produce testosterone and cortisol [11], while aerobic exercise combined with the use of the aqueous extract of saffron has been shown to increase the antioxidants in the liver tissues of the rats with streptozotocin (STZ)-induced diabetes [12], and swimming along with saffron consumption has been reported to improve glycemic indices in diabetic rats [13].

Considering the contradictory findings regarding the effects of physical exercise on IL-17 and IL-18, as well as the scarce data on the interactive effects of crocin and physical exercise on these factors in muscle tissues, such investigations could provide beneficial data for the prevention of the muscle damage induced by diabetes.

The present study aimed to investigate the interactive effects of high-intensity interval training (HIIT) and low-intensity continuous training (LICT) along with crocin consumption on the levels of IL-17 and IL-18 in the soleus muscle tissue of rats with diabetes induced by a high-fat diet and STZ.

Materials and Methods

This experimental study was conducted on 49 male Sprague-Dawley rats aged eight weeks, with the mean weight of 150±30 grams. The animals were purchased from the reproductive center and animal house of Islamic Azad University, Marvdasht Branch, Iran. Afterwards, they were transferred to the animal sport physiology laboratory in standard conditions and kept at the temperature of 22-27°C, relative humidity of 50%, and controlled light (12-hour light/dark cycle) for the seven-day adaptation period. The animals had *ad libitum* access to water and food during this period.

In this study, type II diabetes was induced using the combination of a high-fat diet and STZ injection. To do so, the rats were exposed to a high-fat diet containing 45% of total fat (derived from animal fat), 24 grams of fat, 24 grams of protein, and 41 grams of carbohydrate per 100 grams for eight weeks (15). After eight weeks, diabetes induction was performed intraperitoneally using a single dose of STZ dissolved in sodium citrate buffer (pH=5.4 mg/kg) [14]. Approximately 96 hours after the injection, diabetes was confirmed in the rats with the glucose levels of >300 mg/dl, and these animals were selected as the study samples [14]. Based on blood glucose, the rats were divided into seven groups (n=7), including HIIT, LICT, HIIT with crocin consumption, LICT with crocin consumption, crocin consumption, sham, and control. In order to estimate the maximum running speed, the sport performance test was performed with zero gradient. To perform the test, the rats initially started running at the speed of 10 m/min, followed by the increasing of the treadmill speed to 1 m/min every one minute. This trend continued until the rats were unable to run (i.e., exhaustion) [14]. After estimating the speed of groups one and three for eight weeks, HIIT was performed three sessions per week at the intensity of 80-85% of the maximum running speed for two minutes, along with an active rest period of one minute. The frequency of training reached six sessions within the first week and 12 sessions by the last week.

In groups two and four, training was also performed three sessions per week for eight weeks at the intensity of 50-55% of the maximum running speed. In the first week, the duration of LICT was 25 minutes and reached 50 minutes by the last week. It is also notable that the HIIT and LICT groups were matched in terms of the total volume of physical activity (severity, duration, and repetition) [14]. In addition,

groups three, four, five were intraperitoneally administered with crocin (25 mg/kg) dissolved in normal saline on a daily basis [15].
In order to control the effects of the injection on the study variables, the sham group received daily crocin solvent intraperitoneally. At the end of the eight weeks and 24 hours after the last training session, the rats were surgically treated to measure the study parameters. Initially, the animals were anesthetized with 10% ketamine (50 mg/kg of body weight) and 2% xylazine (10 mg/kg of body weight). After five minutes, their soleus muscle was extracted by specialists. A cryotube was placed in liquid nitrogen and stored for further investigation at the temperature of -70°C.
RNA extraction was carried out in accordance with the instructions of the RNA extraction kit (Yektasaz Tajhiz Company, Iran) using the extraction kit solutions and based on the proposed protocols of the manufacturer. In addition, cDNA synthesis was performed in accordance with the instructions of the Fermentas kit (K1622). The sequence of the applied primers is presented in Table 1.

Table 1. Sequence of Forward-Reverse Primers of Genes in Real-time PCR Reaction

Gene	Forward (5'-3')	Reverse (5'-3')
IL-17	CTGAAAGTCCTCAACTCCCTTAG	CTCATTGCGGCTCAGAGT
IL-18	ACCGCAGTAATACGGAGCAT	GATCAGCTCGGGCACTTTAG

After completing the device activity and observation of the diagrams to increase the number of the provided pieces, several factors were assessed and measured, including the fluresence diffusion based on the calculation of ΔΔCt, changes in the expression of the genes relative to B2m, and control state without distinct environments. Following that, the expression of the genes was estimated using the $2^{-\Delta\Delta Ct}$ formula.
In data analysis, the Shapiro-Wilk test was used to determine the normal distribution of the data. The effects of the crocin solvent on the study variables were evaluated using independent sample t-test between the control and sham groups. In addition, the interactive effects of endurance training and crocin consumption were determined using the two-way analysis of variance (ANOVA), and Bonferroni's mean comparison test was applied to verify the differences between the two training programs ($P \leq 0.05$).

