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Interactive Effects of Swimming Training and Cinnamon Supplementation on Changing Cardiac miR-133a and miR-21 in the Streptozotocin-Induced Diabetic Rats

Marzieh Fazel Najafabadi[1], Saeed Keshavarz[1*], Seyed Ali Hosseini[2], Elham Eftekhari[1]

1. Department of Sports Sciences and Sport Medicine Research Center, Najafabad Branch, Islamic Azad University, Najafabad, Iran.
2. Department of Sport Physiology, Marvdasht Branch, Islamic Azad University, Marvdasht, Iran.

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ABSTRACT

Introduction: This study aimed to review the synergistic effects of swimming training (ST) and cinnamon supplementation (Cin) on changing cardiac miR-133a and miR-21 in streptozotocin-induced diabetic rats.

Methods: A total of 32 diabetic rats were selected as 1) ST+ Cin, 2) Cin, 3) ST and 4) diabetic control (DC) groups, and eight healthy rats were selected as the HC group. Groups 1 and 3 swam three sessions per week and 2-22 minutes each session for eight weeks. Groups 1 and 2 received 200mg/kg/day of aqueous Cin extract. qReal Time PCR method was used to measure the miR-21 and miR-133a gene expression in heart tissue.

Results: MiR-133a and miR-21 gene expression in Cin, ST, and ST+Cin groups increased compared to the DC group (P=0.001), and miR-133a gene expression in the ST+Cin group enhanced compared to Cin and ST groups (P=0.001). MiR-21 gene expression in ST and ST+Cin groups increased compared to the Cin group. In addition, miR-21 gene expression in the ST+Cin group raised compared to the ST group (P=0.001).

Conclusion: Although exercises lead to cardiac adaptations by creating oxidative stress, cinnamon can increase miR-133a as a cardio-protective agent and modulate miR-21 as a marker of cardiac damage. Therefore, cinnamon should be used along with exercises in cases of diabetes and heart disease.

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Introduction

Studies have shown that a large number of people around the world are suffering from diseases such as diabetes, heart diseases and kidney diseases. These diseases, either alone or in combination, are effective in causing severe disorders in people's lives and increasing mortality (1). Researchers estimate that people with diabetes have a greater risk of dying from heart disease than people without diabetes, which is one of the biggest problems facing human society (2). From the pathological point of view, cardiac disorders caused by diabetes can lead to the fibrosis of cardiac smooth muscle and myocardial muscle, causing heart attack due to glucose toxicity and lipid toxicity and increasing inflammatory factors (3).

The dysfunction of molecules in response to sugar disorders is one of the causes of onsetting heart diseases induced by diabetes, in which microRNAs (miRNAs) play an essential role (4,5). Although these non-coding RNAs are not coded in DNA for metabolic actions, they can potentially make crucial changes in heart metabolism. Meanwhile, non-coding RNAs, miR-21, miR-1 and miR-133, are related to heart and glycemic disorders (6). MiR-21 and miR-133 increase following the increase of free radicals in the heart tissue and significantly affect the transcription process of genes that induce apoptosis, fibrosis, and heart attack (7). Although many studies have been conducted concerning the treatment and prevention methods of heart disease in people with diabetes, there is still limited information on these molecular pathways.

Considering the effect of lifestyle on heart health, it has been reported that long-term training with the mechanism of improving sugar metabolism,

* *Corresponding author:* Saeed Keshavarz, Department of Sports Sciences and Sport Medicine Research Center, Najafabad Branch, Islamic Azad University, Najafabad, Iran, Tel: +983142646526, Email: keshavarz1357@gmail.com.

insulin and fat metabolism can effectively control diabetes (8). Researchers believe regular exercise, such as swimming, can decrease diabetes induction by increasing fat tissue lipolysis, mitochondrial biogenesis, and rising sugar fuel in the cell from non-insulin-dependent pathways (9). In other words, single-session exercise training is one of the pillars of adaptation. Based on studies, this training session is considered a factor for increased oxidative stress and can increase miR-133b, miR-133a, and miR-21 levels (10). However, exercise increases resistance to oxidative stress and microRNAs in the body, and physiological hypertrophy, angiogenesis and mitochondrial biogenesis also occur (11). However, detailed information is unavailable on the fluctuation of miR-133 and miR-21 after sports activities. Fathi *et al.* found that cardiac miR-1 and miR-133 gene expression increased following 14 weeks of endurance exercise (12).

