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The Effect of saffron extract and aerobic training on serum HbA1C and Apo A1 in men with Diabetes Mellitus, Type II type 2 diabetes.

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Introduction: Diabetes Mellitus, Type II, is a public health problem which has reached epidemic proportions due to the rapidly increasing rates of this disease worldwide. More than 246 million people in the world have diabetes. Pharmaceutical and non-pharmaceutical strategies for control and treatment of diabetes was provided. Exercise and nutrition, including non-drug strategies for the prevention and control of diabetes are considered.

Materials and Methods: This was a quasi-experimental study. 24 men with type 2 diabetes were selected and randomly divided in four groups (1. control, 2. saffron extract, 3. aerobic exercise, 4.aerobic exercise and saffron extract). Saffron extract was used in amount of 3 mg/kg/BW per daily. Aerobic exercise, three days a week, for eight weeks, with 55-70% of maximum heart rate were performed. At the end, levels of HbA1c and Apolipoprotein A-1 were measured. Data were analyzed by one-way ANOVA and Tukey tests.

Results: Aerobic training (p=0.33), saffron extract (p=0.26) and saffron combined with Aerobic training (p=0.48) was no significant decrease effect on HbA1c levels in diabetic men. But in all three groups, a significant decrease in the amount of Apo A-1, in diabetic men, was observed (p <0.05).

Conclusions: Apolipoprotein A-I, which is the major protein component of high density lipoprotein (HDL) in plasma. Aerobic exercise and saffron extract can increased levels of Apo A-1 in men with type 2 diabetes.

Keywords: Saffron, aerobic, Diabetes Mellitus, Type II Apo A-1, HbA1c.

Introduction

Diabetes is one of the common metabolic diseases in the world that has the dire adverse effects such as nephropathy, retinopathy, cardiovascular problems, gastrointestinal disorders, the deficiencies in the immune system and the skeletal muscle Atrophy (Shirali et al., 2013). The occurrence of type 2 diabetes is increasing with the increased prevalence of obesity, the dietary changes and reduced physical activity.One of non-medicinal ways of prevention and treatment is the use of medicinal herbs. While medicinal herbs and their derivatives have been traditionally discussed in the treatment of diabetes and its complications, valid research evidence has not been found about the effectiveness of a lot of them (Shapiro and Gong, 2002; Sharifat et al., 2014; Mahdizadeh et al., 2015).

Sports activities contribute to the prevention of special complications of diabetes as well (Stewart, 2004). Today, sport and physical activity are also independently or along with other drug treatments for the prevention or treatment of type 2 diabetes , and as well as the balance of metabolic and hormonal factors influencing its occurrence, are important for specialists (Barari et al., 2017).

Obesity and insulin resistance decrease cholesterol- HDL levels, so that obese individuals with body mass index (BMI) over 23 kg/m2, have a lower HDL-cholesterol with the presence or absence of an increase in triglycerides (Mooradian et al., 2008; Shirali et al., 2012; Mahdizadeh et al., 2015). In addition to reducing cholesterol- HDL levelsin the people, HDL protein composition is changed. The researchers found heart protection effects of HDL are associated with proteins such as apolipoprotein E, apolipoprotein A-I and apolipoprotein B, apolipoprotein M (Hu et al., 2010). Apolipoproteins A-1 and B is involved in diabetic retinopathy and according to previous evidence, the amount of the serum apolipoproteins is a much more important indicator compared to the normal lipids for retinopathy and other possible microvascular diabetic complications (Sasongko et al., 2011). Blood sugar can be measured in different ways. Plasma glucose level shows the blood sugar level at the moment of sampling, but HbA1c or glycated hemoglobin that is called "long-term sugar", shows blood sugar levels within two to three months before sampling and if blood sugar has been high durinhe last few weeks, the HbA1c level will be high, as well.So, HbA1c is a better indicator to check the blood sugar levels in diabetic patients (Bathaie et al., 2012). Studies of the aqueous extract of Saffron are limited

in patients with type 2 diabetes. Saffron reduces the capacity of the oxidation of lipoproteins (Verma and Bordia, 1998).

