ORIGINAL ARTICLE

Aerobic and Resistance Exercises Modulate Fibroblast Growth Factor-21 Level in Menopause Women with Type II Diabetes

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ABSTRACT

Objectives: *To determine the relationship between exercises with the serum fibroblast growth factor 21 (FGF21) levels and glucose and lipid profile in menopausal type II diabetic women.*
Methods: *Menopausal women with type II diabetes mellitus were divided into three groups including control (n = 14), aerobic exercise (n = 14) and resistance exercise groups (n = 14). The mean levels of serum glucose, LDL-C, HDL-C, insulin, TG and cholesterol were measured in all participants after 8 weeks of exercise. Serum FGF21 was also measured by ELISA method.*
Results: *The mean of FGF21 levels after exercise was increased significantly in the both aerobic (*p *< 0.001) and resistance exercise (*p *= 0.001) groups. The mean of glucose, LDL-C, TG and cholesterol was decreased significantly after exercise in the both exercised groups (*p *< 0.01). A significant decline had been found for insulin levels and also insulin resistance in the both aerobic (*p *= 0.001) and resistance (*p *= 0.003) groups. There was a negative and significant correlation between FGF21 levels with total cholesterol contents (*p *= 0.001).*
Conclusion: *Aerobic and resistance exercises increase the mean value of FGF21 levels and as the result decline the mean levels of glucose and lipids in blood of menopausal women with type II diabetic mellitus.*

Keywords: Exercise, fibroblast growth factor 21, glucose, lipids, menopausal women

INTRODUCTION

Fibroblast growth factor 21 (FGF21) is an endocrine hormone that belongs to the FGF family and is mainly expressed in the liver and also in adipocytes and the pancreas (15). Recently studies have shown that this protein is involved in metabolic regulations especially glucose uptake, stimulation of gluconeogenesis, activation of free fatty acid (FFA) oxidation, lipolysis, ketogenesis and energy balance through PPARα actions (2). Some studies on animal models demonstrated that fasting leads to increased expression of FGF21 in the liver and stimulates gluconeogenesis, fatty acid oxidation and ketogenesis (2). But in the fed state, it acts as an autocrine hormone in adipocytes, regulating the activity of PPAR-γ through a feed-forward loop mechanism (19). Fibroblast growth factor 21 seems to be a potential therapeutic way for the treatment of type 2 diabetes because pharmacologic studies on animal models have shown that FGF21 administration leads to a significant decrease in fasting blood glucose, insulin and triacylglycerol (TG) levels (15).

Administration of recombinant FGF21 has been also shown to modulate insulin resistance, blood glucose, lipid profile and body mass index (BMI) in obese mice and diabetic monkeys (2, 9–12, 22). Therefore, regarding the previous findings FGF21 can be considered as a therapeutic agent for obesity-related medical conditions. However, in humans its functions are still not clear under physiological conditions. In some clinical studies, a positive correlation between FGF21 plasma levels and several parameters of obesity such as BMI and fat percentage has been shown (15, 20). Some investigators have also reported high-circulating FGF21 levels in fat humans which is associated with cardiometabolic

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disorders including the metabolic syndrome, type 2 diabetes, non-alcoholic fatty liver disease and coronary artery disease (19).

Type II diabetes mellitus causes metabolic changes that may lead to early menopause and worsen climacteric symptoms (3, 6, 13). It seems that exercise is critical for the prevention and treatment of metabolic disorders such as obesity, type II diabetes and atherosclerosis in early menopause. We hypothesized it is maybe mediated by FGF21 levels. Interestingly, it has been recently shown that increased serum FGF21 level is related to regular physical activity in healthy humans (5, 14). However, it is not well-known that whether acute or resistance exercise affects FGF21 expression. Furthermore, the molecular mechanisms by which exercise leads to FGF21 induction have not be elucidated. Therefore, in this study we aimed for the first time to investigate the effects of an 8 weeks of regular aerobic and resistance exercise on serum FGF21 levels and then on glucose and lipid metabolisms, in menopausal women with type II diabetes mellitus.

