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ORIGINAL ARTICLE

The effects of different training modalities on monocarboxylate transporters MCT1 and MCT4, hypoxia inducible factor-1α (HIF-1α), and PGC-1α gene expression in rat skeletal muscles

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Abstract

The research literature suggests that different training modalities cause various patterns in training-induced genes expression. This study aimed to investigate the effects of moderate intensity continuous training (MICT) and isocaloric high intensity interval training (HIIT) on gene expression of monocarboxylate transporter 1 (MCT1) and 4 (MCT4), Peroxisome proliferator-activated receptor γ coactivator-1α (PGC-1α), and hypoxia inducible factor-1α (HIF-1α) in soleus and extensor digitorum longus (EDL) skeletal muscles of rats. Thirty male Sprague–Dawley rats were divided into 3 groups of control, MICT, and HIIT. Training protocols were performed according to the principle of overload for 8 weeks and 5 sessions per week. Then, the soleus and EDL muscles were extracted and the expression levels were analyzed using the real time PCR method. In the MICT group, only the EDL HIF-1α mRNA level was significantly higher than that of the control group ($p < 0.05$). In the HIIT group, however, mRNA levels of MCT4, PGC-1α, and HIF-1α in both muscles were significantly higher than those of the control group ($p < 0.05$). The comparison between the two training methods demonstrated that the gene expression levels of soleus and EDL MCT4, soleus PGC-1α, and soleus HIF-1α were significantly higher in the HIIT group compared to the MICT group ($p < 0.05$). There were also significant positive correlations between all mRNA levels of HIF-1α and corresponding mRNA levels of MCT4 ($p < 0.05$). HIIT caused greater positive responses in the gene expression of MCT4, PGC-1α, and HIF-1α compared to MICT.

Keywords Training modalities · Monocarboxylate transporters · Hypoxia inducible factor-1α · Peroxisome proliferator-activated receptor γ coactivator-1α · Moderate intensity continuous training · High intensity interval training

Introduction

High-intensity exercise causes the production and accumulation of lactate and hydrogen ions in skeletal muscles [1]. During high intensity exercise, the removal of lactate and H^+ from contracting skeletal muscle is essential to maintain force [2]. Much of the lactate produced in glycolytic fibers is taken up and oxidized in adjacent oxidative fibers [3]. Lactate is conveyed across the cell membrane by a family of monocarboxylate transporters (MCTs) [4]. Thus, MCTs have a significant function to maintain pH homeostasis inside the cells [5]. Among the known MCT isoforms, MCT1 and MCT4 are the main transporters in skeletal muscle [6]. MCT1 facilitates lactate influx mostly in oxidative fibers, while MCT4 is responsible for the extrusion of lactate mainly in glycolytic fibers [4, 7]. Contractile activities of skeletal muscles appear to be significant for the regulation of MCTs [8]. Protein contents of MCT1 and MCT4 can rise

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[2, 9] or remain unchanged [10, 11] by exercise training. However, there are limited and inconsistent data regarding the MCT1and MCT4 mRNA responses to training [12, 13]. Training type and intensity appear to be factors influencing changes in both MCT1 and MCT4 content [8]. It has been shown that there is not a simple concordance between alterations in mRNA magnitude and protein levels [8] because skeletal muscle MCT1 and MCT4 protein expression appear to be regulated by transcriptional and post-transcriptional mechanisms [14, 15]

Peroxisome proliferator-activated receptor γ coactivator (PGC)-1α is a transcriptional coactivator, which plays a significant role in the regulation of mitochondrial biogenesis in skeletal muscles [16]. Increased expression of PGC-1α in skeletal muscle causes many aspects of endurance training adaptation including improved oxygen provision to muscles by promoting angiogenesis [17] and increasing mitochondrial biogenesis [18]. HIIT also causes many adaptations related to usual endurance training such as increased muscle mitochondrial content [19]. PGC-1α protein expression increases by endurance exercise training [20] and high intensity interval training [21]. However, it has been indicated that despite an increase in PGC-1α mRNA expression following acute endurance exercise, no changes occur in PGC-1α mRNA responses by endurance exercise training [22]. Furthermore, PGC-1α might be involved in the up-regulation of MCT1 expression in response to the increase of muscle contractile activity [23].