Crocetin of saffron reduces insulin levels and serum lipid levels (Xi et al., 2007). Hosseini and Azerbaijani point out that six weeks of resistance training and the consumption of water extract of Saffron has significant effect alone on the glycemic indexes (fasting glucose and HbA1c)(Hosseini and Azarbayjani, 2013). Other studies have confirmed these findings (Xi et al., 2007; Yang et al., 2010; Arasteh et al., 2011; Shirali et al., 2012). However, consumption of saffron in a concentration of 10 mg/ml in eight week, significant did not have a significant effect in reducing HbA1c. Previous studies the effects of exercise on apolipoproteins and HbA1c were examined (Naderi et al., 2005). The increased formation and size of apolipoprotein A-1 affected by 6 months of endurance training in 39 subjects with a mean age of 57 years who had high blood cholesterol concentrations (Wilund et al., 2002). The increased apolipoprotein A-1 as a result of exercise (Olchawa et al., 2004). In this study by Garekani, no significant changes were reported in HbA1c levels after aerobic exercise on type 2 diabetic subjects (Garekani et al., 2011). The results of a study by Shahrjerdi et al on women with type 2 diabetes showed that strength and endurance training caused a significant reduction in HbA1c level (Shahrjerdi et al., 2009).

While many studies have been conducted on the effects of aerobic exercise training in these patients, results of different studies regarding the impact of sporting activities on HbA1c levels and serum apolipoproteins have been inconsistent. Also, few studies have examined the effect of taking the Saffron extract of the extract. According to our previous studies 2011-2016 on human and animal models of diabetes and given the widespread prevalence of diabetes and the importance of lifestyle changes in controlling and treating this disease, this study aimed to investigate the effect of saffron and practice of endurance exercise on serum levels of apolipoprotein A-1 and HbA1c of patients with type-2 diabetes.

Materials and Methods

Preparation of aqueous extract of Saffron

The dry stigma of edible saffron (Crocus sativus L.) was prepared from Torbat-e Heydarieh County located in the southern province of Khorasan Razavi. First, stigma of saffron is powdered using a pounder; then the resulting powder was dissolved in distilled water and its extract was obtained using a distiller. For this purpose, 100 grams of dried stigmas powder were poured in a glass tank and after the addition of 1000 ml of distilled water were boiled for 10 minutes at 100 ° C. Then, the supernatant was passed through a filter and kept in a bain-marieat a temperature of 55 ° C for a week until gradual evaporation of its water and powdered extract was obtained.

Study method

In this clinical trial study 40 -50 year-old male patients with type II diabetes, who referred to in the Hospital Mahdi, in the Rasht city in recent years, were invited to participate in the study. 50 students volunteered to participate in this study. After interviewing volunteers, 24 men with type 2 diabetes, were selected. Inclusion criteria: personal satisfaction to participate in the study; type II diabetes; lack of chronic obstructive pulmonary disease; lack of heart failure; lack of angina and pulmonary embolism; no hypertension; no kidney or liver disease; hypothyroidism and hyper thyroidism. First, study participants gave written consent. Before the start of aerobic exercise, the blood tests were taken from samples and their serum HbA1c and apolipoprotein A-1 were measured. In addition to measuring these factors, heart rate, blood pressure (systolic + diastolic) subcutaneous fat percentage, VO2max and BMI were measured. After taking the test, subjects were randomly divided in to four groups: 1- control (no exercise and without taking the saffron extract) 2- consumption of aqueous extract of saffron, 3- aerobic exercise, 4-aerobic exercise and the consumption of saffron extract. The control group received no intervention. The group receiving saffron also received saffron 3mg / kg on their body weight daily. Aerobic exercise training groups were present in the Sports Hall of Malavan Javan in Rasht three times a week for eight weeks (a total of 24 sessions) for aerobic exercises with an intensity of 55 to 70 percent under the supervision of a trainer. In addition to attending the training protocol, the aerobic exercise group received an aqueous extract of Saffron daily 3mg / kg on their body weight. After two months, a day after the last training session protocol, blood samples were taken again from the groups and their serum HbA1c and apolipoprotein A-1 levels were measured.

Statistical analysis

In descriptive statistics section, data were calculated with the help of descriptive form of tables and figures. In statistical inference Section, the distribution of the data related to each of the variables was examined using the Kolmogorov–Smirnov test. After ensuring the normal data, the parametric tests were used to analyze the data. Therefore, paired t-test was used to determine the intragroup differences and he one-way analysis of variance (ANOVA) was used to determine the intergroup differences and then if there were significant differences, Tukey's HSD post hoc test was used to identify its value. To analyze the data, SPSS software was used. A significance level of $p \leq 0.05$ was considered for all calculations.