Nevertheless, there was a decrease in miR-133 gene expression in the flexor muscles of the fingers, while there was an increase in miR-133 gene expression in the soleus muscles after 14 weeks of endurance training (13). The consumption of medicinal plants in conjunction with exercises for diabetic patients has caught the attention of researchers. In other words, using medicinal plants with anti-inflammatory and antioxidant properties positively impacts metabolic and heart diseases (14–16).

As a herbal medicine, cinnamon (Cin) is famous for its ability to treat and prevent some diseases. This medicinal plant has the effects of neutralizing free radicals, reducing inflammation, and improving cardiovascular function with anti-diabetic and anti-obesity properties. In addition, researchers have pointed out that cinnamon can enhance the gene expression of miRNAs involved in insulin resistance in visceral fat tissue (17). According to a study, the Isoflavones present in cinnamon can improve free radicals due to their antioxidant capacity. Cinnamon activates the sirtuins pathway by activating deacetylases, which raise the transcription of biological genes, and mitochondrial biogenesis decreases apoptosis and inflammation and necrosis in heart tissue (18). In addition, cinnamaldehyde, as an active ingredient of cinnamon, improves micro-molecules and siRNA is involved in inflammatory factors (19). Despite the anti-inflammatory and antioxidant impacts of cinnamon, the effects of Cin on microRNAs involved in cardiovascular disease are unknown. In addition, using an antioxidant, physical activities, and reviewing two microRNAs in heart tissue vital in preventing and promoting myocardial damage can provide new insights into exercise nutrition. Although numerous studies have been conducted, researchers have not yet found a safe and effective method of preventing heart disease among people with diabetes. Researchers can consider the related pathways in subsequent studies by conducting studies that review the impact of therapeutic interventions on microRNAs. According to the above sentences, this research examined the effects of Cin with swimming training (ST) on miRNA-133a and miR-21 in the heart tissue of rats with diabetes.

Methods

This experimental study was conducted on 40 rats (8 weeks old), purchased and transferred to the exercise physiology lab of the Marvdasht Branch of Islamic Azad University. All rats were kept in standard conditions (22-24°C, 55% relative humidity, and 12/12 hours light-dark cycle). Sterile grated soil was used to absorb animal urine, and animal bedding was cleaned every two days. All ethical procedure of the present study was based on the ethics guidelines of the ethics committee of the Najafabad branch of Islamic Azad University with approved code IR.IAU.NAJAFABAD.REC.1401.084**.** After one week, 32 rats received 55mg/kg streptozotocin (Sigma, USA) intra- peritoneally and according to their fasting blood glucose, divided into 1) ST+ Cin, 2) Cin, 3) ST and 4) diabetic control (DC) groups. Eight healthy rats were selected as the healthy control (HC) group to review the effects of diabetes induction on miR-133a and miR-21.

Swimming Training Protocol

First, rats' ability to swim was investigated in a particular pool. Rats swam 2min daily in the pool for one week to familiarize themselves with the water environment. Then they performed swimming training in water at 36 ± 2°C. The current research protocol was based on Lubkowaska *et al.* (2019). The first week of training lasted for 5min, and 2min were added to each week of training until the exercise lasted 22min in the eighth week, as dictated by the rats' ability. During eight weeks, rats swam five

sessions weekly in a swimming tank (50cm depth, 50cm width, and 100cm length) (20,21).

Cinnamon Consumption

According to Ismail (2014), Cin extract was added to animals' drinking water. Five rats were drinking water containing 200mg/kg Cin in each cage (22).

Sampling

Xylazine and ketamine were injected intra-peritoneally into all rats after a 12-hour fast to measure the effect of Cin and ST. Tests of pain reflexes and touching the tail or belly of rats were conducted to ensure complete anesthesia. Experts carefully removed the heart tissue from the rats' chests after administering anesthesia. The tissue was weighed and cleaned, then placed in a cryotube and immediately stored at -70°C to preserve it.

Measuring miRNA-133a and miR-21

MiRNA-133a and miR-21 were measured with the qReal Time PCR method. First, 50mg of the heart tissue was separated for RNA extraction, and then RNA extraction was performed based on the manufacturer's protocol (Qiagen, Germany). Table 1 shows the primer sequences for miR-133a and miR-2.

