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Effects of High Performance Inulin Supplementation on Glycemic Status and Lipid Profile in Women with Type 2 Diabetes: A Randomized, Placebo-Controlled Clinical Trial

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ABSTRACT

Background: Type 2 diabetes mellitus, as a noncommunicable disease, is the main public health challenge in the 21st century. The prevalence of diabetes mellitus adjusted for the world population in Iran was 8% until the year 2010. Lipid levels are considered as important parameters to be evaluated, as high serum lipid levels are often reported as a complication in patients with diabetes mellitus. It is claimed that functional foods may improve complications of diabetes mellitus, so this study was designed to evaluate the effects of high performance inulin on glycemic status and lipid profile of women with type 2 diabetes.

Methods: The study was a randomized controlled clinical trial. Forty-nine type 2 diabetic females (fiber intake <30g/d, 25<BMI<35 kg/m^2) were divided into two groups. Patients in the intervention group (n=24) received 10g/d inulin and patients in the control group (n=25) received 10g/d maltodextrin for 8 weeks. Glycemic status and lipid profile indices were measured pre and post intervention. Data were analyzed using SPSS software (verision11.5). Paired, unpaired *t*-test and ANCOVA were used to compare quantitative variables.

Results: Supplementation with inulin caused a significant reduction in FBS (8.50%), HbA_{1c} (10.40%), total cholesterol (12.90%), triglyceride (23.60 %), LDL-c (35.30 %), LDL-c/HDL-c ratio (16.25%) and TC/HDL-c ratio (25.20%) and increased HDL-c (19.90%). The changes for the control group parameters were not significant at the end of study.

Conclusion: Inulin may help to control diabetes and its complications via improving glycemic and lipid parameters.

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Introduction

Diabetes mellitus (DM) is considered as a non-communicable disease and main public health challenge in developing and developed countries[1]. The prevalence of diabetes was 171 million in the year 2000. The total number of diabetic patients will be 366 million by the year 2030[2]. The prevalence of DM adjusted

for the world population in Iran was 8%, and its health expenses was approximately 600 million US dollars in the year 2010[3]. Diabetes mellitus is associated with insulin resistance, hyperinsulinemia, hyperglycemia and biochemical alterations in lipid metabolism[4]. Cardiovascular disease (CVD) is the primary cause of death in type 2 diabetes[5]. The relative risk for CVD is 2 to 4 fold higher in DM than in nondiabetic patients[6]. Dyslipidemia has been known as a risk factor for cardiovascular complications in type 2 DM. The typical lipid abnormalities in type 2 diabetic adults comprise low levels of HDL cholesterol, high levels of triglycerides and a dominance of small, dense LDL particles[7].

Recently, functional foods are considered in the management of type 2 diabetes and its complications[8]. Inulin-type fructans are a group of functional foods, which naturally found in leek, wheat, onion, chicory root garlic, and banana. Inulin-type fructans are group of carbohydrate, which is classified as nonviscous, soluble and fermentable fibers. High performance inulin (HP Inulin) is a prebiotic with long-chain; high-molecular weight mixes of inulin-type fructans. This type of inulin is incorporated as sugar and /or fat substitute into drinks and desserts, baked goods, and milk products. Intake of 5-8 g/d inulin should be sufficient to make a positive effect on the gut microflora. Possible side effect of inulin-type fructans intake is gut discomfort due to gas production, reported at doses >20g/d[9].

In animal studies, inulin-type fructans can reduce blood glucose and lipid profile, especially triglycerides[10,11]. According to our knowledge, all human studies have evaluated the effects of fructooligosaccharides on diabetic patients and there is no study to evaluate the impact of inulin HP in these patients[12-14]. The results obtained from several studies on the effects of fructooligosaccharides in diabetic patients are different. One study showed positive effects of oligofructose on blood glucose and lipid profile in diabetic patients[12]. In contrast, some other studies reported no effects for inulin-type fructans supplementation in diabetic patients[13,14]. It has been suggested to design further randomized controlled trials (RCT) in order to determine the effects of inulin-type fructans, inulin, and oligofructose on blood glucose[15] and lipid profile[16] in humans.

The present trial was conducted to assess the effects of HP inulin on serum glucose indices and lipid profile in women with type 2 diabetes.