Results

Table 1

Shows the characteristics of the subjects on the basis of the mean and standard deviation.

Table 1 - describes the characteristics of subjects based on the mean ± SD

Variable	group	Control	saffron	Aerobic exercises	Saffron-aerobic exercis
Number		6	6	6	6
Age (years)		40.3± 4.9	43.7± 1.75	46.5± 1.64	43.8 ± 1.72
Height (cm)		174.8 3.7	175.6 ± 5.6	174.6 ± 3.8	174.5± 1.87
Weight (kg)	pre-test	86.7 ± 11.7	75 ±16.16	81.5 ± 4.1	79.5± 6.3
	post-test	86.5± 1.1	75± 15.40	79± 3.8	77.3 ± 6
*BMI(kg/m2)	pre-test	27.06 ± 1.04	25.5 ±2.4	24.06 ± 3.4	28.3 ± 3.1
	post-test	25.9 ± 0.71	25.4± 2.4	24.1 ± 3.5	28.2± 2.9
maximum oxygen consumption	pre-test	28 ± 3.03	30± 2.7	33.7 ± 2.5	328 ± 4.1
	post-test	36.3± 2.9	37± 2	34± 2	32.7± 3.9

* BMI: body mass index

Table 2 - The mean ± SD of variables, Divided groups , in different stages (pre-test and post-test)

Group	variable	pre-test	post-test
Control	HbA1c	8.85± 1.47	9.23±1.59
	Apo A-1	5.25±0.88	5.17±0.75
saffron	HbA1c	9.75±0.94	9.37±1.55
	Apo A-1	7.42±4.78	16.25±4.83
Aerobic exercises	HbA1c	9.71±1.15	9.33±0.95
	Apo A-1	7.33±3.22	15.41±1.28
Saffron-aerobic exercis	HbA1c	8.53 ± 0.79	8.33 ± 0.90
	Apo A-1	7.67 ± 4.4	13.42 ± 5.48

The descriptive findings related to the variables in the four groups are presented in Table 2.

The results in Table 2 show that:

1. In the pre-test, the highest average HbA1c was for Saffron group, and also in post-test saffron highest average was in this group.

2. In the pre-test, the lowest average was in the group taking aerobic exercises and saffron-posttest is also the lowest average was in the same group.

3. In pre-test, the maximum average ApoA-1 was related to the use of saffron and in post-test, the highest average was in the control group.

4. In the pre-test, lowest average was related to control group and in post-test, lowest average was related to the aerobic exercise group.

Table 3. Comparison of pre-test and post-test HbA1c in groups.

Group		Paired differences				
	Mean	Standard deviation	standard error	t	Df	*p*-value
Control	-0.38	0.25	0.10	-3.78	5	0.33
Saffron	0.38	0.75	0.30	1.26	5	0.26
Aerobic exercise	0.38	0.88	0.36	1.07	5	0.33
Saffron-aerobic exercis	0.20	0.64	0.26	0.77	5	0.48

Paired t- test results showed that the significance level is less than 0.05, so the mean difference indicates that saffron extract and aerobic exercise increases the amount of Apo A-1 in type 2 diabetic men. Saffron extract and aerobic training in combination had no significant effect on the Apo A-1 (P=0.054). As shown in Table 4, no significant difference was seen in the Apo A-1 in pre-test and post-test in the control group (P =0.44).

Table 4. Comparison of pre-test and post-test Apo A-1 in groups

Group		Paired differences				
	Mean	Standard deviation	standard error	t	Df	*p*-value
Control	1.6	4.6	1.89	-0.84	5	0.44
Saffron	8.8	7.1	2.9	-3.06	5	0.028*
Aerobic exercise	8.1	2.7	1.1	-7.3	5	0.001*
Saffron-aerobic exercis	5.7	5.6	2.3	-2.5	5	0.05*

*p < 0.05 level of significance

For a better understanding, information obtained is presented in Figure 1.