Results

Table 1 shows the mean values of the research variables. According to the results of independent sample t-test regarding the differences between the control and sham groups in terms of the effects of the crocin solvent, the levels of IL-17 (P=0.43) and IL-18 (P=0.09) had no significant differences between these groups.

Analysis of IL-17

According to the results of two-way ANOVA to investigate the interactive effects of endurance training and crocin consumption on IL-17, endurance training (P=0.001) and crocin consumption (P=0.001) had significant effects on the increasing of IL-17 levels in the soleus muscle tissues of the rats with diabetes induced by a high-fat diet and STZ. Moreover, the interactive effects of endurance training and crocin consumption in the increasing of IL-17 levels in the soleus muscle tissues of these rats were significant (P=0.001).
According to the results of Bonferroni's comparison of means to examine the differences between the training types (Figure 1), the IL-17 levels in the HIIT groups were significantly higher compared to the animals receiving no training (P=0.001). Furthermore, LICT had no significant effects on the increasing of the IL-17 levels in the soleus muscle tissues of the rats compared to the animals receiving no training (P=0.40). The obtained results also indicated that the IL-17 levels in the HIIT groups were significantly higher compared to the LICT groups (P=0.001).

Analysis of IL-18

The results of the two-way ANOVA are presented in Table 3. Accordingly, endurance training had a significant effect on the changes in the levels of IL-18 in the soleus muscle tissues of the diabetic rats (P=0.001). In addition, crocin consumption could significantly reduce the IL-18 levels in the soleus muscle tissues of the diabetic rats

(P=0.001). Endurance training along with crocin consumption could also significantly increase the levels of IL-18 in the soleus muscle tissues of the diabetic rats (P=0.001).

Figure 2 depicts the results of Bonferroni's comparison of means test. As can be seen, the IL-18 levels in the HIIT groups were significantly higher compared to LICT groups (P=0.001). However, HIIT training had no significant effect on the increasing of the IL-18 levels compared to the animals receiving no training (P=0.001). Moreover, LICT had no significant effect on the reduction of the IL-18 levels compared to the animals receiving no training (P=0.22).

Table 2. Mean IL-17 and IL-18 Gene Expression Levels in Soleus Muscle Tissues of Diabetic Rats in Study Groups

Group	IL-17	IL-18
Control	0.29±0.22	**2.50±0.49**
Sham	0.41±0.31	**2.04±0.44**
Crocin Consumption	0.87±0.49	**1.81±0.40**
HIIT	0.38±0.17	**1.14±0.33**
LICT	0.72±0.27	**1.72±0.63**
HIIT with Crocin Consumption	4.04±1.77	**6.32±1.26**
LICT with Crocin Consumption	1.35±0.32	**1.65±0.44**

Table 3. Results of Two-way ANOVA Regarding Effects of Endurance Training and Crocin Consumption on Research Variables

	Factor	Sum of Squares	Degree of Freedom	Mean of Squares	F	Significant	Size Effect
IL-17	Endurance Training	19.70	2	9.85	16.14	0.001	**0.47**
	Crocin Consumption	27.70	1	27.70	45.40	0.001	**0.55**
	Endurance Training with Crocin Consumption	21.77	2	10.88	17.84	0.001	**0.49**
IL-18	Endurance Training	32.08	2	16.04	35.35	0.001	**0.66**
	Crocin Consumption	22.69	1	22.69	50.02	0.001	**0.58**
	Endurance Training with Crocin Consumption	72.64	2	36.32	80.05	0.001	**0.81**

