

## Type of Aerobic Training Effect on Cardiac Muscles MIR29A and Collagen I Gene Expression in Diabetic Male Rats

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### Abstract

**Objective:** High intensity interval training (HIIT) and continues aerobic training have cardio-protective effects in diabetic rats. The aim of this study was to compare the effect of HIIT and continues aerobic training (CAT) on MIR29A and collagen I gene expression in heart of diabetic male rats.

**Materials and Methods:** In this randomized controlled clinical trial, 18 male diabetic rats were studied. They were divided into 3 groups as HIIT, CAT and control group. Exercise protocol was performed 5 days/week for 5 weeks. The MIR29A and collagen I synthesis were compared between the groups.

**Results:** Findings showed MIR29A expression is statistically higher in HIIT and CAT group than control group ( $P$ -value<0.001) and ( $P$ -value:0.053). Also MIR29A expression is significantly higher in HIIT group compared to CAT group ( $P$ -value:0.034). Collagen I expression was significantly lower in HIIT and CAT group compared to control group ( $P$ -value<0.001) and ( $P$ -value:0.001). Collagen I expression was lower in HIIT group compared to CAT group ( $P$ -value:0.027).

**Discussion:** The results of this study demonstrated that, HIIT increases MIR29A expression which is along with reduction in collagen I synthesis in cardiac muscles increases the risk of myocardial fibrosis in diabetic rats.

**Keywords:** High intensity interval training, Continues aerobic training, Diabetic rats, MIR29A, Collagen I

## Introduction

Diabetes is a very common disease in all countries and about a third of United States adults are pre diabetic (1). Exercise can reduce the blood glucose levels and leads to prevent the progression of diabetes (2). Regan and coworkers (3) showed that patients with diabetes may exhibit extensive perivascular, interstitial, and even

replacement fibrosis in the absence of hypertension or coronary artery disease. The Framingham study (4) demonstrated that a 2-fold higher risk of heart failure in male diabetics and a 5-fold increase of risk in female patients with diabetes. Further animal models of diabetes provide strong support to the association between diabetes and

myocardial fibrosis. It was also found that high intensity interval training (HIIT), leading to improvements in various measures of heart and metabolic health (5).

On the other hand, it is well known that physical activity plays important role in the prevention of type 2 diabetes and cardiovascular disease in individuals with pre-diabetes (6). HIIT is a time efficient and effective exercise for improving cardiac health especially in diabetic patients (5,7). One study showed that a majority of inactive adults because of chronic disease such as diabetes prefer HIIT to moderate continuous training (8).

The molecular basis responsible for cardiac fibrosis in diabetes remains poorly understood (9) the MIRs play important rule in cardiovascular disease [10]. The MIR29As inhibit numerous MIRs which involved in extracellular matrix (ECM) production and fibrosis. Also MIR29As affect cardiac fibrosis through the regulation of collagens (11). One study showed the MIR29A was negatively regulated collagen IV and reduction of MIR29A caused by high glucose level in serum may lead to increase of collagen deposition in proximal tubule of kidney (12)

MIR29A has a key role in physiologic cardiac hypertrophy accompanied by exercise (13). Studies showed different effects of exercise on MIR29A expression. Haram et al. (14) showed HIIT decrease coronary artery disease more than moderate exercise. The results of other studies showed improvement of cardiac function in heart failure and hypertensive patients after HIIT (15).

There are no pharmacologic strategies to inhibit and reverse fibrosis and prevention of heart failure in diabetics. In this study we compared the effect of HIIT and CAT on MIR29A gene and collagen I expression in heart tissue of diabetic male rats.

## Materials and Methods

In this study, 18 mature male Albino Wistar rats were purchased from the Pasteur Institute of Iran (Tehran, Iran), and housed individually

under standard laboratory conditions (temperature:  $22 \pm 2$  °C, humidity:  $50 \pm 10\%$ , 12-h light–12-h dark cycle), with the same nutrition, maintenance weight ( $260 \pm 10$  gr) . They were made diabetic by 50 mg/kg Streptozotocin solution in citrate buffer by intraperitoneal injection. One week after injection, exercises were started by 5 sessions from low to normal speed. Then rats were divided into 3 groups randomly.

1. Control group: The control group (6 rats) did not participate in any exercise program, but to create the same environmental conditions five times a week they were immobilized on a treadmill for 10 to 15 minutes per session.

