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Effect of Moderate Aerobic Exercise on Serum Levels of FGF21 and Fetuin A in Women with Type 2 Diabetes

Exir Vizvari
Department of Exercise Physiology, Faculty of Humanities, Shams Institute of Higher Education, Gonbad Kavous, Iran. ORCID: 0000 0003 0760 4571

Parvin Farzanegi
(Phd)Department of Exercise Physiology, Faculty of Humanities, Sari Branch, Islamic Azad University, Sari, Iran

Hajar Abbas Zade
(Phd)Department of Exercise Physiology, Faculty of Humanities, Sari Branch, Islamic Azad University, Sari, Iran

Corresponding author: Exir Vizvari
Email: vizvariexir@yahoo.com
Tel: +989112756903
Address: Department of Exercise Physiology, Faculty of Humanities, Shams Institute of Higher Education, Gonbad Kavous, Iran

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ABSTRACT

Background and objectives: Fibroblast growth factor 21 (FGF21) and fetuin A are thought to be involved in the pathogenesis of metabolic disorders, such as type 2 diabetes. On the other hand, regular physical activity has an important role in the prevention and management of type 2 diabetes. The purpose of this study was to investigate effect of moderate aerobic exercise on serum levels of FGF21 and fetuin A in women with type 2 diabetes.

Methods: This was a semi-experimental study with a pretest-posttest design. The study was performed on 28 women with type 2 diabetes aged 40-50 years (mean weight: 70.58 ± 2.11) who were randomly divided into an exercise group (n=14) and a control group (n=14). The training intervention consisted of eight weeks of moderate aerobic exercise at 60-70% of maximum heart rate, five times a week. Serum levels of FGF21, fetuin A and some metabolic parameters were evaluated before the first session and 48 hours after the last session. All statistical analyses were performed in SPSS (version 24) using repeated measures ANOVA and at significance of 0.05.

Results: The eight-week aerobic training intervention caused a significant increase in FGF21 and insulin sensitivity as well as a significant decrease in fetuin A, fasting blood sugar and HbA1c (P=0.001).

Conclusion: As a complementary therapy, regular aerobic exercise can be beneficial for type 2 diabetes patients in improving some metabolic parameters as well as FGF21 and fetuin A levels.

Keywords: Diabetes Mellitus Type 2, FGF21, Fetuin A, Exercise

INTRODUCTION

Diabetes refers to a group of metabolic disorders characterized by hyperglycemia, resulting from insulin resistance, loss of insulin secretion or both. Considering the rising prevalence of diabetes worldwide, it is expected that the disease will remain as one of the main causes of mobility and mortality (1). Also, epidemiological evidence indicates that diabetes is an important risk factor for atherosclerosis, which is the leading cause of death in diabetic patients (2). One the other hand, one of the factors affecting the development of chronic diseases, such as type 2 diabetes, is lack of physical activity. Several proteins that are exclusively or predominantly secreted by the liver are now known to directly affect energy metabolism. These liver-derived proteins, known as hepatokines, have important roles in promoting insulin resistance or improving metabolic variables of type 2 diabetes (3). One of these proteins is the fibroblast growth factor$_{21}$ (FGF_{21}), which is mainly expressed in metabolic tissues such as the liver and muscles. Systemic induction of FGF_{21} prevents obesity and decreases hyperglycemia and insulin resistance (4).

Therefore, it can lead to weight loss, decreased triglyceride and low-density lipoprotein (LDL) levels and improved insulin sensitivity (5). Fetuin A plays a major pathogenic role in metabolic diseases. This 64-kDa glycoprotein is elevated in obesity and related disorders, such as metabolic syndrome and type 2 diabetes. Fetuin A concentrations are strongly correlated with impaired insulin sensitivity and glucose intolerance as it directly inhibits the downstream phosphorylation events of the insulin signaling cascade and the translocation of the glucose transporter type 4 (GLUT4) in insulin target tissues. It also affects atherosclerosis in diabetic patients (3,6).

Aerobic exercise involves repeated and continuous movement of large muscles (7). Activities such as walking, cycling, jogging and swimming rely primarily on aerobic energy-producing systems. Regular physical activity has many beneficial health effects, especially on the treatment of chronic diseases, such as diabetes (8-10). Various studies have been carried out to examine effects of training on FGF_{21}. Cuevas-Ramos et al. reported an increase in serum levels of FGF_{21} following physical activity (11). In another study, eight weeks of endurance training did not affect serum level of FGF_{21} in obese men (12). On the other hand, Yang et al. reported a decrease in serum level of FGF_{21} after three months of physical activity in obese women (10). Yong et al. observed no significant change in the fetuin A level following three months of physical activity (13). Another study reported a reduction in serum level of fetuin A in obese, adult women and men following endurance training (14). Schultes et al. also demonstrated that six weeks of aerobic exercise does not significantly change the serum levels of fetuin A in obese women (15). The purpose of this study was to investigate effects of eight weeks of moderate aerobic exercise on serum levels of FGF_{21}, fetuin A and some metabolic parameters in women with type 2 diabetes.

