ORGINAL ARTICLE

The Effect of Continuous and Interval Training on Glycogen Storage of Gastrocnemius Muscle and Serum Levels of Tumor Necrosis Factor-α & Interleukin-6 in Diabetic Rats

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Abstract

Objective: Diabetes mellitus (DM) is the most frequent type of metabolic disorder. Here, we evaluated the effect of continuous and interval training on glycogen storage of gastrocnemius muscle and serum levels of tumor necrosis factor-α (TNF-α) and Interleukin-6 (IL-6) in diabetic rats.

Materials and Methods: This study was experimental. 28 rats were randomly divided into four groups. The interval training included 10 sets of one-minute activity with 50% intensity and continuing training included 8 weeks running at the speed of 15 to 28 m/min. Serum levels of IL-6 and TNF-α and glycogen storage of gastrocnemius muscle were measured using specific ELISA Kits. SPSS 23 software was used.

Results: The level of fast blood glucose and TNF-α in diabetic+continuous training and diabetic+interval training groups were significantly lower than the control-diabetic group (*P*-value< 0.0001). In return, the level of Insulin, IL-6, and glycogen storage in diabetic+continuous training and diabetic+interval training groups were significantly higher than the control-diabetic group (*P*-value< 0.0001). There was a significant difference in value of glycogen storage between diabetic+continuous training and diabetic+interval training groups (*P*-value< 0.0001).

Conclusion: Continuous and interval exercises significantly decreased the levels of these inflammatory mediators in the diabetic rats which were subsequently associated with a significant decrease of blood glucose, insulin tolerance, and improvement of glycogen contents. Both interval and continuous exercises made significant changes, but interval exercises had better effects than continuous exercises.

Keywords: Exercise, Inflammation, Diabetes mellitus

Introduction

Diabetes mellitus (DM) is the most frequent type of metabolic disorder worldwide (1,2). Type II diabetes mellitus (T2DM), which is resulted from the defect in pancreatic beta-cells, may be associated with multiple abnormal conditions

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such as ketoacidosis, hyperlipidemia, hypertension, inflammation, nonalcoholic fatty liver disease, and increased risk of cardiovascular disease (3,4). Obesity, aging, sedentary lifestyle, genetics, and nutritional habitation are the most important risk factors of diabetes development (5,6). Cytokines are small proteins that are released in response to a stimulus and bond to a specific receptor to induce a signaling pathway. Cytokines secreted by adipose tissue modulate insulin secretion and function, hyperglycemia, and weight modulation, and may play a key role in the development of insulin resistance (7). The pathophysiology of diabetes is complex and multifactorial (8). It may be because of mitochondrial damage, oxidative stress and inflammatory processes, cellular damage, and apoptosis (9). Some studies showed that increased expression of inflammatory factors, such as interleukin 6 (IL-6), tumor necrosis factor-alpha (TNF-α), and C-reactive protein (CRP) may be the main reason for the occurrence of diabetes; however, the underlying mechanism is unknown (10). Recent investigations have revealed that the production and secretion of TNF-α and IL-6 have significantly increased in diabetic patients, which in turn increases the levels of other pro-inflammatory cytokines, overproduction of reactive oxygen species (ROS), oxidative stress, and pancreatic cells damage (11,12). Therefore, both IL-6 and TNF-α can be considered as risk factors for the development of insulin resistance and T2DM. However, the exact molecular mechanism is not clear and further investigations are essential to finding the underlying mechanisms (6,13). Exercise training is one of the first clinical approaches for the prevention and treatment of metabolic disorders (14). Some studies showed that mild to moderate exercises improve the antioxidant capacity and protect body cells against ROS, oxidative stress, and inflammatory reactions (15,16). Researchers in the field of sports physiology have discovered innovations in the design of physical activity that lead to profitability in the shortest possible time and seem to be able to have valuable achievements in increasing levels of activity and community health (17). One of them is interval exercises. Today, the potential value of intermittent exercise in developing health and fitness is understood even in people with a variety of disease conditions (18). In general, it seems that metabolic adaptations to this type of exercise can be mediated by the cellular signaling pathway, which ultimately, leads to similar adaptations to adaptation to continuous exercise (17). Given the high prevalence of diabetes and the lack of appropriate treatment, as well as the critical role of IL-6 and TNF-α in the pathogenesis of this disease, finding creative and noninvasive treatment for this disease seems necessary. Therefore, this study aimed to investigate the effect of a period of regular and continuous exercise on the levels of these inflammatory biomarkers, blood glucose and insulin levels, glycogen storage of skeletal muscles, and plasma levels of IL-6 and TNF-α in diabetic rats.

