2023. *Journal of Exercise & Organ Cross Talk*. 2023; 3 (4): 208-215. doi: 10.22122/jeoct.2023.419208.1096

Research Article

The effect of aerobic and resistance exercise on sugar indicators and FGF21 in cardiac tissue of diabetic rat

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Abstract

Training is one of the most effective therapy options for improving the control of type 2 diabetes. FGF21 (fibroblast growth factor) has been identified as a novel metabolic regulating factor with substantial anti-diabetic effects in animal models and humans. The goal of this study was to investigate how four weeks of aerobic and resistance exercise affected fasting blood glucose (FBS) and fibroblast growth factor 21 (FGF21) levels in the cardiac tissue of male Wistar rats with diabetes. In this study, 24 male Wistar rats aged 10 to 12 weeks and weighing 200250 grams were made diabetic with STZ and separated into three groups: diabetes + aerobic exercise (n=6), diabetes + resistance training (n=6), and sham (n=6) and healthy (n=6) were divided. The training lasted four weeks, with the aerobic group working out five days per week and the resistance group working out six days per week. Blood samples and cardiac tissue were collected for analysis before and after 48 hours of the previous exercise and 12 hours of fasting. To conduct statistical analysis, the SPSS version 26 program was employed. We saw an increase in FGF21 in the training groups compared to the sham group, which was significant in the resistance training group (p=0.008) and also in the healthy group (p=0.02). The results showed that resistance trainings can have a bigger influence on sugar indicators and anti-diabetic cardiac factors like FGF21, and will play an effective role in minimizing the consequences of diabetes.

Key Words: **Diabetes, FGF21, Aerobic training, Resistance training, Heart tissue**

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Received 8 October 2023; Accepted 19 December 2023

Introduction

Diabetes is undoubtedly one of the biggest health concerns facing the globe today. It is one of the most prevalent non-communicable diseases and the fourth leading cause of mortality in the majority of high-income countries (Reynolds et al., 2018). Reports indicate that 415 million individuals worldwide had diabetes in 2015, and that number will rise to 642 million by 2040 (Cho et al., 2018). Cardiovascular disease, one of the leading causes of death in these people, is a complication of this diseases (Ernande & Derumeaux, 2012). Diabetes-related oxidative stress, which induces necrosis, apoptosis, and fibrosis in the myocardium and disrupts systolic-diastolic function, is a major factor in heart failure in diabetic patients.

Fibroblast growth factor 21 is a hormone that plays an important role in glucose homeostasis and metabolic regulation (Kim et al., 2023). It is expressed in several metabolically active tissues such as liver, adipocytes, pancreas, brain, skeletal muscle, brown fat, and heart (Kim et al., 2023; Lin et al., 2021; Luo et al., 2023; Tezze et al., 2019). FGF21 is involved in regulating cardiac function and has been shown to protect against pathologic cardiac hypertrophy, oxidative stress, and heart attack (Bo et al., 2021; Planavila et al., 2015; Tezze et al., 2019). One of the mechanisms by which exercise exerts its effects is through the release of myokines, which are cytokines produced by skeletal muscle fibers. Fibroblast growth factor 21 (FGF-21) is a myokine that has been shown to play a role in the crosstalk between muscle, liver, and heart during exercise. In this review, we will examine the current literature on the effect of exercise on FGF-21 crosstalk between muscle, liver, and heart.

Exercise has been shown to increase FGF21 levels in the circulation, liver, skeletal muscle, and heart (Kim et al., 2023; Lin et al., 2021; Luo et al., 2023; Porflitt-Rodríguez et al., 2022; Tanimura et al., 2016). Chronic exercise programs have been found to increase FGF21 levels in adipose tissue, liver, and skeletal muscle, while acute exercise has been shown to incre-

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-ase serum FGF21 levels (Lin et al., 2021; Porflitt-Rodríguez et al., 2022; Tanimura et al., 2016). The effect of exercise on FGF21 crosstalk between muscle and liver and heart has been studied in several research articles (Bo et al., 2021; Porflitt-Rodríguez et al., 2022). Endurance exercise training has been found to enhance FGF21 levels in the liver and skeletal muscle, improve exercise capacity, and shift skeletal muscle fiber size distribution. Aerobic exercise has been suggested to improve metabolism during obesity and overweight by increasing FGF21 levels (Porflitt-Rodríguez et al., 2022). Exercise-induced FGF21 has been shown to play a role in aerobic exercise-induced cardio protection of post myocardial infarction mice (Bo et al., 2021). Several studies have investigated the effect of exercise on FGF-21 levels. A systematic review and meta-analysis found that a 5-week endurance exercise program decreased hepatic fat content and serum FGF-21 levels in overweight and obese individuals (Kim et al., 2023). Another study in mice found that endurance exercise increased FGF-21 expression and improved endurance exercise capacity and fiber conversion of skeletal muscle (Luo et al., 2023). These findings suggest that exercise can increase FGF-21 levels and improve metabolic function. A systematic review and meta-analysis of studies investigating the changes in FGF21 levels after exercise found that resistance exercise significantly increased FGF21 levels in the body (Kim et al., 2023). Another study found that acute resistance exercise increased FGF21 levels in healthy adults (Qian et al., 2022). These findings suggest that resistance exercise may have a positive effect on FGF21 levels in the body.