Table 1. The sequence of primers of miR-133a and miR-21

	Forward	Reverse
U6	*CTCGCTTCGGCAGCACA*	*AACGCTTCACGAATTTGCGT*
miR-133a	*ATAAGAATGCGGCCGCATTCCAAACTAGCAGCACTA*	*AGCTTTGTTTAAACTTAACCATTCTAGCTTTTCC*
miR-21	*GCCGCGTAGCTTATCAGACT*	*CTCAACTGGTGTCGTGGA*

Statistical analysis tests

The normal distribution of data was measured with the Shapiro-Wilk test. One-way ANOVA and Tukey's posthoc tests were used to review the effect of Cin and ST on miR-133a and miR-21 using GraphPad Prism 8.3.3 after ensuring the normality of the data distribution (P≤0.05).

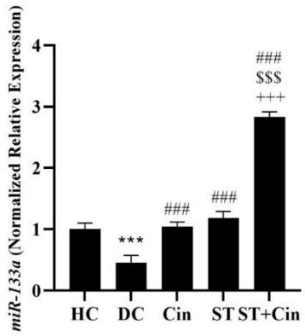

Figure 1. Gene expression of miR-133a
*** (P=0.001) significant decrease rather than HC group
(P=0.001) significant increase rather than HC group
$$$(P=0.001) significant increase rather than Cin group
+++(P=0.001) significant increase rather than Cin group

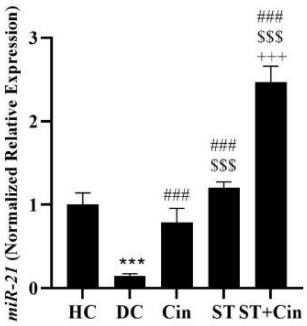

Figure 2. Gene expression of miR-21
***(P=0.001) significant reduction rather than HC group
###(P=0.001) significant rise rather than DC group
$$$(P=0.001) significant rise rather than Cin group
+++(P=0.001) significant rise rather than ST group

Results

According to the one-way ANOVA test results, miR-133a (P=0.001 and F=526.41) and miR-21 (P=0.001 and F=240.72) gene expression significantly differed in the research groups. Tukey's *post hoc* test revealed that miR-133a in the DC group significantly decreased compared to the HC group (P=0.001). However, miR-133a increased in the Cin (P=0.001), ST (P=0.001), and ST+Cin (P=0.001) groups compared to the DC group and raised in the ST+Cin group compared to Cin (P=0.001) and ST (P=0.001) groups (Figure 1).

MiR-21 in the DC group decreased compared to the HC group (P=0.001) but increased in the Cin (P=0.001), ST (P=0.001), and ST+Cin (P=0.001) groups compared to the DC group, raised in the ST (P=0.001) and ST+Cin (P=0.001) groups rather than Cin group, and finally increased in ST+Cin group rather than ST group (P=0.001).

Discussion

In this study, miR-133a and miR-21 gene expression decreased following diabetes induction. Nevertheless, miR-133a and miR-21 gene expression increased following swimming training. According to studies, miR-133 is expressed only in cardiac muscle and causes the differentiation of mesodermal cells into muscle progenitor cells of the heart and cardiomyocytes. In addition, miR-133 can inhibit oxidative stress, affect apoptosis, and protect the heart (23). On the other hand, miR-21 is known as an essential factor in the diagnosis of heart disease. However, conflicting results were reported regarding the levels of this indicator in heart diseases. Researchers believe that oxidative stress in the heart tissue can raise miR-21 gene expression, activating the protective signaling pathway of cardiomyocytes against apoptosis. However, the excessive increase of oxidative stress activates cardiac fibroblasts into myofibroblasts, leading to myocardial fibrosis (7).

On the other hand, sports training increases the cell's energy demand, which is associated with a change in the body's homeostasis. In addition, researchers have shown that sports activities can initiate the pathways of angiogenesis, mitochondrial biogenesis, and myocardial muscle hypertrophy by creating adaptation to oxidative stress in response to training. The role of miRNAs is also significant in these pathways, such that miR-206, miR-133a and miR-1 are related to a rise in mitochondrial biogenesis, and the angiogenesis pathway is programmed with HIF1-α signaling of miR-210 (24). According to the abovementioned mechanisms, training raises miR-133a and modulates miR-21 by modulating intracellular redox. As a confirmation of the present study, single-session exercise training has been shown to increase miR-21 and decrease miR-20a in healthy older men (10). As a result, the intensity and type of training are critical elements in the changes in microRNAs. In addition, miR-133b, miR-133a, and miR-1 levels increased following an acute training session (25). The decrease in the expression of proteins responsible for mitochondrial biogenesis was associated with low levels of miR-133a, and exercise training increased the expression of miR-133a and improved mitochondrial biogenesis (26). In Rezaei *et al.*, 100 days of exercise was associated with increased cardiac miR-133a expression (12). While according to Baggish *et al.,* miR-21 levels decrease after long-term exercise (27).