MATERIALS AND METHODS

This semi-experimental study (clinical trial registrationnumber: IRCT20171104037225N1) was carried out with a pretest and posttest design. The study population included 28 women with type 2 diabetes who were referred to a Diabetes Center in Gorgan, Iran. The study was approved by the ethics committee of Islamic Azad University, Sari Branch (approval code: IR.IAU.SARI.REC.1396.55).

Inclusion criteria were age range of 40-50 years, fasting blood sugar of >126 mg/dl, having type 2 diabetes for at least three years and HbA1c of more than 6.5%. Exclusion criteria included history of insulin injection, fasting blood sugar of >300 mg/dl, regular physical activity in the past six months and history of hepatic and chronic heart disease. The subjects were asked not to perform any other form of physical activity. Insulin sensitivity was calculated based on the following formula: QUICKI=1/ [log (fasting insulin (μU/ml)) + log (fasting glucose (mg/dl))].

Exercise intervention was designed based on the recommendations of the American Diabetes Association and consisted of five sessions of exercise per week at moderate intensity (60-70% of maximum heart rate) for eight weeks (8, 16). Each training session included 10 minutes of warm up and five minutes of cool down. The exercise protocol included aerobic exercise training in forms of walking, jogging, marching, V step, shuffle, mambo chasse, step touch and combination of these exercises (Table 1).

Table 1. Details of the eight-week training program

Week	Saturday (min)	Sunday (min)	Tuesday (min)	Wednesday (min)	Thursday (min)	Intensity (maximum heart rate)
1st	30	31	32	33	34	60%
2nd	35	36	37	38	39	60%
3rd	40	41	42	43	44	60%
4th	45	46	47	48	49	65%
5th	50	51	52	53	54	65%
6th	55	56	57	58	59	65%
7th	60	60	60	60	60	70%
8th	60	60	60	60	60	70%

Metabolic parameters and serum levels of FGF_{21} and fetuin A were evaluated before the first session and 48 hours after the last session. Fasting blood samples were taken between 8:00 and 10:00 AM. Serum levels of FGF_{21} and fetuin A were measured using commercial enzyme-linked immune sorbent assay kits (Bio Vendor, Germany) with sensitivity of 7 pg/ml and 0.104 ng/ml, respectively. Metabolic parameters were measured using an auto analyzer.

Descriptive statistics including mean values and standard deviation were used to describe the data. The Kolmogorov–Smirnov test and Levene's test were applied to determine normality of data distribution and homogeneity of variances, respectively. Statistical analysis was performed using repeated measures ANOVA in SPSS software (Version 24) and at significance level of 0.05.

RESULTS

At baseline, there was no significant difference between the control and exercise groups. Eight weeks of moderate aerobic exercise caused a significant increase in FGF_{21} (P=0.001) and insulin sensitivity (P=0.001). Moreover, there was a statistically significant decrease in serum levels of fetuin A (P=0.001), fasting blood sugar (P=0.001) and HbA_1c following the exercise intervention (P=0.001) (Table 2, Figures 1 and 2).

Table 2. Comparison of metabolic parameters before and after the exercise intervention in woman with type 2 diabetes

Variable	Groups	Pre-test	Post-test	Within groups	Between groups
Fasting blood sugar	Control	165.14 ± 11.82	164.79 ± 12.12	0.778	0.001*
(mg/dl)	Exercise	164.20 ± 10.62	134.29 ± 9.55	0.001¥	
HbA1c (%)	Control	7.94 ± 0.52	7.93 ± 0.55	0.363	0.001*
	Exercise	8.10 ± 0.58	6.88 ± 0.68	0.001¥	
Insulin sensitivity	Control	0.303 ± 0.005	0.303 ± 0.004	0.771	0.001*
(QUICKI)	Exercise	0.303 ± .003	0.319 ± 0.003	0.001¥	

***Significant difference compared to the control group**

¥Significant difference compared to pre-test

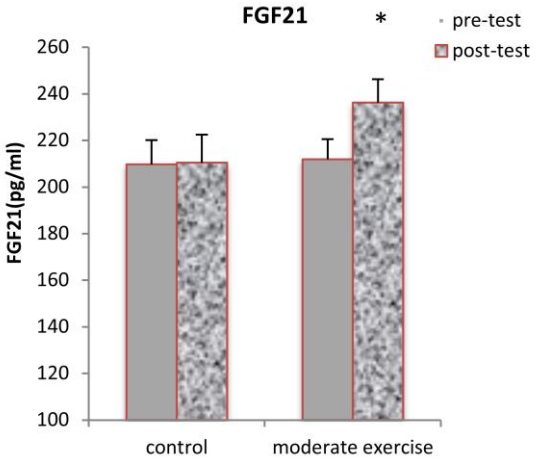

Figure 1. Effect of the training intervention on FGF_{21} levels. * indicates significant difference compared to the control group. ¥ indicates significant difference compared to pre-test (P=0.001).