2. HIIT group (6 rats): Each session consisted of 25 minutes of running on a treadmill by HIIT protocol that implemented by Jung et al (16). The protocol consisted of: Warm up for five minutes with an intensity of 30-40% of VO<sub>2</sub>max then four times intervals (three minutes 85 to 90 percent VO<sub>2</sub>max intensity and one minute recovery with 30 to 35 percent of VO<sub>2</sub>max intensity between intervals), then five-minute cool-down with an intensity of 30-40% of VO<sub>2</sub>max (17).

3. CAT group (6 rats): Each session included 40 minutes of continuous aerobic exercise program running on a treadmill that consist of: five-minute warm-up with 30 to 40 percent of VO<sub>2</sub>max then 30 minutes running with 60- 65% VO<sub>2</sub>max and five-minute cool-down with 30 to 40 percent of VO<sub>2</sub>max.

## Procedures

Twenty four hours after the last training session, after an overnight fasting, rats were anesthetized by intraperitoneal injection of ketamine (90 mg/ kg) and xylazine (10 mg / kg). Then blood samples were collected, direct from the hearts of rats and serum was isolated by centrifugation at 3000 g, 10 C, for 4 min, and Left ventricular heart tissue was removed, freeze in liquid nitrogen and stored for later analysis immediately after washing in saline. cDNA synthesis was performed by 1µg of

RNA using random hexamer primers and full reverse transcriptase enzyme. All materials used in the synthesis of cDNA were obtained from the Roche Company. In this study, qRT-PCR technique was used for gene expression assessment of MIR29A and collagen I expression. The melting curve was given as follow.

### Statistical analysis

In statistical analyzing the mean, standard deviation (SD) and frequency were performed. Also one way analysis of variance (ANOVA) was used for comparing data between three groups. Data analyzed using statistical software PASW V.22 and  $P$ -value $<0.05$  was considered statistically significant.

This study confirmed by animal ethics committee of Tehran University (EC-00312).

### Results

In this study, 18 diabetic rats in three groups were studied for the gene expression of MIR29A and collagen I. Table 1 shows the mean weight and serum glucose of rats in three different groups.

Figure 1 shows, the mean fold changes of MIR29A expression in HIIT group versus control group was 2.67 ( $\pm 1.02$ ) ( $P$ -value $<0.001$ ). CAT affected the MIR29A expression compared to controlled group ( $P$ -value:0.053). The mean fold changes of MIR29A expression in HIIT group versus CAT group was 1.79 ( $\pm 0.49$ ) ( $P$ -value:0.034).

Figure 2 shows, one way ANOVA showed that collagen I expression was significantly lower in HIIT and CAT group compared to control group ( $P$ -value $<0.001$ ) and ( $P$ -value $<0.001$ ). One way ANOVA showed that collagen I expression was lower in HIIT group compared to CAT group ( $P$ -value:0.027).

### Discussion

MIR29A are non-coding RNAs which prohibit translation of messenger RNAs into functional

proteins and down regulate gene expression (18).

Many studies demonstrated that MIR29s are key elements of different physiological or pathological processes (19-22). Some of these MIRs are elevated by coronary disease, (23) myocardial infarction (24) and heart failure (25). MIR29A are regulated during cardiac hypertrophy (26).

MIR29A is produced mostly by fibroblasts, and its family members are key regulators of fibrosis (11,27). In addition, this MIR was found to be a key player in liver (28), pulmonary (29), and kidney fibrosis (30) and in systemic sclerosis (11). Moreover, MIR29A was upregulated along with MIR29C in an animal model of physiological cardiac adaptation to exercise training (31)

Soci et al. showed a correlation between MIR29A and physiological cardiac hypertrophy compared to control group (31). It has been demonstrated that MIR29A family target gene transcripts that encode some proteins involved in fibrotic responses, including different collagen type formation. (10)

These MIRs are involved in virtually all cellular responses. New evidence suggested a critical role for MIR29A in cardiac fibrosis (32).

The severity of cardiac fibrosis and left ventricular dysfunction in experimental models of diabetes is dependent on the species, genetic background, gender and age of the animals studied, the etiology of diabetes and the presence of concomitant pathophysiologic conditions (such as hypertension, dyslipidemia, etc.) (33).