SUBJECTS AND METHODS

Human population

Between April 2014 and December 2014 a total of 42 menopausal women with type II diabetes mellitus aged 40–57 years old and without any contraindication to exercising were included in this study. This study was conducted in accordance with the 'Helsinki declaration'. Participants had no history of smoking, alcohol consumption and other chronic diseases such as cancer, chronic kidney, failure, non-alcoholic steatohepatitis, and autoimmune disorders.

Table 1: The mean of demographic characters of all participants

Variables	Mean ± SD
Height (cm)	161.81 ± 6.05
Weight (kg)	78.24 ± 8.86
Age (year)	51.42 ± 4.43
BMI (kg/m^2)	29.94 ± 2.79
SBP	151.08 ± 9.04
DBP	90.74 ± 8.71

BMI = body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure.

After preliminary considerations of patient's demographic characters and sample selection, subjects were divided randomly into three groups including control, aerobic exercise and resistance exercises groups. The levels of serum glucose, LDL-C, HDL-C, insulin, TG and cholesterol as well as insulin resistance were measured during the day of 1 and after 8 weeks of exercise.

Exercises protocols

The aerobic and resistance exercises test was carried out according to the previous standard methods (18, 25). Before procedures, our experimental team invited participants in a class, and randomly assigned the subjects to one of three groups an aerobic exercise group (n = 14), a resistance exercise group (n = 14) and a control group (n = 14). Then we trained participants in each group regarding the process of each exercise, time of exercise, and all necessary activities. After the subjects became familiar with the procedure of exercises, each group performed the corresponding exercise therapy programme for the 8 weeks.

The training programme for aerobic exercise was performed for 8 weeks, three sessions each week. The intensity of the training programme proceeded from 45% to 50% (in the first 2 weeks), 50% to 55% (in the second 2 weeks), 55% to 60% (in the third 2 weeks) and 60% to 65% of maximum heart rate (in the last 2 weeks). All training programmes included the warm up and cool-down processes for 10 to 15 minutes. The intense training programme was controlled and regulated, using a polar (Polar V 800 made in USA). All subjects performed a warm up (20 minutes) and a cool-down (15 minutes) programme in every training session. The duration of training programmes without the warm up and cool-down was 15 minutes in the first 2 weeks. The first 2 weeks of the programme involved a mild walking, with a mild working intensity. The duration of training programmes without the warm up and cool-down in the second 2 weeks, third 2 weeks and last 2 weeks were 30 minutes, 35 minutes and 40 minutes, respectively. The intensity of programme was increased from mild walking in the first 2 weeks to running and tensional activities in the last 2 weeks. After 8 weeks of exercise, subjects visited the hospital for further examinations.

The training programme for resistance exercise was also performed during 8 weeks, three sessions each week. The duration of training programmes without the warm up and cool-down was 40 minutes. The subjects carried out a 40-minute weight training programme after 10 minutes of warm up. At the end, they performed a 10-minute cool-down programme. The resistance exercise group used resistance bands in their exercise programmes (maximum resistance, RM1 = 40–50%). It included chest press, leg press, back leg, underarm stretch as well as pull down the arms and two-way

stretch receptors in the large muscles of the upper and lower body. The amount of resistance in the band is dependent on the band length. When the bands were stretched 50/70/100%, red bands provided 1.2/1.5/1.8 kg of resistance, green bands provided 1/5/1.9/2.3 kg of resistance, and blue bands provided 2.1/2.7/3.2 kg of resistance, respectively (18, 25).

Biochemical and anthropometric measurements

Blood samples were collected after a 12-hour overnight fast and then centrifuged at 3000 × g at 4°C for 15 minutes. The serum and plasma were collected and stored immediately at −80°C until future analysis. All measurements were performed with commercially available standardized methods. The concentrations of serum total cholesterol (Total-C), LDL cholesterol (LDL-C), HDL cholesterol (HDL-C), triglyceride (TG), and glucose were measured using an enzymatic .assay. The concentrations were determined using commercially available kits purchased from Pars Azmoon Company (Tehran, Iran), including Cholesterol (1 500 010), Glucose (1 500 017), HDL-C (1 050 012), LDL-C (1 050 023), TG (1 500 032) kits. All measurements were determined according to the manufacturer's instructions. The serum FGF21 concentration was determined using a commercially available ELISA kit (FGF21/UNQ3115/PRO10196, Cusabio, China) according to the manufacturer's instructions. The detectable range of the assay and its sensitivity were 15.6 to 1000 pg/ml and 3.9 pg/ml, respectively.