There is evidence to suggest that FGF-21 plays a role in the crosstalk between muscle and liver during exercise. A study in humans found that muscle-derived IL-6 plays a role in triggering glucose output from the liver during exercise. FGF-21 has also been shown to induce browning of white adipose tissue cells, which can improve metabolic function (Severinsen & Pedersen, 2020). These findings suggest that FGF-21 may play a role in the metabolic benefits of exercise. There is also evidence to suggest that FGF-21 plays a role in the crosstalk between muscle and heart during exercise. Follistatin-like 1 (FSTL1) is a myokine produced by both skeletal and cardiac muscle cells that has been shown to positively regulate myocardial substrate metabolism. FGF-21 has also been identified as a hepatokine that is released from the liver during or immediately after an exercise bout (Severinsen & Pedersen, 2020). These findings suggest that FGF-21 may play a role in the metabolic benefits of exercise on the heart.

Few studies have compared these two types of training because of how important different types of training are for diabetes and oxidative stress factors, but recent research and the overall positive impact of training on FGF21 and the existence of a small number of studies on resistance training as well as the absence of comparisons between different types of training on FGF21 and the efficacy of aerobic and resistance training do not support this. Does the ratio of FGF21 in the cardiac tissue and fasting blood (FBS) have a difference from before training, and which of the two trainings is more effective?

Materials and Methods

Animals

In this study, 24 male Wistar rats, average weight 200–250 g, aged 8–12 weeks, were randomly chosen and housed in the animal house of the Shahid Rajaee University's Faculty of Sports Sciences under regular lighting, temperature (18–23 °C), and humidity (50%). 18 of these rats had type 2 diabetes, which allowed them to develop the disease for four weeks while consuming a diet high in fat, with 45% of their total energy coming from fat (produced from animal oil, which has 24 grams of fat, 24 grams of protein, and 41 grams of carbohydrates per 100 grams). By injecting a single dosage of streptozotocin dissolved in sodium citrate buffer with a pH of 4.5 intraperitoneally. A single dose of 30 mg/kg of streptozotocin, dissolved in sodium citrate buffer with a pH of 4.5, was administered intraperitoneally to induce diabetes after 4 weeks. Of the samples, three were in good health.

Exercise training protocol

Every four weeks, an aerobic exercise routine was followed for five days. Before beginning the training, the samples were warmed up for 3 minutes at a pace of 7 m/min, then increased every two minutes to reach the training program of each session (Tanoorsaz et al., 2017). Table 1 shows an aerobic training protocol.

The resistance training regimen was carried out six days a week for four weeks, with the subjects climbing the ladder twice without weights to warm up. After warming up, the training began with three sets of six repetitions, with one-minute pause between each repetition and three minutes' rest between each set. The weight connected to the rats' tails is calculated as a percentage of their body weight (Karimian et al., 2015), which is shown in Table 2.

Table 1. Aerobic training protocol.

Days / Weeks	First Week		Second Week		Third Week		Fourth Week	
	V(m/min)	t (min)	V(m/min)	t (min)	V(m/min)	t (min)	V(m/min)	t (min)
First Day	15	25	16	30	17	35	18	40
Second Day	15	26	16	31	17	36	18	41
Third Day	15	27	16	32	17	37	18	42
Fourth Day	15	28	16	33	17	38	18	43
Fifth Day	15	29	16	34	17	39	18	44

Table 2. Resistance training protocol.

Session	First Set	Second Set	Third Set
First Session	30%	30%	-
Second Session	50%	50%	-
Third Session	50%	50%	50%
Fourth Session	75%	75%	75%
Fifth Session	75%	75%	75%
Sixth Session	75%	75%	75%

In order to check the effectiveness of training, vVO_{2max} tests were used in aerobic training (Boule et al., 2005) and 1RM in resistance training (Davoodi et al., 2018), so that these measurements were taken from the samples before the start of training, two weeks after training and after four weeks.

HOMA-IR

We used the HOMA-IR test (Formula 1) in such a way that four days after the injection, a drop of blood was deposited on the strip of the glucometer gadget (Accu Chek Active) by making a small cut in the rat's tail in order to validate the final diagnosis of diabetes. We administered it, and a glucometer read the strip. Blood glucose levels over 300 mg/dl were seen as a sign of diabetes (Holmes et al., 2015).

$$\text{HOMA-IR}=\frac{Fasting\ insulin\ x\ fasting\ glucose}{22.5}$$

1RM test

The 1RM test was obtained from the resistance training group and the Vvo2max test was taken from the aerobic training group after diabetic rats had been trained for one week and had adapted to the environment. The rats exercised for 3 minutes at a pace of 11 m/min after warming up for 5 minutes at a speed of 6 m/min in preparation for the vVO_{2max} test. If they had the option to continue after three minutes, the speed was increased by five meters per minute. The rats were kept in this task until they became weary, at which point their final speed was recorded (Boule et al., 2005). In order to perform the 1RM test, we considered 30% of the rat's body weight and the weight was attached to the tail of the samples, was added (Davoodi et al., 2018; Molanouri Shamsi et al., 2014).