In both mice and rats, Streptozotocin-induced diabetes is associated with interstitial myocardial fibrosis, accompanied by cardiomyocyte hypertrophy, induction of pro-fibrotic and hypertrophy associated genes, and microvascular rarefaction (34).

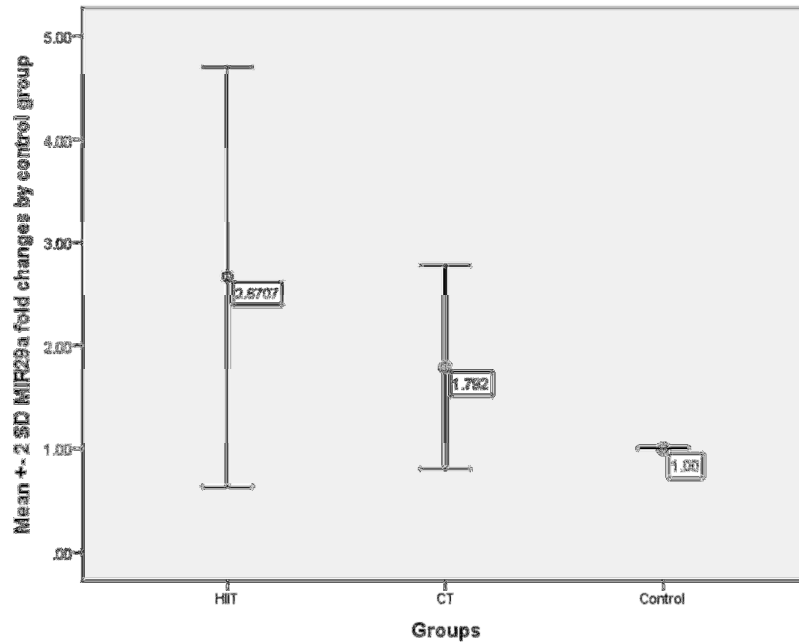


Figure 1. Comparing MIR29A between groups

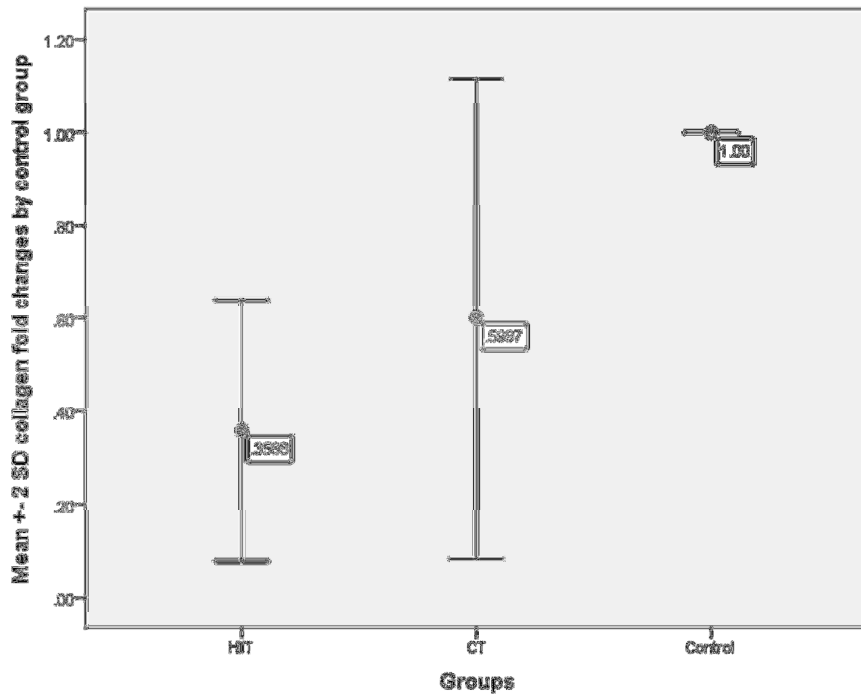


Figure 2. Comparing collagen I between groups

One study shows that fibrosis is the leading cause of organ dysfunction in diseases and results from an imbalance in the turnover of extracellular matrix components. Accumulating studies have also demonstrated that MIR29 family participates in the