Another influential factor involved in activating genes that are expressed with exercise is the hypoxia inducible factor-1 (HIF-1). The main response mechanism to hypoxia in a cell is the transcription factor HIF-1 that increases transcription of a diversity of genes including EPO, HKI and HKII, PFK-L, VEGF, and LDHa [24]. It has been recognized that HIF-1α is increased in hypoxic skeletal muscle [25]. HIF-1α is dependent on oxygen concentrations in the cells, it is hydroxylated and degraded under normoxia, but is stabilized and translocated to the nucleus under hypoxia [26]. In skeletal muscles, the protein contents of HIF-1α are present even under normoxia and greater in fast muscles than in slow muscles [26]. Protein levels of HIF-1α are elevated after acute and long term HIIT [27]. However, the increase in HIF-1α mRNA by acute exercise is blunted with endurance training [24, 28]. HIF-1α mRNA is also elevated in response to hypoxic but not normoxic exercise training [29]. In addition, it appears that MCT4 is increased by hypoxia through a HIF-1α-mediated mechanism [30]. Therefore, taking into consideration the limited literature regarding the effects of exercise training on MCT1, MCT4, PGC-1α, and HIF-1α mRNA levels and also the role of training type and intensity in this regard, the present study aims to compare the effects of MICT and isocaloric HIIT on these mRNA levels in two soleus and EDL muscles as exercise-induced alterations in gene expression can happen in a muscle fiber type-specific manner [31].

Method

Animals

Thirty adult (3 months old) male Sprague–Dawley rats [250–300 g, Razi, Iran] were housed in standard cages of polycarbonate in an air-conditioned room at a temperature of 22 ± 2 ℃ and relative humidity of 55% on a 12:12-h light–dark cycle with the light period beginning at 6:00 am. The rats had free access to water and standard rat food. After two weeks of familiarization with the environment, the rats were randomly divided into 3 equal groups (n = 10) of control, moderate intensity continuous training (MICT), and high intensity interval training (HIIT). All animal experiments were performed in accordance with the National Institutes of Health guide for the care and use of laboratory animals (NIH Publications No. 8023, revised 1978), and the study was approved by the ethics committee of Arak University of Medical Sciences in Iran (IR.Arakmu.REC.1398.141).

Exercise training protocols

All rats in the training groups were familiarized with a rodent 5-lane treadmill on at least 3 occasions (10 m/min, 0% grade, 10–15 min). The moderate continuous training and the high-intensity interval training groups ran for eight weeks and five sessions per week on the treadmill. The control group did not undertake any exercise. These two isocaleric training programs were designed in accordance with the principles of previous studies [32–34]. At the beginning and the end of the training programs, warm-up and cool- down activities were conducted for 3 min at a speed of 16 m/minute. MICT (12–60 min, with the speed of 16–28 m/min) and HIIT (2–10 intervals of intense running with the speed of 28–40 m/min for 4 min, alternated with intervals of slow running with a speed of 16 m/min for 2 min) were performed for 8 weeks and 5 sessions per week (Table 1). The intensities of 16 (68% VO2max), 22 (75% VO2max), 28 (80% VO2max), and 40 (93% VO2max) m/min correspond to estimated energy expenditures of approximately 6.4, 7.2, 7.7, and 8.9 mL O2·100 g^{-1}·min^{-1} for rats, respectively. Based on the O2 uptake of rats at different work intensities, rats in the MICT group expended an estimated total energy (in O2 equivalents) of 11,953 mL O2·100 g^{-1} and rats in the HIIT group expended 11,983 mL O2·100 g^{-1} after an 8-week training period (excluding energy expenditures in warm-up and cool-down). MICT and HIIT protocols were of matched energy expenditures meaning that

Table 1 Moderate intensity continuous training and high intensity interval training protocols

