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Effect of Additional Prebiotics on Glycemia and Lipid Profile in Individuals with Type 2 Diabetes

Ayşe Ayda Demirtaş[1*], Nilüfer Acar Tek[2]

[1] Department of Nutrition and Dietetics, Selçuk University Hospital, Selçuk University, Konya, Türkiye,
[2] Department of Nutrition and Dietetics, Faculty of Health Sciences, Gazi University, Ankara, Türkiye

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Abstract

This study was conducted to determine the effect of prebiotic fiber intake on glycemia and lipemia in individuals with Type 2 Diabetes Mellitus (Type 2 DM). Over a 8-week period, 14 individuals with Type 2 DM between the ages of 20-50 with a Body Mass Index (BMI) above 25 kg/m² were randomly assigned to either an intervention group, in which participants were given additional prebiotic fiber with diabetic diet (n = 8, consuming 10 g/d of oligofructose-enriched inulin to diabetic diet) or to a control group, in which participants were given only with a diabetic diet (n = 6, consuming only diabetic diet). Fasting Plasma Glucose (FPG), fasting insulin, insulin resistance (HOMA-IR), glycosylated hemoglobin (HbA1c), Triglyceride (TG), Total Cholesterol (Total-C), High-Density Lipoprotein Cholesterol (HDL-C), Low-Density Lipoprotein Cholesterol (LDL-C) and Very Low-Density Lipoprotein Cholesterol (VLDL-C) values were measured at the beginning and end of the study. There was no significant difference between the initial and last measurements in HbA1c, fasting insulin, HOMA-IR, and HDL-C values only in the diabetic diet group ($p>0.05$); whereas FPG, TG, Total-C, LDL-C, and VLDL-C levels decreased ($p<0.05$). In the group that received additional prebiotics in the diet, the FPG, HbA1c, TG, Total-C, VLDL-C, and LDL-C levels decreased significantly ($p<0.05$) at the end of the study compared to the beginning; HDL-C ($p<0.05$) was elevated. Prebiotics can be used as a new option in the treatment of many metabolic diseases, especially diabetes. Prebiotics will make a positive contribution to metabolic markers by changing the composition of the microbiota.

Ayşe Ayda DEMİRTAŞ **(Corresponding author);** ORCID: 0000-0002-5969-7549, e-mail: dayseayda@gmail.com.
Nilüfer Acar TEK; ORCID; 0000-0002-8772-9608, e-mail: acarnil@hotmail.com

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1. Introduction

Diabetes has become a serious worldwide health problem that arises with elevated blood sugar levels (Wang et al., 2021). According to the data from the International Diabetes Federation (2021), there are 536.6 million adults with diabetes between the ages of 20-79 in the world, and this number is expected to reach 642.7 million in 2030. In recent years, besides the risk factors such as diet, environmental and genetic factors that affect the development of chronic diseases such as DM, obesity, metabolic syndrome, and cardiovascular disease (CVD) the role of changes in the intestinal microbiota has also been studied (Gholizadeh et al., 2019; Gurung et al., 2020). In the intestinal microbiota of individuals with Type 2 DM, while there is a reduce in functional bacteria number such as *Bifidobacteria* and *Bacteroidetes/Firmicutes* ratio; an raise is observed in both opportunistic pathogenic bacteria and some gram-negative bacteria that produce endotoxin (Larsen et al., 2010; Woldeamlak et al., 2019).

The contribution of the microbiota to the formation of insulin resistance and Type 2 DM is explained by many molecular mechanisms. The intestinal microbiota has an important role in the development of Type 2 DM by influencing metabolic pathways through different potential mechanisms, including intestinal permeability, modulation of inflammation, and glucose and lipid metabolism (Gurung et al., 2020). Therefore, regulation of the microbiome may be a beneficial strategy in the treatment of Type 2 DM (Wang et al., 2021).

Prebiotic fibers are classified as Inulin Type Fructans (ITF) (oligofructose, inulin, fructo-oligosaccharides), galactooligosaccharides, oligosaccharides from starch and glucose (resistant starch), non-carbohydrate oligosaccharides (such as flavanol), and other oligosaccharides (pectic oligosaccharides). Prebiotics are non-digestible nutritional components in the structure of oligosaccharides that enhance host health by selectively stimulating the activity and/or growth of one or more bacteria in the colon (Davani-Davari et al., 2019).