Anthropometric measurements were carried out after participants removed their shoes and upper garments. Bodyweight was quantified with a balance. Height was also obtained using the floor scales stadiometer, again with the patient standing on the central part of the scale. Height was measured to the nearest 0.5 cm. BMI was calculated as weight (kg) divided by height (m^2).

Statistical analysis

All statistical analyses were performed using SPSS version 19.0 (SPSS, Inc., Chicago, IL, USA). The Kolmogorov–Smirnov test was performed to assess the normality of data distribution. The data were expressed as means and standard deviation (± SD). Chi-square, Student's unpaired *t*-test, Wilcoxon signed-rank test or Mann–Whitney *U* test was used as appropriate for comparison of measurements before and after exercises. Correlation coefficients between FGF21 and the other variables were evaluated in all participants. The Pearson correlation test and linear regression were used to analyse and examine the relationship between the parameters and FGF21 concentrations scores. An independent *t*-test was used to compare the mean of the serum variables between the two groups. The ANOVA model was utilized for statistical analyses of parameters concentration between all groups. The value $p < 0.05$ was considered statistically significant.

RESULTS

Patient profile and information on some demographic characteristics are summarized in Table 2. The mean age of all participated patients was 51.42 ± 4.43 years. The mean of systolic and diastolic blood pressure, weight, height and body mass index (BMI) were calculated in each patient at specified intervals of time and compared. There is no significant difference regarding the basic information of participated patients between all groups.

Table 2: Demographic characters of patients in each group

Variables	Aerobic exercise	Resistance exercise	Control group	*p*-Value
Height (cm)	165.5 ± 6.53	159.28 ± 5.08	160.66 ± 6.54	0.192
Weight (kg)	79.5 ± 8.96	79.57 ± 8.18	75.66 ± 9.44	0.158
Age (year)	50.83 ± 6.79	53.28 ± 1.17	50.17 ± 5.34	0.103
BMI (kg/m^2)	30.71 ± 3.44	29.76 ± 3.84	29.37 ± 4.55	0.885
SBP	152.43 ± 8.18	148.11 ± 9.39	152.71 ± 9.56	0.937
DBP	92.14 ± 8.80	88.67 ± 7.42	91.42 ± 9.93	0.995

BMI = body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure.

Effect of exercises on the serum FGF21 level

The mean of FGF21 levels during the pre- and post-examinations in all three groups is shown in Table 3. The mean of FGF21 concentration was higher in exercise groups in compare with control group ($p < 0.001$). The mean of FGF21 concentration after post-examination was increased significantly in the both aerobic ($p < 0.001$) and resistance exercise ($p = 0.001$) groups. However, in the control group there was no significant difference in FGF21 concentration during the pre- and post-examination ($p = 0.269$).

Table 3: The mean of FGF21 concentrations in each group

	Aerobic exercise	Resistance exercise	Control group	p-Value
FGF21 (pg/ml)				
Before exercise	267.57 ± 28.62	289.0 ± 21.41	353.28 ± 24.63	< 0.001
After exercise	393.43 ± 33.39	364.71 ± 19.55	367.57 ± 28.62	0.132
p-Value	< 0.001	0.001	0.269	–

Effect of exercises on blood metabolic parameters

The mean of some metabolite factors during the pre- and post-examinations in all three groups is demonstrated in Table 4. Our findings showed that there is a significant difference regarding the mean of all studied metabolite levels from pre-examination to post-examination in the both exercised groups, but these differences were not significant in the control group. The mean of glucose was decreased significantly after exercise in the both aerobic ($p = 0.002$) and resistance exercise ($p = 0.001$) groups. The mean of insulin level declined from 9.28 ± 2.03 µg/ml to 7.74 ± 1.05 µg/ml in the aerobic exercise group ($p = 0.001$) and from 9.13 ± 1.85 µg/ml to 7.67 ± 1.39 µg/ml in the resistance exercise group ($p = 0.001$). Besides that, a significant decline had been found for insulin resistance in the both aerobic ($p = 0.001$) and resistance ($p = 0.003$) groups after exercise. Lipid metabolic factors were also compared between all groups during the pre- and post-examinations. The mean level of HDL-C was also increased significantly in both