Week	Day	MICT	mL O_2 100 g^{-1} $week^{-1}$	HIIT	mL O_2 100 g^{-1} $week^{-1}$
Week1	1	12 min, 16 m/min	512	2 intervals, 28 m/min, 4 min	523
	2	14 min, 16 m/min		2 intervals, 28 m/min, 4 min	
	3	16 min, 16 m/min		2 intervals, 28 m/min, 4 min	
	4	18 min, 16 m/min		3 intervals, 28 m/min, 4 min	
	5	20 min, 16 m/min		3 intervals, 28 m/min, 4 min	
Week2	1	22 min, 22 m/min	936	4intervals, 28 m/min, 4 min	959
	2	24 min, 22 m/min		4 intervals, 28 m/min, 4 min	
	3	26 min, 22 m/min		4 intervals, 28 m/min, 4 min	
	4	28 min, 22 m/min		5 intervals, 28 m/min, 4 min	
	5	30 min, 22 m/min		5 intervals, 28 m/min, 4 min	
Week3	1	31 min, 28 m/min	1270	5 intervals, 40 m/min, 4 min	1210
	2	32 min, 28 m/min		5 intervals, 40 m/min, 4 min	
	3	33 min, 28 m/min		5 intervals, 40 m/min, 4 min	
	4	34 min, 28 m/min		5 intervals, 40 m/min, 4 min	
	5	35 min, 28 m/min		5 intervals, 40 m/min, 4 min	
Week4	1	36 min, 28 m/min	1463	6 intervals, 40 m/min, 4 min	1452
	2	37 min, 28 m/min		6 intervals, 40 m/min, 4 min	
	3	38 min, 28 m/min		6 intervals, 40 m/min, 4 min	
	4	39 min, 28 m/min		6 intervals, 40 m/min, 4 min	
	5	40 min, 28 m/min		6 intervals, 40 m/min, 4 min	
Week5	1	41 min, 28 m/min	1655	7 intervals, 40 m/min, 4 min	1694
	2	42 min, 28 m/min		7 intervals, 40 m/min, 4 min	
	3	43 min, 28 m/min		7 intervals, 40 m/min, 4 min	
	4	44 min, 28 m/min		7 intervals, 40 m/min, 4 min	
	5	45 min, 28 m/min		7 intervals, 40 m/min, 4 min	
Week6	1	46 min, 28 m/min	1844	7 intervals, 40 m/min, 4 min	1839
	2	47 min, 28 m/min		7 intervals, 40 m/min, 4 min	
	3	48 min, 28 m/min		8 intervals, 40 m/min, 4 min	
	4	49 min, 28 m/min		8 intervals, 40 m/min, 4 min	
	5	50 min, 28 m/min		8 intervals, 40 m/min, 4 min	
Week7	1	51 min, 28 m/min	2040	8 intervals, 40 m/min, 4 min	2032
	2	52 min, 28 m/min		8 intervals, 40 m/min, 4 min	
	3	53 min, 28 m/min		8 intervals, 40 m/min, 4 min	
	4	54 min, 28 m/min		9 intervals, 40 m/min, 4 min	
	5	55 min, 28 m/min		9 intervals, 40 m/min, 4 min	
Week8	1	56 min, 28 m/min	2233	9 intervals, 40 m/min, 4 min	2274
	2	57 min, 28 m/min		9 intervals, 40 m/min, 4 min	
	3	58 min, 28 m/min		9 intervals, 40 m/min, 4 min	
	4	59 min, 28 m/min		10 intervals, 40 m/min, 4 min	
	5	60 min, 28 m/min		10 intervals, 40 m/min, 4 min	
			Total: 11,953		Total: 11,983

MICT moderate intensity continuous training, *HIIT* high intensity interval training

these two training protocols had nearly equal total energy expenditures.

Tissue preparation

To avoid misinterpreting the data due to acute effects of the last exercise session, 48 h after the last exercise session the rats were anesthetized with Ketamine (60–80 mg/kg) and Xylazine (8 mg/kg). After cleaning the surgical area, the

soleus and EDL muscle tissues of the rats were removed and placed in liquid nitrogen. Then, the tissues were kept in a freezer at a temperature of − 80 °C.