Materials and Methods

Animals and treatments

This study was experimental. To determine the number of statistical population, (N: 28) effect size: 0.55, α: 0.05, power: 0.8 were used. 28 male Wistar rats (with a mean age of 40-45 weeks and bodyweight of 250-300 gram) were randomly divided into four groups: control-healthy, control-diabetic, diabetic+interval training, diabetic+continuous training.

The study was approved by the animal care and use committee at Islamic Azad University, Sari branch. Rats in the diabetes group received an intravenous injection of streptozotocin (1000 mg, ZellBio Company, German) with a concentration of 50 mg/kg (19). 48 hours after the injection, diabetes was induced in these animals (blood glucose>250 mg/dl).

Exercises training

To decrease environmental stresses, diabetic rats in exercise groups were habituated with a rodent treadmill (Six Lines, Iranian Scholars

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Company) for 5 successive days (with a speed of 10 m/min at 0% inclination for 5 min/day) (20, 21). In the previous study, the exercise training protocol was described (22). Rats in the interval exercise group were performed 3 days/week for eight weeks, with an intensity of 85-90% of VO2 max. Two minutes per week was added to the training time, as well as a training speed of 2 m/min. The speed of training was eventually reached 28 m/min in the last week. A rest time (two minutes) was also performed between each interval. Rats in the continuous exercise group were trained 5 days/week for 8 weeks, with an intensity of 65-70% of VO2 max. In the first week, the training time was 5 minutes and the training speed was 15 m/min, in the eighth week, the training speed had reached 28 m/min and the training time had reached 20 minutes. In both types of training, at the beginning and end of the training to warm-up and cool-down, the rats trained on the treadmill for 2 minutes and a speed of 5 m/min.

Blood and tissue Samples collection and measurements

48 hours after the end of exercise training, rats were anesthetized with ketamine (30-50 mg/kg) and xylazine (3-5 mg/kg). The gastrocnemius muscle (100-150 g) was isolated and homogenized in phosphate buffer (pH 7.0) at 4°C with a homogenizer (Hielscher, UP100H). The homogenized tissue was centrifuged at 12000 rpm, 4 °C for 15 min (23). The supernatant was then collected for glycogen (nmol/g) content measurement. Furthermore, blood sample was collected from the abdominal aorta for measurement of fast blood glucose and insulin levels. Blood insulin (mU/l) level was measured by the Rat insulin ELISA Kit (provided by ZellBio Company). Fasting blood glucose (mg/dl) was determined by the Autoanalyzer apparatus. The levels of TNF-α (pg/ml) and IL-6 (pg/ml) were measured by the Rat TNF-α and IL-6 ELISA Kits, provided by ZellBio Company (ZB-0764-R9648 and ZB-0522-R9648, respectively).

Statistical analysis

The mean of all data is presented as mean (±SD). Comparison of the mean of all data between four groups was performed using the one-way ANOVA. Data were analyzed using SPSS 23. A *P*-value≤ 0.05 was considered significant.

Ethical considerations

This research was approved by the animal care and use committee at the Islamic Azad University of Sari (R.IAU.SARI.REC. 1397.011).

