The Effect of Aqueous Extract of Barberry and Selected Training on some Blood Factors in Men with Type2 Diabetes (A Quasi-Experimental Study)

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Abstract

*Background and Objective***:** Although the efficacy of selected training and antioxidant herbs in the treatment of diabetes mellitus has been determined, the interactive effect of selected training and aqueous extract of barberry on insulin resistance and risk factors of type2 diabetes mellitus is not well understood. The aim of the present study was to investigate the effect of aqueous extract of barberry and selected training on some blood factors in men with type2 diabetes.

Material and Methods: In this study, 48 middle-aged men an age range of 40-50 years with type2 diabetes participated in the study. The participants were randomly divided into four groups of 12 subjects, including (1) control, (2) aqueous extract of barberry consumption, (3) aerobic training, and (4)aerobic training+ barberry consumption, based on insulin resistance index. The participants in the aqueous extract of barberry consumption group received200 ml of barberry juice daily for8 weeks and the training and training+ barberry consumption groups performed the training protocol designed in the study for 8 weeks, while the control group did not receive any intervention.

Results: After 8 weeks of exercise training and consumption of aqueous extract of barberry, insulin resistance index, fasting insulin level, fasting blood glucose level, triglyceride level, low density lipoprotein (LDL) and total cholesterol were significantly decreased compared to the control group and high density lipoprotein (HDL) had a significant increase; on the other hand, regarding the intergroup changes, only the levels of LDL and CHO were significant compared to the aqueous extract of barberry consumption and aerobic training.

Conclusion: In general, aqueous extract of barberry consumption and regular exercise training seems to be effective in improving insulin resistance index and blood lipids levels in type2 diabetic patients.

Keywords: Berberis Vulgaris, Training, Lipid Profile, Type 2 Diabetes

Introduction

Diabetes is a serious, common and costly disease that many people worldwide have it and optimal control of diabetes is not sufficient yet worldwide. The World Health Organization has labeled diabetes a "latent epidemic" and predicts that the incidence and prevalence of diabetes in all societies, especially developing countries, is increasing for a number of reasons, including changes in lifestyle and overall population growth (1). Type2 diabetes, also known as non-insulin dependent diabetes mellitus (NIDDM) and adult diabetes, accounts for about 85 to 90 percent of all types of diabetes. Impairment of insulin or glucose receptors on the cell membrane, that is, increased insulin resistance, is a major problem in these patients (2). Although currently the main and effective treatment for type2 diabetes is insulin use and hypoglycemic agents, these compounds have numerous adverse effects such as increased adipose deposits, fatty tissue loss at injection site, and incidence of hypoglycemic shock, and in the long run, they do not have an effect on the process of diabetes mellitus. Therefore, the need to find effective compounds with fewer side effects in the treatment of diabetes is felt (3).

Recently; research on herbs used in traditional medicine has received much attention because natural compounds may be a better treatment with fewer side effects against synthetic drugs. Barberry, scientifically known as Berberisvulgaris,which has a long history in traditional medicine and is used in the treatment of infectious fever, typhus, and diarrhea, is widely grown in the northeastern mountains of Iran and is variously used (4). Studies have shown that barberry juice is rich in antioxidant compounds (5), most notably berberine, berbamine, palmatine, oxacanthin,

malic acid and berberobine (6). Studies on the effects of barberry root extract and its major alkaloid, berberine, have found this plant to have antioxidant and anti-inflammatory effects; it also decreases blood pressure,hypoglycemiaand lowers blood lipids (7) and strongly improve pulmonary hypertension (8). The results of previous studies on the effect of this herb on the risk factors of type2 diabetes are inconsistent. For example, Lazavi et al. (2018) suggested that consuming 200ml of barberry juice daily for 8weeks improves blood pressure in type2 diabetic patients (9), while Ebrahimi Mamghani et al.(2008) observed no change in the blood pressure and inflammatory factors of type2 diabetic patients after a period of consuming barberry (10).

