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The Effect of High-intensity Interval Training and L-carnitine on the Expression of Some Pro-inflammatory Genes in the Liver and Cardiac Tissues of Rats

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Abstract

Background: Inflammation is characterized by interactions between cytokines and inflammatory pathogens. Cytokines are glycoproteins involved in inflammation. Exercise training and physical activity are associated with a healthy lifestyle. In the current study, we aimed to determine the effects of high intensity interval training (HIIT) and L-Carnitine (LCAR) on the expression of genes involved in inflammation and inflammatory pathways in the liver and heart of rats.

Method: Thirty-two male Wistar rats were randomly divided into the four groups (n = 8): 1. Untreated control group, 2. LCAR group (received 200 mg/kg LCAR daily), 3. HIIT group (performed high intensity interval training), 4. Exercise training + LCAR.

Results: The results of our study showed that HIIT + LCAR significantly reduced the expression of IL-1β in the liver compared to the HIIT group ($p = 0.038$). The combination of HIIT and LCAR decreased IL-6 expression in the liver tissue compared to the control ($p < 0.001$), LCAR ($p < 0.001$), and HIIT ($p = 0.002$) groups. The HIIT + LCAR group decreased Cox 2 gene expression in the liver tissue compared to the untreated control group ($p < 0.001$), and LCAR group ($p = 0.007$). The combination of HIIT and LCAR reduced IL-1β expression in the cardiac tissue compared to the untreated control ($p < 0.001$), LCAR ($p = 0.034$), and HIIT ($p = 0.041$) groups. The combination of HIIT and LCAR increased IL-6 expression in the cardiac tissue compared to the other three groups ($p < 0.001$).

Conclusion: According to the obtained results, HIIT combined with LCAR administration is very useful in reducing the expression of pro-inflammatory genes in the heart and liver tissues.

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Introduction

Inflammation is a response that has major effects on body tissues. It is characterized by interactions between cytokines and inflammatory pathogens. Cytokines are glycoproteins that are involved in inflammation and immunity (1, 2). Cytokines are generally divided into two groups, the first of which include pro-inflammatory cytokines that promote inflammation, such as interleukin-1 (IL-1), tumor necrosis factor-α (TNF-α), interferon-gamma (IFN-γ), and IL-12, while the second group are anti-inflammatory cytokines including IL-4, IL-10, IL-13, interferon-alpha (IFN-α), and tumor growth factor-beta (TGF-β) that act against inflammation (1-3). Exercise and general physical activity are associated with a healthy lifestyle and increased longevity, as well as decrease of pro-inflammatory cytokines and increase of anti-inflammatory cytokines (1). Interleukin cytokines, including IL-1β, IL-6, and IL-10, are key immune system factors and are involved in the systemic response to inflammation. Single training sessions with varying intensity and time have been shown to induce systemic inflammatory responses similar to injury-related responses (2, 3).

The acute phase response (APR) is the body's immediate response to inflammatory stimuli such as strenuous exercise, which involves a complex cascade of mediators for reducing tissue damage and enabling recovery from the pre-inflammatory process. Exercise activates monocytes and macrophages and then increases the expression of pro-inflammatory cytokines such as IL-1β and IL-6 (4, 5). MCP-1 and IL-10 levels increase during exercise as well as after exercise and limit inflammation and restore normal physiological function in the affected tissue. IL-1β has also been shown to be effective in the acute phase response and stimulation of the expression of genes involved in the acute phase. Despite its major role in the acute phase response, the findings about IL-1β elevation after exercise are uncoordinated and controversial (6-8). When IL-1β increases, not only IL-1β but also IL-6 and CRP increase, and this increase may have detrimental effects on the process of limiting inflammation (4, 9). High-intensity interval training (HIIT) has recently become popular, and one of the reasons is that it is effective at a specific time compared to traditional methods that are time-consuming (such as endurance training). HIIT has been shown to increase mitochondrial enzyme activity and increase the oxidative capacity of muscle compared to conventional endurance training methods by compensating for the decrease in exercise volume through increasing the intensity of exercise (8, 10-12). Of course, it is also important to note that low-volume HIIT leads to inflammatory responses similar to endurance exercise (13).

L-Carnitine [beta-hydroxy-gamma trimethylammonium butyrate (LCAR)] is known as a vitamin-like and amino-acid-like substance, and the L-isoform of LCAR has physiological activity. The main role of LCAR in the body is to facilitate the oxidation of lipids by transferring long-chain fatty acids to the mitochondrial matrix (the site of beta oxidation). Therefore, without LCAR, most dietary lipids cannot be used as a food source, and fatty acids accumulate in the body and eventually lead to obesity. LCAR is absorbed through active sodium-

dependent transport and inactive transport through the intestines (14, 15).