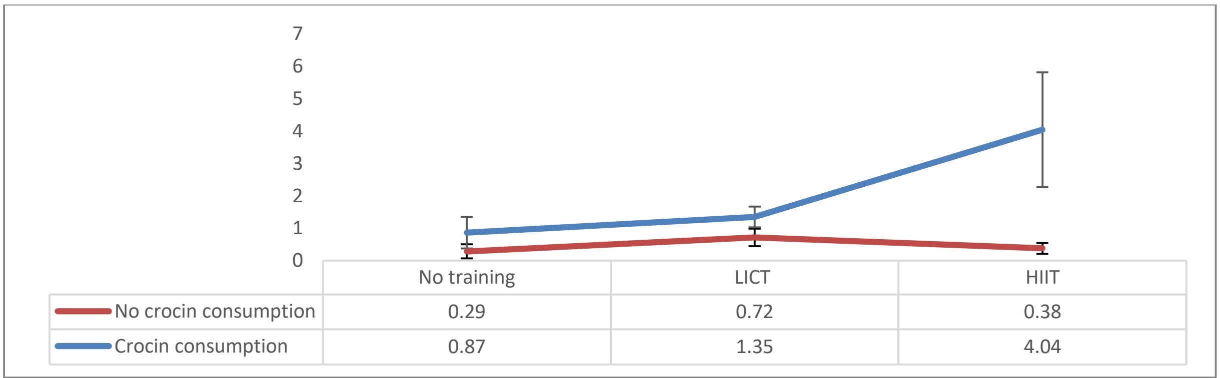

Figure 1. IL-17 Gene Expression in Soleus Muscle Tissues of Research Groups

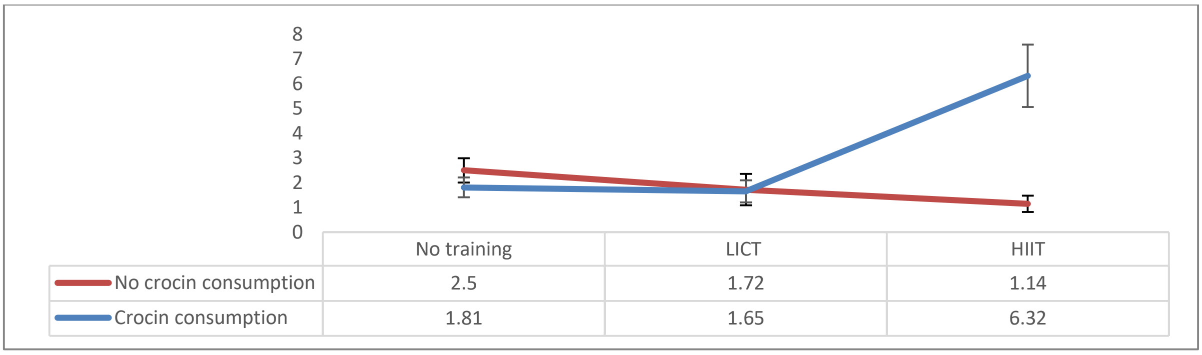

Figure 2. IL-18 Gene Expression in Soleus Muscle Tissues of Research Groups

Discussion

According to the literature, obesity and type II diabetes are associated with mild-to-severe inflammation. The risk of obesity and metabolic syndrome increases with the secretion of IL-18 from the adipose tissue and smooth muscle cells and secretion of IL-17 from macrophages, TH-17, natural killer cells, and other pro-inflammatory [16]. In the pathogenesis of type II diabetes, diabetic nephropathy is involved in the activation of the Kappa B nuclear transcription factor and the provocation of the factors that promote the pathways of cell damage [17].

Scientists believe that cytokines variably affect different tissues, and some cytokines could exert anti-inflammatory effects as well. Since IL-17 and IL-18 are both anti-inflammatory cytokines, the skeletal muscles seem to release some IL-6 into the bloodstream during physical exercise although this cytokine leads to increased insulin resistance in the liver and adipose tissue. However, the metabolic effects of this cytokine on skeletal muscles have also been confirmed. The increase in this cytokine in the skeletal muscles is associated with the higher levels of IL-17 and IL-18, which in turn increase insulin sensitivity in the skeletal muscle tissues. As such, previous studies have denoted that muscle contractions could result in the positive expression of the levels of some cytokines, such as IL-18, TNF-α, and IL-8 [5].

The changes in IL-17 seem to be influenced by the intensity of physical exercise. According to the results of the present study, HIIT could increase the secretion of the anti-inflammatory cytokines that express IL-17 in the skeletal muscles [18]. Several studies have investigated the effects of various sports with variable intensity on the expression of these cytokines. In line with the current research, previous findings have demonstrated that high-intensity training could increase the serum and protein levels of IL-17 in the skeletal muscles of rats, while moderate-intensity training has been reported to have no significant effects on the changes in IL-17 [19].

According to a study in this regard, resistance training and endurance training had no significant effects on the changes in the serum IL-17 levels in athletes [18, 20]. However, 12 weeks of resistance training was reported to significantly decrease the IL-18 levels in elderly men [21]. On the other hand, eight weeks of swimming has been reported to have no significant effects on the changes in the serum levels of IL-18, while 10 weeks of swimming has been shown to reduce the serum levels of IL-18 in rats [22]. Although the findings of most of the studies in this regard suggest that these cytokines are pro-inflammatory agents in some tissues, their pathway and mechanism of expression following physical exercise in the skeletal muscles remain unknown. Therefore, further investigations are required in this regard.

