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Research Article

Glycemic Control by Exercise and Urtica Dioica Supplements in Men With Type 2 Diabetes

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Abstract

Background: Type 2 diabetes is a metabolic disease in which hyperglycemia is a major symptom, and is associated with numerous vascular and non-vascular complications. People with diabetes use medicinal treatment to exert glycemic control, as well as exercise training and herbal remedies, such as urtica dioica (UD).

Objectives: This study aimed to compare the effects of 8 weeks of aerobic training and UD supplementation alone, and in combination, on glycemic control in men with type 2 diabetes mellitus (T2DM).

Patients and Methods: This semi-experimental study was conducted in 2014, in the city of Dezful, Iran. A total of 40 males (aged 30 - 50 years) with T2DM were selected and randomly divided into one of four groups in equal numbers (n = 10): 1 - aerobic training (Ae), 2 - UD supplements (UD), 3 - a combination of aerobic training and UD supplements (Ae + UD), and 4 - a control group. Blood samples were taken 24 hours before and 48 hours after the intervention period, following 10 - 12 hours of fasting. A t-test and analysis of variance was used to analyze the changes in the measured parameters, and $P \leq 0.05$ was considered statistically significant.

Results: A significant decrease in fasting blood sugar (FBS) was observed in the Ae group (-9.50 ± 6.96 mg/dl; P = 0.002), the UD group (-7.60 ± 6.04 mg/dL; P = 0.001), and the Ae + UD group (-18.30 ± 6.63 mg/dL; P < 0.001) after 8 weeks. There was a significant difference in FBS between the three intervention groups and the control group. In addition, a significant difference in FBS (P < 0.05) was shown between the UD and Ae + UD groups.

Conclusions: The findings confirmed the positive influence of UD supplements and aerobic training on glycemic control in males with T2DM. When aerobic training was combined with a UD supplement, a greater degree of glycemic control was observed.

Keywords: Type 2 Diabetes Mellitus, Aerobic Exercise, Urtica Dioica, Blood Glucose

1. Background

Diabetes is a chronic metabolic disorder that continues to be a major worldwide epidemic (1, 2). In developing countries, the incidence of type 2 diabetes mellitus (T2DM) is rising, as a result of a proportionate increase in numerous risk factors, such as dietary changes, increasing prevalence of obesity, and a decrease in physical activity (3). The prevalence of type 2 diabetes is growing rapidly, from 135 million in 1995 to an estimated 380 million in 2025 (1). In numerous countries, at least 10% of total healthcare costs are spent on this disease, and according to the latest statistics from the Iranian Ministry of Health, more than 40 milliard Rial from the Department of Health budget has gone to controlling diabetes. Furthermore, life expectancy in people with diabetes and in hospitalized patients is 5 - 15 years less than others (4).

T2DM is closely associated with both acquired and genetic risk factors. A sedentary lifestyle is an example of an acquired factor that is an independent predictor of poor quality of life, and should be considered as a modifiable risk factor in the general population (3). T2DM elevates the risk of microvascular complications, such as retinopathy and nephropathy, and people with this disease often die as a result of macrovascular complications, including coronary artery disease and stroke (5, 6). Despite their undeniable benefits, most of the drugs used to treat diabetes also have serious side effects, which is why the use of alternative therapies or supplements is an important research consideration (7). Increasing growth of chronic disease has led to an increased use of complementary medicine in recent years. Previous studies have shown that several complementary therapies have been used in people with T2DM, along with diet and lifestyle changes: herbal drugs that contain anti-diabetic agents and magnetic therapy, mental and physical exercise, laughter therapy, massage therapy, and music therapy (1, 8).

Treatment based on herbal remedies is usually cheaper, easier, and more readily available than treatment via pharmaceutical agents, and, in some cases, has fewer side

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effects. In addition, people prefer to use herbal, rather than pharmaceutical, remedies. In response to people's increasing likelihood to use medicinal plants, the American diabetes association has encouraged research to evaluate the efficacy of such plants, as used by people with T2DM. To date, over 1,200 medicinal plants that may be effective in treating this disease have been identified (9), and more than 400 traditional herbal treatments have been reported with regard to T2DM. However, the efficacy of very few of these plants has been scientifically investigated and approved. Urtica dioica (UD) is one of the medicinal plants that has been traditionally used in Morocco, Turkey, Brazil, Jordan, Iran, and many other countries. Numerous studies have shown that UD has a noticeable effect on reducing blood glycemic level (10). This effect has been mentioned in ancient texts, such as the writings of Avicenna, and UD has been introduced as an auxiliary drug for treating diabetes in traditional medicinal in Iran (10, 11). According to studies in animal models, UD is safe to use, and has been introduced as a hypoglycemic agent in people with T2DM (10, 12). However, some studies, such as Swanston et al. (13) and Gunes et al. (14) reported no significant differences in blood glycemic level following UD consumption.