Materials and Methods

Subjects

In this trial, sixty- five DM females aged between 20-65 yr were voluntarily recruited from Iran Diabetes Society and Endocrinology as well as Metabolism clinics of Tabriz University of Medical Sciences. Inclusion criteria were: having DM > 6 months, using anti-diabetic drugs, normal diet and Body Mass Index (BMI) >25 kg/m^2 during and in the last 3 months. Diabetes mellitus was defined as a fasting glucose ≥126 mg/dl[17]. Patients were excluded if they had history of gastrointestinal, cardiovascular, renal, thyroid, liver, pancreatic diseases, being pregnant or lactating, consuming pre or probiotics products during and 2 weeks prior to the intervention, antibiotics, antacids, alcohol, anti-diarrheal, anti-inflammatory, lipid-lowering, laxatives drugs and individual with a typical fiber intake >30g. At the beginning of trial, demographic data including age, drugs, diabetes duration (years) were collected using a questionnaire. The Ethics Committee of the Tabriz University of Medical Sciences provided ethical approval for the trial, and written informed consent was obtained from each patient. The approval of trial was registered on the Iranian Registry of Clinical Trials website (www.irct.ir/, IRCT201110293253N4).

Experimental design

Participants were randomly divided into 2 groups using a block randomization procedure based on BMI and age. Intervention group received 10 g/d inulin HP supplement (Sensus, Borchwef 3, 4704 RG Roosendaal the Netherlands) and control group received similar amounts of maltodextrin as placebo (Jiujiang Hurirong Trade CO., LTD, China (mainland)) for 8 weeks. Both maltodextrin and inulin have similar taste and appearance[18], which were provided to subjects in similar opaque packages. Patients received half of packages at the beginning and the remaining at 4th week of the study. In order to minimize withdrawal and ensure to consumption of supplements, the patients received a phone call every week. Throughout the trial, subjects were asked to have usual physical activity and diet.

Anthropometric and dietary intake assessment

Anthropometric indices including body weight and height were measured at baseline and at the end of the trial. Dietary intakes were evaluated using a 3-day food dairy (two usual days and one weekend day) at baseline and at the end of the trial. Before the intervention, all patients were provided instructions how to use food scale and record their food intake. After recording day, each patient received a phone call for renewed recording food intake by trained person. Dietary intakes were analyzed using the nutritionist 4 software (First Databank Inc., Hearst Corp., San Bruno, CA) containing the database from tables of content and nutritional value of Iranian food products.

Biochemical indices

At baseline and at the end of trial, after an overnight fasting 10 ml venous blood samples were collected and transferred into two vacutainer tube, one containing EDTA for measurement of blood HbA1c and the other containing sodium fluoride for glucose and lipid profile. Serum samples were separated from whole blood by centrifugation at 2500 rpm for 10 min (Beckman Avanti J-25; Beckman Coulter, Brea, CA) at room temperature. All parameters were analyzed on the day of sampling. FBS concentration was measured by the enzymatic methods using an Abbot Model Aclyon 300, USA auto analyzer with kits from Pars-Azmone (Tehran, Iran). Glycosylated hemoglobin (HbA1c) was determined in whole blood using an automated high performance liquid chromatography analyzer with comm.-ercially Bio-Rad D-10 Laboratories, Schiltigheim, France kit.

The levels of serum total cholesterol (TC), high-density lipoprotein (HDL-c) and triglyceride (TG) were measured by enzymatic colorimetric methods with commercial kits (Cholesterol CHOD-PAP and Triglycerides GPO-PAP; Pars-Azmone, IRI) on an automatic analyzer (Abbott, model Alcyon 300-USA)[19]. Serum Low-density lipoprotein (LDL-c) was calculated according to the Friedewald equation[20]. Since the TC/HDL-C and LDL-C/HDL-C ratios determine the relative risk of coronary artery disease, they were also calculated in this trail[21].

Statistical Analyses

Data were analyzed using SPSS software (version 11.5; SPSS Inc., Chicago, IL). The results were expressed as mean ± standard deviation. The normality of the distribution of data was evaluated by the one-sample Kolmogorov-Smirnov test. Paired, independent *t* test and ANCOVA were used to compare numerical data. Drugs used in two groups were compared using the Mann-Whitney U test. Analysis of covariance was used to identify any differences between the two groups post intervention, adjusting for baseline measurements and covariates. For calculating mean changes of markers between groups, first mean changes of markers from baseline were calculated by [(8wk values-baseline values) / baseline values)] * 100. Then, mean changes of markers between groups were calculated. $P<0.05$ were considered to be statistically significant.