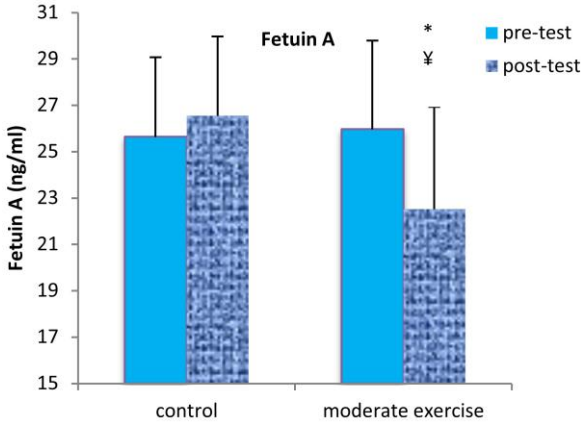

Figure. Effect of the training intervention on fetuin A levels. * indicates significant difference compared to the control group. ¥ indicates significant difference compared to pre-test (P=0.001).

DISCUSSION

In this study, the effect of eight weeks of moderate aerobic exercise was evaluated on serum levels of FGF_{21} and fetuin A in women with type 2 diabetes. Based on the results, the exercise intervention caused a significant increase in FGF_{21} and insulin sensitivity and a decrease in fetuin A, fasting blood sugar and HbA1c. Regular physical activity controls blood glucose, fat and insulin resistance, which reduces the complications of diabetes. In accordance with these results, Vizvari et al. also observed a reduction in fasting blood sugar, HbA1c and insulin resistance in diabetic patients following regular exercise (17). The improvement in insulin sensitivity could be due to the increased expression of GLUT4 and improved insulin signaling cascade. Moreover, FGF_{21} has been shown to decrease blood glucose levels by increasing GLUT 1 expression in human primary adipocytes (18).

In the present study, the eight-week moderate aerobic exercise increased serum levels of FGF_{21}, which is consistent with results of two previous studies (19, 20). However, a study reported that plasma level of FGF_{21} reduces after three weeks of training (21). The positive effects of regular physical activity on the metabolic parameters of diabetics may be exerted partly through mitochondrial biogenic proteins and glucose regulators, such as FGF_{21}. Physical activity increases glucagon and free fatty acids release, which simultaneously increases the secretion of FGF_{21} from hepatocytes (22). In addition, FGF_{21} increases insulin-independent glucose uptake in adipose tissues (5) via expression of GLUT 1 and regulation of lipolysis (23). This protein also increases the mitochondrial oxidative capacity in adipose tissue, which is characterized by increased oxygen consumption and upregulation of key metabolic genes (24). In other tissues such as the liver and pancreas, FGF_{21} helps homeostasis (4). Increased phosphorylation of 5' AMP-activated protein kinase by FGF_{21} ultimately increases fat oxidation, glucose uptake and mitochondrial biogenesis (25, 26).

We also observed that the eight-week moderate aerobic training significantly reduced the serum levels of fetuin A. In line with this finding, Lee et al. reported 11% reduction in fetuin A after 12 weeks of training in middle aged men (27). Similarly, Salama and El-Damarawi demonstrated that regular exercise significantly decreases fetuin A in diabetic rats (28). On the other hand, observed study reported an increase in serum levels of fetuin A in men in response to six months of aerobic exercise (29). However, a study reported no significant change in fetuin A levels of non-diabetic obese women after six weeks of training (15). The inconsistency between the results could be attributed to differences in the exercise protocol, duration and intensity of exercise as well as factors, such as health of subject. Fetuin A inhibits *insulin receptor* tyrosine kinase activity in skeletal muscle and adipose tissue (30). It also stimulates cytokines expression and lipogenesis while reducing adiponectin, which may consequently lead to insulin resistance (29).

CONCLUSION

As a non-pharmacological therapy, physical activity may exert beneficial effects on some metabolic parameters in diabetics through improvement of serum FGF_{21} and fetuin A levels.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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