Meanwhile, miR-21 expression increased in response to acute and chronic training (28). Most of these studies have examined circulating values in human subjects. In Habibi *et al.,* swimming training could norm and increase miR-133a gene expression in the cardiac muscle of ovariectomized and diabetic rats. Further, the increase in the expression of this microRNA was related to the inhibition of myocardial apoptotic markers (29). According to published studies, the function and changes of some microRNAs are different in different tissues and even in the blood. Therefore, exercise with dual effects (increasing stress and creating cardiac adaptation) can increase the protective microRNAs such as miR-133a. At the same time, each training session can lead to a rise in microRNAs indicating cellular damage like miR-21 (29). Therefore, the present study is consistent with most of the studies conducted about miR-133, while regarding miR-21, the results are generally contradictory, and the reasons for the inconsistency can be attributed to the effect of duration, type, and intensity of training as well as the baseline levels of miR as a redox regulator.

In this research, Cin consumption significantly increased miR-133a and miR-21 gene

expression. According to the studies, Cin consists of isoflavones, flavonoids, and cinnamaldehyde, which have potent antioxidant effects. Cin can improve lipid profile, lipolysis, and heart damage indicators such as creatine kinase and troponin T in the heart tissue. In this regard, researchers believe this happens after consuming cinnamon by reducing lipid oxidation and MDA, as well as increasing antioxidants. Cin activates the nuclear transcription factor cAMP-activated protein kinase (AMPK), leads to mitochondrial biogenesis and inhibits oxidative and inflammatory factors from the TGF-β/Smad pathway (30). According to Naghiaee *et al.,* cinnamon extract modulated miR26b, miR29a, and miR233 levels in adipose tissue insulin resistance, and this study demonstrated cinnamon's regulatory role in microRNA-dependent insulin metabolism (31). In another study, the same researchers examined cinnamon with metformin and their effect on miR-320 and miR-26b in the insulin resistance pathway of adipose tissue. Based on this study, cinnamaldehyde, like metformin, decreased miR-320, increased miR-26b, and improved glucose metabolism in the fat tissue (17,31). Qu *et al.* also showed that cinnamaldehyde consumption significantly decreased miR-155 and miR-21 gene expression and inhibited apoptosis (32). Therefore, these researchers stated that cinnamaldehyde could increase the interleukin one beta by inhibiting AKT, mTOR, and cyclooxygenase-2 (COX-2) phosphorylation inhibitor via inhibiting reactive oxygen species, miR-21 and miR-155. Finally, this pathway prevents inflammation and apoptosis (32). Meanwhile, studies have shown that miR-21 is an essential factor for activating macrophages, which has a suitable biological function in reconstructing the ischemic heart muscle (7). Therefore, the increase of miR-21 following Cin and equal level compared to the HC group indicates the adjustment and normalization of its expression.

In addition, the present study showed that Cin and ST significantly increased miR-133a and miR-21 gene expression. Further training seems to challenge the oxidative system, and this response to sports activities leads to adaptation due to exercise (24). However, these two variables can regulate the cellular redox and microRNAs through similar pathways, such as increasing lipolysis, improving fat profile, and improving mitochondrial biogenesis (13,30). Researchers have found that exercise and Cin consumption enhance lipid profiles and increase antioxidant levels (33). In addition, the combination of training and Cin consumption improved the activity of catalase, glutathione peroxidase, and superoxide dismutase cardiac muscle (34). Reviewing the data shows that performing exercise is a challenge in cardiac function that may have oxidative effects or favorable adaptations, which can increase the expression of miR-133a as an inhibitor of apoptosis. At the same time, good adaptations (via oxidative stress) can increase the miR-21 as a promoter of apoptosis.

Meanwhile, cinnamon and increasing miR-133a can lead to the modulation of miR-21 expression in heart tissue for cardiac muscle regeneration. Sufficient information about ST and Cin is one of the limitations of the present research. Therefore, it is suggested to conduct more studies in this field. Furthermore, another limitation of the present study is the need to evaluate the pathways under apoptosis or cardiac protection. Therefore, measuring other functional indicators besides miR-21 in the following studies is suggested.

Conclusion

Based on the results, Cin and ST alone and together improve miR-133a gene expression. However, more studies are needed due to the nature of miR-21 and conflicting results related to this microRNA. In addition, Cin antioxidants can be recommended with caution in addition to exercises for diabetes and the risk of heart disease.

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