A study by Carnevali *et al.* showed that HIIT increases mitochondrial fat transfer capacity (by increasing the activity of the enzyme carnitine palmitoyltransferase), which facilitates the oxidative process (16). It has also been reported that HIIT improves the oxidative direction in the muscles of animals with hypertension (17). Overall, HIIT increases energy efficiency and physical function (18). In Nayebifar *et al.* study, 10 weeks of HIIT alone and with ginger improved MCP-1 in overweight women (19). Zwetsloot *et al.* (2014) also showed that HIIT caused an inflammatory response in young men, albeit to a small extent (8). In a study by Kaspar *et al.*, HIIT decreased IL-1β, IL-10 and MCP-1and increased IL-6 (20). De Souza *et al.* (2018) reported that HIIT reduced the IFNγ / IL-4 ratio and was actually anti-inflammatory (21). A single bout of HIIT has been shown to be able to induce transient anti-inflammatory states in healthy individuals and overweight individuals (20). In Gerosa-Neto *et al.* study, after 16 weeks of training, serum IL-6 levels decreased in the HIIT group, while TNF-α increased after 16 weeks of intense interval training (22). Ono and Koshartani showed that HIIT (4 times a week and for 6 weeks) increased TNF-α and IL-6 (23).

As it turns out, there is no consensus on the effects of HIIT exercise on inflammatory markers, and the information outlined above is challenging. There are not many studies on the expression of inflammatory genes during HIIT. Today, LCAR is offered as a supplement and its most important effects are weight loss and improving physical condition. On the other hand, our current society is facing another important problem called inactivity and laziness, which along with unsafe diet leads to chronic diseases. In the coming years, we will eventually face an increased trend of inflammation and diseases such as diabetes and obesity which are accompanied by inflammation.

Most studies are reports that have not thoroughly examined the effects of LCAR. In fact, despite several studies on the effect of exercise and LCAR on inflammatory factors and the limited studies in the field, we performed this study to determine the effects of HIIT in the presence of LCAR on the expression of genes involved in inflammation and inflammatory pathways in the liver and heart of male rats.

Materials and Methods

The materials and kits used in this study were L-carnitine (C0283, Sigma, USA), SYBR green (Ampliqon, Denmark), RNA extraction kit (BS414, BioBasic, Canada), cDNA synthesis kit (RR037A, TAKARA, Japan), and Primers (Metabion, Germany).

All animal cares and procedures were conducted in accordance with the European Convention for the protection of animals used for experimental and other scientific purposes. This study was approved by Ethics Committee of Kerman University of Medical Sciences (IR.KMU.REC.1398.233).

Thirty-two male Wistar rats in the age range of 8 weeks were purchased from the pet center of Kerman Physiology Research Center and kept in the laboratory at a temperature of 22 ± 2°C and a light-dark cycle of 12:12 hours. The animals had free access to water and food. The rats were first allowed for two weeks to be familiarized with the laboratory environment. Finally, rats were randomly divided into the four groups of 8 rats (23, 24):

1. Untreated control group (no exercise and no LCAR intake)

2. LCAR group (received 200 mg / kg body weight LCAR intraperitoneally, 4 weeks)

3. Exercise Training (HIIT for 4 weeks)

4. HIIT exercise training group that received LCAR (HIIT + LCAR)

Exercise protocol

HIIT included 5 days of high-intensity training, which performed at a speed of 10 to 25 meters per minute and increasingly. Interval training program performed by 10 repetitions of 1- minute with 2 minutes of active rest. Training time for each rat lasted 30 minutes. The rats started training at 20 meters per minute and ended at 45 meters per minute. In addition to the time spent on the main workout, 5 minutes for warm-up and 5 minutes for cooling were included. Interval training lasted 4 weeks (5 days a week) in the groups 3 and 4 (25). Forty-eight hours after the end of the last training session, the animals were anesthetized and their liver and heart tissues were extracted and stored at -80°C for Real Time-PCR measurements (21, 23).

Real time PCR

About 50 mg of each tissue (Heart and Liver) was dissected and homogenized at a specific lysis buffer by Heilscher Sonicator (Heilscher H200, Germany). Total RNA was extracted according to the kit procedure and then after, the complementary DNA (cDNA) was synthesized by cDNA synthesis kit according to the kit's protocol (500 ng of extracted RNA was used). In Real-time PCR measurements, we used specific primer as shown in Table 1. The Real-time PCR reactions were performed by ABI Step one plus instrument. The Real-time PCR reaction contained 10 µl SYBR green, cDNA (100 ng), forward and reverse primers (1µl of each primer), and the reaction volume was reached to 20 µl by distilled DNase free water. The annealing temperature was determined according to each primer's Tm and gradient PCR. Finally, the thermal protocol in Real-time PCR was as follow; 95 °C (10 min), 95 °C (15 sec), annealing temperature (40 sec), 40 cycles, and after the thermal cycles were finished the melt curve analysis was performed. We used 18S rRNA as a housekeeping gene. The relative expression of genes was determined by $2^{-\Delta\Delta Ct}$ method (26, 27).

