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A comparative study on the changes in plasma levels of fetuin-A, fat profile, and insulin resistance in healthy women and type 2 diabetic patients after 12 weeks of aerobic exercise

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Abstract- Aim: The present study compared the changes in plasma levels of fetuin-A, fat profile, and insulin resistance in healthy women and type 2 diabetic patients after 12 weeks of aerobic exercise.
Methods: In this study, 18 healthy type 2 diabetic women with an age range of 40-45 years were selected using a purposeful sampling method. Then, they were divided into two groups: type 2 diabetic patients (n = 10) and healthy people (n = 8). Both groups performed aerobic exercises for 12 weeks (3 sessions per week, each session lasting 40-60 minutes) under the supervision of a trainer. The hypotheses were tested in SPSS software. Statistical significance was considered at the level of $\alpha \leq 0.05$.
Results: The results revealed that exercise caused a significant decrease in the mean of the fetuin-A variable in the patient group (P=0.008) after the exercise period. However, it had no significant effect on the mean of this variable in the healthy group (P=0.26). Although the exercise period decreased the mean level of high-density lipoprotein variable significantly in the patient group (P=0.002), it did not cause a significant effect in the means of other fat profile variables of this group including triglyceride (P=0.28), cholesterol (P=0.1), low-density lipoprotein (P=0.77), and all the fat profile variables of the healthy group including triglyceride (P=0.11), cholesterol (P=0.61), high-density lipoprotein (P=0.37), and low-density lipoprotein (P=0.88). Exercise caused a significant decrease in the mean insulin resistance variable in the healthy group (P=0.024). However, no significant change was observed in the mean insulin resistance variable of the patient group after the exercise period (P=0.33).
Conclusion: The results suggest that a 12-week period of aerobic exercise causes a significant decrease in fetuin-A levels in type 2 diabetic women. Additionally, the present study revealed that aerobic exercises had no significant effect on fetuin-A in healthy women.

Keywords- Aerobic exercise, Fetuin-A, Fat profile, Insulin resistance, and Type 2 diabetes.

Introduction

Diabetes is considered the most common disease caused by metabolic disorders and the fourth cause of mortality in Western countries. The pathogenicity of this disease, in terms of treatment costs and high disability, is one of the major health-treatment problems of humans. It will be more significant with the expansion of urbanization and lifestyle changes toward inactivity and improper nutrition (Alavinia, 2012). The rate of diabetes disease follows an increasing trend. It had a 122% increase in the number of patients from 1995 to 2025. It caused direct costs of 2.5% to 15% of the total health budget and its indirect costs are very high and inestimable. It causes some complications such as ischemic heart diseases, hypertension, types of heart failure, retinopathy, neuropathy, nephropathy, cataract, etc. It causes 4 million deaths per year and accounts for 9% of all deaths worldwide. Its prevalence is 7.2% in the population over 30 years in Tehran and 6.5% in Isfahan. In Iran, there are at least 2 million diabetic patients and half of them are unaware of their disease (Delaware, 2004). Decreased response to the metabolic effects of insulin, including stimulation of glucose consumption or inhibition of hepatic glucose production is called insulin resistance. Insulin resistance plays a significant pathophysiological role in type 2 diabetes. Moreover, it is closely associated with other problems such as obesity, hypertension, coronary artery disease, dyslipidemia, and other disorders that are defined as metabolic syndrome (Williams, 1986).

The major problem in type 2 diabetes is not the lack of insulin, but the problem is in the target tissues, especially the muscles, so insulin resistance is high in these tissues. Since sugar cannot enter the target tissues, its level in the blood increases, and this issue stimulates the pancreas, and more insulin is produced by beta cells and enters the blood, resulting in hyperglycemia or hyperinsulinemia. It is often associated with symptoms such as frequent urination, polyuria, and weight changes (Lumber et al., 2008). Hyperglycemia causes complications such as cardiovascular diseases and damage to the eyes and kidneys. Increased insulin along with lipid disorders and hypertension provide the conditions for atherosclerosis (Grundy et al., 2005). Although insulin resistance is typically asymptomatic, it is directly associated with an increased risk of coronary heart disease (Lempiainen et al., 1999), cardiovascular dysfunction (Ingelsson et al., 2006), and mortality caused by them (Laaka et al., 2006). Thus, the evaluation of factors affecting insulin resistance is significant. Despite the clear need for new treatments for insulin resistance, its mechanisms and treatment have not been fully understood and clarified yet (Patrick et al., 2010).