Results

From 65 subjects recruited, 49 subjects completed the trial (n= 24 in the intervention group; n=25 in the control group; (Fig.1). As shown in Table 1, initial characteristics were similar at baseline in both groups.

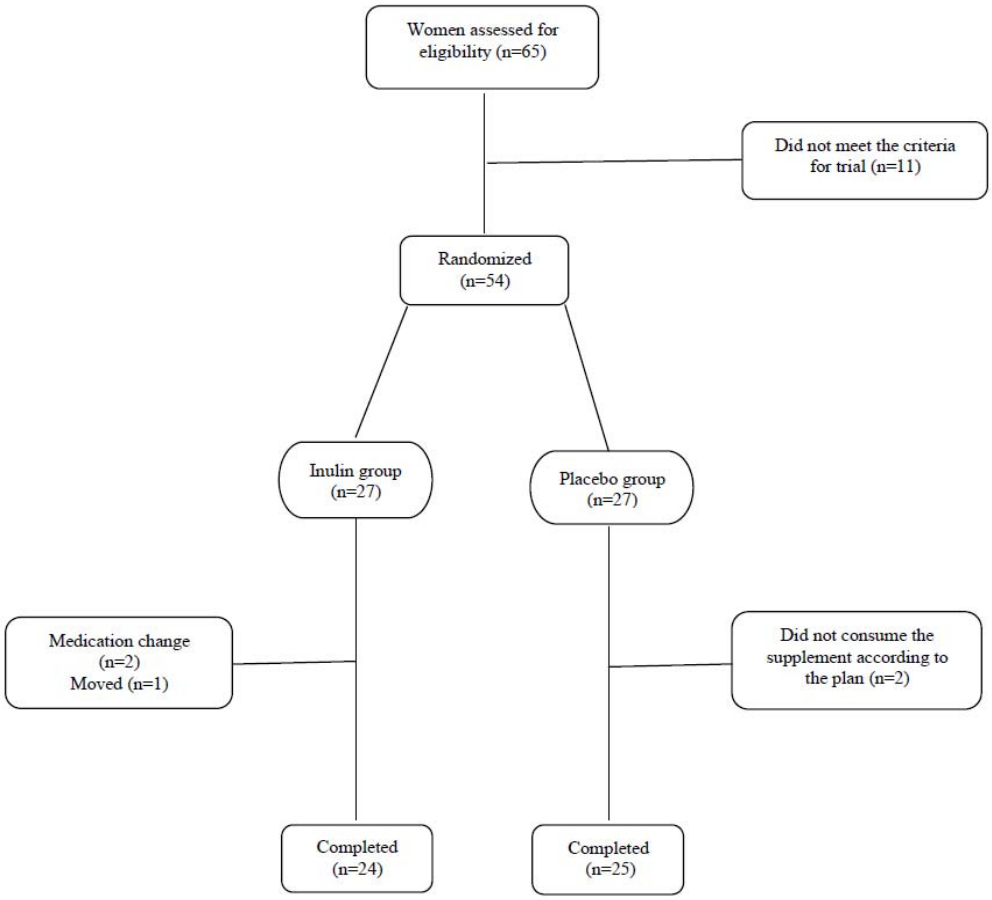

Fig. 1: Trial design implemented in this study

Effect of inulin supplementation on anthropometric indices and dietary intakes

As shown in Table 1, there was no significant difference at baseline body weight and BMI between two groups. Two groups did not show significant difference in baseline dietary intakes, except for dietary fiber which was significantly higher in control group than in the intervention group (data not shown, presented in another paper[22]). Post intervention, body weight and BMI were significantly decreased in inulin group (75.45 ± 11.35 to 72.85 ± 11.20 kg, 31.60 ± 4.09 to 30.50 ± 4.02 kg/m^2, respectively; $P<0.05$) while they remained unchanged in maltodextrin group. These changes were significant in inulin group compared to baseline ($P<0.05$). The results for dietary assessment are presented in detail in another paper[22].