Zahra Safari et al. (2020) also stated in their research that although barberry supplementation significantly improves insulin levels, it may not affect other glycemic indexes (11). Rasoul Nasiri et al. in their research showed that the use of barberry extract can be effective as a new treatment method in the treatment of diabetes and prevention of cardiovascular diseases and hypertension (12). On the other hand, the results of meta-analysis of Amini et al showed that consumption of barberry has significant effects on WHR index and it seems that the use of barberry as a medicinal supplement is useful in certain health conditions (13).On the Other exercise training is a major therapeutic modality in the treatment of diabetes mellitus (14). Regular physical exercise has been reported to be effective in the prevention and delay of onset of type 2 diabetes, increases insulin sensitivity, and ameliorates glucose metabolism (15). Some benefits of exercise are could be useful for cardiovascular disease by favorable changes in blood lipid profile, improved blood pressure, increased insulin

sensitivity, weight loss, maintaining optimal weight, glycemic control and improved quality of life (16). Therefore, exercise can be used to manage this disease, as physical activity can lead to severe fluctuations in blood glucose levels; so that regular exercise may have a lowering effect on glucose levels and consequently lowers insulin requirements (17). Given the contradictory results regarding the effects of this medicinal plant on the risk factors of diabetes on the one hand and the lack of interactive research on the interactive effects of barberry juice and exercise training on the risk factors of type2 diabetes in human specimens on the other hand, the present study aimed to examine the effect of aqueous extract of barberry and exercise training on some blood factors in men with type2 diabetes.

Materials and Methods

Subjects

In this quasi-experimental study, from among all type2 diabetic men referring to Gachsaran Hospital Diabetes Center, 48middle-aged patients(with test power 0.90 and effect size 0.80 using G power software to estimate the sample size)with age range of40 to50 years (mean ± SD: 44.9 ±1.9 years) whose blood sugar was above 125mg /dl, with at least one year of type2 diabetes, no history of cardiovascular disease, no smoking, and no insulin use, were purposively selected as the sample of study.

Prior to conducting the research, all participants completed the consent form. After measuring fasting blood sugar and insulin, the insulin resistance index was calculated and the participants were randomly divided into four groups of12 subjects, including (1) control, (2) extract of barberry consumption, (3) exercise training, and (4) training+ barberry consumption, based on insulin resistance index. The individual and anthropometric characteristics of the subjects are presented separately in Table1.

Measurement of the indicators

In this study, pure barberry extract was prepared in coordination with Tarvand saffron company laboratory in Qaen city without any preservatives and additives, and based on the recommendation of the laboratory; the beverage was prepared by mixing a concentration of10 ml of juice with 200ml of water. Subjects of the barberry juice extract group received 200cc of the drink twice a day in the morning and evening (each time 100cc) for8 weeks (6), whereas the control group did not receive any intervention. During the study, subjects were advised to control their diet and avoid dietary changes. They were also advised to refrain from taking any supplements without a doctor's prescription and to inform the researchers if prescribed. To determine insulin resistance index and blood lipid levels, blood samples were taken after at least 12hours fasting and fasting blood glucose was measured by enzymatic calorimetry with glucose oxidase technology using glucose kit(Pars Azmoon Co., Iran).The coefficient of variation between test and sensitivity of measurement was 1.3%and 1mg/dl, respectively. ELISA method was used to measure fasting insulin using DSL kit. HOMA-IR method was used to measure insulin resistance index (18). In this method, fasting glucose and insulin were measured and put in the following formula:

HOMA-IR = [Plasma Insulin (Micro unit/dL) × Plasma Glucose (mmol/L)] ÷22.5

To determine the total cholesterol, triglyceride and high density lipoprotein (HDL) concentrations, enzyme assay and ParsAzmoon Co. kit were used. Low-density

lipoprotein (LDL) levels were also calculated with respect to total cholesterol, triglyceride and HDL levels.

Training protocol

In this study, aerobic training at 60-70% of maximal heart rate intensity was used to evaluate the biochemical responses of the subjects in the aerobic training + aqueous extract of barberry consumption groups. The training protocol consisted of 10 minutes of general stretching and warm-up and 30 minutes of aerobic activity at an intensity of 60 to 65% of the individual's calculated maximum heart rate. During the exercise, the researcher controlled the training intensity through the Polar heart rate monitor for each subject and appropriate feedback was given to the subjects if the intensity of the training was to be increased or decreased. At the end of the

training, the subjects performed activities including stretching and walking to cool and return to baseline (19).

Statistical procedures

In the present study, the Kolmogorov-Smirnov test was used to investigate the homogeneity of the variables in different groups. Parametric tests were used because there were no significant differences in pretest between groups in terms of different factors (P>0.05).Correlation t-test was used to analyze the hypotheses on within-group differences, and one-way analysis of variance (ANOVA)and Tukey's post hoc test were used to compare between-group differences. All statistical calculations were carried out using SPSS software version24 at p<0.05.