**Table 1. Weight and serum glucose in studied groups**

| Variable                      | HIIT             | CT               | C                 |
|-------------------------------|------------------|------------------|-------------------|
| Weight (gr) mean $\pm$ SD     | 276.4 $\pm$ 16.5 | 250.1 $\pm$ 13.1 | 238.17 $\pm$ 17.9 |
| Glucose (mg/dl) mean $\pm$ SD | 502.8 $\pm$ 10.2 | 518.4 $\pm$ 13.4 | 577.6 $\pm$ 11.5  |

development of liver, renal, pulmonary and cardiac fibrosis. Considering the potentially critical involvement of high glucose in the pathogenesis of fibrosis, it would be reasonable to hypothesize that tight glycemic control may be effective in attenuation of cardiac fibrosis. Although poor glycemic control is associated with an increased incidence of heart failure (35), intensive glucose lowering failed to reduce cardiovascular events (36), the risk of heart failure (37) and the incidence of new-onset atrial fibrillation (38).

Collagen fibers are one of the key elements in the remodeling process, since these proteins are the main loadbearing component of many soft tissues. In particular, collagen fiber orientation and bundle formation through cross-linking (39) play a significant role in valvular tissue mechanics. As a consequence, the architecture of the collagen network has a major influence on the mechanical functionality of soft tissues, as well as on mechanically induced growth and remodeling processes. Therefore, a deeper knowledge of collagen remodeling will greatly benefit our understanding of healthy tissue development as well as pathological adaptations such as seen during fibrosis, aneurysm formation (40) and wound healing (41).

American College of Sports Medicine recommended that healthy adults participate in moderate to vigorous intensity activities with the minimum goal of 450 to 750 MET-minutes weekly to promote and maintain health (42).

The benefits of exercise for overall health are incontrovertible. As such physical activity has favorable effects on hypertension (43) and insulin resistance (44). Namely, it is associated with reduction of adiposity and improvement of several metabolic risk factors including hypertriglyceridemia, low high density lipoprotein-cholesterol, hyperinsulinemia and

elevated homeostasis model assessment insulin resistance index (HOMA-IR) (45). These health benefits are evident at moderate level of fitness, such as brisk walk for 20-40 min most of week days for middle age and older individuals (46).

One study stated that HIIT leads to improvements in various markers of cardio metabolic health but adherence to HIIT following a supervised laboratory intervention has yet to be tested. Studied shows that HIIT makes more cardio metabolic adaptation compared to continuous training (46).

In this study we compared the effect of HIIT and CAT in MIR29A expression and collagen synthesis. Results of this study showed that HIIT group has more MIR29A expression compared to control and CAT group. Exercise leads to MIR29A expression and more MIR29A expression inhibits fibrosis of cardiac muscles. In HIIT group more expression of MIR29A was along with less collagen compared expression with CAT and control group. Collagen I in cardiac muscle leads to fibrosis and cardiac damage.

One study showed that MIR29A regulates proinflammatory cytokines secretion by effecting on lipoprotein lipase receptor (47) their finding suggested the effect of MIR29A on preventing of atherosclerosis. Overexpression of MIR29 in atrial fibroblasts decreased expression of collagen and fibronectin, and down regulation of MIR29 increased collagen and fibronectin gene expression (48).

Jung et al showed that HIIT is more effective and accepted compared to moderate intensive continuous training for prediabetic adults (49). Other study showed, insulin levels can regulates the MIR29 expression, and reduce insulin levels leads to cardiac structural damage in diabetic patients (49). Drigney et al showed that HIIT effects on ventricular

repolarization indices, and HIIT might be associated with greater improvements in certain cardio-metabolic risk factors compared to moderate intensity continuous exercise. (50) Adaptations to HIIT occur with less exercise time commitment than traditional exercise guidelines (51).

The results of this study demonstrate, HIIT increases MIR29A expression which is along with reduction in collagen I synthesis in cardiac muscles which may reduce the risk of myocardial fibrosis in diabetic rats. HIIT is better compatible for diabetic rats other than CAT and it have better effects on cardiac function. Further studies can compare the HIIT

and CAT in human for use of this method in diabetic patients for better cardiac function and inhibit the diabetic cardiomyopathy and fibrosis.

## Conclusions

HIIT is well tolerated exercise and is effective in MIR29A expression and by the results of this study MIR29A expression influence the collagen I expression which is a key factor in cardiac fibrosis. So HIIT particularly in diabetics can be a modality for lowering the risk of cardiac fibrosis.

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