Evaluation of Glycemic Control in Women with Type 2 Diabetes Mellitus Treated with Ziziphus Fruit

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Abstract

Objective Diabetes mellitus (DM) as a metabolic disorder is becoming a serious threat of health. In recent years, there has been renewed interest in the treatment against different diseases using medicinal plants. The present randomized clinical trial was carried out to evaluate the efficacy of Ziziphus in improving glucose control in women with type 2 diabetes mellitus (T2DM).

Materials and Methods: Women were randomized to treatment with Ziziphus (30 gr/day) or control group (age match). This trial was done during three months. Fasting blood sugar (FBS), 2-hour postprandial blood glucose (2hpp) and glycated hemoglobin (HbA1c) were measured before and after the intervention.

Results Ziziphus consumption was associated with significant reductions in serum levels of 2hpp glucose and HbA1c (P<0.05) in women with T2DM. As well as marginally significant effect was observed from Ziziphus of serum levels of FBS (P=0.06) after the intervention.

Conclusion: Consumption of Ziziphus for 3 months has anti-diabetic effects on women with T2DM. These findings suggest Ziziphus as a beneficial supplement for diabetic women.

Keywords: Type 2 diabetes mellitus, Women, Glycemic control, Ziziphus fruit

Introduction

Type 2 diabetes mellitus (T2DM) is one of the most common chronic diseases in nearly all countries. It is estimated that prevalence of T2DM will grow, so the health and economic burden will worsen significantly (1,2). Middle East countries will have the greatest relative increase in the prevalence of diabetes by 2030 (3). The prevalence of T2DM is about 14.52% in over 30 years old population of Yazd provinces (4). Diabetes management without side effect is still a challenge. Natural products as sources of modern drug discovery and ethnopharmacology is important issues. According to the world health organization (WHO), nearly three-quarters of the world

population rely on traditional remedies for their health care (5).

Prospective longitudinal cohort studies have suggested an inverse association between consumption of fruits and vegetables rich in flavonoids and complications and risk of T2DM (6,7). Ziziphus is a fruit that has curative properties. This fruit is used by local population for the treatment of some diseases such as digestive disorders, obesity, antidiabetic, urinary diseases, sedative, liver diseases and skin infections (8-10).

Ziziphus contains vitamin A, B, and C and minerals. Several bioactive phytochemicals like tannins, sterols, phenolic, flavonoids, saponin, alkaloids, and fatty acids were found in this fruit. The presence of these vitamins and phytochemicals in Ziziphus have antioxidant activity that may be beneficial to counterbalance the heightened state of oxidative stress in T2DM (11-13).

The results of some studies have shown that consumption of this fruit may be associated with improving glycemic control (14,15). There have been very few studies on the anti-diabetic effects of Ziziphus fruit (ZF) in clinical setting. The aim of this study was to determine whether supplementation with ZF could influence plasma glucose levels in women with T2DM.

Materials and Methods

Sixty women with T2DM aged 32–65 years were recruited for this trial. Patients were selected from the Diabetes Research Center, Yazd, Iran. The Ethics Committee at the Shahid Sadoughi University of Medical Sciences (Yazd, Iran) approved the study protocol, and each woman signed an informed consent form prior to commencement of the study. Inclusion criteria were female with T2DM, glycated hemoglobin (HbA1c) between 6.5 to 9.5 percent, body mass index (BMI)$\geq$ 25 kg/m^2. Exclusion criteria were type 1 diabetes, pregnant women, chronic pancreatitis, liver and kidney disease, insulin therapy, use of vitamin supplements, changing physical activity during trial, being vegetarian or having any restrictive dietary requirements.

Study design

The current study was designed as a single-blinded clinical trial. Included participants (n=60) were randomly assigned assigned to control or intervention groups. Intervention group consumed ZF (30 g/day) before breakfast, lunch and dinner and control group did not receive any intervention. Previous study showed that dose of 30 g/day of Ziziphus jujuba powder is safe without any negative impact on other organs (16), so intervention group used 30 g/day of Ziziphus jujube every day. The statistician and laboratory staff remained blind to the intervention type.