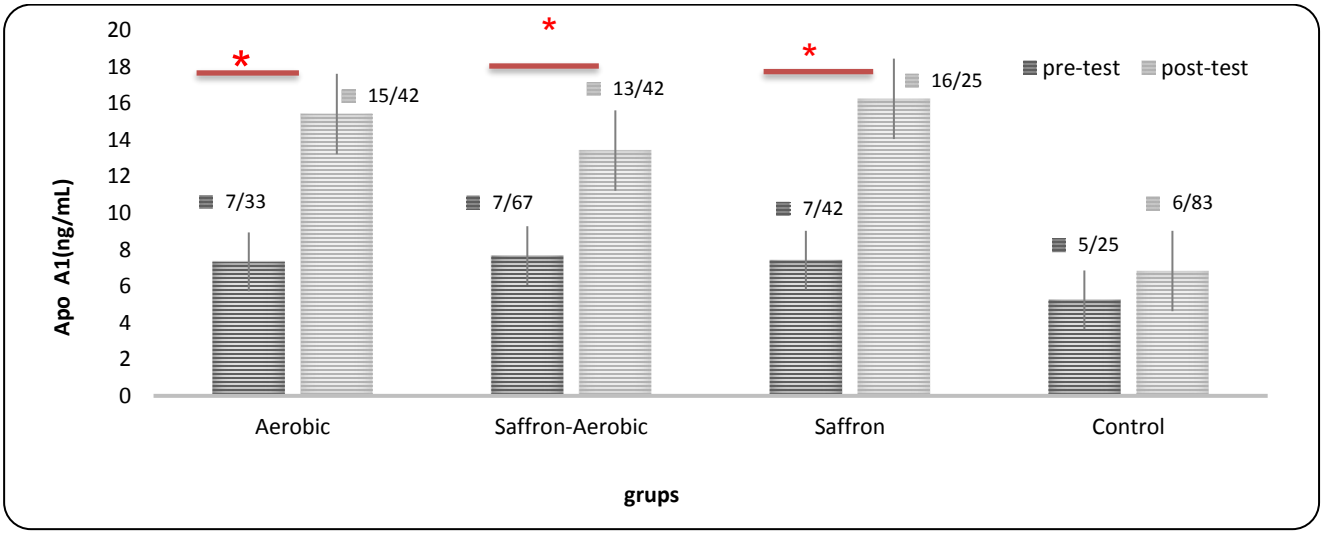

Fig. 1. Comparison of pre-test and post-test Apo A1 concentrations, in four groups.

Discussion

This study aimed to investigate the effect of aerobic exercise on the extract and index glycosylated hemoglobin and serum apolipoprotein A-1 was conducted in patients with type 2 diabetes.

The effect of the Saffron extract on HbA1c

Saffron extract (10mg / kg) had no significant effect on HbA1c levels in type II diabetic men. Saffron extract in a concentration of 10 mg has no significant effect on HbA1c and their results are consistent with the results of this research (Naderi et al., 2005). The methanolic extract of saffron (80-240mg / kg), crocin (50-150mg / kg) and saffron (0.25-0.5ml / kg / 0) decreased HbA1c (Kianbakht and Hajiaghaee, 2011). Consumption of saffron has led to a significant decrease in HbA1c in diabetic rats. In this study, rats were given 25 milligrams per kilogram of saffron extract that different our research in terms of concentrations (Hosseini and Azarbayjani, 2013).

Also results of other studies in this area reported the reduction in HbA1c, as a result of the consumption of the Saffron extract (Xi et al., 2007; Yang et al., 2010; Hosseini and Azarbayjani, 2013). The results of more studies are not consistent with the results. This inconsistency could be as a result from the use of different samples and different concentrations of the Saffron extract. The mechanism of the effect of the Saffron extract on HbA1c cannot be described in this study, but previous research noted that Saffron caused the renewal of beta cells in the diabetic mice (Mohajeri et al., 2009). In addition, it seems that more studies are needed to understand the mechanisms of the extract.

The effect of aerobic exercise on HbA1c

The results showed that eight-week aerobic training has no significant effect on HbA1c levels in type 2 diabetic men. Various studies have examined the effects of physical exercise on HbA1c levels. Some of these studies are consistent with the results of this study.

Wallberg stated that four months of training for 60 minutes per session, two to three times a week, did not change HbA1c in nine subjects with mean age 35 years. In this study, exercise intensity was uncertain (Wallberg-Henriksson et al., 1998). The results of a study on 20 patients showed that training for three months with the intensity of the 60 to 85 percent of maximum heart rate for 45 minutes per session, three times a week, did not change HbA1c (Zinman et al., 1984). The results of a study by Georgia (2011), did not report any significant change in HbA1c levels after aerobic exercise in patients with type 2 diabetes as well (Jorge et al., 2011).