Result

Table1. Individual characteristics of the four groups participating in the study (mean±standard deviation).

Variable	Control=12 (M±SD)	Training=12(M±SD)	Barberry=12(M±SD)	Barberry + Training=12(M±SD)
Age(year)	44.0±1.9	43.2.3	45.9±1.5	43.68 ±2.3
Height(cm)	171.1±3.6	172.45	176.0±3.6	174.4±3.82
Weight(kg)	76.6±3.4	77.4.66	75.7±5.6	74.91±4.16

Results of the biochemical variables of the subjects in the study

After data analysis, the results of dependent sample t-test showed that eight weeks of aerobic training had a significant effect on LDL(P = 0.025), HDL(P = 0.001), CHO(P = 0.027), TG(P = 0.013), glucose(P = 0.010), insulin(P = 0.010) and HOMA-IR(P = 0.031).

Also, the results of dependent sample t-test showed that eight weeks of aqueous extract of barberry consumption had a significant effect on LDL(P = 0.031), HDL(P = 0.028), CHO(P

= 0.030), TG(P = 0.002), glucose(P = 0.006), insulin(P = 0.022) and HOMA-IR(P = 0.006).

On the other hand, consumption of aqueous extract of barberry and aerobic training for two months had a significant effect on LDL(P = 0.001), HDL(P = 0.010), CHO(P = 0.001), TG(P = 0.016), glucose(P = 0.001), insulin(P = 0.01) and HOMA-IR(P = 0.012).

The results of one-way ANOVA showed significant differences in LDL(P = 0.001, F = 8.135), HDL(P = 0.002, F = 5.793), CHO(P = 0.001,F = 10.744), TG(P = 0.001, F = 8.228), glucose (P = 0.001, F = 9.218), insulin(P =

0.005, F = 4.865) and HOMA-IR(P = 0.001, F = 9.371),

Therefore, Tukey's post hoc test was used to determine the exact place of mean of differences, as shown in Figures 1 to 7.
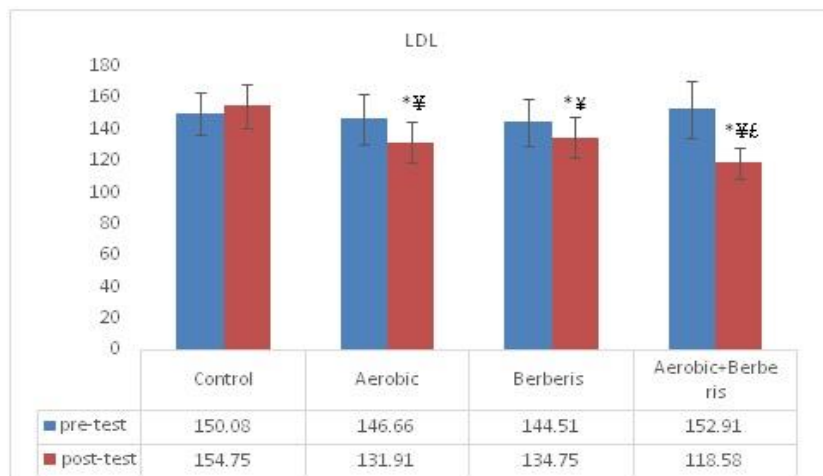

Figure 1. LDL changes in the four study groups
*Indicates the significance of within-group changes (P ≤ 0.05)
¥Indicates the significance of between-group changes compared to the control group
£Indicates the significance of between-group changes compared to the aqueous barberry extract and aerobic training
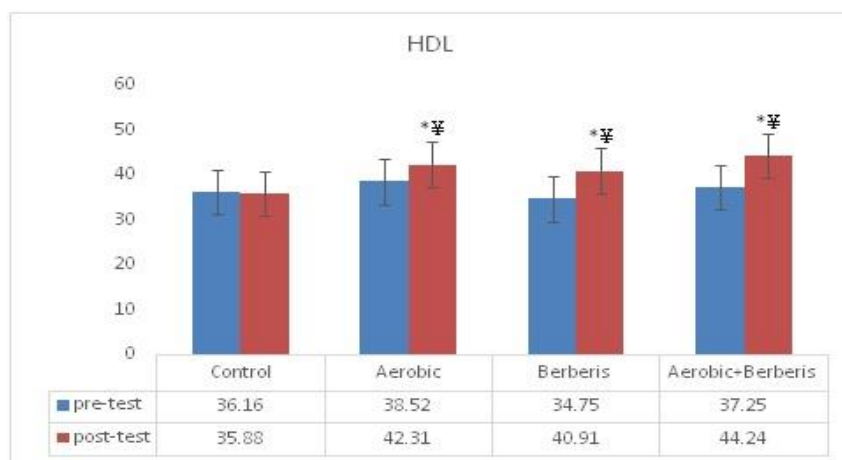