With the understanding of the role of intestinal microbiota in the pathophysiology of metabolic diseases, it was thought that prebiotics could be used as a new option in the treatment of diabetes (Davani-Davari et al., 2019; Wang et al., 2021). It has been stated that prebiotics have a positive contribution to metabolic markers by transforming the structure of the microbiota. It has been shown that prebiotic treatment improves intestinal microbiota fermentation, reduces hunger, and improves postprandial glucose response (Cani et al., 2009; Parnell & Reimer, 2012).

Prebiotics produce short-chain fatty acids (SCFA) by fermentation in the colon, which can slow down gastric discharge by regulating stomach movements. In studies conducted on people with Type 2 Diabetes, it has been shown that ITF have an improving impact on serum glucose levels by delaying gastric emptying, reducing postprandial glucose levels (Dehghan et al., 2014; Wang et al., 2019), and significantly decreasing FPG, HbA1c (Dehghan et al., 2016; Dehghan et al., 2014) TG, Total-C and LDL-C, while increasing HDL-C (Dehghan et al., 2016; Roshanravan et al., 2017). In order to show these effects, it is recommended that ITF supplementation be 10 g daily for 6 weeks or more (Dehghan et al., 2016; Dehghan et al., 2014; Roshanravan et al., 2017; Wang et al., 2019).

Therefore, dietary interferences can be recommended as a beneficial strategy to prevent, delay or treat Type 2 DM by causing positive variations in the gut microbiota. It has been proposed that additional prebiotics to diet may be an effective method to change the composition of the intestinal microbiota in individuals with pre-diabetes (Larsen et al., 2010; Wang et al., 2021).

In our study we planned in light of this information, it was aimed to evaluate the effect of prebiotic fiber intake on glycemia and lipemia in individuals with Type 2 DM. Certain limitations existed in the present study. The sample size of our study was small. Additionally, the duration of the intervention was 2 months. The intervention period is insufficient in terms of evaluation of biochemical markers such as HbA1c. Therefore, randomized controlled trials with larger samples are needed to determine the short and long-term effects of prebiotics on microbiota.

2. Materials and Methods

2.1. Individuals

This study was conducted with 14 individuals with Type 2 DM who were diagnosed and treated by the Department of Endocrinology at Selçuk University Hospital, between the ages of 20-50 y, with a BMI above 25 kg/m². Inclusion criteria for the study: diagnosed with Type 2 DM for more than 6 months, having a regular diabetic diet, and currently using oral antidiabetic drug. A history of any diagnosed pancreatic, gastrointestinal, thyroid, cardiovascular, kidney and liver disease, using insulin, regular use of probiotics, prebiotics, antibiotics, antacids, alcohol, antidiaretic and anti-inflammatory medications, being pregnant or breastfeeding, daily fiber intake of 30 g and above, and changing antidiabetic medication during the study are the exclusion criteria of the study.

2.2. Study Design

The intervention group received 10 g of prebiotic fiber (inulin+fructooligosaccharide) daily in addition to the diabetic diet (n=8), and the control group received a diabetic diet (n=6) for 8 weeks. The prebiotic supplement given to the volunters has been met by the researchers. The diabetic diet programs previously applied by the individuals in the study and control groups were rearranged by the researchers according to current body weight and height. The 'Mifflin-St. Jeor Equation' based on current weight was used to calculate the Basal Metabolic Rate (BMR) of individuals (Mifflin et al., 1990). The macronutrient pattern of the diabetic diet is organized so that 45-60% of energy comes from carbohydrates, 15-20% from protein and 25-30% from fat (TEMD, 2022). The volunteers were randomly assigned to two groups. At the beginning and end of the study, all participants' FPG, fasting insulin, HOMA-IR, HbA1c, TG, Total-C, LDL-C, and VLDL-C values were measured. The study was initiated after determining the sample size within the population with 95% confidence interval and 80% power and a total sample size of at least 14. The study has been approved by the ethics committee of Gazi University (Decision No: 14.06.2021 / 578).

