

## Effect of High Intensity Interval Training with Metformin on Lipid Profiles and HbA<sub>1c</sub> in Diabetic Rats

Yadollah Mahmoudi<sup>1,2</sup>, Mandana Gholami\*<sup>3</sup>, Hojatollah Nikbakht<sup>4</sup>, Khosrow Ebrahim<sup>5</sup>, Salar Bakhtiyari<sup>6</sup>

1. Ph.D. Student, Department of Sport Physiology, Faculty of Humanities and Social Sciences, Islamic Azad University, Science and Research Branch, Tehran, Iran.

2. Instructor, Department of Physical Education, Payame Noor University, Tehran, Iran.

3. Assistant Professor, Department of Physical Education and Sport Sciences, Science and Research Branch, Islamic Azad University, Tehran, Iran.

4. Associate Professor, Department of Sport Physiology, Faculty of Humanities and Social Sciences, Islamic Azad University, Science and Research Branch, Tehran, Iran.

5. Professor, Department of Sport Physiology, Faculty of Humanities and Social Sciences, Islamic Azad University, Science and Research Branch, Tehran, Iran.

6. Associate Professor, Department of Clinical Biochemistry, Faculty of Basic Sciences, Ilam University of Medical Sciences, Iran.

### \*Correspondence:

Mandana Gholami, Assistant Professor, Department of Physical Education and Sport Sciences, Science and Research Branch, Islamic Azad University, Tehran, Iran.

**Tel:** (98) 912 149 1868

**Email:** m.gholami@srbiau.ac.ir

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### Abstract

**Objective:** Type2 diabetes (T2DM) as a metabolic disease is associated with absolute or relative insulin deficiency, increased blood glucose and carbohydrate metabolism disorders which is considered as risk factors of other diseases such as cardiovascular diseases. In the present study, the effect of eight weeks of high intensity interval training (HIIT) on lipid profile (TG, LDL and HDL), glucose and glycated hemoglobin (HbA<sub>1c</sub>) levels in streptozotocin-induced diabetic rats was investigated.

**Materials and Methods:** Sixty male Wistar rats were randomly divided into six groups: healthy, diabetic, diabetic + metformin, healthy + training, diabetic + training and diabetic + training + Metformin. The training groups performed eight weeks of HIIT. Metformin was given 150 mg / kg to the rats by gavage every day. T2DM was induced by injection of nicotinamide and streptozotocin and 48 hours after the end of last training session, the rats were sacrificed. Then lipid profile, blood glucose and HbA<sub>1c</sub> were measured. One way analysis of variance (ANOVA) test was used for statistical analysis.

**Results:** The results of this study showed that TG levels were low in diabetic training and diabetic + training + metformin groups compared to the diabetic group (*P*-value: 0.0001). There weren't any significant differences between total cholesterol, LDL-c and HDL-c levels between groups. Blood glucose levels were significantly lower in diabetic + training and diabetic + training + metformin groups compared to diabetic controls (*P*-value: 0.0001). HbA<sub>1c</sub> levels were significantly lower in diabetic + training and diabetic + training + metformin than in diabetic group (*P*-value: 0.0001).

**Conclusion:** According to the results of this study, it seems that severe periodic exercise can be considered as an important strategy for improving lipid profiles and blood glucose control in T2DM patients.

**Keywords:** High intensity interval training (HIIT), Lipids, HbA<sub>1c</sub>, Diabetes mellitus

### Introduction

Type 2 diabetes mellitus (T2DM) is a metabolic disease and associated with absolute or relative insulin deficiency, increased blood glucose and carbohydrate, fat and protein metabolism disorder (1). The prevalence of T2DM is about 6.8% without

gender segregation worldwide (2,3,4). According to the recent studies in Iran, 7.7% of the population aged 25-64 is diagnosed with diabetes and 16.8% suffer from impaired glucose tolerance (5). Diabetes is the risk factor of cardiovascular disease by atherosclerotic origin (6). The prevalence of cardiovascular disease in T2DM patients is four times higher than normal population (7). Lipid disorder is prevalent in T2DM patients which causes and exacerbates the short-term and long-term complications which is a risk factor of cardiovascular disease (3). The most common pattern of dyslipidemia in T2DM patients is the increase of triglyceride (TG) levels and decrease of high density lipoprotein (HDL) levels (9). High blood sugar increases insulin, low density lipoprotein (LDL) and very low density lipoprotein (VLDL) and decreases HDL, provides the basis for atherosclerosis (10).