Laboratory measurements

After four weeks of training, the rats were fasted for 10 to 12 hours before being prepared for dissection by first anesthetizing them with Ketamine (75mg/kg) and Xylazine (10mg/kg), and then blood was collected from the samples' hearts and their hearts were extracted. The tissues were transported to a special kit and subsequently to a -80°C freezer once the heart was removed (Nourbakhsh et al., 2015). ELISA method was used to check glycemic indices and FGF21, the kits used to check glycemic indi--ces were DA-3200 model and the kits used for FGF21 were from Zell Bio with Cat No.: ZB-10034C-R9648.

Statistical analysis

To perform statistical calculations, SPSS version 26 software was used with Shapiro-Wilk test and LSD one-way and post hoc analysis of variance. Also, since the data were normal, Pearson's correlation was used. We used Prism software to draw graphs. A significant value at the level of $p \leq 0.05$ was considered to reject the null hypothesis

Results

The mean and standard deviation of the Lee index for all groups are reported in Table 3.

The mean and standard deviation of the one repetition maximum test and maximum oxygen consumption before and after training are given in Table 4.

Tables 3 and 4 reveals that the training groups have a lower Lee's index than the sham group, and the assessment of 1RM and vVO_{2max} tests before and after training shows that these factors improve and grow after training.

There was a positive correlation between FGF21 and 1RM (rp=0.889), meaning that an increase in 1RM led to an increase in FGF21, and this relationship was significant (P=0.044). There was also a positive correlation between FGF21 and vVO2max (rp=0.908), indicating that an increase in vVO_{2max} resulted in an increase in FGF21, and this relationship was significant (P=0.012).

In the inferential section, one-way analysis of variance and the LSD post hoc test were utilized to validate the research hypotheses.

Figure 1 depicts the hypothesis test of fasting blood sugar level.

Fasting blood sugar levels decreased significantly in the aerobic (p=0.02) and resistance (p=0.04) training groups compared to the sham group, according to figure 1. In the comparison of these two

Table 3. Resistance training protocol.

Groups	Aerobic Training	Resistance Training	Sham	Healthy
Lee Index	0.44 ± 0.12	0.47 ± 0.06	0.50 ± 0.06	0.42 ± 0.03

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Table 4. Mean and standard deviation of the 1RM and vVO_{2max}

Variables	Before Training	After Training
1RM (gr)	51.30 ± 2.26	71.00 ± 9.63
vVO2max (m/min)	20.17 ± 5.84	27.67 ± 5.16

trainings, aerobic training resulted in a greater reduction in blood sugar, but the difference was not shown to be significant in this study.

The result of FGF21 data is shown in Figure 2.

According to the findings, there was an increase in FGF21 in the training groups as compared to the sham group, which was significant in both the resistance training group (p=0.008) and the healthy group (p=0.02). The amount of FGF21 increased more in the resistance group than in the aerobic group when the two trainings were compared, although the difference was not significant.

Discussion

Type 2 diabetes is one of the most common metabolic illnesses of the twentieth century, characterized by an increase in blood glucose and an increase in oxidative stress. It may be important in the etiology of cardiovascular disorders (Mohammadi et al., 2017). According to the findings of this study, aerobic and resistance training can both have a good influence on blood glucose levels, although there was no significant difference between the two trainings. The level of FGF21, on the other hand, increased in both forms of exercise, although this rise was significant only in the resistance group.

FGF21 has also been shown to prevent diabetic cardiomyopathy via AMPK-mediated antioxidation and lipid-lowering effects in the heart (Yang et al., 2018). The study concluded that FGF21 has a protective effect on the heart, and its activation and involvement in cardiac protection may facilitate increased glucose uptake in

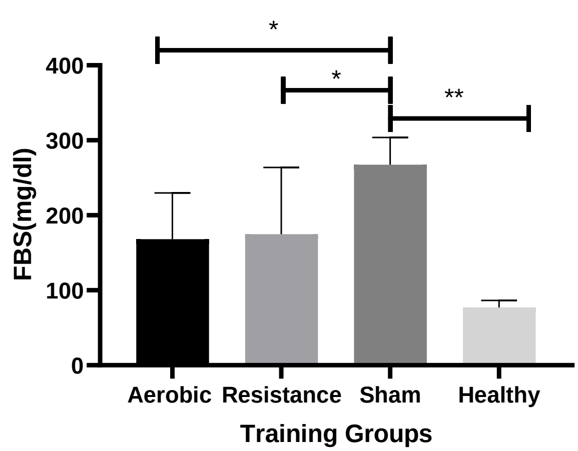

Figure 1. Comparison of fasting blood sugar in different groups. Data were show as mean ± SD. *Shows significant difference at P ≥ 0.05