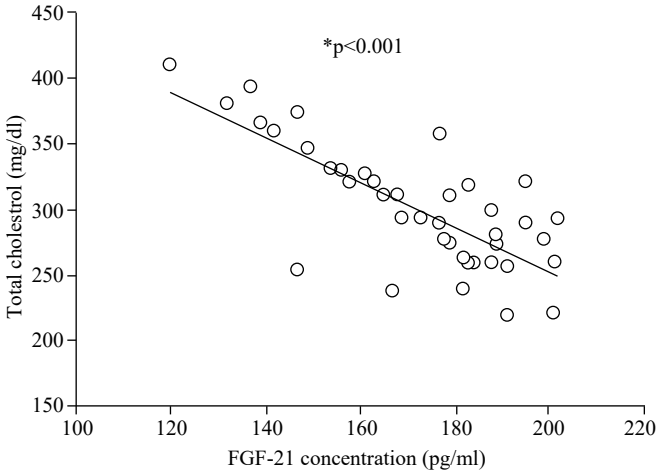

Figure: Correlation between FGF21 levels and serum total cholesterol concentrations. A negative significant correlation was found between FGF21 and serum total cholesterol ($p = 0.001$).

Table 4: The mean of some blood factors in each group

Variables	Aerobic exercise	Resistance exercise	Control group	*p*-Value
Glucose (mg/dl)				
Before exercise	176.43 ± 42.69	172.86 ± 32.73	163.71 ± 39.31	0.818
After exercise	142.43 ± 49.51	145.14 ± 31.63	171.0 ± 42.59	0.392
p-Value	0.002	0.001	0.232	–
Insulin (µg/ml)				
Before exercise	9.28 ± 2.03	9.13 ± 1.85	8.9 ± 1.84	0.932
After exercise	7.74 ± 1.05	7.67 ± 1.39	8.88 ± 1.25	0.136
p-Value	0.001	0.001	0.944	–
Insulin resistance				
Before exercise	4.21 ± 1.82	4.02 ± 1.62	3.72 ± 1.61	0.861
After exercise	2.71 ± 1.34	2.83 ± 1.62	3.88 ± 1.63	0.253
p-Value	0.001	0.003	0.496	–
LDL-C (mg/dl)				
Before exercise	86.30 ± 4.35	87.53 ± 5.28	84.37 ± 4.50	0.496
After exercise	75.31 ± 5.10	80.52 ± 6.20	81.63 ± 6.81	0.158
p-Value	< 0.001	< 0.001	0.226	–
HDL-C (mg/dl)				
Before exercise	38.68 ± 2.64	39.03 ± 4.59	37.5 ± 5.24	0.788
After exercise	44.64 ± 2.92	44.32 ± 5.55	38.1 ± 4.71	0.024
p-Value	< 0.001	< 0.001	0.397	–
Cholesterol (mg/dl)				
Before exercise	176.71 ± 11.6	182.71 ± 15.51	190.0 ± 10.92	0.181
After exercise	151.14 ± 10.69	164.0 ± 11.12	193.86 ± 12.52	< 0.001
p-Value	< 0.001	< 0.001	0.068	–
TG (mg/dl)				
Before exercise	176.28 ± 23.08	172.57 ± 20.25	167.43 ± 42.24	0.767
After exercise	142.71 ± 18.45	143.71 ± 23.52	171.14 ± 20.43	0.033
p-Value	< 0.001	< 0.001	0.193	–

exercised groups, but the mean of LDL-C, cholesterol and triglyceride concentrations was declined significantly in both exercised groups ($p < 0.001$). We did not find a significant difference between two exercised groups during the pre- and post-examinations, but a significant difference was found between the mean of measured parameters between control and exercised groups.

Linear regression and the Pearson correlation tests have shown a negative and significant correlation between serum FGF21 concentrations and total cholesterol levels (Figure; $p = 0.001$; $r = 0.423$). However, we did not find a significant correlation between FGF21 with the other serum biochemical parameters.