The increasing prevalence of overweight and an inactive life style is also important in the pathogenesis of T2DM. For several years, exercise has been considered as one of the three therapeutic methods to treat the disease, along with diet and medical therapy. Its low expense and absence of a medicinal nature, has led to an increase in the treatment importance of physical activity (15, 16). Experts believe that diet and drugs are not effective in in curing T2DM and controlling glycemic levels alone, and that physical activities and exercise training should be added to a diabetic individual's daily program (2, 17). A series of interventional studies has consistently supported engagement in physical activity as a way of improving glycemic control in individuals with T2DM (3), and it has been shown that regular exercise training controls blood glycemic levels, decreases cardiovascular risk factors and weight, and improves quality of life (2, 18, 19). Studies have shown that repeated muscle contractions in people with T2DM who have an insulin sensitivity problem facilitate glucose entry to muscle cells in the absence of insulin. Furthermore, exercise increases glucose transport protein (GLUT4) levels and decreases insulin resistance (2, 17). Other research has shown that exercise training had a significant effect on reducing hyperglycemia in people with T2DM (2, 6, 20, 21). However, in some studies, such as those conducted by Karstoft et al. (22) and Hamedinia et al. (23), no significant changes in blood glycemic control were reported following exercise training.

Lack of awareness regarding T2DM, as well as lack of access to medicines and healthcare, could lead to blindness, amputation, and renal insufficiency. However, with blood glucose control, short- and long-term diabetes complications can occur (4, 24). Although there is now effective treatment for diabetes mellitus, via insulin and blood glucose-lowering agents, these combinations exert multiple adverse effects, such as increased fat deposits, a shrinking of fat tissue at the injection site, and hypoglycemic shock. The long-term complications of diabetes do not affect treatment. The need for effective compounds with fewer side effects for the treatment of diabetes is now recognized (25). We believe that UD is associated with a lower cost and fewer complications than the pharmaceutical agents used by people with T2DM (9, 10). In addition to being one of the pillars of treatment of T2DM, exercise has a positive role in blood glucose control (17, 18, 24, 26), and aerobic exercise has been introduced as a low-cost, convenient way to address diabetes complications (17, 18). Given the prevalence of diabetes in the world (24) and in Iran (18), it appears necessary to find effective methods to control blood glucose in the treatment of diabetes (2, 4, 24).

Since there are conflicting results regarding the effects of exercise training and UD on reducing blood glycemic levels, it is necessary to study the effect of aerobic exercise and UD on blood glucose in people with T2DM.

2. Objectives

According to mentioned matters more researches about UD are performed on experimental animals is safe (10). The present research was designed to investigate the effects of aerobic training and UD supplementation alone, and an exercise and diet combination on fasting blood sugar (FBS) in males with T2DM.

3. Patients and Methods

3.1. Sample Selection

In this semi-experimental study, 40 males with T2DM were selected, using available sampling methods, and randomly divided into four groups (n = 10): a UD supplement group, an aerobic training group, a UD supplement + aerobic training group, and a control group (27) and sample size equation was calculated:

$$n = \frac{\left(z_{1-\frac{\alpha}{2}} + z_{1-\beta}\right)^2 \left(s_1^2 + s_2^2\right)}{\left(\bar{x}_1 - \bar{x}_2\right)^2} \quad (1)$$

In the present study, all participants gave their informed consent and were assured that there would be no fee for participation in the design of all the exercises, and that the laboratory supplements were free. They were also allowed to leave the trial whenever they wished, for personal reasons or health problems. The patients were assured that the data were confidential, and that the results would be generally described.

Inclusion criteria were: being male, aged 30 to 50 years old with T2DM, FBS < 200 mg/dL, nonsmokers, no insulin injections, no history of cardiovascular or respiratory diseases or muscular and skeletal problems, an inactive life style, and no regular exercise within the 6 months prior to the beginning of the study. Exclusion criteria were: the use of drugs from a doctor for any reason, a positive effect of medicinal supplementation on blood glucose, and regular participation in the exercise sessions. All participants signed the informed consent form.