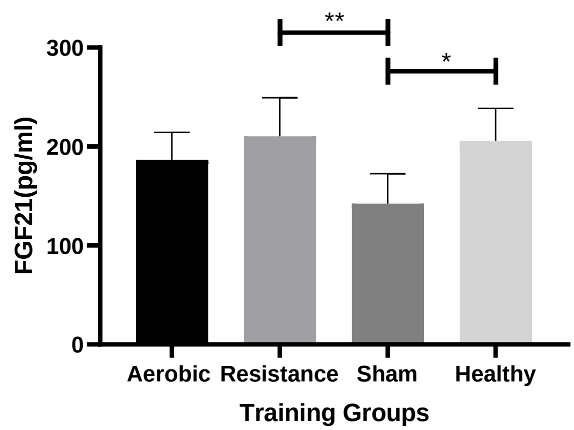

Figure 2. Comparison of FGF21 in different groups. Data were show as mean ± SD. *Shows significant difference at P ≥ 0.05

ischemic stress (Patel et al., 2014). The study also found that resistance exercise was more effective than aerobic exercise in improving sugar indicators and FGF21 levels in diabetic rat cardiac tissue (Patel et al., 2014). Therefore, resistance exercise may be a more effective intervention for diabetic patients with cardiovascular complications.

The effect of aerobic and resistance exercise on sugar indicators and FGF21 in diabetic rat cardiac tissue has been studied in various research articles. The studies show that exercise can improve insulin resistance, increase insulin sensitivity, and reduce blood insulin concentration (Lin et al., 2021). Exercise can also reduce circulating FGF-21 and myostatin levels, which are potential therapeutic targets for insulin resistance in age-related metabolic disorders, including type 2 diabetes (Shabkhiz et al., 2021). Aerobic exercise can increase the sensitivity of FGF21 by upregulating the expression of the downstream receptor adiponectin (ApN), and the serum FGF21 level after exercise increases initially and then decreases (Li et al., 2022). Resistance exercise improves cardiac function and mitochondrial efficiency in the hearts of diabetic rats, which are accompanied by higher FGF21 content in the soleus muscle (Khajehlandi et al., 2021). Both aerobic and resistance exercise training significantly decreased serum fetuin-A and fetuin-B and increased FGF-21 levels in males with type 2 diabetes mellitus, but more significant alterations in serum factors were observed from resistance training (Keihanian et al., 2019). In the case of resistance exercise, FGF-21 levels decreased after exercise in all but one study (Kim et al., 2023).

The research on the effect of exercise on FGF21 crosstalk between muscle, liver, and heart suggests that endurance exercise increases the expression of FGF21 in skeletal muscle, which promotes fiber conversion through TGF-β1 and p38 MAPK signaling pathways (Luo et al., 2023). Both clinical and preclinical studies have shown that aerobic exercise can change circulatory and tissue FGF21, along with its receptors (Porflitt-Rodríguez et al., 2022). Exercise-induced elevation of circulating FGF21 affects both muscle and liver, but the dominance of one over the other remains unclear (Yue & Jianping, 2022). Exercise can also improve obesity-induced metabolic disorders by enhancing FGF21 sensitivity in adipose tissues (Geng et al., 2019). Acute exercise can increase FGF21 in metabolic organs and circulation, and the activation of Akt induced by acute exercise might increase circulation FGF21(Tanimura et al., 2016). Overall, the research suggests that exercise can have a positive effect on FGF21 crosstalk between muscle, liver, and heart, but more studies are needed to fully understand the mechanisms involved.

The studies cited in the search results suggest that aerobic and resistance exercise can have positive effects on sugar indicators and FGF21 in diabetic rat cardiac tissue. Aerobic exercise has been shown to alleviate oxidative stress and apoptosis by activating the FGF21/FGFR1/PI3K/AKT pathway (Bo et al., 2021). Both clinical and preclinical studies have shown that aerobic exercise can lead to changes in circulatory and tissue FGF21, along with its receptors and co-receptor (Porflitt-Rodríguez et al., 2022). Resistance training has been found to attenuate circulating FGF-21 and myostatin and improve insulin resistance in elderly men with and without type 2 diabetes mellitus (Vecchiatto et al., 2022). Another study found that insulin and exercise increase FGF21 in plasma, and that induced expression and secretion of FGF21 from muscle may improve glucose tolerance, lipid metabolism, and energy expenditure in rodents (Kruse et al., 2017).

In the research of Abbasi Daloii and colleagues, a period of aerobic training caused a significant increase in FGF21 in the serum of obese men (Abbassi Daloii & Maleki Delarestaghi, 2017). In the research of Yaghubi et al., who investigated the effect of eight weeks of aerobic training on the level of FGF21 in diabetic women, they saw an increase in the level of FGF21(Yaghubi & Abedi, 2021). It appears that aerobic and resistance exercises improve glucose disposal by increasing insulin action and by activating the AMPK pathways, causing GLUT4 translocation to the muscle cell surface and glucose uptake in subjects (Pereira & Lancha, 2004). We speculate that increased FGF21 mediates some of the beneficial effects of aerobic and resistance exercises on glucose and lipid metabolism in menopausal women with type II diabetes mellitus. Another study by Kim et al reported that serum FGF21 level is increased in mice after a single bout of acute exercise and that this is accompanied by increased serum levels of free fatty acid, glycerol and ketone body. They also observed that FGF21 gene expression was induced in the liver but not in skeletal muscle and white adipose tissue of mice after acute exercise, and further, the gene expression levels of hepatic peroxisome proliferator-activated receptor α (PPAR α) and activating transcription factor 4 (ATF4) were also increased. They proposed that FGF21 may also be associated with exercise-induced lipolysis in addition to increased catecholamines and reduced insulin (Kim et al., 2013).