2.3. Statistical Analysis

Data were analyzed using Statistical Package for the Social Science (SPSS) version 23.0 software. Non-parametric methods were used for the measurement values that did not conform to the normal distribution. In accordance with non-parametric methods, the "Mann-Whitney U" test method was used to compare the measurement values of two independent groups. The "Wilcoxon" test method was used to compare the double-repeated measurements of two dependent groups.

3. Results

There was no statistically significant difference between the groups in terms of gender, educational status, and occupation ($p>0.05$) (Table-1).

There was no statistically significant difference between the groups in terms of age and diabetes duration ($p>0.05$). There was no statistically significant difference between the groups in the FPG, HbA1c, fasting insulin, HOMA-IR, TG, HDL-C, and VLDL-C values measured at the beginning and end of the study ($p>0.05$). At the beginning of the trial, Total-C and LDL-C values were lower in the diet group than in the prebiotic fiber group ($p<0.05$). In the diet group, FPG, TG, Total-C, LDL-C, and VLDL-C values were significantly lower compared to the baseline values at the end of the study ($p<0.05$); while there was no significant difference between the first and last measurement in HbA1c, fasting insulin, HOMA-IR and HDL-C values ($p>0.05$).

Fasting plasma glucose, HbA1c, fasting insulin, HOMA-IR, TG, Total-C, LDL-C, and VLDL-C values decreased significantly at the end of the study compared to baseline in the group receiving additional prebiotics in the diet; whereas HDL-C increased ($p<0.05$) (Table- 2).

Table 1. Distribution of Individuals by General Characteristics

Variables	Diet group [n=6]	Diet+prebiotic group [n=8]	p
	n (%)	n (%)	
Gender			
Female	4 (%66.7)	2 (%25.0)	0.119
Male	2 (%33.3)	6 (%75.0)	
Educational status			
Middle school	3 (%50.0)	-	
High school	2 (%33.3)	3 (%37.5)	0.058
University	1 (%16.7)	5 (%62.5)	
Occupation			
Officer	-	3 (%37.5)	
Employee	2 (%33.3)	3 (%37.5)	0.171
Self-employment	2 (%33.3)	2 (%25.0)	
Housewife	2 (%33.3)	-	

Data are presented as number (percent)
p values for chi-square test

4. Discussion

Medical Nutrition Therapy (MNT), together with exercise and drug therapy, forms the basis of the medical treatment of diabetes patients. In order to provide effective glycemic and metabolic control in diabetes and to delay or prevent complications of diabetes, MNT should continue to be a part of the treatment throughout life (ElSayed et al., 2023). Regular and adequate intake of soluble fiber is one of the important dietary factors that play a role in the clinical management of diabetes by lowering the postprandial blood glucose level and reducing insulin resistance (Xie et al., 2021).

The presence of Type 2 Diabetes is related with the deterioration of the balance in the intestinal microbiota. Dysbiosis in the microbiota causes inflammation and affects glucose metabolism, insulin sensitivity, and tissue fatty acid composition. Dietary interventions such as increasing prebiotic fiber consumption have a dominant therapeutic effect in the prevention and management of Type 2 DM by changing the intestinal microbiota (Birkeland et al., 2021; Liu et al., 2017; Pourghassem Gargari et al., 2013).

It has been shown in many studies that soluble dietary fiber added to the diet plays an important role in glucose homeostasis with its positive effects on HbA1c, postprandial blood sugar, insulin resistance (Liu et al., 2017; Xie et al., 2021), and FPG (Liu et al., 2017; Silva et al., 2013) in individuals with Type 2 DM. In a meta-analysis study, 33 randomized clinical studies were evaluated, and it was shown that ITF, which is 10 g of soluble dietary fiber added to the diet for 6 weeks and longer, is effective in improving glycemic control (Wang et al., 2019).