Results

The results showed that there is a significant difference in the amount of glucose, Insulin, glycogen storage, IL-6 (*P*-value< 0.0001), and TNF-α (*P*-value= 0.001) between the research groups. The control-diabetic group had significantly higher fast blood glucose and TNF-α level compared to the control-healthy group, whereas the level of fast blood glucose and TNF-α in diabetic+continuous training and diabetic+interval training groups were significantly lower than control-diabetic group (*P*-value< 0.0001). Although there was no significant difference in the mean value of fast blood glucose and TNF-α between diabetic+continuous training and diabetic+interval training groups, interval training was more effective (Table 1). In return, the control-diabetic group had significantly lower Insulin, IL-6, and glycogen storage levels compared to the control-healthy group, whereas the level of Insulin, IL-6, and glycogen storage in diabetic+continuous training and diabetic+interval training groups were significantly higher than that in the control-diabetic group (*P*-value<0.0001). Although there was no significant difference in the value of Insulin and IL-6 between diabetic+continuous training and diabetic+interval training groups, interval training was more effective (Table 1). There was a significant difference in the value of glycogen storage between diabetic+continuous

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Table 1. The research variables and comparisons between groups

Variable	Groups	Mean (±SD)	F	*P*-value
Fasting blood glucose (mg/dl)	Control-healthy	100.50 (±8.52)	61.390	[a]<0.0001
	Control-diabetic	362.02 (±58.19) *P*-value< 0.0001*		
	Diabetic+continuous training	222.66 (±32.78) *P*-value< 0.0001#		
	Diabetic+interval training	214.17 (±26.40) *P*-value< 0.0001#		
Insulin (mU/l)	Control-healthy	15.52 (±1.13)	21.287	[a]<0.0001
	Control-diabetic	11.15 (±1.26) *P*-value< 0.0001*		
	Diabetic+continuous training	12.79 (±0.95) *P*-value= 0.007#		
	Diabetic+interval training	13.18 (±0.71) *P*-value= 0.001#		
Glycogen storage (nmol/g)	Control-healthy	6.87 (±0.88)	13.268	[a]<0.0001
	Control-diabetic	4.59 (±0.86) *P*-value< 0.0001*		
	Diabetic+continuous training	7.54 (±1.19) *P*-value< 0.0001# p-value= 0.001$		
	Diabetic+interval training	5.67 (±0.83) *P*-value= 0.043#		
IL-6 (pg/ml)	Control-healthy	5.61 (±0.99)	56.044	[a]<0.0001
	Control-diabetic	4.81 (±0.94) *P*-value< 0.0001*		
	Diabetic+continuous training	10.04 (±0.86) *P*-value<0.0001#		
	Diabetic+interval training	9.54 (±0.98) *P*-value< 0.0001#		
TNF-α (pg/ml)	Control-healthy	0.61 (±0.09)	7.692	[a]0.001
	Control-diabetic	0.93 (±0.16) *P*-value< 0.0001*		
	Diabetic+continuous training	0.80 (±0.15) *P*-value= 0.07		
	Diabetic+interval training	0.78 (±0.10) *P*-value= 0.033#		

a: Significant results for ANOVA test
*: Significance relative to control-healthy
#: Significance relative to control-diabetic
$: Significance relative to diabetic+interval training

training and diabetic+interval training groups (Table 1).

Discussion

In this study, we considered the effect of continuous and interval exercises on blood glucose and insulin levels, as well as serum TNF-α and IL-6 levels and glycogen content in the skeletal muscle of diabetic rats. Our findings had revealed that continuous and interval exercises are associated with a significant decrease in blood glucose and a significant increase in the blood insulin level in diabetic rats. We also found that both types of exercise training significantly increased the mean of glycogen contents in the skeletal muscle of diabetic rats. Both interval and continuous exercises made significant changes, but interval exercises had better effects than continuous exercises. Chavanelle et al. (2017) reported that interval training improves glucose metabolism in a superior manner to continuous training. Skeletal muscle insulin signaling and glucose transporter type 4 (Glut-4) content were only improved in the interval training group, suggesting that skeletal muscle insulin sensitivity would be more altered by the effects of interval training than by those of continuous training. This could account for the better improvement of glucose homeostasis following interval-training intervention (24). Ostler et al. demonstrated