3.2. Anthropometric Indices and VO_{2max}

The participants' height was measured using a SECA with an accuracy of 1 mm, weight was measured using SECA digital model with an accuracy of 1 gram. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared (kg/m^2). The Rakport test was used to measure the aerobic capacity (VO_{2max}) of the participants (18):

VO_{2max}= 132.853 - (weight × 0.0769) - (age × 0.3877) + (gender × 6.315) - (time × 3.2649) - (HR × 0.1565)

3.3. Biochemical Indices

A day before the intervention (pre-test) after 10 to 12 hours of fasting, a laboratory nurse took a 5cc blood sample from the medical radial vessel of the right hand of each participant between 8 and 9 am, based on a standard program in a sitting situation. Two days after intervention (post-test), blood was taken under the same conditions in order to measure aforementioned biochemical factors, and was centrifuged 30 - 45 minutes after sampling. FBS was measured by pars azmoon kits made in Iran, and biochemical measurements were carried out using photometric techniques.

3.4. UD Supplements

The bought UD leaves, washed and dried in sunlight, were gathered and packaged. In the experimental groups, 10 grams of this powder was dissolved in yogurt 15 minutes before breakfast over a period of 8 weeks. In order to avoid a possible effect of using yogurt, allotment of yogurt was considered for every group were added.

3.5. Aerobic Training

In the exercise training groups, the exercise program included supervised aerobic training that was conducted in safety (2, 18). The warm-up consisted of fast walking, jogging, and static stretching for 10 minutes, after which running (the main training program) was begun at 50% of the heart rate reserve (HRR) for 10 minutes in the first week, and increased to 70% of the HRR for 30 minutes in the final week (Table 1). The HRR was determined using the Karvonen Formula (18). At the end of every training session, walking fast and stretching movements were undertaken for 5 minutes to cool down. In order to avoid potential hazards, a nurse was present during all training sessions. The participants were advised to have a sweet snack if they had hypoglycemia. Their blood glucose and blood pressure were measured using a digital glucometer and blood pressure machine before they began the training, and if they had a high glucose level or high blood pressure they were not permitted to participate in training.

Table 1. Aerobic Training Program

Weeks	Duration, min	Intensity (HRR%)
1	10	50 - 60
2	15	50 - 60
3	15	50 - 60
4	20	50 - 60
5	20	60 - 70
6	25	60 - 70
7	25	60 - 70
8	30	60 - 70

Abbreviation: HRR, heart rate reserve.

3.6. Statistical Methods

Statistical Package for the Social Sciences (version 19.0) software was used to analyze the data. Normality of data distribution was assessed using the Kolmogorov Smirnov test, which indicated that all the data had a normal distribution before and after the 8-week study period. Experimental data were compared between groups. The Levene test for homogeneity of variance was used and evaluated, and the data were analyzed using a paired samples t-test and a one-way analysis of variance, the finding of Tukey post hoc test was significant. The level of statistical significance in all the tests was $P \leq 0.05$.

4. Results

This study investigated the effects of UD supplements and aerobic training alone and in combination in FBS males with T2DM. Table 2 shows the pre-test demographic characteristics of the participants.

After 8 weeks of intervention, a significant decrease was observed in FBS in the three intervention groups (Table 3).

There was a significant difference ($P < 0.001$) in FBS between the groups (Table 4).

The Tukey post hoc test (Table 5) showed a significant difference ($P < 0.05$) in the level of FBS between the three intervention groups (Ae, UD, and Ae + UD) and the control group. There was also a significant difference ($P < 0.05$) in FBS between the UD group and the Ae + UD group.

Table 2. The Basic Characteristics of the Participants at Baseline

Variables	Ae	UD	Ae + UD	Control	f	P
Age, y	42.20 ± 3.97	45.20 ± 3.23	41.30 ± 4.37	42.90 ± 2.47	1.997	0.132
Height, cm	168.71 ± 5.13	167.49 ± 6.14	165.71 ± 5.86	168.78 ± 6.30	0.466	0.708
Weight, kg	76.89 ± 4.49	75.30 ± 5.04	76.38 ± 6.15	75.10 ± 8.70	0.416	0.742
BMI, kg/m2	27.05 ± 1.88	26.97 ± 2.91	27.79 ± 1.34	27.80 ± 2.00	0.469	0.706
Disease duration, y	3.50 ± 1.18	3.00 ± 1.49	2.50 ± 1.43	3.00 ± 1.10	1.212	0.319
VO_{2max}, $ml.kg^{-1}.min^{-1}$	27.48 ± 2.39	27.45 ± 4.30	27.92 ± 1.64	28.57 ± 2.36	0.336	0.799
FBS, mg/dL	142.80 ± 10.21	150.40 ± 8.81	150.90 ± 10.84	146.00 ± 8.27	1.528	0.224