Physical activity is effective in reducing the incidence of diabetes and is the primary factor or one of the significant factors in the lower prevalence of the disease among rural people compared to urban residents. Recent studies suggest that the prevalence of type 2 diabetes is higher in people living in urban areas who have less physical activity (Wahabi, 2009). The effect of physical activities and exercises in the control and treatment of diabetes has been proven since many years ago. Studies have indicated that in type 2 diabetic patients who have an insulin sensitivity problem, repeated muscle contractions in the absence of insulin facilitate the entry of sugar into the muscle cells and thus its consumption. Additionally, physical activities and exercises increase the levels of Glugouse transporter-4 proteins and reduce insulin resistance (Kim et al., 2004).

Differences in response to glucose transport in specific skeletal muscle fiber types might be related to the levels of Glut4 protein. Since this protein plays a key role in the transport of glucose to skeletal muscle, any disturbance in its expression may contribute to insulin resistance (Kern et al., 1999). Therefore, it can be stated that muscle contractions have an insulin-like effect and send large amounts of glucose into the cells to be used for energy production. It also allows muscle fibers during exercise to have a relatively low glycogen concentration for a relatively long period. Also, with the completion of an exercise, muscle cells try to restore their glycogen reserves, so blood glucose concentration remains at a lower level for several hours after exercise (Kart et al., 1989, Garto et al., 1984).

Regular exercise or physical activity can reduce significantly the complications of diabetes such as obesity, hypertension, hyperlipidemia, and hyperinsulinemia, and increase the sensitivity of the target tissue to insulin. Aerobic exercises can reduce insulin resistance and glycosylated hemoglobin (Tokmakidis et al., 2004). Studies suggest that aerobic exercise improves insulin sensitivity in subjects with insulin resistance. Its reason has been attributed to the simultaneous weight loss and positive regulation of the expression of glucose transporter protein (GLUT4) in skeletal muscle (Dumortier et al., 2003). Most studies have reported that endurance exercise can be effective in controlling type 2 diabetes (Boule et al., 2002).

Sigal et al. (2007) showed that 22 weeks of aerobic exercise, three sessions per week, improved blood sugar control in type 2 diabetic patients (Sigal et al., 2007). Giannopoulo et al. (2005) reported that 14 weeks of aerobic exercise, three sessions per week, 50 minutes per session, with an intensity of 65 to 70% of VO2 Peak, reduced body fat percentage and improved sensitivity to insulin in type 2 diabetic women (Giannopoulo et al., 2005). Aerobic exercise program causes positive changes in the significant risk factors of cardiovascular diseases including HDL-c, LDL-c, TC, BMI, DBP, and HC in obese women. It can also be stated that exercise improves fat profile and reduces insulin resistance. All these effects are useful for controlling obesity and its related diseases (Robert et al., 2013).

Fetuin-A is one of the blood proteins produced in the liver and secreted into the bloodstream. Bovine fetuin was first described in 1944 as the most abundant plasma protein in fetal bovine serum (Pedersen, 1994). In 1960, this protein was described in humans and named alpha-2-HS-glycoprotein. The reason for choosing this name was the alpha-2 globulin fraction of serum proteins in cellulose acetate gel electrophoresis (Hermans et al., 1960). Fetuin-A is a liver-derived plasma protein expressed highly for the proteolytic process of glycosylation, phosphorylation, and sulfation after translation. Fetuin is seen as a single-chain precursor to the mature double-chain form in blood circulation (Dichen et al., 2011). Fetuin-A belongs to the cystatin family of protease inhibitors and natural insulin receptor inhibitors (Rauth, 1992). Some studies have reported that the serum level of fetuin-A, like albumin, can be used as a marker of nutritional status and a general marker of hepatic protein synthesis, especially in dialysis patients (Block et al., 2007). Several articles have also reported its high concentration in metabolic syndrome, which may be considered a risk factor for this syndrome (Fisher et al., 2009). Regarding the effect of this protein on the insulin receptor, it has been stated that fetuin inhibits its activity by inhibiting tyrosine kinase of this receptor and inhibiting autophosphorylation (Akhoundi, 1994). Reports suggest that fetuin-A causes insulin resistance in muscle and fat tissue since it binds to insulin tyrosine kinase receptors in these tissues (Barclay, 2008). Moreover, its serum concentration is directly associated with insulin resistance and dyslipidemia due to the inhibition of insulin receptor autophosphorylation (Singh et al., 2012).