On the other hand, control of HbA<sub>1c</sub> levels is a reliable indicator in diabetes control (11). Physical activity may be a potential cause of changes in HbA<sub>1c</sub> levels (12). Ghiathi et al. reported that eight weeks of aerobic activity in diabetic women did not significantly change the HbA<sub>1c</sub> level (13,14). The use of glucose-lowering drugs including metformin in T2DM patients can reduce fasting blood glucose (FBS) levels. One of the natural and safe solutions for diabetes treatment is physical activity, which is always available.

Several studies have pointed to the role of exercise in fat metabolism. Regular physical activity leads to an increase in lipid and glucose metabolism by increasing insulin sensitivity and HDL and decreasing TG and LDL. Ghalavand et al. showed that continuous aerobic exercise significantly reduced the level of blood glucose, LDL and a significant increase in HDL plasma levels in diabetic patients. Also, there was a significant decrease in blood glucose and a significant increase in plasma HDL after vigorous training (15). Most studies have investigated the effect of endurance and resistance training on lipid

profile and other parameters related to diabetes.

One of the sport protocols is interval training that is associated with a greater variety and less fatigue, and attracts many enthusiasts. In the present study, the effect of eight weeks of high intensity interval training (HIIT) on lipid profile (TG, LDL and HDL), FBS and HbA<sub>1c</sub> levels in streptozotocin-induced diabetic rats was investigated

## Materials and Methods

In this experimental study, 60 male Wistar rats (mean weight ( $\pm$ SD) 256 ( $\pm$  9.6) grams) were randomly divided into six groups; healthy, diabetic, diabetic + metformin, healthy + training, diabetic + training and diabetic + training + metformin. After two weeks of training, the training groups were prepared to work on the treadmill of the mouse to prepare the desired protocols. T2DM was induced by injection of nicotinamide and streptozotocin. Intra-peritoneal injection was performed on rats after 12 hours of fasting, 45 mg / kg streptozotocin dissolved in 500-300  $\mu$ l saline serum physiology. For 15 minutes before streptozotocin injection, 110 mg / kg of nicotinamide was dissolved in the physiologic serum and injected. After 7 days, blood glucose was measured. A glucose tolerance test was also performed to ensure the accuracy of blood glucose test. Rats with the blood glucose greater than 150 mg / dL were considered as diabetic.

The rats were practiced for one week and three days each day, and 15 minutes each day, at speeds of 20 m / min, were practiced on the treadmill. Subsequently, an increasing number of tests were performed to determine the maximum working load of rats in the training groups. The test started at speeds of 6 m / min, and every three minutes, the speed was increased until the animal was not able to run (three times remaining and falling from the speed of treadmill) and determined the maximum load for each rat. After diagnosing the maximum work, the speed required for the desired intensity was calculated. The

beginning of the training was done at 9 AM. Two similar treadmills were used to control the training time. After every two weeks, the maximum sever of rats activity was set again, and the principle of overload was applied in this way. The training process started with 10minutes warming (50 to 60 percent of maximum work load), and then the main exercise was performed according to table 1 (16,17).

To eliminate the effects of exercise and uncontrollable variables, 24 hours after the last training session, the weight of the rats was first measured using a digital scale. Then, with ethical principles and with intraperitoneal injection, a combination of ketamine (30 to 50 mg / kg body weight) and xylazine (3 to 5 mg / kg body weight), the rats were anesthetized and directly 10 ml of blood of the heart was taken from the rats and centrifuged for 15 minutes at a speed of 3,000 rpm. The lipid profile (LDL, HDL, TG and total cholesterol) and glucose were measured by colorimetric method using Pars Test (Iran) and HbA<sub>1c</sub> kits by chromatography.

This study was ethically approved according IR.MEDILAM.RES.1396.29 in Ilam University of medical sciences.

The Kolmogorov-Smirnov test was used to check the normal distribution of data. One-way ANOVA and post-hoc post hoc test were used to examine the differences between groups of each indicator. SPSS 16 was used to examine the data.

## Results

TG of the diabetic control and the diabetic + training group was not significantly different (*P*-value: 0.07). TG levels were low in diabetic training and diabetic training + metformin in comparison with the diabetic control group (*P*-value: 0.001). It was also lower in the diabetic training group in comparison with the diabetic

training + metformin (*P*-value: 0.01). However, this was controlled by the diabetic + metformin group more than the diabetic group (*P*-value: 0.001).

LDL level were reported in diabetic and exercise diabetic groups + metformin higher than the diabetic control group (*P*-value: 0.01).Cholesterol level in the diabetic training group was less than those of diabetes control and diabetic training + metformin (*P*-value: 0.034).This was also lower in the diabetic training + metformin group than in diabetic control (*P*-value: 0.01). The blood glucose level differs between the diabetes control group, the diabetes + HIIT groups (*P*-value: 0.004) and diabetes + HIIT + metformin (*P*-value: 0.01).