Table 1. The primers' sequences that used in this study in order to perform Real-Time PCR

Genes name	Forward primer (5' to 3')	Reverse primer (5' to 3')	Product size (bp)
IL-1β	AGGCTTCCTTGTGCAAGTGT	TGAGTGACACTGCCTTCCTG	200
Cox-2	TGTATGCTACCATCTGGCTTCGG	GTTTGGAACAGTCGCTCGTCATC	94
IL-6	CCGGAGAGGAGACTTCACAG	CAGAATTGCCATTGCACAAC	134
TNF-α	AGATGTGGAACTGGCAGAGG	CCCATTTGGGAACTTCTCCT	178
18s	CGGCTACCACATCCAAGGAA	TTTTCGTCACTACCTCCCCG	90

Statistical analysis

Data analysis was performed through SPSS software. One-way analysis of variance (ANOVA) was used to determine the differences in variables between groups along with Tukey's post hoc test. In all statistical comparisons, a significance level of P <0.05 was considered as significant.

Results

Gene expression in the liver

According to the obtained results, HIIT + LCAR significantly reduced the expression of IL-1β in the liver compared to the HIIT group (p = 0.038), while the expression level in other groups did not show any significant change (Figure 1). IL-6 expression in the liver tissue decreased in HIIT + LCAR group compared to that in the untreated control (p <0.001), LCAR (p < 0.001), and HIIT (p = 0.002) groups (Figure 2). TNF-α expression did not show any significant change among different groups (Figure 3). As it is seen in figure 4, in the HIIT +LCAR group Cox 2 gene expression in the liver tissue decreased compared to the untreated control (p < 0.001), and LCAR groups (p = 0.007).

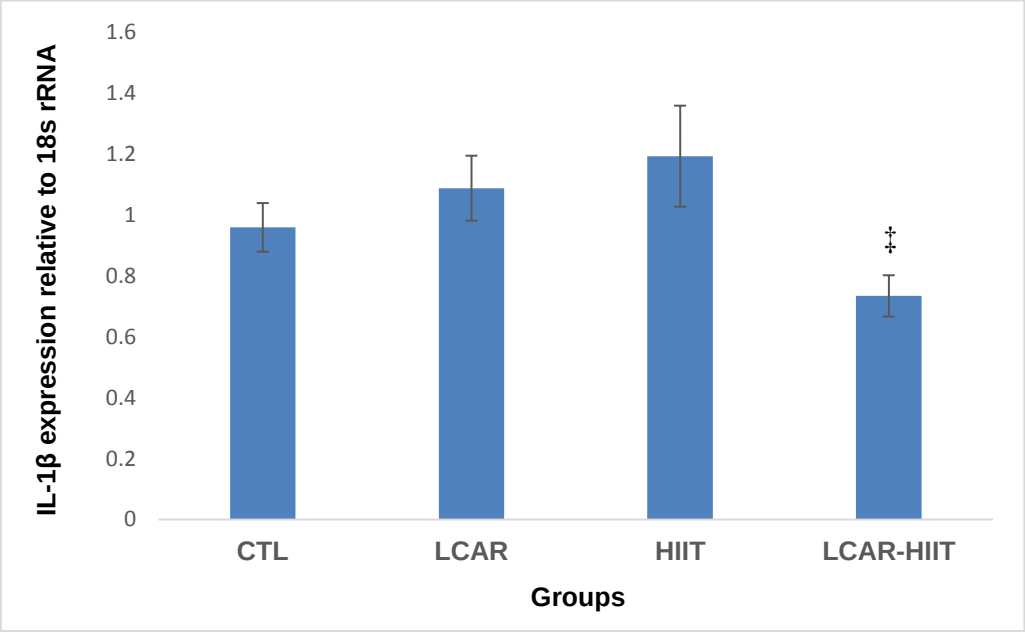

Figure 1. Relative IL-1 gene expression quantified by Real-Time PCR method in the liver of studied groups

The groups (n=8) were as follow; Untreated control (CTL); received L-carnitine (LCAR), performed High intensity interval training (HIIT) and LCAR + HIIT (LCAR-HIIT). Data have been expressed as Mean± SEM and p<0.05 was considered as significant. ‡ Statistically significant compared to HIIT group