Fetuin-A can be used as a marker of vascular disease in type 2 diabetic patients (Roos, 2010). It is an independent predictor of type 2 diabetes due to its high concentration in insulin resistance cases. Different proteins such as fetuin-A and adiponectin regulate insulin sensitivity. Many studies have also reported an association between fetuin and atherosclerosis due to vascular calcification caused by this substance deficiency (Gorji et al., 2014). Several epidemiologic studies have reported that increased fetuin-A serum levels are associated with insulin resistance, metabolic syndrome, and type 2 diabetes (Song et al., 2011, Lx et al., 2008).

Given insufficient information on the association between fetuin-A serum level and insulin resistance, metabolic syndrome, and type 2 diabetes, and some contributing factors, more studies are needed to evaluate the cellular mechanism of fetuin-A action since this hepatocyte is associated with the risk of developing type 2 diabetes. Hence, the present study compares the changes in plasma levels of fetuin-A and fat tissue, and insulin resistance in healthy women and type 2 diabetic patients after 12 weeks of aerobic exercise.

Methods

The present study was quasi-experimental and was implemented as a pretest-posttest design. The statistical population of this study included type 2 diabetic women who were referred to the diabetes clinic of Fatemieh Hospital and those who were referred to the laboratory of the Javaheri Comprehensive Health Service Center of Khansar City and the healthy women who had health records in comprehensive health service centers. Among them, 25 patients who were between 40 and 45 years old and willing to cooperate in the project, and met the inclusion criteria of the study were selected by purposeful sampling method (after reviewing the medical records, face-to-face interviews, and measuring the ability to perform physical activity). Then, they were divided into two groups, patients and healthy. Both groups performed walking aerobic exercises, rhythmic aerobic movements (low impact aerobics), and basic calisthenics movements with music for 12 weeks, with a frequency of 3 sessions per week, and each session lasted 40-60 minutes. Each exercise session consists of 3 parts: warm-up (10 minutes), the implementation of walking, aerobic movements in preliminary chains of 4 in a standing position, and basic and calisthenics movements (25-45 minutes), and cooling down with final movements back to the initial state in a sitting and lying position (5 minutes).

Blood sampling was done by a laboratory expert. He took 10 ml of blood samples from the brachial vein of the subjects in a sitting position, 48-72 hours before the start of the exercise period, and 48-72 hours after the end of the 12-week exercise program, after about 10 hours of fasting. The tests were performed by specialized devices in two laboratories of the Javaheri Health Center in Khansar and the laboratory of Al-Zahra Hospital in Isfahan. Some anthropometric indices were measured and recorded by a nutritionist before blood sampling, and some other indices were measured and recorded by a trainer 2 days after blood sampling. Due to the dropout of 7 subjects, posttest data were collected from 18 subjects (10 subjects in the diabetic group and 8 subjects in the healthy group).

The collected data were analyzed at two levels of descriptive and inferential statistics. In the inferential statistics section, the Shapiro-Wilk test was used to examine the normal distribution of the data. Paired t-test would be used to examine the intra-group differences, if the data were normal, and the Wilcoxon signed-rank test would be used to examine the difference between the pretest and posttest if the data were not normal. Graphs were drawn by Excel software and statistical processes were done by SPSS software to test hypotheses. The data were analyzed at a significance level of equal or less than 0.05.

Results

All the variables were tested at two different times, before performing aerobic exercises and after performing aerobic exercises in two groups of healthy people and diabetic patients. Since the statistical sample includes two independent groups, all descriptive statistics indices, central index (mean), and dispersion index (standard deviation) were calculated separately for each group.