But a lot of research reported different findings with this study's results. Research on 25 patients with an average age of 52 years showed that the implementation of four months of exercise at 70% maximal oxygen consumption for 45 minutes per session and 5 to 7 times a week reduced HbA1c (Rönnemaa et al., 1988). The results of the research by Mosher on 10 patients with an average age of 17 years showed that implementation of three months of aerobic exercise for 45 minutes per session, three times a week reduced HbA1c (Mosher et al., 1998). The results of the research on 110 people with an average age of 55 years showed that the implementation of the four months of training by 60 to 75 percent of maximum heart rate for 40 to 60 minutes per session, 4 sessions per week reduced HbA1c (Schwartz et al., 1992). The increase 6/1% HbA1c in diabetic and non-diabetic without physical activity is a good predictor of the risk of coronary artery disease (Aczel et al., 2003).

HbA1c in non-diabetic patient's active was significantly lower than passive patients (Sloma et al., 2003; Dela et al., 2004). Also the reduced levels of HbA1c in patients with type II diabetes mellitus as a result of physical activity (Maiorana et al., 2002; Boulé et al., 2003; Sigal et al., 2004; Lecumberri et al., 2007). Also showed that 8-week aerobic exercise caused a significant reduction in HbA1c in diabetic patients (Yousefi pour P, 2015).

As we see the results of research conducted in this field have been contradictory and some studies address the lack of impact of the of physical activity on levels and HbA1c and numerous research put an emphasis on reducing HbA1c levels as a result of physical activity.

In this study, aerobic exercise, and a combination of aerobic exercises and consumption of saffron extract on HbA1c did not show a significant effect. In general, it can be said that contrast in research results can be caused by several factors. For example, you can note type, severity and duration of the exercise, the initial level of HbA1c, age of the participants, their gender and use of drugs that impress exercise effects. For example, the average age of the study subjects was about 10 to 13 years and they reported a significant decrease in HbA1c (Schwartz et al., 1992; Dela et al., 2004; Yousefi pour P, 2015). Strength and endurance training caused a significant reduction in HbA1c level (Shahrjerdi et al., 2009). The reduced HbA1c, as a result of strength training (Hosseini and Azarbayjani, 2013).

Several studies have confirmed exercise as a way to control weight and Glycemiccontrol followed by the reduction of HbA1c. Improvement in glycosylated hemoglobin levels and lipid profiles as a result of aerobic exercise training causes a reduction in inflammatory markers secreted by adipose tissue as well, and given that these inflammatory markers causes insulin resistance, reduced glycosylated hemoglobin and lipid profile is followed by insulin resistance. Furthermore, possibly muscle contraction increases permeability of the membrane to glucose due to the increased number of vehicles of glucose in the plasma membrane. By performing sports activities, rates of 4 glutamines in the muscles trained are increased that improves insulin action on glucose metabolism and can reduce HbA1c levels (Shahrjerdi et al., 2009).

In fact, disorders contributing incidence of insulin resistance are returned with weight loss, diet and physical activity. By increasing carriers of glucose into muscle cells, glutamine 4, insulin receptor substrates and also increasing muscle mass, exercise can increase the body's response to insulin. Fatty acids produced from adipose tissue, by an accumulation in muscle cells, disrupt the transfer of GLUT-4 cells into the surface of these cells; by increasing fatty acid oxidation, exercises prevent their accumulation in muscle cells. Hence, Changes in lifestyle with a focus on weight loss and increased physical activity, is one of the main strategies of coping with diabetes in people with impaired glucose tolerance (Tadibi and Bayat, 2012).

Comparison of the effect of Saffron extract, aerobic exercise, and a combination of Saffron extract - aerobic exercise on the HbA1c

The combination of Saffron extract - aerobic exercise had no significant effect on HbA1c levels in the groups. A comparison of the effects of different interventions showed that there is no

significant difference between the consumption of Saffron extract, aerobic exercise, and the combination of Saffron extract-aerobic exercise in the HbA1c groups. No research was found to compare the protocols. Hosseini, Nikbakht and Azerbaijani compared the effects of resistance training and saffron extract in diabetic rats (Hosseini and Azarbayjani, 2013).

They showed that the HbA1c of test groups (resistance exercise group, combined resistance exercise- saffron extract group and saffron extract group) is lower than the control group, but there was no significant difference between the experimental groups. Although the results are in line with the results of this study, the exercises used in the study are different. Morerecognition about this issue needs to greater preceding studies.