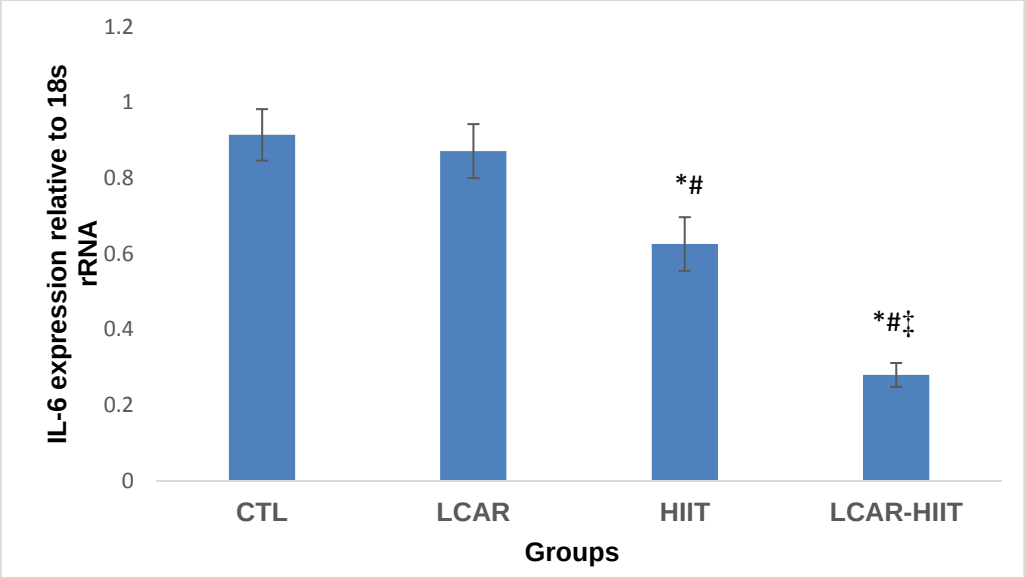

Figure 2. Relative IL-6 gene expression quantified by Real-Time PCR method in the liver of studied groups

The groups (n=8) were as follow; Untreated control (CTL), received LCAR, performed High intensity interval training (HIIT) and LCAR + HIIT (LCAR-HIIT). Data have been expressed as Mean± SEM and $p<0.05$ was considered as significant. * Statistically significant compared to the control group, # Statistically significant compared to the LCAR group, ‡ Statistically significant compared to the HIIT group

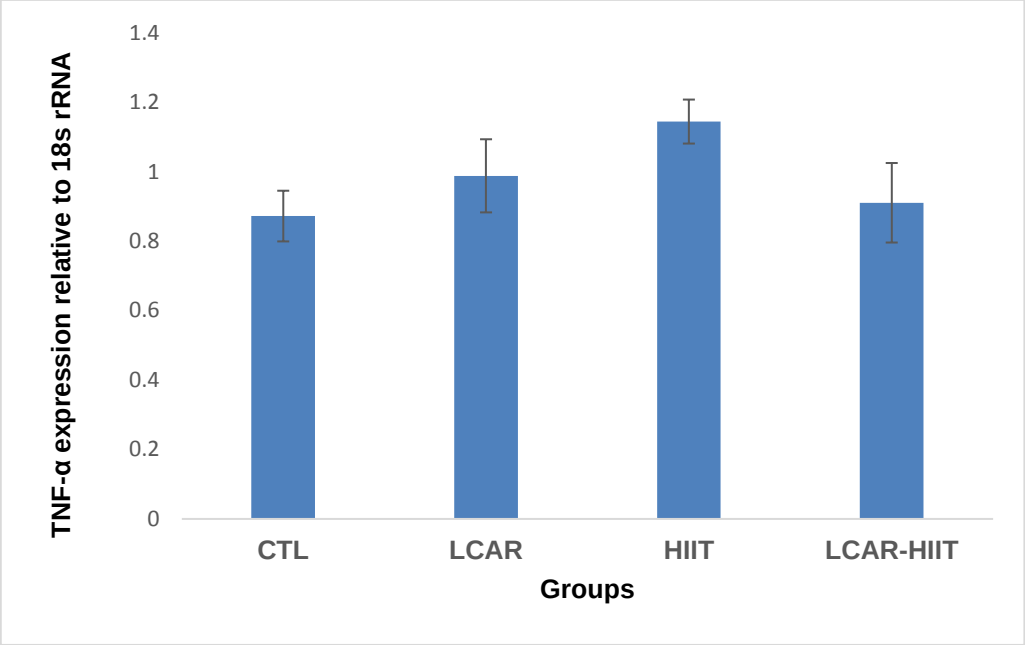

Figure 3. Relative TNF-α gene expression quantified by Real-Time PCR method in the liver of studied groups

The groups (n=8) were as follow; Untreated control (CTL), received LCAR, performed High intensity interval training (HIIT) and LCAR + HIIT (LCAR-HIIT). Data have been expressed as Mean± SEM and $p<0.05$ was considered as significant.