Table1: Baseline characteristics of trial patients[1]

Characteristics	Control group (n=25)	Intervention group (n=24)
Age (yr)	48.70 ± 9.70	47.80 ± 10.10
Weight (kg)	70.50 ±11.05	75.45 ± 11.30
Height (cm)	153.50 ± 6.50	154.40 ± 5.80
BMI (kg/m^2)	29.90 ± 4.20	31.60 ± 4.09
Diabetes duration (yr)	5.30 ± 4.60	7.30 ± 5.40
Metformin 500 mg (tablets/d)	2.70 ± 0.90	2.85 ± 1.08
Glibenclamide 5mg (tablets/d)	1.90 ±1.20	2.35 ± 0.99

BMI: body mass index. [1]Rsults are presented as means ± standard deviation. / For all Characteristics, there were no significant differences between Maltodextrin and Inulin groups (all Non significant, based on independent samples *t* tests)

Briefly, there was no significant difference between groups regarding to intakes of energy, carbohydrate and total fat at the end of trial. The intake of energy and macronutrients remained unchanged in control group, while intake of energy and total fat decreased significantly in intervention group[22].

Effects of inulin supplementation on fasting blood sugar and lipid profile

At the beginning of trial, we did not observe a significant difference between intervention and control groups in FBS, HbA_{1c} and lipid profile (Table 2). At the end of trial, there was a significant decrease in FBS (8.50%), HbA_{1c} (10.40%), TC (12.90%), TG (23.60 %), LDL-c (35.30 %), LDL-c/HDL-c ratio (16.25%) and TC/HDL-c ratio (25.20%) in the intervention group compared with the control group (P<0.05). Inulin supplementation caused a 19.90% increase in HDL-c, compared with the control group after adjusting for dietary intakes and baselines values (P<0.05). In the control group FBS, HbA_{1c}, TC, TG, LDL-c, HDL-c, TC/HDL-c ratio and LDL-c/HDL-c ratio were not significantly changed at the end of trail.

Table 2: The effects of 8 weeks of inulin supplementation on anthropometrics indices, FBS and lipid profile during trial[1]

Variables	Period	Control group (n=25)	Intervention group (n=24)
FBS (mg/dl)	Initial	157.80 ± 10.60	161.70 ± 15.10
	End	156.10 ± 14.20	146.60 ± 19.90 [a,b]
HbA_{1c} (%)	Initial	8.20 ± 0.90	8.40 ± 0.90
	End	8.30 ± 1.09	7.70 ± 0.70 [a, b]
TC (mg/dl)	Initial	197.90 ± 37.80	192.50 ± 42.80
	End	203.10 ± 45.60	171.00 ± 39.70 [a, b]
TG (mg/dl)	Initial	213.10 ± 68.10	223.30 ± 84.20
	End	216.80 ± 59.80	169.95 ± 65.60 [a,b]
LDL-c (mg/dl)	Initial	114.60 ± 35.30	110.60 ± 40.90
	End	116.30 ± 42.96	89.60 ± 41.40 [a,b]
HDL-c (mg/dl)	Initial	40.60 ± 5.65	37.20 ± 6.05
	End	43.50 ± 4.20	47.40 ± 7.65 [a,b]
TC / HDL-c	Initial	4.90 ± 0.90	5.30 ± 1.40
	End	4.70 ± 0.10	3.70 ±1.09 [a,b]
LDL-c / HDL-c	Initial	2.80 ± 0.80	3.00 ± 1.20
	End	2.70 ± 0.95	1.95 ± 0.10 [a,b]

BMI: body mass index; FBS: fasting blood sugar; TC: total cholesterol; TG: triglyceride; HDL-c: high-density lipoprotein; LDL-c: low-density lipoprotein. / [1]Values are presented as mean ± standard deviation. [a] P<0.05, paired t test. [b] P<0.05 analysis of covariance adjusted for dietary intakes and baseline values.

Discussion

Beneficial effects of high fiber diets on prevention and management of diabetes are claimed[23]. Therefore, we assayed the effects of inulin on glycemic status and lipid profile in type 2 diabetic patients. Our results showed that the inulin supplementation significantly decreased body weight and BMI, FBS and HbA_{1c} in intervention group compared to control group. In addition, we observed inulin consumption caused a significant decrease in TC, TG, LDL-c, TC/HDL-c ratio and LDL-c/HDL-c ratio in intervention compared to control group. The inulin supplementation significantly increased HDL-c compared to the control group.

Pourmoradian et al. reported that royal jelly supplementation significantly decreased the mean body weight (72.45 ± 4.42 vs. 71.00 ± 6.44 kg)[24]. The addition of royal jelly improves the growth of L. acidophilus and B. bifidum. Probably, royal jelly supplementation may decrease weight via microfloura change[25].