Similarly, FGF21 causes a significant decrease in fasting plasma glucose, fructose, triglyceride, insulin, and glucagon in diabetic monkeys. In addition, FGF21 causes a small but significant decrease in weight (Taniguchi et al., 2014). Another study has shown that serum FGF21 increases in impaired glucose tolerance and type 2 diabetes and is associated with liver and whole-body insulin resistance (Schuler et al., 2013). In animal studies, the existence of FGF21 resistance has been investigated in obese mice with a diet; Therefore, the high serum level of FGF21 probably indicates the resistance and reduction of the therapeutic effect of FGF21, which may lead to glucose and fat burning. In addition, the basal level of FGF21 is positively related to the daily amount of physical activity, while the FGF21 induced by training in normal weight individuals increases with increasing cardio-respiratory fitness. Cuevas-Ramos et al showed that in healthy young women, the level of FGF21 increased significantly from an average of 276.8 ng/l to 460.8 ng/l after two weeks of training (Cuevas-Ramos et al., 2012). In Rajabi et al.'s research, a significant increase in serum FGF21 was observed after 12 weeks of aerobic training on inactive women (Eckardt et al., 2014). Kim et al showed that even one session of acute exercise increases serum FGF21 levels in both healthy mice and men. However, Kharitonen and colleagues reported that FGF21 therapeutic prescription causes a decrease in plasma glucose and triglyceride levels close to the normal level (Kharitonenkov et al., 2007). In the study of Semba and colleagues, high serum concentrations of FGF21 were related to abnormal glucose metabolism and insulin resistance (Semba et al., 2012). Similarly, in the study of Mraz and colleagues, the plasma level of FGF21 in diabetic patients was significantly higher than in the healthy control group (Mraz et al., 2009). Based on these results, FGF21 has been proposed as a hormonal regulator of metabolism and may be a promising key target for the treatment of insulin resistance and other aspects of metabolic syndrome. Experiments on mice treated with FGF21 showed that this protein regulates the entire body's insulin response and increased glucose uptake in skeletal muscles, white adipose tissue, and brown adipose tissue (Camporez et al., 2013).

The results of the present research are consistent with the findings of Cuevas-Ramos et al. (2012) (Cuevas-Ramos et al., 2012) and Abbasi et al. (2016) (Abbassi Daloii et al., 2016) and are not consistent with the findings of Taniguchi et al. (2016) (Taniguchi et al., 2016). It seems that FGF21 is a determining factor in the response of metabolic adaptation to energy deficiency and also as an excellent therapeutic molecule for the treatment of type 2 diabetes in laboratory animals. Performing sports activity leads to an increase in FGF21 serum level in healthy mice and humans. Recent findings show that FGF21 is

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an important endogenous regulator for blood glucose. Also, FGF21 increases glucose consumption in an insulin-dependent manner. The therapeutic use of FGF21 in diabetic mice led to the improvement of blood glucose levels (Raschke & Eckel, 2013). In most type 2 diabetes patients, the goal of doing sports exercises is to increase energy expenditure, and this topic is directly related to the amount of muscle mass involved during sports activities. For this reason, activities that involve more muscle mass have better results for type 2 diabetes patients (Poirier et al., 2002). In general, it can be said that regular aerobic and resistance trainings have a positive effect on the heart function and sugar indices of diabetic people, but according to the results of the present study, resistance training can be recommended to improve the heart function of type 2 diabetics.

Conclusions

According to the results of the present research, resistance trainings can have a bigger influence on sugar indicators and anti-diabetic cardiac factors like FGF21, and will play an effective role in minimizing the consequences of diabetes.

What is already known on this subject?

Based on the available research, it is known that both aerobic and resistance exercise can have a significant impact on fibroblast growth factor 21 (FGF21) levels and its associated pathways in cardiac tissue. Additionally, both aerobic and resistance exercise training have been found to decrease serum fetuin-A and fetuin-B levels while increasing FGF-21 levels in men.

What this study adds?

Resistance Trainings can have a bigger influence on sugar indicators and anti-diabetic cardiac factors like FGF21, and will play an effective role in minimizing the consequences of diabetes.

Organ Cross-Talk Tips:

- The cross-talk between damaged heart muscle and metabolic responses following eccentric exercise needs to be carefully identified (future perspective).

Acknowledgements

The following article is taken from the master's thesis of Amir Mounesan, which was carried out at Shahid Rajaee University's Faculty of Sports Sciences. We thank and appreciate all the people who helped us in the implementation of this research.

Funding

None.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The ethics code of this research was IR.SRTTU.SSF,2020.112 taken from Shahid Rajaee Teacher Training University of Tehran.

Informed consent Animal study.

Author contributions

Conceptualization: A.M; Methodology: A.M; Software: F.N; Validation: A.M; Formal analysis: F.N; Investigation: A.M; Resources: A.M; Data curation: F.N; Writing - original draft: A.M; Writing - review & editing: A.M; Visualization: A.M; Supervision: A.M; Project administration: A.M; Funding acquisition: A.M

References

Abbassi Daloii, A., Hedayatzadeh, S., Abdi, A., & Abbaszadeh Sourati, H. (2016). The effect of 8 weeks of aerobic exercise on serum levels of FGF21, Apolipoprotein A-1 and LDL-C to HDL-C ratio in obese women. Sport physiology & management Investigations, 8(1), 77-87.

