

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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Received: 14 January 2021

Accepted: 07 July 2021

Published in September 2021

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

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

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 (\pm 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 \leq 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

Table 1. The research variables and comparisons between groups

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

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

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- β) 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.

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.

Acknowledgments

We would like to appreciate the staff of the exercise physiology centers of Islamic Azad University, Sari, Iran.

Conflict of Interest

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

References

- Whiting DR, Guariguata L, Weil C, Shaw J. IDF diabetes atlas: global estimates of the prevalence of diabetes for 2011 and 2030. *Diabetes research and clinical practice*. 2011;94(3):311-21.
- Yaghini N, Mahmoodi M, Asadikaram G, Hassanshahi G, Khoramdelazed H, Arababadi MK. Serum levels of interleukin 10 (IL-10) in patients with type 2 diabetes. *Iranian Red Crescent Medical Journal*. 2011;13(10):752-3.
- Barbot M, Ceccato F, Scaroni C. Diabetes mellitus secondary to Cushing's disease. *Frontiers in endocrinology*. 2018;9:284.
- Kharroubi AT, Darwish HM. Diabetes mellitus: The epidemic of the century. *World journal of diabetes*. 2015;6(6):850.
- Fletcher B, Gulanic M, Lamendola C. Risk factors for type 2 diabetes mellitus. *Journal of Cardiovascular Nursing*. 2002;16(2):17-23.
- Lowe G, Woodward M, Hillis G, Rumley A, Li Q, Harrap S, et al. Circulating inflammatory markers and the risk of vascular complications and mortality in people with type 2 diabetes and cardiovascular disease or risk factors: the ADVANCE study. *Diabetes*. 2014;63(3):1115-23.
- Jokar MH, Sedighi S, Mohamadkhani A, Moradzadeh M. Inflammatory Cytokines and type 2 diabetes. *Kooshesh*. 2020;22(3):396-403. (in Persian)
- Ju J, Huang Q, Sun J, Zhao X, Guo X, Jin Y, et al. Correlation between PPAR- α methylation level in peripheral blood and atherosclerosis of NAFLD patients with DM. *Experimental and therapeutic medicine*. 2018;15(3):2727-30.
- Mantovani A. NAFLD and risk of cardiac arrhythmias: Is hyperuricemia a neglected pathogenic mechanism?. *Digestive and Liver Disease*. 2018;50(5):518-20.
- Ryan JD, Armitage AE, Cobbold JF, Banerjee R, Borsani O, Dongiovanni P, et al. Hepatic iron is the major determinant of serum ferritin in NAFLD patients. *Liver International*. 2018;38(1):164-73.
- VanWagner LB. New insights into NAFLD and subclinical coronary atherosclerosis. *Journal of hepatology*. 2018;68(5):890-2.
- Scheller J, Chalaris A, Schmidt-Arras D, Rose-John S. The pro-and anti-inflammatory properties of the cytokine interleukin-6. *Biochimica et Biophysica Acta (BBA)-Molecular Cell Research*. 2011;1813(5):878-88.
- Spranger J, Kroke A, Möhlig M, Hoffmann K, Bergmann MM, Ristow M, et al. Inflammatory cytokines and the risk to develop type 2 diabetes: results of the prospective population-based European Prospective Investigation into Cancer and Nutrition (EPIC)-Potsdam Study. *Diabetes*. 2003;52(3):812-7.
- Yanai H, Adachi H, Masui Y, Katsuyama H, Kawaguchi A, Hakoshima M, et al. Exercise therapy for patients with type 2 diabetes: a narrative review. *Journal of clinical medicine research*. 2018;10(5):365-9.
- Rietman A, Sluik D, Feskens EJ, Kok FJ, Mensink M. Associations between dietary factors and markers of NAFLD in a general Dutch adult population. *European journal of clinical nutrition*. 2018;72(1):117-23.
- Bellantini F, Villani R, Tamborra R, Blonda M, Iannelli G, di Bello G, et al. Synergistic interaction of fatty acids and oxysterols impairs mitochondrial function and limits liver adaptation during nafld progression. *Redox biology*. 2018;15:86-96.
- Rahimi R, Nikfar S, Larijani B, Abdollahi M. A review on the role of antioxidants in the management of diabetes and its complications. *Biomedicine & Pharmacotherapy*. 2005;59(7):365-73.
- Gibala MJ. Interval training for cardiometabolic health: why such a HIIT?. *Current sports medicine reports*. 2018;17(5):148-50.
- Akbarzadeh A, Norouzian D, Mehrabi MR, Jamshidi SH, Farhangi A, Verdi AA, et al. Induction of diabetes by streptozotocin in rats. *Indian Journal of Clinical Biochemistry*. 2007;22(2):60-4.