Table 1: Descriptive information of diabetic subjects

Diabetic subjects						
Variable	Mean ± SD		Min		Max	
Age	42.40±1.17		41		45	
height (cm)	155.80±4.80		146		161	
weight (kg)	78.43±10.48	76.20±11.01	65.8	64.5	104.7	102
Body mass index (Kg/m2)	32.29 ± 3.99	31.36±4.04	28.13	27.15	41.41	40.35
resting heart rate (beats per minute)	78.60±7.72	75.60±7.04	66	66	90	84
Maximum oxygen consumption	30.22±4.46	30.50±6.84	23.95	14.42	39.14	39.60

Table 2: Descriptive information of healthy subjects

healthy subjects						
Variable	Mean± SD		Min		Max	
Age	41.75±1.75		40		45	
height (cm)	175.12±6.57		145		165	
weight (kg)	73±6.63	71.83±6.50	63.50	62.70	80	79
Body mass index (Kg/m2)	29.53±1.37	29.05±1.06	27.48	27.57	31.25	30.55
resting heart rate (beats per minute)	76.50±8.33	69±7.85	66	60	90	78
Maximum oxygen consumption	30.81±4.55	35.86 ± 9.33	25.45	27.99	39.08	57.08

Table 3: Examining the pretest and posttest differences in fetuin-A levels in diabetic women and healthy women

Group	Variable	Stage	Mean±SD	Test statistic (Z)	Sig (p)
Diabetic women	Fetuin-A(μg/ml)	Pretest	734.56±173.47	-2.6	*0.008
		Posttest	522.74 ± 199.13		
Healthy women	Fetuin-A(μg/ml)	Pretest	990±865.20	-1.12	0.263
		Posttest	988.02±870.52		

* Statistical significance was considered at the level of α ≤ 0.05

Based on the results, the mean fetuin-A of diabetic women after performing aerobic exercises in the posttest stage decrease significantly to 0.008. It means that performing 12 weeks of aerobic exercise affected the mean fetuin-A. Although the mean of this variable in the posttest stage also decreased in healthy women, its decrease was not significant (Table 3).

Table 4: Examining the difference between pretest and posttest fat profiles in diabetic women and healthy women

Group	Variable(mg/dl)	Stage	Mean± SD	Test statistic		sig
				(T)	(Z)	(p)
Diabetic women	High-density lipoprotein (HDL)	Pretest	55.50 ± 5.01	4.35		*0.002
		Posttest	48±5.35			
Healthy women	High-density lipoprotein (HDL)	Pretest	51.37±8.15	0.95		0.37
		Posttest	49.25±5.82			
Diabetic women	Low-density lipoprotein	Pretest	93±21.65	0.29		0.77
		Posttest	91.72±18.31			
Healthy women	Low-density lipoprotein	Pretest	114.07±22.73	-0.159		0.88
		Posttest	115.25±29.12			
Diabetic women	triglyceride	Pretest	138 ± 76.86		-1.07	0.28
		Posttest	111.90±69.15			
Healthy women	triglyceride	Pretest	136.50±26.67	1.79		0.11
		Posttest	117.25±33.57			
Diabetic women	Cholesterol	Pretest	176.10±27.68	1.79		0.1
		Posttest	162.10±29.47			
Healthy women	Cholesterol	Pretest	192.75±28.99	0.52		0.61
		Posttest	188±37.04			

* Statistical significance is considered at the level of $\alpha \leq 0.05$.

Regarding the fat profile variables, as shown in Table 4, the mean of HDL in diabetic women in the posttest stage compared to the pretest stage was associated with a decrease at a significance level of 0.002. The mean of this variable in the posttest of the healthy group also decreased, although the difference was not significant compared to the pretest. The mean LDL decreased in the posttest of the patient group and increased in the posttest of the healthy group. However, the difference in the means was not significant. Thus, performing 12 weeks of aerobic exercise did not affect the mean LDL of both groups. Changes in the mean blood triglyceride in both patient and healthy groups were not statistically significant. Regarding the mean cholesterol variable, although it decreased in both groups in the posttest stage, the decrease did not have a significant difference between the two groups. It means that performing 12 weeks of aerobic exercise did not affect blood cholesterol levels.