Abbreviations: Ae, aerobic training group; Ae + UD, combined aerobic training and urtica dioica group; BMI, body mass index; FBS, fasting blood sugar; UD, urtica dioica group.

Table 3. Pre-Test and Post-Test Values For Fasting Blood Sugar[a]

Variable/Group	Pre-Test	Post-Test	t	P Value
FBS, mg/dl				
Ae	142.80 ± 10.21	133.30 ± 8.93	4.330	0.002 [b]
UD	150.40 ± 8.81	141.40 ± 9.03	4.502	0.001 [b]
Ae + UD	150.90 ± 10.84	132.60 ± 12.12	8.723	0.000 [b]
Control	146.00 ± 8.27	146.50 ± 5.58	-0.170	0.869

Abbreviations: FBS, fasting blood sugar; Ae, aerobic training group; UD, urtica dioica group; Ae + UD, combined aerobic training and urtica dioica group.
[a]Data are presented as mean ± SD.
[b]The comparison of in-group values of body composition and biochemical parameters before and after the intervention (Means ± SD).

Table 4. Comparison of the Mean Differences of Fasting Blood Sugar Between Two Groups[a]

Group	Ae	UD	Ae + UD	Control	f	P Value
FBS, mg/dL	-9.50 ± 6.96	-7.60 ± 6.04	-18.30 ± 6.63	+0.50 ± 9.02	9.30	0.000 [b]

Abbreviations: Ae, aerobic training group; Ae + UD, combined aerobic training and urtica dioica group; FBS, fasting blood sugar; UD, urtica dioica group.
[a]Data are presented as mean ± SD.
[b]There was a significant difference (P < 0.05) between the groups.

Table 5. Results of the Tukey Post Hoc Test[a]

Group I	Group J	P Value
Ae	UD	0.990
Ae	Ae + UD	0.056
Ae	Control	0.020 [b]
UD	Ae + UD	0.027 [b]
UD	Control	0.042 [b]
Ae and UD	Control	0.000 [b]

Abbreviations: Ae, aerobic training group; Ae + UD, combined aerobic training and urtica dioica group; FBS, fasting blood sugar; UD, urtica dioica group.
[a]Data are presented as mean ± SD.
[b]There was a significant difference (P < 0.05) between the groups.

5. Discussion

5.1. Exercise Training

A significant decrease was observed in the level of FBS (-9.50 ± 6.96) in the aerobic exercise intervention group after 8 weeks (Table 3). With regard to decreasing blood glycemic level, the findings were in accordance with the results of some previous studies (6, 20, 21, 26), but not with the findings of Karstoft et al. (22). A possible reason for this may be differences in the characteristics of the tests. Since Karstoft et al. used older patients (aged over

57 years) with a high BMI (29 kg/m^2), it is possible that the study participants were not capable of effectively carrying out exercises, due to being overweight and to muscular weakness as a result of senility. In addition, the research protocol included 4 months' walking, while aerobic running was used in the present study.

Previous research has indicated that muscular contraction has an insulin-like effect and helps with the diffusion of glucose from the blood into cells to be consumed for energy production (18, 28). Muscular contraction results in a higher membrane permeability to glucose, due to an increase in the number of glucose transporters (GLUT4) in the plasma membrane. Exercise can increase the number of GLUT4s in a muscle; furthermore, it improves glucose metabolism and can help lower blood glycemic level (15, 29). It is believed that accumulation of free fatty acids in muscular cells interferes with transportation of GLUT4 to the cells' surfaces. Exercise may prevent the accumulation of fatty acids in muscular cells, via increasing their oxidation (30). An increase in insulin action and insulin signals is the other positive mechanism for adjusting glucose metabolism (17, 31, 32). Another possible reason for favorable changes in glycemic control is that the protein content of the insulin receiver, as well as the activity of protein kinase B, which plays a crucial role in transporting insulin signals, increases after exercise, which in turn, can lead to a decrease in blood glucose (31). In addition, it is possible that exercise training, or the weight loss resulting from exercise, improves beta cells function, indirectly and through other biochemical mediators or peptide hormones that are reported to express genes and their receivers in pancreas cells, which is followed by a decrease in the level of blood glycemic level in people with diabetes (33-36).