The effect of the saffron extract on Apo A-1

A period of daily intake of aqueous extract of saffron at an amount of 150 mg / kg caused a significant increase in the Apo A-1 in type 2 diabetic men. No research was found to investigate the effects of the saffron extract on Apo A-1. Most studies done about saffron are focused on its antioxidant properties. It is believed that saffron has antioxidant properties and also the active ingredient such as crocin and Safranal (Kanakis et al., 2007). Verma and Bordia are believed that the use of saffron can prevent the increased oxidative stress and the development of type 1 diabetes (Verma and Bordia, 1998). However, more research is required to determine the effect of the extract on Apo A-1.

The effect of aerobic exercise on Apo A-1

Eight weeks of aerobic exercise significantly increased plasma levels of Apo A-1 type 2 in diabetic men. Endurance exercise (5 days per week for 6 months) has increased quantities of Apo A-1 in both young and middle-aged men groups (Schwartz et al., 1992). After 24 weeks of training, aerobic exercise and a combination of aerobic and resistance exercises have shown significant increase in the Apo A-1. The increase was higher in the combination group, but the difference was not significant (Park et al., 2003). The increased formation and size of apolipoprotein A-1 by a 6- month endurance training in 39 subjects with a mean age of 57 years, who had high blood cholesterol concentrations (Wilund et al., 2002). Increase in apolipoprotein A-1 as a result of exercise, but exercise protocol was not performed in this study, and through completing a questionnaire the subjects were classified into the exercised and non-exercised groups (Olchawa et al., 2004). The effects of progressive resistance training on the concentration of plasma apolipoprotein A-1 rats. Results showed a significant increase in serum levels of apolipoprotein A-1 as a result of resistance exercise (Safarzadeh, 2014). The effect of progressive resistance exercise on serum concentrations of apolipoprotein A-1 in diabetic rats and showed that after 4 weeks of resistance exercise, serum levels of apolipoprotein A-1 in the exercise group increased significantly compared to the control group (Rohi et al., 2013). Aerobic and resistance exercise on overweight women has significantly improved Apolipoprotein A-1. However, there are also studies that have presented conflicting results (Saadatnia et al., 2015). The implementation of a short-term endurance exercise Protocol on Wistar male mice (for three weeks with an intensity of 26meter per minute and for 90 minutes, five days a week on revolving bar). No difference was seen in the amount of apolipoprotein A-1 (Khabazian et al., 2009).

The moderate resistance and intense exercise on Apolipoprotein A-1 in non-athlete students has not created a significant difference (Sheikholeslami Vatani et al., 2011). Also did not observed significant difference in the apo A-1 in obese women owing to 8 weeks of resistance exercise (Segal et al., 1991). While many factors such as age, gender and background of samples as well as initial levels of Apo A-1 can affect research results, but the low intensity of exercises has been known as a main reason of a significant increase in Apo A-1 as a result of sports activities (Ghanbari et al., 2012).

The mechanisms of the effects of intensive exercise on changes in the circulating of Apo A-1 are not determined yet. However, it seems that the level of circulating and tissue caused by intensive training on adiponectin (Tadibi and Bayat, 2012) factors affecting changes in circulating levels of Apo A-1 as a result of exercises (Khabazian et al., 2009) changes in the concentration of circulating factors such as Lecithincholesterol acyltransferase (LCAT), acyl CoA cholesterol acyl transferase of (ACAT) and cholesterol ester transfer protein (CETP) as a result of exercise can be result in increased concentrations of Apo A-1(Khabazian et al., 2009).

Comparison of the effect of Saffron extract, aerobic exercise, and acombination of Saffron extract- aerobic exercise on the Apo A-1

Results of a comparison between the effects of interventions made in the Apo A-1 showed that no significant difference is present between the interventions in increasing Apo A-1, but all three interventions significantly increased in the Apo A-1compared to the control group. The effect of each of these interventions was described earlier, but because of the lack of similar studies, there isno longer a possibility to compare these results with other studies' results.

In general, it can be said that while the consumption of Saffron extract, aerobic exercise and a mixed of consumption of saffron extract and aerobic exercises had not had a significant effect on the level of HbA1c in type 2 diabetic men, but taking Saffron extract, aerobic exercises and the combination of consumption of Saffron extract - aerobic exercises have increased the level of APO A-1 in type 2 diabetic men.

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