Figure 2. HDL changes in the four study groups
*Indicates the significance of within-group changes (p ≤ 0.05)
¥Indicates the significance of between-group changes compared to the control group

Figure 3. CHO changes in the four study groups
*Indicates the significance of within-group changes (p ≤ 0.05)
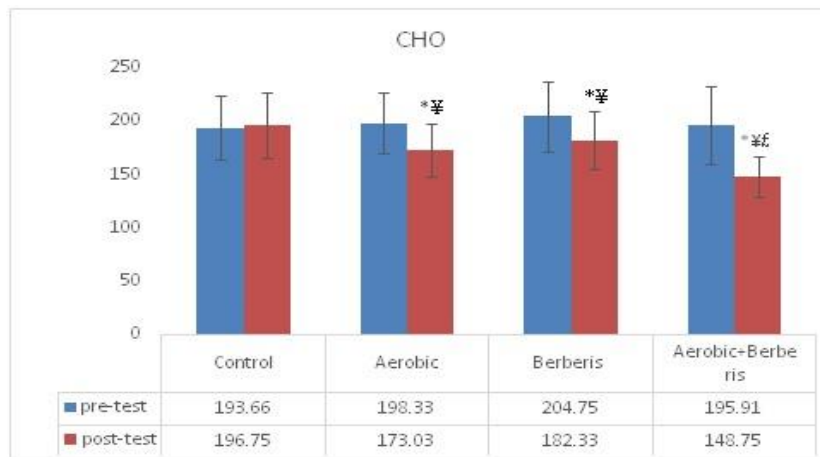¥Indicates the significance of between-group changes compared to the control group
£Indicates the significance of between-group changes compared to the aqueous barberry extract and aerobic training

Figure 4. TG changes in the four study groups
*Indicates the significance of within-group changes (p ≤ 0.05)
¥Indicates the significance of between-group changes compared to the control group

Figure 5. Glucose changes in the four study groups
*Indicates the significance of within-group changes (p ≤ 0.05)
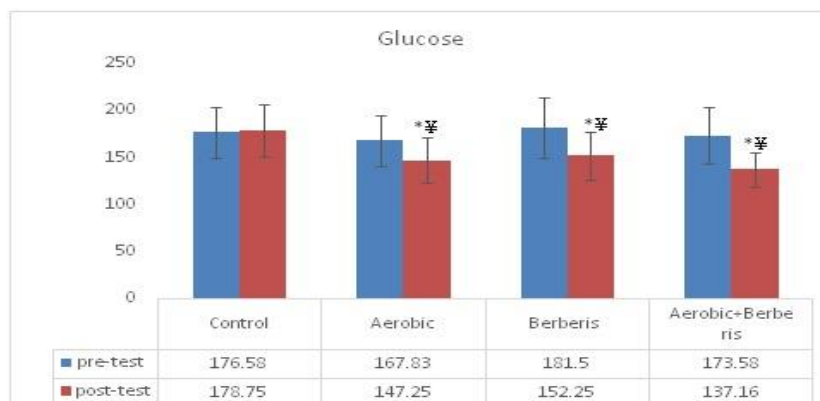¥Indicates the significance of between-group changes compared to the control group

Figure 6. Insulin changes in the four study groups
*Indicates the significance of within-group changes ($p \leq 0.05$)
¥Indicates the significance of between-group changes compared to the control group
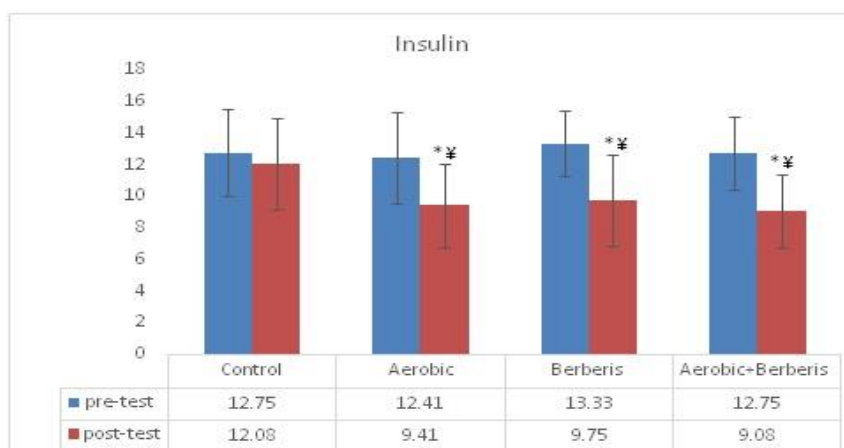
	Control	Aerobic	Berberis	Aerobic+Berberis
pre-test	12.75	12.41	13.33	12.75
post-test	12.08	9.41	9.75	9.08