20. Batacan Jr RB, Duncan MJ, Dalbo VJ, Connolly KJ, Fenning AS. Light-intensity and high-intensity interval training improve cardiometabolic health in rats. *Applied physiology, nutrition, and metabolism*. 2016;41(9):945-52.
21. Freitas DA, Rocha-Vieira E, Soares BA, Nonato LF, Fonseca SR, Martins JB, et al. High intensity interval training modulates hippocampal oxidative stress, BDNF and inflammatory mediators in rats. *Physiology & behavior*. 2018;184:6-11.
22. Hajjighasem A, Farzanegi P, Mazaheri Z. Effects of combined therapy with resveratrol, continuous and interval exercises on apoptosis, oxidative stress, and inflammatory biomarkers in the liver of old rats with non-alcoholic fatty liver disease. *Archives of physiology and biochemistry*. 2019;125(2):142-9.
23. Ma Z, Chu L, Liu H, Wang W, Li J, Yao W, et al. Beneficial effects of paeoniflorin on non-alcoholic fatty liver disease induced by high-fat diet in rats. *Scientific reports*. 2017;7(1):1-0.
24. Chavanelle V, Boisseau N, Otero YF, Combaret L, Dardevet D, Montaurier C, et al. Effects of high-intensity interval training and moderate-intensity continuous training on glycaemic control and skeletal muscle mitochondrial function in db/db mice. *Scientific reports*. 2017;7(1):1-0.
25. Ostler JE, Maurya SK, Dials J, Roof SR, Devor ST, Ziolo MT, et al. Effects of insulin resistance on skeletal muscle growth and exercise capacity in type 2 diabetic mouse models. *American Journal of Physiology-Endocrinology and Metabolism*. 2014;306(6):E592-605.
26. Stølen TO, Høydal MA, Kemi OJ, Catalucci D, Ceci M, Aasum E, et al. Interval training normalizes cardiomyocyte function, diastolic Ca²⁺ control, and SR Ca²⁺ release synchronicity in a mouse model of diabetic cardiomyopathy. *Circulation research*. 2009;105(6):527-36.
27. Lee S, Park Y, Zhang C. Exercise training prevents coronary endothelial dysfunction in type 2 diabetic mice. *American journal of biomedical sciences*. 2011;3(4):241.
28. Trask AJ, Delbin MA, Katz PS, Zanesco A, Lucchesi PA. Differential coronary resistance microvessel remodeling between type 1 and type 2 diabetic mice: impact of exercise training. *Vascular pharmacology*. 2012;57(5-6):187-93.
29. Broderick TL, Parrott CR, Wang D, Jankowski M, Gutkowska J. Expression of cardiac GATA4 and downstream genes after exercise training in the db/db mouse. *Pathophysiology*. 2012;19(3):193-203.
30. Chiş IC, Mureşan A, Oros A, Nagy AL, Clichici S. Protective effects of Quercetin and chronic moderate exercise (training) against oxidative stress in the liver tissue of streptozotocin-induced diabetic rats. *Acta Physiologica Hungarica*. 2016;103(1):49-64.
31. Mohammad P, Esfandiar KZ, Abbas S, Ahoora R. Effects of moderate-intensity continuous training and high-intensity interval training on serum levels of resistin, chemerin and liver enzymes in streptozotocin-nicotinamide induced type-2 diabetic rats. *Journal of diabetes & metabolic disorders*. 2019;18(2):379-87.
32. Jiang LQ, Duque-Guimaraes DE, Machado UF, Zierath JR, Krook A. Altered response of skeletal muscle to IL-6 in type 2 diabetic patients. *Diabetes*. 2013;62(2):355-61.
33. Kim KB. Effect of different training mode on Interleukin-6 (IL-6) and C-reactive protein (CRP) in type 2 diabetes mellitus (T2DM) patients. *Journal of exercise nutrition & biochemistry*. 2014;18(4):371.
34. Pattamaprapanont P, Muanprasat C, Soodvilai S, Srimaroeng C, Chatsudthipong V. Effect of exercise training on signaling of interleukin-6 in skeletal muscles of type 2 diabetic rats. The review of diabetic studies: RDS. 2016;13(2-3):197.
35. Hall B, Zebrowska A, Kaminski T, Stanula A, Robins A. Effects of hypoxia during continuous and intermittent exercise on glycaemic control and selected markers of vascular function in type 1 diabetes. *Experimental and Clinical Endocrinology & Diabetes*. 2018;126(04):229-41.
36. Zebrowska A, Hall B, Maszczyk A, Banas R, Urban J. Brain-derived neurotrophic factor, insulin like growth factor-1 and inflammatory cytokine responses to continuous and intermittent exercise in patients with type 1 diabetes. *Diabetes research and clinical practice*. 2018;144:126-36.