RNA isolation and cDNA synthesis

After sampling, the expression of MCT1, MCT4, PGC-1α, and HIF-1α genes in all groups was studied by quantitative reverse transcriptase polymerase chain reaction (qRT-PCR). Total RNA was extracted from the tissues using RNX-Plus solution [CinnaGen Co, Iran] based on the manufacturer's instructions. The pelleted RNA was dissolved in diethylpyrocarbonate-treated water [DEPC treated water; SinaClon, Iran] and quantified using a Nano Drop device with a wavelength range of 260–280 nm. The mean ratio of OD in the wavelength of 260 to 280 nm was approximately 1.90, which revealed the suitable purity of the extracted RNA. This was followed by using 1 µg of total RNA for cDNA synthesis by utilizing RevertAid ™ First Strand cDNA Synthesis Kit [Pars Tous, Iran] in a total volume of 20 µl. The samples were then loaded into the thermal cycler for 10 min at 25 °C, 60 min at 47 °C, 5 min at 85 °C, and 10 min at 4 °C. The cDNA was subsequently stored at − 80 °C.

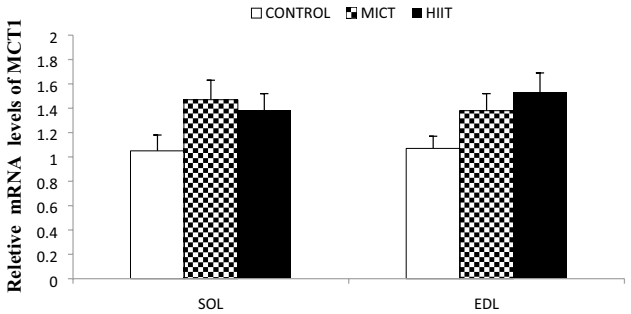

Fig. 1 Monocarboxylate transporter 1 (MCT1) mRNA in Soleus (SOL) and Extensor Digitorum Longus (EDL) muscles in control, moderate-intensity continuous training (MICT), and high-intensity interval training (HIIT) groups. The values are mean ± SEM; n = 10 per group

Quantitative RT-PCR

qRT-PCR was performed using a Life Cycle Real time PCR [Roche, Switzerland]. qRT-PCR was carried out in a total volume of 20 µl comprising 10 µl of 2 × SYBR green DNA PCR Master Mix [Yekta Tajhiz Azma, Iran], 0.5 µl of 5 mmol/l solutions of each one of the forward and reverse primers, and 2 µl of cDNA (fivefold diluted). Samples were run in duplicate. The primer sequences were as follows:

MCT1, 5-GCAGCCGTCCAGTAATGATT-3 (forward), 5-CAAGACCTCCAATGACACCAA-3 (reverse); MCT4, 5-ACAGGGGTCATCACTGGCTTG-3 (forward), 5-GCA CAAAGGAACACGGGACT-3 (reverse); PGC-1α, 5-ATC CTCTTCAAGATCCTGTTACT-3 (forward), 5-CGTGCT CATTGGCTTCATAG-3 (reverse); HIF-1α, 5-CAGGAC AGTACAGGATGCT-3 (forward), 5-CGTGCTGAATAA TACCACTTACA-3 (reverse); and Cyclo A, 5- GGCAAA TGCTGGACCAAACAC-3 (forward), 5- TTAGAGTTG TCCACAGTCGGAGATG-3 (reverse).

Non-specific PCR products and primer dimers were checked by Melt curve analysis after each run. All samples were normalized against Cyclo A as an internal control gene applying the comparative CT method (ΔΔCT).