Abbassi Daloii, A., & Maleki Delarestaghi, A. (2017). The Effect of Aerobic Exercise on Fibroblast Growth Factor 21 and Adiponectin in Obese Men. Journal of Sport Biosciences, 9(1), 109-121. https://doi.org/https://doi.org/10.22059/jsb.2017.61917

Bo, W., Ma, Y., Xi, Y., Liang, Q., Cai, M., & Tian, Z. (2021). The Roles of FGF21 and ALCAT1 in Aerobic Exercise-Induced Cardioprotection of Postmyocardial Infarction Mice. Oxid Med Cell Longev, 2021, 8996482. https://doi.org/10.1155/2021/8996482

Boule, N. G., Weisnagel, S. J., Lakka, T. A., Tremblay, A., Bergman, R. N., Rankinen, T., . . . Study, H. F. (2005). Effects of exercise training on glucose homeostasis: the HERITAGE Family Study. Diabetes care, 28(1), 108-114. https://doi.org/10.2337/diacare.28.1.108

Camporez, J. P. G., Jornayvaz, F. R., Petersen, M. C., Pesta, D., Guigni, B. A., Serr, J., . . . Jurczak, M. J. (2013). Cellular mechanisms by which FGF21 improves insulin sensitivity in male mice. Endocrinology, 154(9), 3099-3109. https://doi.org/https://doi.org/10.1210/en.2013-1191

Cho, N. H., Shaw, J. E., Karuranga, S., Huang, Y., da Rocha Fernandes, J. D., Ohlrogge, A. W., & Malanda, B. (2018). IDF Diabetes Atlas: Global estimates of diabetes prevalence for 2017 and projections for 2045. Diabetes Res Clin Pract, 138, 271-281. https://doi.org/10.1016/j.diabres.2018.02.023

Cuevas-Ramos, D., Almeda-Valdes, P., Meza-Arana, C. E., Brito-Cordova, G., Gomez-Perez, F. J., Mehta, R., . . . Aguilar-Salinas, C. A. (2012). Exercise increases serum fibroblast growth factor 21 (FGF21) levels. PloS one, 7(5), e38022. https://doi.org/10.1371/journal.pone.0038022

Davoodi, S. H., Vahidian-Rezazadeh, M., & Fanaei, H. (2018). The effect of endurance and resistance exercises and consumption of hydro-alcoholic extract of nettle on the changes in weight and plasma levels of nesfatin-1 in type 1 diabetic rats. KAUMS Journal (FEYZ), 22(4), 362-369.

Eckardt, K., Gorgens, S. W., Raschke, S., & Eckel, J. (2014). Myokines in insulin resistance and type 2 diabetes. Diabetologia, 57(6), 1087-1099. https://doi.org/10.1007/s00125-014-3224-x

Ernande, L., & Derumeaux, G. (2012). Diabetic cardiomyopathy: myth or reality? Arch Cardiovasc Dis, 105(4), 218-225. https://doi.org/10.1016/j.acvd.2011.11.007

Geng, L., Liao, B., Jin, L., Huang, Z., Triggle, C. R., Ding, H., . . . Xu, A. (2019). Exercise Alleviates Obesity-Induced Metabolic Dysfunction via Enhancing FGF21 Sensitivity in Adipose Tissues. Cell Rep, 26(10), 2738-2752 e2734. https://doi.org/10.1016/j.celrep.2019.02.014

Holmes, A., Coppey, L. J., Davidson, E. P., & Yorek, M. A. (2015). Rat Models of Diet-Induced Obesity and High Fat/Low Dose Streptozotocin Type 2 Diabetes: Effect of Reversal of High Fat Diet Compared to Treatment with Enalapril or Menhaden Oil on Glucose Utilization and Neuropathic Endpoints. J Diabetes Res, 2015, 307285. https://doi.org/10.1155/2015/307285

Karimian, J., Khazaei, M., & Shekarchizadeh, P. (2015). Effect of Resistance Training on Capillary Density Around Slow and Fast Twitch Muscle Fibers in Diabetic and Normal Rats. Asian J Sports Med, 6(4), e24040. https://doi.org/10.5812/asjsm.24040

Keihanian, A., Arazi, H., & Kargarfard, M. (2019). Effects of aerobic versus resistance training on serum fetuin-A, fetuin-B, and fibroblast growth factor-21 levels in male diabetic patients. Physiol Int, 106(1), 70-80. https://doi.org/10.1556/2060.106.2019.01

Khajehlandi, M., Bolboli, L., Siahkuhian, M., Rami, M., Tabandeh, M., Khoramipour, K., & Suzuki, K. J. B. (2021). Endurance training regulates expression of some angiogenesis-related genes in cardiac tissue of experimentally induced diabetic rats. 11(4), 498. https://doi.org/https://doi.org/10.3390/biom11040498