Similarly, there was a significant difference between diabetes+ metformin and diabetes + HIIT + metformin groups (*P*-value: 0.009). Blood glucose levels were lower in diabetic training and diabetic training + metformin groups in comparison with diabetic controls. However, this was higher in the diabetic training group compared to the diabetic training+ metformin. The HbA<sub>1c</sub> level was significantly different in the diabetic and diabetes control + metformin (*P*-value: 0.01), diabetes + HIIT (*P*-value: 0.001) and diabetes + HIIT + metformin (*P*-value: 0.001). Also, this level was not significant in the diabetic control + metformin with diabetic+ HIIT + metformin group (*P*-value: 0.6). The mean and standard deviation of the studied groups are shown in Table 2.

## Discussion

Diabetes is a chronic disease, and the main symptom of the disease is the increase in serum glucose, which itself causes the emergence and exacerbation of its short-term and long-term complications. Sport activity can be considered as an appropriate strategy to

Table 1. The high intensity interval training instructions

Variables	Training steps	Warming up	Main body (three interval)		Cooling down
			high	low	
Training time (min)		6	4	2	6
Training levels		50 to 60 %	90 to 100 %	50 to 60 %	50 to 60 %

**Table 2. Lipid profile and blood glucose in studied groups after intervention**

Variables	Healthy	Diabetic	Diabetic + Metformin	Healthy+ HIIT	Diabetic + HIIT	Diabetic + HIIT + Metformin	P-value
Weight (g) mean ( $\pm$ SD)	262( $\pm$ 5.8)	222( $\pm$ 12.5)	204( $\pm$ 10.7)	274( $\pm$ 6.6)	288( $\pm$ 11.1)	288( $\pm$ 6.9)	0.0001
TG (mg/dl) mean ( $\pm$ SD)	45.8( $\pm$ 9)	131( $\pm$ 24.7)	121.4 $\pm$ 26.2	47 $\pm$ 7.8	58.2 $\pm$ 10.04	71 $\pm$ 9.3	0.0001
HDL (mg/dl) mean ( $\pm$ SD)	41 $\pm$ 2.4	34.4 $\pm$ 2.4	25.4 $\pm$ 3.04	42.2 $\pm$ 1.2	32.2 $\pm$ 2	33 $\pm$ 2.1	0.003
LDL- (mg/dl) mean ( $\pm$ SD)	16.2 $\pm$ 0.66	19 $\pm$ 0	20 $\pm$ 0.44	19.6 $\pm$ 0.4	19.6 $\pm$ 0.8	19.6 $\pm$ 0.5	0.0001
Cholesterol (mg/dl) mean ( $\pm$ SD)	41 $\pm$ 3.79	60. 6 $\pm$ 3.5	52 $\pm$ 4.2	61.2 $\pm$ 4.9	58.4 $\pm$ 2.9	58.6 $\pm$ 1.3	0.014
Blood sugar (mg/dl) mean ( $\pm$ SD)	162.2 $\pm$ 33.2	481.6 $\pm$ 9.1	406 $\pm$ 91.6	151.4 $\pm$ 6.1	215.6 $\pm$ 9.6	131 $\pm$ 8.1	0.0001
HbA <sub>1c</sub> (%) mean ( $\pm$ SD)	3.06 $\pm$ 0.04	6.5 $\pm$ 0.58	4.8 $\pm$ 0.24	3.14 $\pm$ 0.1	3.48 $\pm$ 0.4	3.36 $\pm$ 0.16	0.0001

improve lipid and glycemic control and reduce the complications of diabetes in T2DM patients (18). A very intense periodic exercise that is accompanied by a greater variety and less fatigue is one of the activities that attracted a lot of enthusiasts. Therefore, the aim of this study was to determine the effect of HIIT on lipid profile, glucose and HbA<sub>1c</sub> in diabetic rats with streptozotocin. The results of this study were consistent with the study by Chen et al (19) and Hordern et al. (20). But the results of the research by Mercuri et al. (21) and Yanget al (22) were inconsistent. This difference between the results of various studies can be attributed to the difference between the severity, duration and the difference between the age and gender of the research samples. On the other hand, TG levels in the exercise group were much lower than that of the diabetic + metformin indicating that the training efficiency in reducing TG was much higher than the efficacy of just taking the medication. This can be a significant benefit of exercising in reducing the TG in diabetic people compared to using only medication in these individuals. The findings of this study showed that the HDL level in the diabetic group (32.2  $\pm$  2) and diabetic training + metformin (33  $\pm$  2.1) was lower than diabetic (34.4 $\pm$ 2.4). This non-significant reduction in the training group is in contradiction with the findings of some researchers. (23,24). It is also consistent with the findings of Iglayet al (25) and Karstoft et al (26). Karstoft et al. did not find a significant

difference in HDL and LDL after four months of continuous aerobic exercise, which is in line with the current study. Earlier studies have shown that aerobic exercise and resistance training increased the HDL level and did not significantly changing in LDL levels (27). The possible reason for this difference is because of the difference in the test characteristics or the difference in the practice protocol.