Statistical method

The collected data was analyzed in SPSS 20 software and presented as means ± SEM. Shapiro–Wilk's and Levene's tests were used to evaluate the normality and equality of variances, respectively. To analyze the data and to determine the inter-group differences, one-way analysis of variance

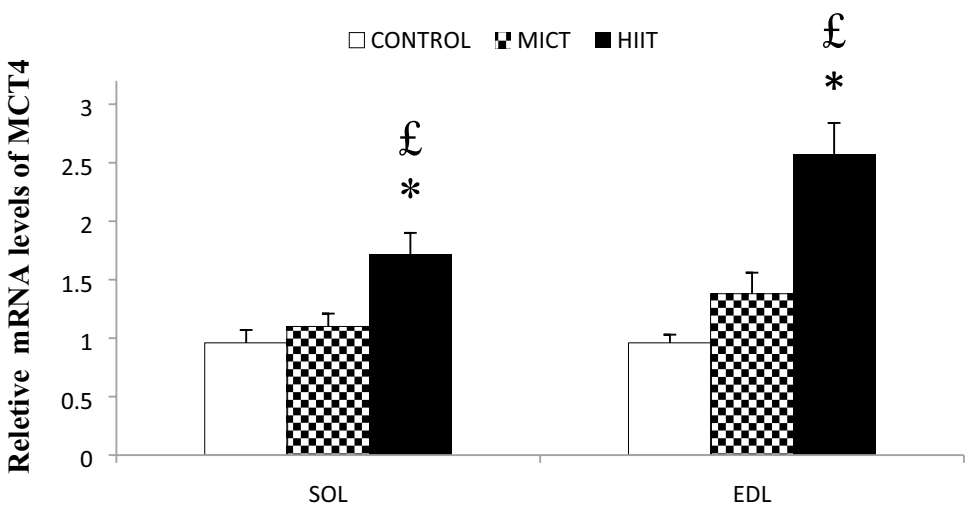

Fig. 2 Monocarboxylate transporter 4 (MCT4) mRNA in Soleus (SOL) and Extensor Digitorum Longus (EDL) muscles in control, moderate-intensity continuous training (MICT), and high-intensity interval training (HIIT) groups. The values are mean ± SEM; n = 10 per group. * Significantly different from control group ($p < 0.05$). £ Significantly different from MICT group ($p < 0.05$)

(ANOVA) followed by Tukey's and Tamhanés post hoc tests were used. In addition, Pearson's correlation coefficient was calculated in order to determine the relationship between variables. Statistically significant difference was set at $p < 0.05$.

Results

Effects of training modalities on MCT1 mRNA

There were not any significant differences between MCT1 mRNA levels of MICT and control groups in both soleus ($p = 0.13$) and EDL ($p = 0.28$) muscles. Similarly, the differences between MCT1 mRNA levels of HIIT group and control group were not significant in soleus ($p = 0.28$) and EDL ($p = 0.075$). The findings also revealed that in both muscles, there were not any significant differences between MCT1 mRNA levels of the two training groups ($p = 0.89$ for soleus, $p = 0.74$ for EDL) (Fig. 1).

Effects of training modalities on MCT4 mRNA

MCT4 mRNA levels of the MICT group were not significantly different from those of the control group in soleus ($p = 0.75$) and EDL ($p = 0.14$) muscles. In contrast, compared to the control group, MCT4 mRNA levels of the HIIT group were higher in soleus ($p = 0.002$) and EDL ($p = 0.001$) muscles. The comparison between training groups also revealed that MCT4 mRNA levels of the HIIT group were significantly higher than those of the MICT group in both soleus ($p = 0.013$) and EDL ($p = 0.007$) muscles (Fig. 2).