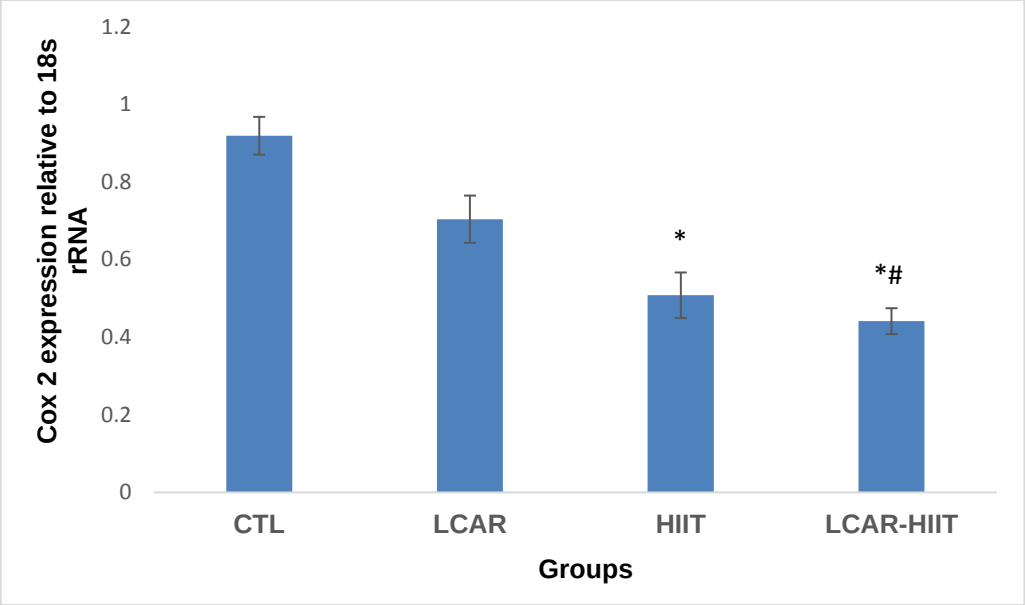

Figure 4. Relative Cox 2 gene expression quantified by Real-Time PCR method in the liver of studied groups

The groups (n=8) were as follow; Untreated control (CTL), received LCAR, performed High intensity interval training (HIIT) and LCAR + HIIT (LCAR-HIIT). Data have been expressed as Mean± SEM and p<0.05 was considered as significant. * Statistically significant compared to the control group, # statistically significant compared to the LCAR group

Gene expression in the heart

The results of the present study also showed that the combination of HIIT and LCAR significantly reduced IL-1β expression in the cardiac tissue compared to the untreated control ($p < 0.001$), LCAR ($p = 0.034$), and HIIT ($p = 0.041$) groups (Figure 5). The combination of HIIT and LCAR increased IL-6 expression in the cardiac tissue compared to the other three groups ($p < 0.001$) (Figure 6). We also found that HIIT + LCAR significantly reduced TNF-α expression in the cardiac tissue compared to the other groups ($p < 0.05$) (Figure 7). Finally, as it is shown in figure 8, HIIT + LCAR significantly reduced the expression of Cox 2 in the cardiac tissue compared to other groups ($p < 0.05$).

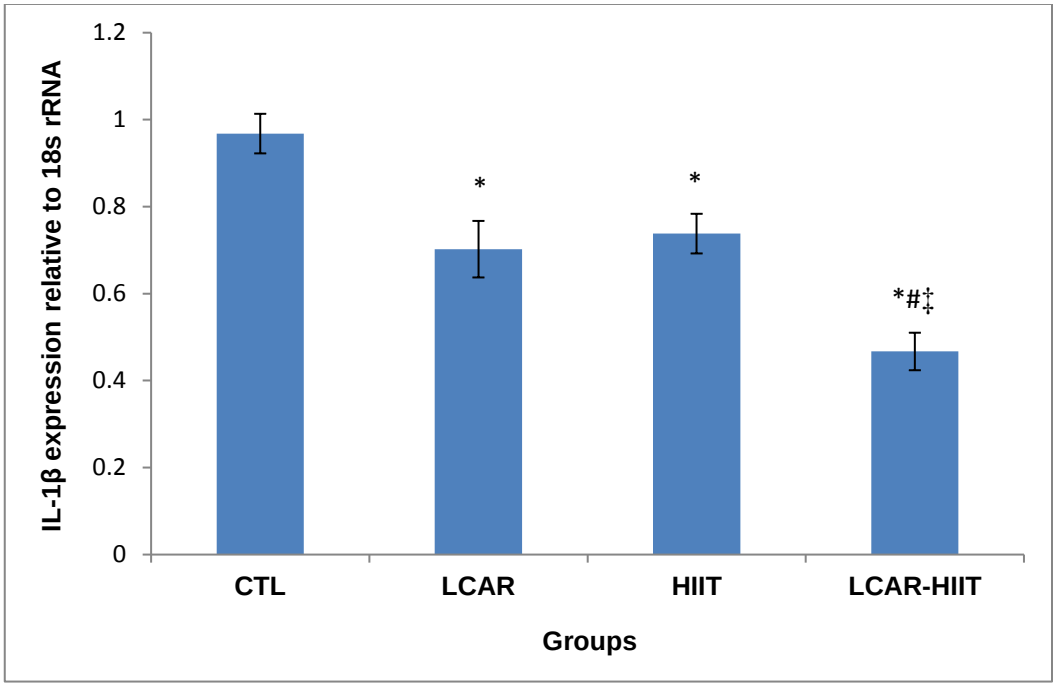

Figure 5. Relative IL-1β gene expression quantified by Real-Time PCR method in the heart of studied groups