5.2. UD Supplementation

A significant decrease was observed in FBS (-7.60 ± 6.04) in the UD group after 8 weeks in the present study, which is in agreement with the findings of some previous studies (12, 37, 38), which have reported the effectiveness of UD in controlling blood glycemic level. Although this finding is not in accordance with those of Swanston-Flatt et al. (13), the latter used mice in which diabetes had been induced with streptozotocin. In addition, the period and type of interference was respectively shorter than, and different from, the interference period used in the present study. Gunes et al. (14) also observed no significant difference after 10 days of UD use in mice with streptozotocin-induced diabetes. Therefore, one can point to the differences in participants and duration of intervention period in both of the latter studies compared to the present study. There are several reports on the usefulness of the tail or other parts of UD leaf extract, or by injection or oral use, in T2DM (10, 39). Animal studies have shown that active UD compounds can enhance the level of blood insulin in natural diabetes and in streptozotocin-induced disease (38, 40, 41). Fakhraee et al. stated three possible mechanisms that may be involved in the effects exerted by UD on reducing blood glycemic levels in T2DM: (A) an effect of UD and an increase of muscle cells increases formation of permeable pores, which leads to increased glucose uptake in muscle, and, ultimately to reduction of high blood glucose levels. (B) The effects of UD stimulate the release of insulin and beta cells to increase insulin secretion, leading to a decrease in blood glucose. (C) The effect of UD on carbohydrate hydrolysis inhibitor (alpha-amylase inhibitory activity) finally to leads to a reduction of high blood glucose levels (10). There are several natural compounds in the leaf of UD (flavonoids, peptides, and amines), some of which have a known anti-diabetic effect. The reported ways in which these compounds exert their effects are: excitation of glycogen, blocking the potassium channels of beta cells of the pancreas, and interfering in glucose absorption from the intestine wall (42). Kavalali et al. also reported a protective effect of UD on pancreas cells in an histopathologic investigation of diabetic mice, in addition to investigating the effect of UD in lowering blood glucose in rats with streptozotocin-induced diabetes (37). Bnouham et al. also justified a decrease in the activity of UD in blood glucose through a decrease in observed glucose in the intestine (12).

5.3. Combined UD Supplementation and Exercise Training

A significant decrease was observed in FBS (-18.30 ± 6.63) in the Ae + UD group. With regard to the simultaneous effect of consuming complementary UD and carrying out aerobic training, the current study is the first to show an improvement of two combined interference methods on blood glycemic level. This glycemic improvement may be due to a decreasing effect of UD on blood glycemic level (10), accompanied by a decreasing role of exercise in lowering this level because of decreasing resistance to insulin and an improvement in the energy balance in people with T2DM (2, 6).

In the present study, significant reductions in fasting blood glucose were observed in all three intervention groups. The greatest blood sugar changes were reductions of 12.12% in the Ae + UD group, 6.57% in the Ae group, and 5.68% in the UD group, and an increase of 0.61% in the control group.

In general, the findings of the current research indicate a positive effect of aerobic training and UD alongside the medicinal treatment of diabetic patients. In a comparison of the various types of interference in the current study, it was found that combining two methods had a greater effect on glycemic control in men with T2DM. The study was the first to examine the effect of aerobic training combined with UD supplement consumption on blood glycemic level in people with diabetes, therefore the lack of similar studies means that there is a need for further investigations of this topic.

5.4. Research Limitations

In the present study, training requirements (time, duration, and intensity of training), the participants (age, gender, severity of illness), and conducting the pre-test and post-test measurements at particular times of day to avoid possible effects of the body's circadian rhythm on the results were controlled. In addition, the status of glycemic control and medication were fixed. However, there were some variables that were not controllable. These included the individual differences of the participants resulting from heredity and lifestyle, and their culture of dietary habits. In addition, the diet of the participants could not be controlled, which could have affected the results. Finally, another limitation was the short duration and low sample volume that was used.

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Footnotes

Authors' Contribution: Saeid Dabagh and Masoud Nikbakht contributed equally to this research, performed the literature search, and wrote the first draft. Saeid Dabagh and Masoud Nikbakht provided expert opinion and reviewed the paper.

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