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mild betterments in glucose tolerance and vital Akt Ser473 phosphorylation (25). Stølen et al. (2009) reported a change for better in lipid profile (26). However, none of these studies reported lower fasting blood sugar. Among researchers having demonstrated more common continuous endurance training on diabetes rats, Lee et al. indicated reforms on insulin tolerance, with no changes on fasting blood sugar, applying a comparable continuous training as ours (27). Also, similar studies using this type of continuous exercise have failed to alter blood sugar control (28, 29). Therefore, Chavanelle et al. confirmed that exercise-training adaptations as to glucose homeostasis are difficult to receive in diabetes rats, augmenting the opinion that these animals could be used as a "training resistance" pattern. It is noteworthy, established effects of interval training on glucose homeostasis were found in this ground. These outcomes fasten the concern to research the effects of interval training in diabetic context and highlight this training condition as an applicant to traverse the training-resistant situation (24). Exercises and sport activities create different adaptations in the body at different levels or different intensities so that such activities increasing the antioxidant capacity, and play two roles of prevention and therapy in oxidative stress-related diseases (30,31). Our study revealed that the mean levels of IL-6 and TNF-α in the serum of diabetic rats are significantly higher than healthy rats. Interestingly, we found that continuous, interval exercises significantly decrease the mean of TNF-α, and IL-6 levels in the serum of diabetic rats, but the results in the interval-training group were better than the continuous exercises. Several studies reported increased levels of TNF-α and IL-6 in the serum of diabetic subjects. For instance, Jiang et al., (32) showed that regular exercise training significantly decreases the expression of IL-6 in the skeletal muscle of diabetic rats which was subsequently associated with increased cellular response to insulin and glucose clearance. Kim et al., (33) showed that diabetes is associated with a significant increase in the level of serum IL-6, whereas doing regular exercise significantly decreases the expression of IL-6 in diabetic rats. In contrast, Pattamaprapanont et al., (34) showed that exercise training has no significant effect on the expression pattern of IL-6 in diabetic rats. It means that the type and severity of exercises are likely important. The blood sugar decline in replication to an interval training could be a result of metabolic and hormonal responses (epinephrine, norepinephrine and GH). These replications seem to append GLUT-4 translocation to the sarcolemma, hence an enhanced glucose uptake (35). The benefit of the interval training was corroborated by evaluating proangiogenic agents (VEGF, TGF-b) and proinflammatory cytokine (IL-6, TNF- α) levels in diabetic specimens. This perception has symbolization that the addition of interval training by the specimens with diabetes to the modernization program can help to defend against potentially serious hypoglycemia cases (36). The absence of TNF-α enhancement in response to an interval training could show an adaptive decrease in inflammatory replication to metabolic stress induced by training (35). Exercise training probably downregulates IL-6 and TNF-α expression from skeletal muscle which in turn stimulates glucose clearance and diabetes improvement. However, further studies are needed to find the exact mechanism of exercise action either at gene and protein expression levels.

Conclusions

Results of the current study revealed that diabetes is significantly associated with increased levels of serum TNF-α and IL-6. Continuous and interval exercises significantly decreased the levels of these inflammatory mediators in sera of diabetic rats which was subsequently associated with a significant decrease of blood glucose, insulin tolerance, and improvement of glycogen contents. Both interval and continuous exercises made significant changes, but interval exercises had better effects than continuous exercises.

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Therefore, pharmacologic activation of TNF-α and IL-6 by exercise training, which has been implicated in the pathogenesis of diabetes mellitus, maybe a potential therapeutic target for treating this disease.

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Conflict of Interest

All contributing authors declare that there is no conflict of interest.

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