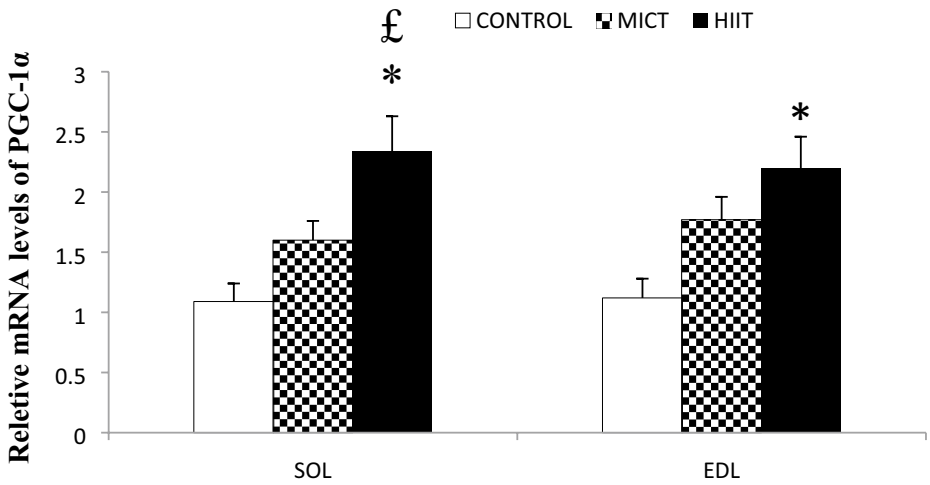

Fig. 3 Peroxisome proliferator-activated receptor γ coactivator (PGC)-1α mRNA in Soleus (SOL) and Extensor Digitorum Longus (EDL) muscles in control, moderate-intensity continuous training (MICT), and high-intensity interval training (HIIT) groups. The values are mean ± SEM; n = 10 per group. * Significantly different from control group ($p < 0.05$). £ Significantly different from MICT group ($p < 0.05$)

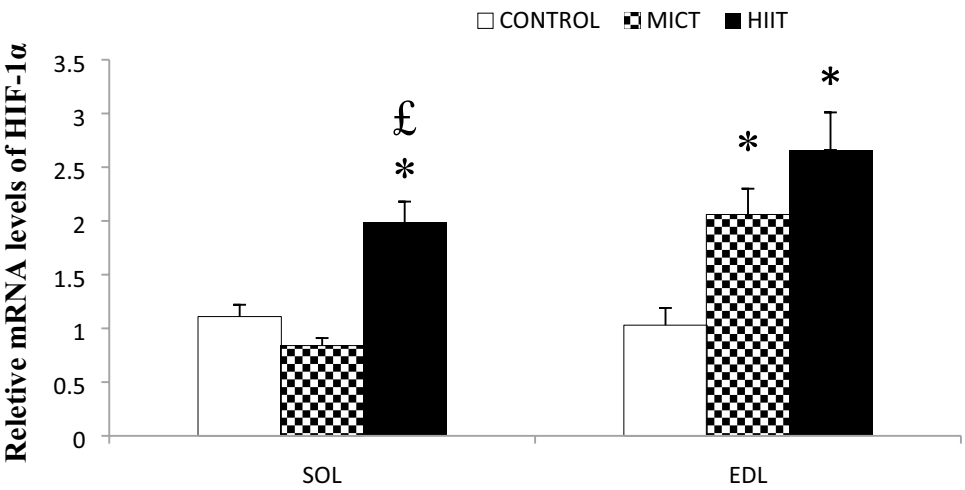

Fig. 4 Hypoxia inducible factor-1α (HIF-1α) mRNA in Soleus (SOL) and Extensor Digitorum Longus (EDL) muscles in control, moderate-intensity continuous training (MICT), and high-intensity interval training (HIIT) groups. The values are mean ± SEM; n = 10 per group. * Significantly different from control group ($p < 0.05$). £ Significantly different from MICT group ($p < 0.05$)

Effects of training modalities on PGC-1α mRNA

PGC-1α mRNA levels of the MICT group were not significantly different from those of the control group in soleus ($p=0.23$) and EDL ($p=0.13$) muscles. In contrast, PGC-1α mRNA expression levels of the HIIT group were greater in soleus ($p=0.001$) and EDL (0.005) muscles compared to those in the control group. The findings also indicated that soleus PGC-1α mRNA level of the HIIT group was significantly higher than that of the MICT group ($p=0.04$), while there was no significant difference between the two training groups in EDL PGC-1α mRNA levels ($p=0.33$). (Fig. 3).

Effects of training modalities on HIF-1α mRNA

HIF-1α mRNA level of the MICT group was significantly greater than that of the control group in EDL ($p=0.016$), but the difference was not significant in soleus ($p=0.34$). However, HIF-1α mRNA levels of the HIIT group were significantly higher in both soleus ($p=0.001$) and EDL ($p=0.001$) in comparison with those of the control group. The present study also revealed that soleus HIF-1α mRNA level was significantly higher in the HIIT group compared to the MICT group ($p=0.001$), while there was not any significant difference between the two training groups in EDL HIF-1α mRNA levels ($p=0.21$) (Fig. 4).