Participants were asked to prepare the infusion by pouring 100 mL of boiling water onto 10 g of dried ZF and drink it after 10 *minutes* three times a day (30 g/day).

Anthropometric measurements

Height without shoes was measured to the nearest 0.1 cm with a Seca Stadiometer. Body weight was measured by a digital scales (Hamburg, Germany) with 0.01 kg sensitivity. The subjects were wearing light clothing and no shoes. BMI was calculated as body weight/height^2 and expressed in kilograms per square meter.

Venous blood collection and biochemical analysis

After 12 hours overnight fasting, 5 ml blood samples were taken from the left antecubital vein between 7:00 and 8:30 A.M. Serum was separated from blood by centrifugation at 3000 RPM for 10 minutes. Serum samples were stored at -80^o C until analysis. Fasting blood sugar (FBS) and 2-hour postprandial blood glucose (2hpp) were determined using an automated enzymatic assay (Pars Azmoon Kit, Iran) on a Hitachi 902 auto-analyser. A

colorimetric method was used to measure glycated hemoglobin (HbA1c) after primary separation via ion exchange chromatography (biosystems).

Statistical analysis

All statistical analyses were performed using SPSS for Windows version 16.0 (SPSS Inc., Chicago, IL, USA). Kolmogorov- Smirnov test was used to determine quantitative data distribution. Data were expressed as means ± Standard Deviation (SD) for normally distributed continuous. Skewed variables (FBS and 2hpp glucose) was treated as a log-transformed value in all analyses and reported as the geometric mean. Between-group comparisons were performed using independent samples t-test. Within-group comparisons were made using paired t-test for normally distributed data. The percentage of changes in variables after intervention was determined by the following formula: [(after values – before values)/before values] × 100. Bivariate correlations between changes in body weight, FBS, 2hpp glucose , HbA1c and duration of diabetes were evaluated using Pearson's (For normally distributed data) and Spearman's (For non-normally distributed data) correlation coefficient. A *P*-value of less than 0.05 was considered as statistically significant.

Results

In this study, three participants were excluded for different reasons: one subject for complaining of hypotention in the ZF group and 2 persons for starting insulin in the control group.

Finally, 57 women with T2DM completed this trial. Participants did not report any adverse effects or symptoms with the ZF consumption during the study.

Demographic findings

Baseline demographic and anthropometric parameters of ZF and control groups are summarized in Table 1. The mean age of the women in the ZF and control groups showed to be 46.88 ± 7.34 and 49.20 ± 7.69 respectively. There were no significant differences between two groups in age, weight, height, BMI, and duration of diabetes at the beginning of the study ($P>0.05$).

Effect of ZF on glycemic control

Glycemic indexes of participants before and after intervention are shown in Table 2. FBS, 2hpp and HbA1C were not different between two groups before the intervention. Results of analysis showed statistically significant differences between two studied groups in 2hpp glucose ($P<0.05$) and HbA1C ($P=0.008$) levels at the end of the study. Further, marginally significant differences were seen between the two groups in serum levels of FBS ($P=0.06$) after the intervention.

FBS levels and 2hpp glucose decreased in the intervention group by 10.35 % (vs. 5.8 % decrease in control group) and 13.07 % (vs. 10.07 % decrease in control group), respectively, at the end of the study in comparison to baseline values. Based on the findings set out in Table 2, serum levels of HbA1C significantly decreased in the intervention group by 0.5 % (vs. 0.33 % decrease in control group).

Table 1. Demographic and anthropometric characteristics of participants before the intervention

Variables	Ziziphus group (n=29)	Control group (n=28)	*P*-value
Age (y)	46.88 ± 7.34	49.20 ± 7.69	0.40
Weight (kg)	76.17 ± 15.46	78.42 ± 12.97	0.51
Height (cm)	158.42 ± 4.58	158.16 ± 6.77	0.09
BMI (kg/m2)	30.22 ± 5.13	30.43 ± 6.75	0.88
Duration of diabetes (year)	3.81 ± 2.96	3.26 ± 2.27	0.65

Values are expressed as mean ± SD. *P*-value is reported based on the analysis of independent sample T-test for continuous variables and Chi-square for categorical ones.