Figure 7. HOMA-IR changes in the four study groups
*Indicates the significance of within-group changes ($p \leq 0.05$)
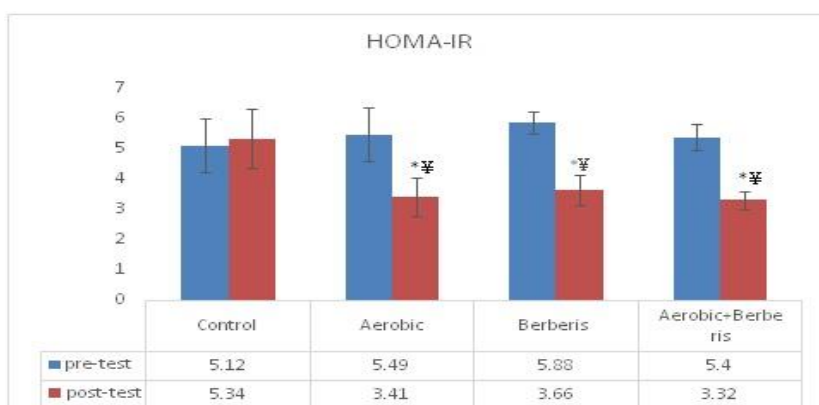¥Indicates the significance of between-group changes compared to the control group

	Control	Aerobic	Berberis	Aerobic+Berberis
pre-test	5.12	5.49	5.88	5.4
post-test	5.34	3.41	3.66	3.32

Discussion

Lipid disorders are one of the common complications of type 2 diabetes. Recently, the use of medicinal plant for the improvement and treatment of many diseases has been welcomed because natural compounds may be the best treatment with the least side effects compared to other industrial drugs. Barberry juice is an antioxidant compound that some studies have shown can be effective in improving some of the complications of diabetes, including hypertension (6).

The effects of this medicinal plant on blood sugar, insulin resistance index, and blood lipid levels in human samples of type2 diabetes have not been well documented, and further research is needed on animal samples of type1 diabetes (20). Therefore, the aim of this study was to investigate the effect of aqueous extract of barberry and aerobic training on insulin resistance and blood lipid levels in men with type 2 diabetes. The results of this study showed that after8 weeks of aerobic training and consumption of aqueous extract of barberry at a dose of 200cc daily, insulin levels and levels of insulin resistance, glucose and blood lipid index significantly decreased in men with type2 diabetes

compared to the control group.Recently, Lazaviet al. (2018) have shown that consuming 200ml of barberry juice daily for 8weeks significantly reduced fasting blood sugar in the barberry juice extract group (9). From the results of the present study and other similar studies, it is deduced that the effects of glucose reduction by the extract of barberry are related to the presence of secondary metabolites of barberry. These metabolites include saponins, flavonoids, alkaloids, and especially berberine (6), so that berberine is able to increase glucose uptake via AMPK and AMPK-P38 pathway through activation of protein kinase B, thereby reducing blood glucose (21). In addition, the use of barberry extract in diabetic patients can improve insulin sensitivity and function due to the determining role of berberinein barberry juice extract and consequently decrease glucose (22). Studies on the effect of barberry juice extract on changes in insulin resistance index are few and controversial. Consistent with the results of the present study, Bije et al. (2015) showed that short-term supplementation of barberry extract improved insulin resistance index in type2 diabetic patients following an aerobic exercise session (19); contrary to this finding, Ebrahimi Mamghani et al.(2009) observed that after long-term consumption of black barberry, insulin resistance index in type 2 diabetes patients did not change significantly (23). Differences in the dose of barberry extract, sex of subjects and severity of disease can be the reasons for the difference between the present study and the study of Ebrahimi Mamghani et al. (2009). It should be noted that in the study conducted by Ebrahimi Mamghani, the amount of barberry was300 grams of black barberry dissolved in 770cc cider vinegar and the subjects were both male and female patients. The results of Bweir