Kharitonenkov, A., Wroblewski, V. J., Koester, A., Chen, Y.-F., Clutinger, C. K., Tigno, X. T., . . . Etgen, G. J. (2007). The metabolic state of diabetic monkeys is regulated by fibroblast growth factor-21. Endocrinology, 148(2), 774-781. https://doi.org/https://doi.org/10.1210/en.2006-1168

Kim, H., Jung, J., Park, S., Joo, Y., Lee, S., Sim, J., . . . Lee, S. (2023). Exercise-Induced Fibroblast Growth Factor-21: A Systematic Review and Meta-Analysis. Int J Mol Sci, 24(8), 7284. https://doi.org/10.3390/ijms24087284

Kim, K. H., Kim, S. H., Min, Y. K., Yang, H. M., Lee, J. B., & Lee, M. S. (2013). Acute exercise induces FGF21 expression in mice and in healthy humans. PloS one, 8(5), e63517. https://doi.org/10.1371/journal.pone.0063517

Kruse, R., Vienberg, S. G., Vind, B. F., Andersen, B., & Hojlund, K. (2017). Effects of insulin and exercise training on FGF21, its receptors and target genes in obesity and type 2 diabetes. Diabetologia, 60(10), 2042-2051. https://doi.org/10.1007/s00125-017-4373-5

Li, X. H., Liu, L. Z., Chen, L., Pan, Q. N., Ouyang, Z. Y., Fan, D. J., . . . Huang, H. Q. (2022). Aerobic exercise regulates FGF21 and NLRP3 inflammasome-mediated pyroptosis and inhibits atherosclerosis in mice. PloS one, 17(8), e0273527. https://doi.org/10.1371/journal.pone.0273527

Lin, W., Zhang, T., Zhou, Y., Zheng, J., & Lin, Z. (2021). Advances in Biological Functions and Clinical Studies of FGF21. Diabetes Metab Syndr Obes, 14, 3281-3290. https://doi.org/10.2147/DMSO.S317096

Luo, X., Zhang, H., Cao, X., Yang, D., Yan, Y., Lu, J., . . . Wang, H. (2023). Endurance Exercise-Induced Fgf21 Promotes Skeletal Muscle Fiber Conversion through TGF-β1 and p38 MAPK Signaling Pathway. International Journal of Molecular Sciences, 24(14), 11401. https://doi.org/https://doi.org/10.3390/ijms241411401

Mohammadi, R., Matin Homaee, H., Azarbayjani, M., & Baesi, K. (2017). The effects of 12 weeks endurance training on glucose amount, blood insulin and heart structure in type 2 diabetic rats. community health, 9(3), 29-36.

Molanouri Shamsi, M., Hassan, Z. H., Gharakhanlou, R., Quinn, L. S., Azadmanesh, K., Baghersad, L., . . . Mahdavi, M. (2014). Expression of interleukin-15 and inflammatory cytokines in skeletal muscles of STZ-induced diabetic rats: effect of resistance exercise training. Endocrine, 46(1), 60-69. https://doi.org/10.1007/s12020-013-0038-4

Mraz, M., Bartlova, M., Lacinova, Z., Michalsky, D., Kasalicky, M., Haluzikova, D., . . . Haluzik, M. (2009). Serum concentrations and tissue expression of a novel endocrine regulator fibroblast growth factor-21 in patients with type 2 diabetes and obesity. Clin Endocrinol (Oxf), 71(3), 369-375. https://doi.org/10.1111/j.1365-2265.2008.03502.x

Nourbakhsh, A., Ardakani, M. z., davood, A., Javid, S., Mobashsher, zahedi, N., . . . Ramin. (2015). A comprehensive guide to the care and use of laboratory animals. medical scholar, 23(3), 1-10.

Patel, V., Adya, R., Chen, J., Ramanjaneya, M., Bari, M. F., Bhudia, S. K., . . . Randeva, H. S. J. P. o. (2014). Novel insights into the cardio-protective effects of FGF21 in lean and obese rat hearts. 9(2), e87102. https://doi.org/https://doi.org/10.1371/journal.pone.0087102

Pereira, L. O., & Lancha, A. H., Jr. (2004). Effect of insulin and contraction up on glucose transport in skeletal muscle. Prog Biophys Mol Biol, 84(1), 1-27. https://doi.org/10.1016/s0079-6107(03)00055-5

Planavila, A., Redondo-Angulo, I., & Villarroya, F. (2015). FGF21 and Cardiac Physiopathology. Front Endocrinol (Lausanne), 6, 133. https://doi.org/10.3389/fendo.2015.00133

Poirier, P., Tremblay, A., Broderick, T., Catellier, C., Tancrède, G., & Nadeau, A. (2002). Impact of moderate aerobic exercise training on insulin sensitivity in type 2 diabetic men treated with oral hypoglycemic agents: is insulin sensitivity enhanced only in nonobese subjects? Medical science monitor: international medical journal of experimental and clinical research, 8(2), CR59-65.