Furthermore, our results showed significantly positive correlations between soleus HIF-1α and MCT4 mRNA levels of MICT ($r=0.76$, $p=0.010$) and HIIT ($r=0.80$, $p=0.005$) groups. Similarly, significantly positive correlations between EDL HIF-1α and MCT4 mRNA levels of MICT ($r=0.70$, $p=0.024$) and HIIT ($r=0.74$, $p=0.013$) groups were observed. However, the correlation between PGC-1α and MCT1 indicated that there was only a significantly positive correlation between soleus PGC-1α and MCT1 mRNA levels of the MICT group ($r=0.66$, $p=0.036$).

Discussion

To the best of our knowledge, this is the first study to investigate MCT1, MCT4, PGC-1α, and HIF-1α mRNA expression in soleus and EDL skeletal muscles of rats under MICT and isocaloric HIIT conditions. The main findings of the present research revealed that the expression levels of selected genes altered in different patterns depending on the muscle fiber type-specific responses to the type and intensity of the exercise training.

The current study showed that MCT1 mRNA levels did not change in soleus muscle after both MICT and HIIT. In agreement with these findings, Bonen et al. (2000) indicated that in type I skeletal muscles of rats, one week of chronic muscle stimulation did not alter MCT1 mRNA [14]. The results of the present study also demonstrated that both MICT and HIIT did not alter EDL MCT1 mRNA levels, which are inconsistent with the findings of Bonen et al. (2000) who reported that one week of chronic muscle stimulation increased MCT1 mRNA level in type II skeletal muscles of rats [14]. However, the results of the present study support the findings of Nordsborg et al. (2003) who reported no change in MCT1 mRNA after high-intensity training in human muscles [13]. In our study, the comparison between the two performed training methods indicated that in both muscles there were no significant differences between MCT1 mRNA levels after MICT compared to HIIT. Some studies have indicated that MCT1 protein expression levels are increased in response to training [9, 35]. This increase in MCT1 by training can increase lactate uptake from circulation. However, the discrepancies in MCT1 protein and corresponding mRNA expression levels in response to training could be attributed to the regulation of MCT1 protein expression by post-transcriptional mechanisms [14]. Bonen et al. (2000) also demonstrated that in type I and type 2 skeletal muscles of rats, three weeks of chronic muscle stimulation did not alter MCT4 mRNA and protein levels [14]. Similarly, the findings of the current study revealed no significant changes in MCT4 mRNA in both oxidative and glycolytic muscles in response to MICT. However, our results indicated that MCT4 mRNA in both type 1 and type 2 muscles increased significantly after HIIT, which are in agreement with that of Arabmomeni et al. (2015) who suggested that long term intermittent training increased MCT4 mRNA levels in the muscles of rats [36]. It appears that this increase in MCT4 facilitates the removal of lactate. In our study, the large increments in MCT4 mRNA levels after HIIT revealed that training intensity can be an effective factor in MCT4 mRNA alterations. In some studies, MCT4 protein content increased only following maximal or supra maximal training [9, 37]; however, MCT4 protein expression appeared to be regulated by both transcriptional and post-transcriptional mechanisms [15]. Our results also demonstrated that in both oxidative and glycolytic muscles, MCT4 mRNA levels increased significantly after HIIT compared to MICT. In the current study, greater MCT4 expression magnitudes in EDL compared to that of soleus following training is supported by the fact that MCT4 is mainly expressed in glycolytic fibers [6].