(2009) revealed a significant decrease in blood glucose levels following aerobic training (24). In people with diabetes, impaired glucose uptake is usually caused by impaired GLUT4function (25). Following exercise, contracting muscles are able to withdraw more glucose from the blood without the effect of insulin. Thus, performing aerobic activity in diabetic patients stimulates and transforms the resulting GLUT4 and transfers it to the cell membrane, resulting in rapid glucose uptake by active skeletal muscles, which reduces glucose levels in diabetics (26). Also, regarding insulin level changes, the results of the present study showed significant differences in insulin levels in the barberry aqueous extract groups and a significant difference in the training and training with barberry aqueous extract groups compared to the pre- and post-protocol stages. In line with the findings of this study on the effect of aerobic training on insulin depletion, Albright's (2009) study confirm the effect of regular low intensity training on reduced insulin levels (27). During exercise, blood insulin secretion decreases and reduces baseline insulin and stimulated insulin levels. It also leads to a decrease in the mRNA required for the production of insulin and glucokinase in the pancreas and results in a decrease in insulin secretion (28). Therefore, the reasons for the decrease in insulin levels in the training as well as training with aqueous extract of barberry consumption groups in the pre- and post-protocol stages, as well as the comparison of the insulin levels of these groups with the control group, can be attributed to the important role of barberry extract and the decreasing effect of aerobic training.

The results of this study also showed that consumption of aqueous extract of barberry

for 8 weeks significantly decreased total cholesterol and triglyceride levels and significantly increased HDL compared to the control group. LDL levels, despite significant decrease in the barberry juice group, were not significantly different compared to the control group. Past studies have shown that some natural antioxidants such as berberine and natural phenols (such as lycopene and vitamin E) reduce blood lipids (29). Medicinal herbs and antioxidants have been shown to decrease fat absorption, stimulate bile cholesterol secretion and increase cholesterol excretion through the stool (20). Research has also shown that a number of medicinal plants inhibit the glycation of lipoproteins, enzymes and proteins that are involved in the metabolism of lipids and lipoproteins, thereby reducing serum lipids (30). The lipid-lowering properties of barberry may be due to the antioxidant compounds identified in this plant, especially the alkaloid berberine (6). It has been reported that berberine may lower blood cholesterol levels by a different mechanism than statin drugs, and if statin and berberine are used together, a decrease in cholesterol levels is more likely to occur (20).Kong (2004) has suggested that berberine increases the production of a type of protein receptor in the liver that binds to cholesterol and facilitates its excretion (31). On the other hand, studies have shown that barberry can improve liver function and bile secretion and decrease blood lipids (32). In addition, research has shown that phenolic compounds, which are also present in barberry, decrease LDL and triglyceride and increase HDL (33).The mechanisms of action of polyphenolic compounds in increasing HDL concentrations remain unknown. It is likely that its effect is due to increased activity of paraoxonase-1 enzyme (23). Paraoxonase-1 is associated with serum HDL

levels and is often secreted by the liver. It has been suggested that phenolic compounds such as quercetin increase the activity and level of paraoxonase mRNA in humans (34). Because this enzyme inhibits HDL oxidation; it is likely that increasing its level by phenolic compounds will increase HDL concentration (23). In addition, studies have shown that phenolic compounds decrease plasma cholesterol concentrations by inhibiting intestinal absorption of cholesterol and hydroxylmethylglutaryl CoA reductaseenzyme (35). Also, phenolic compounds can decrease apolipoprotein B levels and decrease plasma triglyceride levels by decreasing plasma levels of chylomicrons and their postprandial leftovers (33).

Conclusion

In general, with respect to the results of the present study regarding decreased insulin resistance and harmful lipid levels as well as increased HDL levels, it is suggested that type 2 diabetic patients should use aerobic training and aqueous extract of barberry to the amount used in the present study in order to control diabetes, regulate blood sugar and prevent cardiovascular disease.

Ethical Considerations

This article comes from a master's thesis of Sport Physiology. It has been registered at the Research Committee of Islamic Azad University with code IR.IAU.KAU.REC.1399.009. All of the subjects in this study gave voluntary informed consent to participate in this research.

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