According to the results of the present study, crocin consumption could significantly increase IL-17 gene expression and reduce IL-18 gene expression in the muscle tissues of the rats with diabetes induced by a high-fat diet and STZ. It is believed that crocin consumption could also protect unsaturated fatty acids in the cell membrane by decreasing free radicals. Moreover, crocin has been reported to inhibit the activation of reactive oxygen species by inhibiting oxidative stress and reducing lipid peroxidation. Crocin consumption may also increase NF-κB and decrease lipid peroxidation, exerting lipid-lowering effects on diabetic patients. However, most of the studies in this regard have indicated that the antioxidant and anti-inflammatory effects of crocin are dose-dependent [23, 24].

In the current research, the administration of 25 mg/kg of crocin increased IL-17 and decreased IL-18 in the muscle tissues of the diabetic rats. Despite extensive research in this regard, no data is available on the effects of crocin on IL-17 and IL-18 levels, especially in the skeletal muscle tissues. Inconsistent with our findings, 60 days of crocin consumption at the concentration of 40 mg/kg was reported to significantly reduce the expression of IL-17 in an arthritic model of rats. In the mentioned study, the concentrations of 10 and 20 mg/kg of crocin had no significant effects on IL-17 changes [25]. According to another research, the administration of 500 mg/kg of the hydroalcoholic extract of saffron was reported to significantly decrease the IL-17 levels in diabetic laboratory rats [26]. Studies have shown that the increased level of IL-6 is one of the pathways that could stimulate IL-10 and IL-1ra expression, as well as TNF-α inhibition, thereby resulting in the decreased levels of IL-18 [6]. It seems that factors such as ambient temperature, level of obesity, and mobility may influence the changes in IL-17 levels, which could justify the increased IL-17 level in the present study [22].

According to the current research, endurance training with crocin consumption had interactive effects on the increased levels of IL-17 and IL-18 in the muscle tissues of diabetic rats. However, the results of Bonferroni's comparison of means test indicated that HIIT training could significantly increase the IL-17 and IL-18 gene expression in the muscle tissues of the rats, while continuous training had no significant effects on these pro-inflammatory factors. Therefore, it could be inferred that the intensity of physical activity is a major influential factor in reducing the expression of IL-17 and IL-18 in muscle tissues [18, 22]. On the other hand, the crocin concentrations used in most studies indicates that the reductive effects of IL-17 and IL-18 are most likely associated with the administration of the higher doses of this natural compound [23, 24].

Few studies have been focused on these pro-inflammatory factors and their mechanism of action in muscle tissues. Moreover, there have been no studies to simultaneously examine the effects of training and crocin consumption on the levels of IL-17 and IL-18 in muscle tissues. Such example is the study by Hassanpour et al., which showed that endurance training and crocin consumption had interactive effects on the reduction of cell death-promoting factors and increasing anti-apoptotic proteins in the cardiac muscle cells of rats with type II diabetes [27]. In the mentioned study, HIIT and crocin consumption were reported exert interactive effects to increase hematological factors in doxorubicin-poisoned rats, while doxorubicin could diminish these factors [28]. On the other hand, moderate-intensity continuous training along with the consumption of crocin (100 mg/kg) has been reported to decrease inflammatory factors and increase antioxidants in the brain tissues of rats with Parkinson's disease [29]. This is inconsistent with the results of the present study, and the discrepancy could be due to the differences in the intensity of training and crocin concentration.

According to the results of the present study, the ineffectiveness of crocin as a potent antioxidant could be attributed to pharmacologic interference, which is specifically discussed in medical sciences. Although such interferences cause the positive effects of medications, they may occasionally induce adverse side-effects. Therefore, it is suggested that in the further investigations in this regard, the consumption of crocin not be considered before and during training, and the effects of crocin consumption be examined after the training period.

Considering the studies conducted in this respect, it is noteworthy that the levels of IL-6 expressed in the muscles may indicate increased insulin sensitivity and be considered a potent stimulant for the expression of IL-17 and IL-18. One of the limitations of the current research was the lack of the measurement of the gene expression of this cytokine in the muscle tissues. Therefore, it is recommended that further studies in this regard investigate the gene expression of this cytokine in the muscle tissues along with physical exercise. Additionally, since both these variables are known as pre-inflammatory factors, and data is scarce regarding their function in the muscle tissues, the levels of anti-inflammatory agents should be measured in further research in order to obtain accurate results.

Conclusion

According to the results, HIIT could have inflammatory effects on the skeletal muscle tissues in the rats with type II diabetes, while LICT had no significant effects on the changes in the inflammatory factors of the muscle. In addition, crocin consumption could decrease IL-18 expression and increase IL-17 expression in the skeletal muscles. However, endurance training and crocin consumption had significant interactive effects on the increment of inflammatory factors in the muscle tissues of the rats.

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