Another meta-analysis study managed by Paul et al. (2022) reported a decrease of 0.45% in HbA1c, 13.98 mg/dl in FPG, 0.75 µU/mL in fasting insulin, and 0.88 units in HOMA-IR with the addition of prebiotics in individuals with type 2 DM. In this study, it was also observed that ITF supplementation used in addition to the diet for 8 weeks significantly reduced the glycemic indicators; FPG, HbA1c, HOMA-IR, and fasting insulin ($p<0.05$). While the change in HbA1c, fasting insulin, and HOMA-IR values was not significant in the diet intervention group ($p>0.05$); the decrease in fasting blood sugar was significant ($p<0.05$). These results suggest that prebiotics may contribute to glucose metabolism by positively changing the intestinal microbiota. Inulin-type fructans can improve serum glucose levels by delaying gastric discharge, reducing postprandial serum glucose, and slowing the entry of glucose into the bloodstream. In addition, prebiotics may indirectly affect hepatic glucose metabolism by decreasing the concentration of plasma fatty acids. In addition, it has been shown that oligofructose can improve blood glucose metabolism by increasing the levels of GLP-1 and Glucagon-Like Peptide 2 (GLP-2) (Wang et al., 2019). Prebiotics increase the production of GLP-2, which decreases intestinal permeability, thereby reducing endotoxemia and reducing insulin resistance (Ho et al., 2016).

Table 2. Comparison of the Groups by Demographic Characteristics and Pre and Post-Treatment Biochemical Results

	Diet group [n=6]	**Diet+prebiotic group [n=8]**	**p[1]**
	Median (I-III QR)	**Median (I-III QR)**	
Age (years)	41.5 (31.2-50.0)	42.0 (37.0-46.7)	0.897
Diabetes duration (years)	1.0 (0.87-8.75)	6.0 (5.0-9.7)	0.268
FPG (mg/dl)			
Initial	130.5 (95.0-196.0)	132.0 (107.5-172.0)	0.561
End	98.0 (91.2-122.5)	117.5 (94.5-147.5)	0.517
p[2]	0.046	0.012	
HbA1c			
Initial	6.6 (6.2-8.6)	8.1 (6.6-8.5)	0.243
End	6.1 (5.9-6.6)	6.6 (5.8-7.5)	0.603
p[2]	0.093	0.012	
Fasting Insulin			
Initial	17.4 (9.2-29.4)	10.2 (5.7-15.9)	0.245
End	9.3 (7.4-12.0)	8.3 (7.0-11.5)	0.519
p[2]	0.116	0.050	
HOMA-IR			
Initial	3.7 (2.4-10.6)	4.3 (1.9-4.9)	0.698
End	2.7 (2.4-3.9)	2.7 (1.8-3.3)	0.796
p[2]	0.173	0.036	
TG(mg/dl)			
Initial	201.5 (142.7-221.0)	215.0 (151.5-299.0)	0.366
End	142.0 (116.0-193.2)	165.5 (121.0-195.0)	0.699
p[2]	0.028	0.012	
Total-C (mg/dl)			
Initial	211.0 (201.5-218.2)	253.0 (235.5-279.2)	0.002
End	184.5 (168.2-200.2)	218,5 (195.2-231.5)	0.014
p[2]	0.028	0.012	
LDL-C (mg/dl)			
Initial	129.5 (107.5-136.5)	160.5 (152.7-181.7)	0.002
End	114.5 (102.0-119.2)	134.5 (125.7-165.5)	0.004
p[2]	0.028	0.012	
HDL-C (mg/dl)			
Initial	43.0 (40.2-50.7)	42.0 (38.0-45.0)	0.361
End	45.5 (42.5-53.0)	52.0 (44.5-54.0)	0.476
p[2]	0.279	0.017	
VLDL-C (mg/dl)			
Initial	40.3 (28.5-44.2)	43.1 (30.3-59.8)	0.366
End	28.4 (23.2-38.6)	33.1 (24.2-39.0)	0.699
p[2]	0.028	0.012	

Values are given as median.
FPG, fasting plasma glucose; HbA1c, glycosylated hemoglobin; HOMA index, insulin resistance; TG, triglyceride; Total-C, total cholesterol; LDL-C, low-density lipoprotein cholesterol; VLDL-C, very low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol.
$p^1<0.05$, "Mann-Whitney U" test for comparison of measurement values of two independent groups
$p^2<0.05$, "Wilcoxon" test statistics were used to compare the difference between baseline values and post-treatment measurements.