Parnell et al. reported oligofructose at a dose of 21 g/day for 12 weeks decreased body weight in healthy adults[18]. We have showed that supplementation with inulin significantly decreased energy intake of the intervention group (1693.60 ± 250.60 to 1417.90 ± 236.70 kcal/day, $P<0.05$)[22]. The mechanism(s) of weight reduction by inulin is not fully understood. Probably, some gut hormones such as GLP-1, PYY, and ghrelin are involved in weight reduction caused by inulin[18].

Only three studies investigated the effects of fructans on glucose, insulin and lipid profile in type 2 DM[12-14].Yamashita et al showed that oligofructose (OFS) supplementation (8 g/day for 2 weeks) decreased fasting blood glucose, TC and LDL-c in type 2 DM patients[12]. Chen et al. demonstrated that glucomannan, as a prebiotic, at a dose of 3.6 g/day for 4 weeks, reduced fasting blood glucose, TC and LDL-c in type 2 DM patients[26]. Jackson et al. showed that prebiotic supplementation (10 g/d inulin for 8 weeks in individuals with mild hyperlipidaemia) decreased fasting insulin and TG[27]. Introducing of inulin-enriched pasta to healthy young volunteers showed a significant decrease in glycemic status and improved lipid profile[28]. Luo et al. and Alles et al. did not find significant changes with OFS supplementation (20g/d for 4 weeks, 15g/d for 3 weeks, respectively), on FBS and lipid profile in type 2 DM patients[13,14]. Additionally, the finding of increased HDL-c concentrations is in agreement with data previously obtained in vitro[29]. In our trial, the TC: HDL-c ratio and LDL-c/HDL-c ratio, as atherogenic indices were significantly reduced in the intervention group compared with the control group. It is indicated that these ratios CVD were better than either serum TC or LDL-c[30].

The difference in results obtained in several studies may be due to pathologic state and basal levels of fasting blood sugar and lipid profile in type 2 DM patients and type and dose of supplementation.

Hypoglycemic effect of fibers can be explained by several mechanisms. Inulin can control the level of serum glucose by decreasing the post-meal rise of serum glucose and delaying entry of glucose into blood and retarding gastric emptying[31]. Furthermore, modification of the gut hormones such as glucagon-like peptide1 (GLP-1)[32], short- chain fatty acids (SCFA) which are produced from colonic fermentation of prebiotics[33,34] and reduction in the body weight and BMI[35] can affect glucose metabolism in the body. SCFA can delay gastric emptying[33]. Oligofructose can improve glucose metabolism by rising of plasma insulin, β cell mass, pancreatic insulin, GLP-1[36] and GLP-2[37].

Based on what is already known about the properties of inulin- fructans, it seems that beneficial effects of inulin on lipid profile mainly mediated by short chain fatty acids (SCFA). Butyrate inhibits liver cholesterol synthesis and provides a source of energy for human colon epithelial cells[38]. Acetate may act as precursor for cholesterol synthesis, while propionate could

inhibit hepatic cholesterol synthesis by decreasing the use of acetate as a precursor of cholesterol[39]. Rossi et al. found that butyrate was the major fermentation product from inulin[40]. Reduction of plasma TG may be resulted from decreased hepatic lipogenic capacity[41], a reduction in the hepatic lipogenic enzyme gene expression such as acetyl -COA carboxylase, malic enzyme, ATP citrate lyase, glucose6- phosphate, 1-dehydrogenase and fatty acid synthase, increase triacylglycerol-rich lipoprotein catabolism[10,42]. Glucose and insulin are main stimulator in the control of lipogenesis, reduction in fasting blood sugar and insulin levels can result in reduction lipogenesis[43]. Moreover, prebiotics may contribute to cholesterol reduction by increasing fecal bile acid excretion[38], reducing in intestinal cholesterol absorption by increasing the thickness of the unstirred layer in the small intestine[44], increase in the expression of 3-hydroxy-3-methylglutaryl-COA reductase (HMG-COA reductase) and increase in the sterol regulatory element-binding proteins[42].

Our trial had some limitations, including duration of the intervention, which seems to be short, lack of measurement of serum SCFA, serum free fatty acids and plasma apolipoprotein.

Conclusion

Inulin supplementation may control levels of glycemic status and improve lipid profile in type 2 diabetic patients. These findings support the use of inulin as a safe treatment for managing diabetes. Our findings must be scrutinized in further clinical trials.

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Competing interests

The authors declare that there is no conflict of interests.

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