The groups (n=8) were as follow; Untreated control (CTL), received LCAR, performed High intensity interval training (HIIT) and LCAR + HIIT (LCAR-HIIT). Data have been expressed as Mean± SEM and $p<0.05$ was considered as significant. * Statistically significant compared to the control group, # statistically significant compared to the LCAR group, ‡ statistically significant compared to the HIIT group

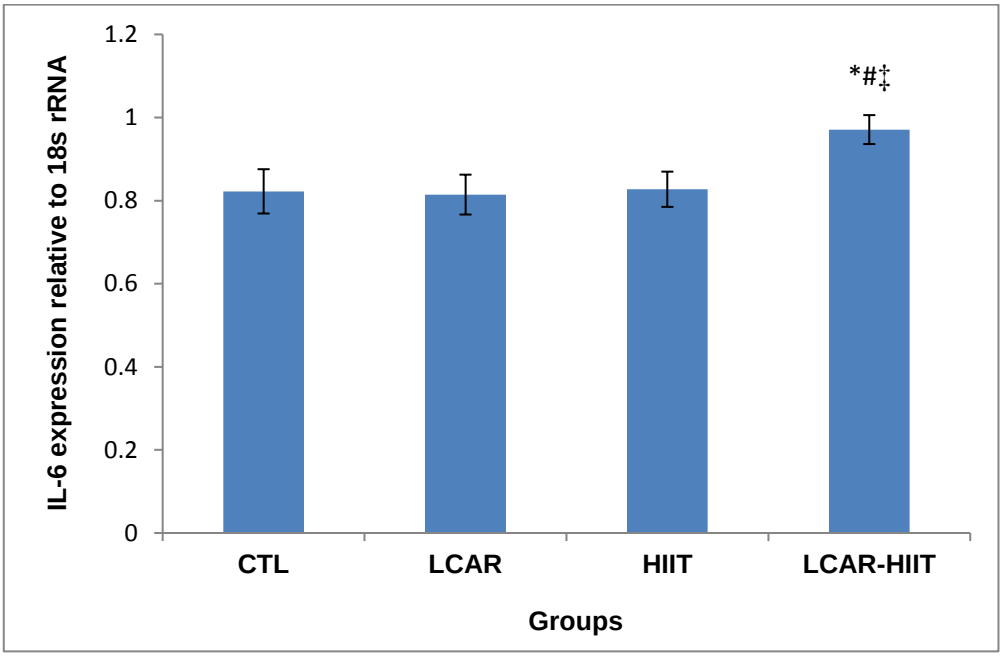

Figure 6. Relative IL-6 gene expression quantified by Real-Time PCR method in the heart of studied groups

The groups (n=8) were as follow; Untreated control (CTL), received LCAR, performed high intensity interval training (HIIT) and LCAR + HIIT (LCAR-HIIT). Data have been expressed as Mean± SEM, $p<0.05$ was considered as significant. * Statistically significant compared to the control group, # statistically significant compared to the LCAR group, ‡ statistically significant compared to the HIIT group