Table 5: Examining the pretest and posttest differences in the level of insulin resistance in diabetic women and healthy women

Group	Variable	Stage	Mean± SD	Test statistic		Sig (p)
				(T)	(Z)	
Diabetic women	Insulin resistance index	Pretest	5.66 ± 3.56		-0.96	0.33
		Posttest	5.28 ± 3.42			
Healthy women	Insulin resistance index	Pretest	3.26 ± 1.19	2.85		*0.024
		Posttest	2.52±1.002			

*Statistical significance is considered at the level of $\alpha \leq 0.05$.

The results showed that although the mean insulin resistance in diabetic women decreased after 12 weeks of aerobic exercise, it was not statistically significant. The mean difference of this variable in the posttest and pretest stages in healthy women was at a significant level of 0.024. Thus, performing 12 weeks of aerobic exercise had a significant effect on the mean insulin resistance of healthy women (Table 5)

Discussion

The results revealed that after 12 weeks of aerobic exercise, the mean of the fetuin-A variable in the patient group (type 2 diabetic women) decreased in the posttest stage compared to the pretest stage, and this decrease was statistically significant (P=0.008). Also, in the healthy women group, the mean of this variable decreased in the posttest stage compared to the pretest stage, although the decrease was not significant (P=0.26). These results are consistent with those of the study conducted by Schultes et al. (2010). However, they are inconsistent with the results of the studies conducted by Bahrami et al. (2011), Rezaeian et al. (2000), and Shevandi et al. (2009). These differences in the results may be attributed to the type and intensity of exercises and number of exercise sessions, age range, and the disease of the studied subjects.

Fetuin-A is a multi-functional protein with several functions. It is a protein whose low level can be both beneficial and harmful (Mehrotra et al., 2005). Studies suggest that fetuin-A levels decrease especially in healthy people or in diabetic patients after performing exercises. In the present study, fetuin-A significantly decreased in diabetic patients, which may be due to the reduction of insulin resistance owing to the exercise of these patients. The results of studies have shown that in type 2 diabetic patients who have an insulin sensitivity problem, repeated muscle contractions in the absence of insulin facilitate the entry of sugar into the muscle cells and thus its consumption. Also, exercise increases the levels of Glugouse transporter-4 proteins and reduces insulin resistance (Kim et al., 2004). Studies also suggest that aerobic exercise improves insulin sensitivity in subjects suffering from insulin resistance. It is attributed to the simultaneous weight loss and positive regulation of the expression of glucose transporter protein (GLUT4) in skeletal muscle (Dumortier et al. 2003).

Regarding the effect of this protein on the insulin receptor, it has been reported that fetuin inhibits the tyrosine kinase activity of this receptor and inhibits autophosphorylation (Akhoundi, 1994). The results revealed that after 12 weeks of aerobic exercise, only the mean of high-density lipoprotein (HDL) in the patient group decreased significantly (P=0.002). Although the mean of other fat profile variables of both groups decreased in the posttest stage compared to the pretest stage, the decrease was not significant. Accordingly, it can be concluded that 12 weeks of aerobic exercise did not have a significant effect on the fat profile parameters of patients and healthy women. These results are consistent with those of studies conducted by Belom and Chang (2008) and Goldhaber et al. (2003). However, they are inconsistent with the results of the studies conducted by Wahabi et al. (2008) and Rezaeian (2009).

In the study conducted by Belom and Chang, the duration of the exercise was short (7 days of moderate-intensity aerobic exercise. However, much time is needed for the effect of aerobic exercise on blood fats. Regarding the HDL variable, high-intensity exercise is effective. The exercise intensity in our study was not as high as in Belom's study (Belom and Chang, 2008).

In the study by Goldhaber et al., the changes in the measured values of lipids after three weeks of the walking program were very small and insignificant

(Goldhaber et al., 2003), which was consistent with the results of this study. In the study by Wahabi et al. (2009), the level of triglycerides and HDL in the group of diabetic patients decreased significantly compared to the control group, which is not consistent with our study (Wahabi et al., 2009). The study by Rezaeian Najmeh (2010) showed that performing 10 weeks of endurance exercise (3 sessions per week, each session lasted 45 minutes with an intensity of HRmax 40-60%) in sedentary obese postmenopausal women was associated with a significant decrease in triglycerides, cholesterol, and LDL compared to the control group. the results obtained for the lipid variables are not consistent with the results of our study. Its reason may be the type of subjects and exercises (Rezaeian Najmeh, 2010).