DISCUSSION

FGF21 plays a critical role in carbohydrate and lipid metabolisms and as the result in energy balance (16). It induces the process of lipolysis in adipose tissue, as well as fatty acid oxidation and ketogenesis in liver (17, 21, 29). However, its physiological functions in human subjects are not well-known. More recently studies have shown that FGF21 levels are associated with the number of physical activities but the mechanism is not clear. Similar to starvation state, exercise also induces the process of lipolysis in adipose tissue, and subsequently FFAs in serum that are utilized as a major fuel for ATP production in peripheral tissues such as skeletal muscle and the liver (17).

It has been recently reported that serum FGF21 level is increased after 2 weeks of exercise (5). However, the relationship between aerobic and resistance exercises with FGF21 levels in menopausal women with type II diabetes mellitus has not been considered. In this study, we evaluated the effects of aerobic and resistance exercises on FGF21 levels as well as carbohydrate and lipid metabolism in menopausal women with type II diabetes mellitus. We identified a direct relationship between daily physical activities with carbohydrates and lipid metabolisms as well as serum FGF21 levels. Our findings showed that physical training either as aerobic or resistance exercises, improve the lipid and glucose metabolism in studied subjects. Both aerobic and resistance exercises significantly decreased the mean of serum glucose, insulin, LDL-C, total cholesterol and TG after 8 weeks of trainings. On the other hand, the mean of HDL-C has been increased significantly in training groups.

Furthermore, insulin resistance was decreased significantly in trained subjects, suggesting the positive effects of aerobic and resistance exercises on carbohydrate and lipid metabolisms in menopausal women with type II diabetes mellitus. In addition to metabolic factors, we considered the mean of serum FGF21 level after trainings in all subjects. Our results demonstrated that the mean of serum FGF21 levels was increased significantly after 8 weeks of trainings in both exercised groups. Therefore, we observed that both aerobic and resistance exercises increase the mean of serum FGF21 levels in studied patients. In addition, we demonstrated a significant correlation between increased FGF21 levels and declined total cholesterol value after exercises. Previous studies have also reported FGF21 is related to cholesterol metabolism (17). Another potential finding of this study was related to the decreased insulin response observed after exercises. Insulin inhibits lipolysis and blocks the main mechanism by which exercise stimulates FGF21 secretion (1, 26).

Our results were consistent with other studies (28). In a study by Yang *et al*, they reported that a 3-month combined exercise programme decreases the serum FGF21 levels as well as arterial stiffness in obese Korean women (28). They also showed that BMI, waist circumference, SBP, diastolic blood pressure and triglyceride levels were significantly decreased after the exercise programme. Similarly, our results are in accordance with other findings that have shown a positive association between exercises and serum FGF21 levels (4, 5, 7, 8, 24, 27). Cuevas-Ramos *et al* observed that serum FGF21 levels significantly increased after 2 weeks of physical activity in women. This increment correlated positively with clinical parameters related to the adrenergic and lipolytic response to exercise (5).

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 (14).

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 (23). Therefore, the FGF21 response to exercise could be involved in the beneficial effects of increased physical activity in lipids, cholesterol and carbohydrate utilization, in menopausal women with type II diabetes mellitus, FGF21 seems to be an excellent therapeutic molecule for the treatment of type II diabetes and obesity in menopausal women with type II diabetes mellitus. In the present study, we showed that aerobic and resistance exercises lead to the systemic increase of serum FGF21 levels as well as a decrease of insulin resistance in menopausal women with type II diabetes mellitus. 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. However, some limitations of our study should be recognized. First, we could not provide a large number of participants for this study. In addition, the results may not be applicable to men. Finally, we did not register the caloric consumption during the study. However, no major changes in BMI and body composition were observed. Therefore, further study with a larger group of participants is necessary to evaluate the physiological role of FGF21 on aerobic and resistance exercise-induced changes in glucose and lipid metabolism.

ETHICAL CONSIDERATIONS

The Human Biomedical Research Institutional Committee of Islamic Azad University of Sari, Iran approved the study protocols, and written informed consent was obtained from all participants. The mean of demographic characteristics of all participants is shown in Table 1.

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