The obtained data of the present study indicated that despite increases in PGC-1α mRNA levels after MICT in both oxidative and glycolytic muscles, these increments were not significant. Similarly, Tunstall et al. (2002) and Pilegaard et al. (2003) failed to elicit any significant change in the PGC-1α mRNA level in human skeletal muscles after moderate intensity endurance training [22, 38]. Nevertheless, it

has been indicated that mRNA expression level of PGC-1α is enhanced after moderate intensity acute endurance exercise [22, 39]. Several studies have indicated that PGC-1α protein expression is enhanced following endurance exercise training [20, 40]. However, training-induced increase in PGC-1α protein expression appears to result from the cumulative effects of transient bursts in its mRNA expression after successive exercise sessions [41]. Our results revealed that HIIT increased PGC-1α mRNA levels significantly in both muscles. Consistent with the current study, Shirvani and Arabzadeh (2018) showed that 8 weeks of HIIT increased PGC-1α mRNA levels in skeletal muscles of rats significantly [42]. It appears that PGC-1α mRNA abundance is enhanced in an intensity-dependent manner after exercise [43]. Our results also demonstrated that in the soleus muscle, PGC-1α mRNA level increased significantly in HIIT compared to MICT, while there was no significant difference in EDL PGC-1α mRNA levels between the two training groups.

The results of the current study illustrated that although MICT caused no significant change in soleus HIF-1α mRNA, a slight decrease was observed. In accordance with the present study, regular endurance training [24] and aerobic training [44] have been reported not to affect HIF-1α mRNA in human skeletal muscles. These outcomes support the hypothesis that as a result of the negative influence of HIF activation on oxidative capacity, long-term endurance training regulates HIF negatively [45]. In agreement, Lindholm et al. (2014) demonstrated that negative regulators of HIF are increased in response to endurance training [46]. However, the data from the current study indicated that MICT increased the HIF-1α mRNA level significantly in glycolytic EDL muscle. The reason for this difference in soleus and EDL muscles might be due to the greater amounts of negative regulators in skeletal muscles with high oxidative capacity [45]. It has been shown that HIF-1α mRNA expression is up-regulated following hypoxic but not normoxic training [29, 47]. Abe et al. (2015) also demonstrated that HIF-1α is a main transcription factor in the regulation of glycolytic metabolism. They stated that the elevated expression of genes associated with glycolytic capacity following HIIT results from enhanced levels of HIF-1α [27]. These findings verify the results of the current study that revealed HIF-1α mRNA levels increased significantly in both soleus and EDL muscles following HIIT. In addition, greater expression of HIF-1α mRNA in EDL compared to soleus muscle is supported by the finding that showed HIF-1α mRNA and protein expression levels were higher in the more glycolytic muscles compared to the more oxidative muscles [48]. The comparison between the two training groups also showed that there was a significant difference between HIF-1α mRNA levels only in the soleus muscle. Furthermore, it has been demonstrated that the main regulatory mechanism identified for MCT4 expression is hypoxia implicating transcriptional regulation by HIF-1α [23, 30]. In the present study, strong positive relationships between mRNA levels of HIF-1α and MCT4 also revealed that the changes in MCT4 expression were associated with the changes in HIF-1α expression. On the other hand, some studies have shown that MCT1 expression is regulated by PGC-1α in skeletal muscles [23, 49]. In our study; however, strong positive relationship between soleus PGC-1α and MCT1 mRNA levels of MICT group demonstrated that the changes in MCT1 expression were associated with the changes in PGC-1α expression only in the oxidative muscle.

Conclusion

In summary, the present study indicated that in both soleus and EDL muscles, gene expression levels of MCT4, PGC-1α, and HIF-1α increased in response to HIIT, whilst MCT1 gene expression was not affected. However, gene expression levels of MCT1, MCT4, and PGC-1α remained unaltered in both muscles following MICT, whereas HIF-1α gene expression was enhanced in EDL. The comparison between the two training methods revealed that HIIT caused greater positive responses in the gene expression of MCT4, PGC-1α, and HIF-1α compared to MICT. Furthermore, strong positive correlations between mRNA levels of MCT4 and HIF-1α showed that MCT4 expression is associated with HIF-1α expression.

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Author contributions AA was involved in literature review and data collection. DS-V performed study design, data analysis, interpretation and writing of the manuscript. MB and SG were involved in data collection.

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Data availability The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

Ethical approval The study was approved by the ethics committee of Arak University of Medical Sciences in Iran (IR.Arakmu.REC.1398.141).

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