In the present study, there was no significant difference between LDL levels between exercise and control groups. However, it was lower in the training group (19.6  $\pm$  0.4) than in the control group + metformin (20  $\pm$  0.44), indicating the efficacy of HIIT than taking the drug in reducing the amount LDL. Lipid disorders are very common in patients with T2DM. Increasing LDL and decreasing HDL leads to increased cardiovascular disease in these patients (28). One of the most common forms of dyslipidemia in people with T2DM is high TG and HDL reduction (29). Many studies have also shown that increased TG, LDL and HDL reduction are the most important risk factors for cardiovascular disease (30). As shown, an approximately 5% reduction in LDL levels is clinically important. For example, 1% reductions in LDL lead to a 1.7 % reduction in the risk of coronary artery disease. In this study, exercise did not reduce LDL, but it is possible that by modifying the intensity and duration of exercise, it can reduce the amount of it and prevent cardiovascular disease. According to the data in Table 2, cholesterol levels in training

diabetic groups ( $58.4 \pm 2.9$ ) and training diabetic + metformin ( $58.6 \pm 1.3$ ) were lower than that of the diabetic group ( $6 \pm 5.3 / 60$ ) but was not significant. These findings are consistent with the results of the study by Marwick et al. (31) and Dunstan et al. (32), which showed that a period of training reduces total cholesterol in patients with T2DM. A study showed that aerobic exercise reduced total cholesterol in diabetic patients (27), which was consistent with the results of this study. Reducing cholesterol is probably due to increased reverse transmission of cholesterol and conversion to HDL, which can prevent cardiovascular disease. Reverse transfusion leads to the accumulation of excess cholesterol from peripheral tissues, including arterial wall macrophages, and their return to the liver for metabolism, with the re-development of immature HDL, which can prevent atherosclerosis (33). Researchers find that the main mechanism of reducing plasma TG, total cholesterol and LDL concentrations after exercise is due to increase the amount of lipoprotein lipase (LPL) enzymes and reduce TG lipase enzyme (34). The LPL enzyme is one of the most important enzymes in the process of regulating the metabolism of TG and lipoproteins, often found in adipose tissue and skeletal muscle (19). In the present study, increased LPL activity may be due to increased muscle activity followed by increased demand for free fatty acids as a substrate for energy production. As a result of this, the cholesterol withdrawal increases, followed by a decrease in TG and total cholesterol and its plasma level decreases. This study showed that HbA<sub>1c</sub> levels were significantly lower in the training groups ( $3.48 \pm 0.4$ ) than in the control group ( $6.5 \pm 0.58$ ) and diabetic + drug consuming ( $4.8 \pm 0.24$ ). This result was not consistent with the Ghiasi et al investigation that shown eight weeks of aerobic training had a significant effect on glycosylated hemoglobin in diabetic women

(13). A more effective exercise in reducing the amount of HbA<sub>1c</sub> compared with merely using metformin can be considered as a significant advantage. The results of this study showed that eight weeks of high interval training lead to a significant decrease in blood plasma glucose. The results of this study were consistent with the preview research by Amitas et al (35,36). Sports activities increase the number of glucose carriers and, as a result, increase the entrance of sugars into muscle cells and the consumption of sugars (8). Sports activities have an insulin-like effect and send a lot of glucose into the cell to spend on energy production. In this study, blood glucose levels in the diabetic group were significantly lower than that of the diabetic control group and diabetic + metformin which suggested that intense activity may be a good alternative instead of medication to reduce glucose in diabetic rats.

## Conclusions

In general, the findings of this study showed that HIIT can reduce blood glucose, TG, cholesterol and HbA<sub>1c</sub> in T2DM patients. Similarly, the decrease in TG, glucose and HbA<sub>1c</sub> levels in these patients was more severe after HIIT than metformin consuming alone. Therefore, HIIT can be considered as an important strategy for improving lipid profiles, controlling blood glucose levels in T2DM. It can be considered as an effective interventionist approach. However, further studies are needed to clarify other mechanisms involved.

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