Studies have shown that aerobic exercise with an appropriate intensity causes positive and significant effects on the fat profile. However, in this study, a period of aerobic exercise did not affect the fat profile. The difference between the results of our study and other studies might due to the type of subjects, the length of the exercise period, exercise intensity, and the lack of control over the diet of these subjects. The results revealed that after 12 weeks of aerobic exercise, the mean variable of insulin resistance in the healthy women group decreased in the posttest stage compared to the pretest stage and this decrease was statistically significant (P=0.024). However, the mean of this variable in type 2 diabetic women decreased in the posttest stage compared to the pretest stage. However, the decrease was not significant (P=0.33). The results of the present study are consistent with those of studies conducted by Shevandi et al. (2008), and Dunstan et al. (2002), but inconsistent with the results of the study conducted by Terry et al. (2009).

In the study by Shevandi et al. (2009), 30 type 2 diabetic men performed aerobic exercise. The results revealed that insulin resistance decreased significantly after exercise. Dunstan et al. (2002) showed that high-intense aerobic exercise improves insulin resistance, but resistance exercise does not change insulin resistance. Terry et al. (2009) investigated the effect of long-term exercises on the concentration of peptide hormones and insulin resistance in overweight youth. In the mentioned study, youths participated in regular aerobic exercise for 8 months. The result of this study showed that exercise did not cause a change in insulin and glucose. In the study by Lee et al. (2008), the effect of two types of exercise methods (intermittent exercise with 90% intensity and continuous exercise with 70% intensity of maximum heart rate) was investigated in patients with metabolic syndrome. It has been reported that intermittent aerobic exercise, especially when performed with greater intensity, increases cell response to insulin and improves insulin resistance in fatty muscle tissues. However, Houmards suggested that the number of exercise sessions per week rather than the intensity of exercise is associated with improved insulin sensitivity. Mayer et al. (1998) indicated that both intensity and duration of exercise were effective, so when the duration of an exercise was at the highest level, an improvement in insulin sensitivity was observed (Sattar et al., 2006).

It has also been reported that fetuin-A causes insulin resistance in muscle and fat tissue since it binds to insulin tyrosine kinase receptors in these tissues (Barclay, 2008). Also, its serum concentration is directly associated with insulin resistance and dyslipidemia due to the inhibition of insulin receptor autophosphorylation (Singh et al., 2012). Thus, the reduction in insulin resistance in the diabetic women group can be related to the significant reduction of fetuin-A (P=0.008). Regarding the relationship between physical activity and its effect on insulin resistance, most studies have shown that physical activity reduces insulin resistance and its consequences (Thompson, 2001). Regular exercise leads to a decrease in plasma glucose levels, a significant increase in insulin sensitivity, an improvement in insulin resistance, and an overall improvement in sugar control (Thompson, 2001). Epidemiological evidence suggests that physical activity prevents and delays the onset of insulin resistance and type 2 diabetes (Tomilto, 2001). Regarding the significance of insulin resistance in the healthy women group and the significant difference between the means of the two groups of type 2 diabetic women and healthy women, it seems that 3 sessions of aerobic exercise per week for 12 weeks were sufficient to achieve a significant change in the insulin resistance index.

Conclusion

The results of the present study revealed that a 12-week period of aerobic exercises causes a significant reduction in the level of fetuin-A. Additionally, the present study showed that aerobic exercises had no significant effect on the fetuin-A variable in healthy women. Regarding the effect of aerobic exercise on fetuin-A level and insulin resistance in type 2 diabetic women, it is suggested to use this type of exercise along with drug therapy to improve the condition of diabetes in diabetic patients. Also, further studies with a longer period are needed to evaluate the simultaneous effect of aerobic exercise and drug therapy. The results revealed that aerobic exercise improves fetuin-A levels and insulin resistance in type

2 diabetic patients. Thus, it is recommended that these patients use this type of aerobic exercise to improve their condition since these exercises are useful, safe, and enjoyable and they can encourage patients to perform physical exercises.

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