Studies have shown that ITF consumption enhances the serum lipid profile and thus helps to reduce the risk of CVD (Brighenti, 2007; Reis et al., 2014). Inulin is a viscous and soluble compound that inhibits cholesterol absorption. As a result of colonic fermentation of prebiotics, short-chain fatty acids butyric acid, propionic acid, and acetic acid are produced. These acids, in addition to providing energy to colon epithelial cells, are involved in supporting the survival of beneficial bacteria by lowering the ambient pH, regulating blood sugar, and secreting satiety intestinal hormones. It also plays an important role in improving the profile of lipids, including Total-C, HDL-C, LDL-C, and VLDL-C. Inulin-type fructans decrease the expression of genes encrypting liver enzymes required for de novo synthesis of lipids, increase muscle lipoprotein lipase enzyme mRNA transcript and activity, increase the production of SCFAs, excretion of fecal bile salt and cholesterol, and increase *Bifidobacterium spp* growth (Liu et al., 2017; Tawfick et al., 2022).

Uncontrolled diabetes patients typically have low HDL-C and high TG level. High triglyceride levels affect LDL cholesterol metabolism and lead to the formation of smaller and denser LDL particles, which are atherogenic (Mach et al., 2020). Some randomized placebo-controlled studies have reported that ITF intake improves the lipid profile therefore has a possible influence on reducing the risk of CVD (Dehghan et al., 2016; Dehghan et al., 2014; Reis et al., 2014; Roshanravan et al., 2017). Dehghan et al. (2014) announced that intake of 10 g/d inulin over 8 weeks had significant impacts on lowering FPG, fasting insulin, Total-C, LDL-C, and TG, increasing HDL-C. In this study, ITF supplement used in addition to the diet significantly decreased TG, Total-C, LDL-C, and VLDL-C values at the end of the study compared to the beginning ($p<0.05$); It was found to increase HDL-C ($p<0.05$). The change in HDL-C values was not significant ($p>0.05$); The decrease in TG, Total-C, LDL-C, and VLDL-C values was significant ($p<0.05$) in the diet group only. The recommended LDL-C value for individuals with diabetes at moderate cardiovascular risk is <100 mg/dL. In the 2019 EAS/ESC guideline, lowering the LDL-C level is recommended as the primary treatment to reduce the risk of CVD (Mach et al., 2020). With the addition of ITF, this reduction in LDL-C constitutes 2.7% of the recommended value (Liu et al., 2017). It has been shown that each 40 mg/dL decrease in LDL-C provides a 23% reduction in cardiovascular conditions (Baigent et al., 2005). Therefore, ITF supplementation with diet may be a preventive measure for CVD mainly through the reduction in LDL-C concentration and other positive effects on lipid homeostasis.

5. Conclusion

According to the results of this study, it has been shown that a daily intake of 10 g oligofructose-enriched inulin in addition to the diabetic diet for approximately 8 weeks improves the glycemic status and lipid profile in Type 2 DM. It suggests that the use of a prebiotic (ITF) that supports the positive effects of a diabetic diet may be an effective way to change gut microbiota and/or function. All these findings show that ITF can be used as adjunctive treatment for glycemic and lipemic control, particularly for patients with Type 2 DM in clinical practice.

Ethical Statement

Ethical approval for this study was obtained from Ethics Committee of Gazi University on 14.06.2021 with approval number 578.

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Presentation Information

The data from this study were presented as an oral presentation at I. International Congress on Medical Sciences and Multidisciplinary Approaches. The presentation date was February 20th, 2021.

Conflicts of Interest

The authors declare no conflicts of interest regarding this study. Any institution or organization providing funding for this research did not have any role in the design, data collection, analysis, interpretation, or publication to influence or distort the findings.

Author Contributions

The contributions of the authors are as follows: Ayşe Ayda Demirtaş participated in data collection and analysis, prepared the draft of the paper; Nilüfer Acar Tek conducted the supervision and final revision of the manuscript.

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