Porflitt-Rodríguez, M., Guzmán-Arriagada, V., Sandoval-Valderrama, R., Tam, C. S., Pavicic, F., Ehrenfeld, P., & Martínez-Huenchullán, S. (2022). Effects of aerobic exercise on fibroblast growth factor 21 in overweight and obesity. A systematic review. Metabolism, 129, 155137. https://doi.org/https://doi.org/10.1016/j.metabol.2022.155137

Qian, Z., Zhang, Y., Yang, N., Nie, H., Yang, Z., Luo, P., . . . Yan, J. (2022). Close association between lifestyle and circulating FGF21 levels: A systematic review and meta-analysis. Frontiers in endocrinology, 13, 984828. https://doi.org/https://doi.org/10.3389/fendo.2022.984828

Raschke, S., & Eckel, J. (2013). Adipo-myokines: two sides of the same coin—mediators of inflammation and mediators of exercise. Mediators of inflammation, 2013. https://doi.org/https://doi.org/10.1155/2013/320724

Reynolds, K., Saydah, S. H., Isom, S., Divers, J., Lawrence, J. M., Dabelea, D., . . . Hamman, R. F. (2018). Mortality in youth-onset type 1 and type 2 diabetes: The SEARCH for Diabetes in Youth study. J Diabetes Complications, 32(6), 545-549. https://doi.org/10.1016/j.jdiacomp.2018.03.015

Schuler, G., Adams, V., & Goto, Y. (2013). Role of exercise in the prevention of cardiovascular disease: results, mechanisms, and new perspectives. Eur Heart J, 34(24), 1790-1799. https://doi.org/10.1093/eurheartj/eht111

Semba, R. D., Sun, K., Egan, J. M., Crasto, C., Carlson, O. D., & Ferrucci, L. (2012). Relationship of serum fibroblast growth factor 21 with abnormal glucose metabolism and insulin resistance: the Baltimore Longitudinal Study of Aging. J Clin Endocrinol Metab, 97(4), 1375-1382. https://doi.org/10.1210/jc.2011-2823

Severinsen, M. C. K., & Pedersen, B. K. (2020). Muscle–organ crosstalk: the emerging roles of myokines. Endocrine reviews, 41(4), 594-609.

Shabkhiz, F., Khalafi, M., Rosenkranz, S., Karimi, P., & Moghadami, K. J. E. j. o. s. s. (2021). Resistance training attenuates circulating FGF-21 and myostatin and improves insulin resistance in elderly men with and without type 2 diabetes mellitus: A randomised controlled clinical trial. 21(4), 636-645. https://doi.org/https://doi.org/10.1080/17461391.2020.1762755

Taniguchi, H., Tanisawa, K., Sun, X., Cao, Z. B., Oshima, S., Ise, R., . . . Higuchi, M. (2014). Cardiorespiratory fitness and visceral fat are key determinants of serum fibroblast growth factor 21 concentration in Japanese men. J Clin Endocrinol Metab, 99(10), E1877-1884. https://doi.org/10.1210/jc.2014-1877

Taniguchi, H., Tanisawa, K., Sun, X., Kubo, T., & Higuchi, M. (2016). Endurance Exercise Reduces Hepatic Fat Content and Serum Fibroblast Growth Factor 21 Levels in Elderly Men. J Clin Endocrinol Metab, 101(1), 191-198. https://doi.org/10.1210/jc.2015-3308

Tanimura, Y., Aoi, W., Takanami, Y., Kawai, Y., Mizushima, K., Naito, Y., & Yoshikawa, T. (2016). Acute exercise increases fibroblast growth factor 21 in metabolic organs and circulation. Physiol Rep, 4(12), e12828. https://doi.org/10.14814/phy2.12828

Tanoorsaz, S., Behpoor, N., & Tadibi, V. (2017). Changes in Cardiac Levels of Caspase-8, Bcl-2 and NT-proB-NP Following 4 Weeks of Aerobic Exercise in Diabetic Rats. International Journal of Basic Science in Medicine, 2(4), 172-177. https://doi.org/http://dx.doi.org/10.15171/ijbsm.2017.32

Tezze, C., Romanello, V., & Sandri, M. (2019). FGF21 as Modulator of Metabolism in Health and Disease. Frontiers in physiology, 419. https://doi.org/https://doi.org/10.3389/fphys.2019.00419

Vecchiatto, B., de Castro, T. L., Muller, C. R., Azevedo-Martins, A. K., & Evangelista, F. S. J. O. (2022). Physical exercise-induced FGF-21 to fight obesity: An update review. 2(4), 372-379. https://doi.org/https://doi.org/10.3390/obesities2040031

Yaghubi, & Abedi. (2021). Effect of eight weeks of aerobic exercise with ginger supplementation on FGF21, irisin and insulin resistance in women with type 2 diabetes. Iranian journal of diabetes and metabolism, 21(2), 111-118.

Yang, H., Feng, A., Lin, S., Yu, L., Lin, X., Yan, X., . . . Zhang, C. (2018). Fibroblast growth factor-21 prevents diabetic cardiomyopathy via AMPK-mediated antioxidation and lipid-lowering effects in the heart. Cell Death Dis, 9(2), 227. https://doi.org/10.1038/s41419-018-0307-5

Yue, S., & Jianping, C. (2022). Hepatic FGF21: its emerging role in inter-organ crosstalk and cancers. International Journal of Biological Sciences, 18(15), 5928. https://doi.org/https://doi.org/10.7150%2Fijbs.76924