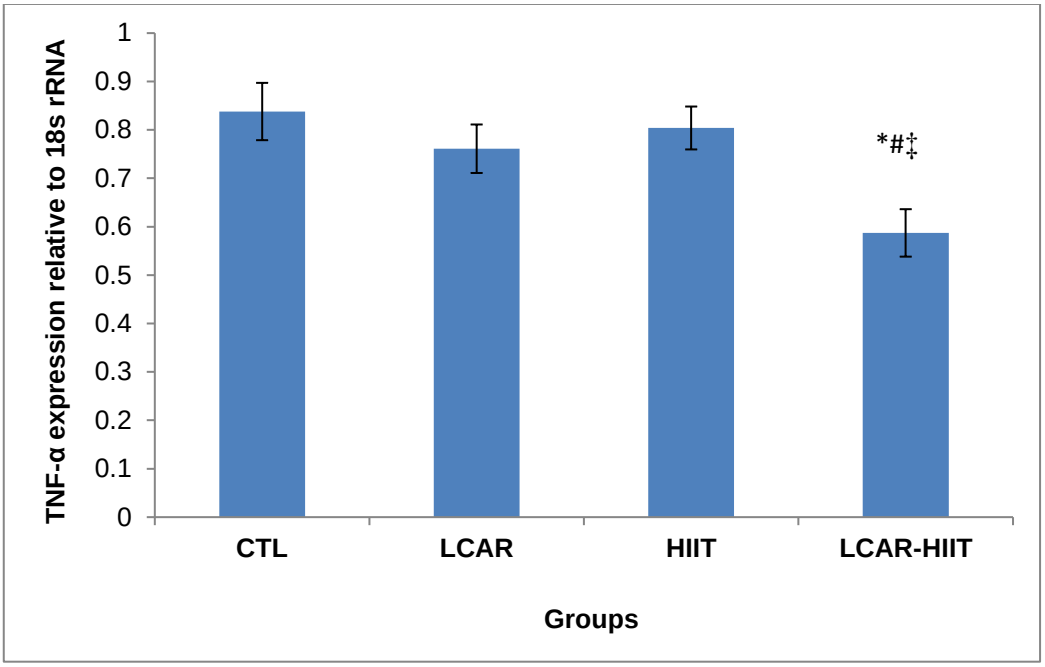

Figure 7. Relative TNF-α gene expression quantified by Real-Time PCR method in the heart of studied groups

The groups (n=8) were as follow; untreated control (CTL), received LCAR, performed high intensity interval training (HIIT) and LCAR + HIIT (LCAR-HIIT). Data have been expressed as Mean± SEM and p<0.05 was considered as significant. * Statistically significant compared to the control group, # statistically significant compared to the LCAR group, ‡ statistically significant compared to the HIIT group

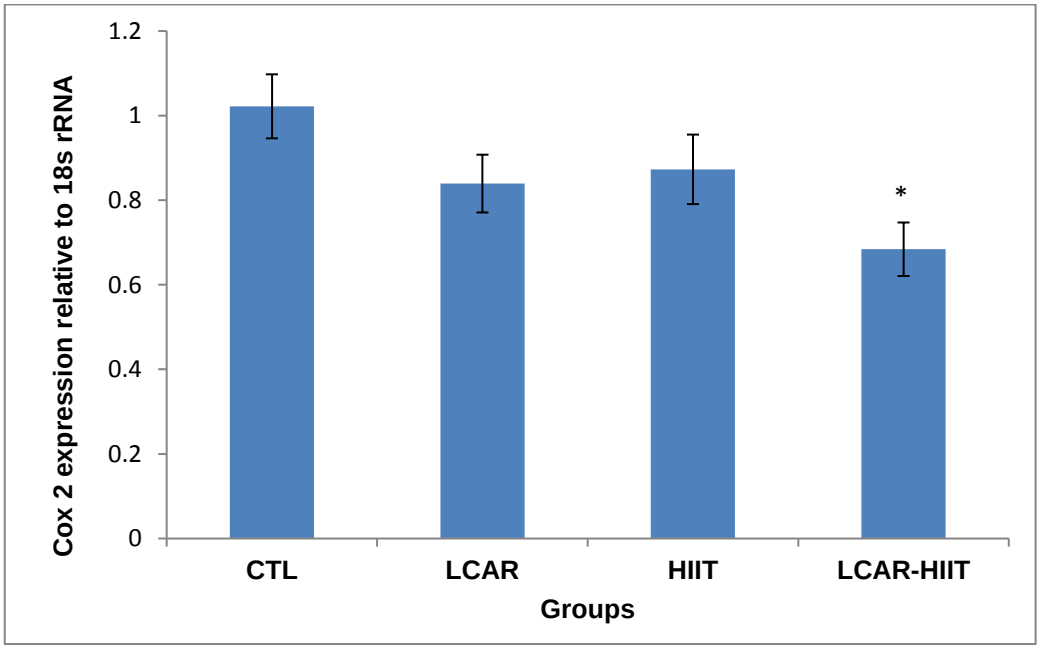

Figure 8. Relative Cox 2 gene expression quantified by Real-Time PCR method in the heart of studied groups

The groups (n=8) were as follow; Untreated control (CTL), received LCAR, performed High intensity interval training (HIIT) and LCAR + HIIT (LCAR-HIIT). Data have been expressed as Mean± SEM and p<0.05 was considered as significant. * Statistically significant compared to control group, # statistically significant compared to the LCAR group, ‡ Statistically significant compared to the HIIT group

Discussion

There is no consensus on the effects of HIIT exercise on inflammatory markers and the information is challenging (18-23). There are not many studies on the expression of inflammatory genes during HIIT. Today, LCAR is offered as a supplement and its most important effects are weight loss and improving physical condition (14). On the other hand, our current society is facing another important problem called inactivity, which along with an unsafe diet leads to chronic diseases, which in the coming years can eventually cause an increased trend of inflammation and diseases such as diabetes and obesity (14). In the present study, we targeted the heart and liver tissues for the expression of pro-inflammatory genes, whereas previous studies have often investigated serum levels of these factors. In this study, we determined the effects of HIIT on the expression of genes involved in inflammation and inflammatory pathways in the presence of LCAR in the liver and heart of male rats. The results of our study showed that LCAR and HIIT can be effective in reducing pro-inflammatory agents, but the effect of combination of the two is much stronger than each of them alone. Considering Cox 2 expression, we found that HIIT and the combination of HIIT and LCAR are more effective in the liver than in the heart tissue.