Correlation analyses

Correlations between the changes of body weight and FBS, 2hpp glucose and HbA1C in two studied groups were analysed using Pearson's correlation coefficient test. There was significant positive correlation between the changes of body weight and HbA1C (r=0.393, P=0.02) in ZF group at the end of the study. No other significant correlations were found between changes of body weight and FBS, 2hpp glucose and HbA1C in both groups.

Discussion

The results of this study demonstrated that consumption of ZF is associated with a significant reduction in 2hpp glucose and HbA1C compared to the control. However, within-group comparisons revealed a significant decrease in FBS levels, 2hpp glucose and HbA1C in both groups. According to the results of Hemmati et al. (14) showed that treating diabetic rats with aqueous and hydroalcoholic extracts of Ziziphus. jujuba effectively decreased their elevated FBS levels. The anti-diabetic effects of the medicinal plants were previously reported (17). It is clear that diabetes and hyperglycemic conditions increase formation of reactive oxygen species and decrease the cellular antioxidant defence capacity (18). It is suggested that Ziziphus Jujube extract prevent hyperglycemic toxicity by elevating the intracellular antioxidant system and detoxify the generation of the high glucose-induced mass of free radical and the generation of apoptosis (19).

Our results are consistent with the findings of a previous study of Jarald et al. (20) that reported, aqueous extract and the non-polysaccharide fraction of the aqueous extract of Ziziphus could exhibit significant anti-hyperglycemic and hypoglycemic activities. Also petroleum ether extract (contained fats and triterpenoids) exhibited significant anti-diabetic effect. Treatment of diabetic rats with petroleum ether extract, aqueous extract, and non-polysaccharide fraction of Ziziphus restored the increased biochemical parameters, glucose, urea, creatinine, total cholesterol, HDL-C, LDL-C, triglyceride and HbA1c significantly to the near normal level. Eventually, the non-polysaccharide fraction of the aqueous extract was more effective than the aqueous extract and the petroleum ether extract.

The present study has several limitations, including its single blind design, the study population size was small, and this might have negatively influenced the power of study to detect significant differences differences in FBS parameter. Therefore, it is suggested randomized double-blinded trials in larger populations and over a longer period of time. It is recommended to determine if different ZF doses are associated with enhanced anti-diabetic effect.

Table 2. Glycemic status in women with T2DM before and after the intervention

Variables		Ziziphus group (n=29)	Control group (n=28)	*P*-value
FBS	Baseline [a]	144.18 ± 26.34	147.17 ± 23.79	0.63
	After intervention [a]	128.32 ± 21.47	137.53 ± 23.03	0.06
(mg/dL)	Mean difference(MD) (95 % CI),	−16.57 (−22.88, -10.25),	−9.82 (−16.06, -3.58),	
	P-value [b]	<0.005	0.003	
2hpp glucose	Baseline [a]	184.67 ± 48.92	196.39 ± 50.45	0.29
	After intervention [a]	157.16 ± 43.20	174.64 ± 35.09	
(mg/dL)	MD (95 % CI),	−28.48 (−41.95, -15.01),	−23.97 (−35.65, -12.28),	0.041
	P-value [b]	<0.005	<0.005	
HbA1C (%)	Baseline [a]	7.79 ± 0.71	8.05 ± 0.76	0.15
	After intervention [a]	7.19 ± 0.60	7.71 ± 0.67	
	MD (95 % CI),	−0.5 (−0.64, -0.36), <0.005	−0.33 (−0.45, -0.21),	0.008
	P-value [b]		<0.005	

Values are expressed as mean ± SD. [a and b] *P*-value is reported based on the analysis of independent sample T-test and paired sample T-test, respectively

Conclusion

The present study demonstrates that short term intake of Ziziphus fruit had beneficial effects on glycemic control in women with T2DM. A larger sample size and a longer intervention period may be needed to illustrate significant clinical improvement.

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Conflict of Interest

The authors have declare that there was no conflict of interest.

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