Despite it is a major role in the acute phase response, the findings about IL-1β elevation after exercise are uncoordinated and controversial (6-8). When IL-1β increases, not only IL-1β but also CRP increases, and this increase may have detrimental effects on the process of limiting inflammation (4, 9). Injection of TNF-α or IL-1 in animals has been shown to cause hemodynamic changes and shock (28). In the present study, IL-1β expression in the cardiac and hepatic tissues decreased in HIIT +LCAR group, whereas it seemed to be slightly increased in the exercise group. A study by Carnevali and colleagues showed that HIIT increases mitochondrial fat transfer capacity (by increasing the activity of the enzyme carnitine palmitoyltransferase), which facilitates the oxidative process (16). It has also been reported that HIIT improves the oxidative direction in the muscles of animals with hypertension (17). Overall, HIIT increases energy efficiency and physical function (18). Our results showed that HIIT in combination with LCAR could work better and plays an important role in exercise-induced inflammation by reducing IL-1β and increasing IL-6 expression (IL-6 is considered as a myokine and can act as an anti-inflammatory cytokine in muscles) and limiting the inflammatory response. In Nayebifar *et al.* (2016) study, 10 weeks of HIIT alone and with ginger improved MCP-1 in overweight women (19). Zwetsloot *et al.* (2014) also showed that HIIT causes an inflammatory response in young men, albeit to a small extent (8). In a study by Kaspar *et al.*, HIIT decreased IL-1β, IL-10 and MCP-1 and increased IL-6 in the blood (20). Our data about the expression of inflammatory genes are in accordance with data of a previous study on the serum level of cytokines (8, 19, 20). De Souza *et al.* (2018) have reported that one session of HIIT reduced the IFNγ / IL-4 ratio and actually acted against inflammation (21). A single bout of HIIT has been shown to be able to induce transient anti-inflammatory states in healthy individuals and overweight individuals (20). Due to the fact that previous studies had focused more on serum levels, we had to use them in this area. In the present study, TNF-α was not significantly affected by interfering factors (LCAR and HIIT) but IL-6 gene expression in the liver was reduced by HIIT and LCAR (groups 3 and 4) but in the heart tissue, the combination of HIIT and LCAR

increased IL-6 expression. The study by Gerosa-Neto *et al.* showed that after 16 weeks of training, serum IL-6 concentration decreased in the HIIT group, while TNF-α increased after 16 weeks of intense interval training (22) that is the same as the expression pattern in the liver but different from IL-6 expression in the heart tissue. In Ono and Kushartani (2018) study, HIIT for six weeks (4 times a week) increased TNF-α and IL-6 levels (23). These results are consistent with our results in relation to IL-6but in terms of TNF-α, they are contrary to the findings of our study. The study of Amanollahi *et al.* (2020) showed that 8 weeks of HIIT training did not change serum TNF-α levels, while reduced IL-6 levels, but the decrease was not significant (29). The liver IL-6 expression was reduced and TNF-α was unchanged in the liver after HIIT that is consistent with the results of Amanollahi et al (29).

Two studies examined the expression of inflammatory genes (30, 31). Khademi et al. (2018) showed that 10 weeks of HIIT training had no effect on IL-1β expression in rat heart tissue (30) which is contrary to our results; we found that IL-1β gene expression in cardiac tissue was significantly reduced by HIIT, also the combination of HIIT and LCAR reduced its expression in an additive manner. Another study found that combining 6 weeks of exercise with 100 mg/kg of LCAR daily reduced the expression of TNF-α and IL-1β in rat heart tissue (31). Interestingly, the results of this study are consistent with our study, in which the combination of HIIT and LCAR reduced the expression of IL-1β, and TNF-α gene in the heart tissue. The limitation of this study is that only one type of training exercise was used and the effect of other types of training was not investigated. Future studies, by directly comparing HIIT with classical endurance exercise in animals will help to draw possible differences between the two types of training methods.

Conclusion

HIIT exercise combined with LCAR administration is very useful in reducing the expression of pro-inflammatory genes in heart and liver tissues. The results of the present study can also provide the interactive effect of HIIT in the presence of LCAR administration as a newly proposed solution to improve the condition during exercise as well as the anti-inflammatory and metabolic status.

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Conflict of interest

Authors declare that there is no conflict of interest.

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