Consumption of fructooligosaccharides does not favorably affect blood glucose and serum lipid concentrations in patients with type 2 diabetes[1–3]

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ABSTRACT

Background: Fructooligosaccharides have been claimed to lower fasting glycemia and serum total cholesterol concentrations, possibly via effects of short-chain fatty acids produced during fermentation.

Objective: We studied the effects of fructooligosaccharides on blood glucose, serum lipids, and serum acetate in 20 patients with type 2 diabetes.

Design: In a randomized, single-blind, crossover design, patients consumed either glucose as a placebo (4 g/d) or fructooligosaccharides (15 g/d) for 20 d each. Average daily intakes of energy, macronutrients, and dietary fiber were similar with both treatments.

Results: Compliance, expressed as the proportion of supplements not returned, was near 100% during both treatments. Fructooligosaccharides did not significantly affect fasting concentrations (mmol/L) of serum total cholesterol (95% CI: −0.07, 0.48), HDL cholesterol (−0.04, 0.04), LDL cholesterol (−0.06, 0.34), serum triacylglycerols (−0.21, 0.44), serum free fatty acids (−0.08, 0.04), serum acetate (−0.01, 0.01), or blood glucose (−0.37, 0.40).

Conclusions: We conclude that 20 d of dietary supplementation with fructooligosaccharides had no major effect on blood glucose, serum lipids, or serum acetate in patients with type 2 diabetes. This lack of effect was not due to changes in dietary intake, insufficient statistical power, or noncompliance of the patients. *Am J Clin Nutr* 1999;69:64–9.

KEY WORDS Fructooligosaccharides, serum cholesterol, serum triacylglycerol, serum acetate, blood glucose, type 2 diabetes, Netherlands, adults, humans

INTRODUCTION

Fructooligosaccharides are nondigestible oligosaccharides that occur naturally in various edible food plants, such as onions and leeks (1, 2). The recent use of fructooligosaccharides as a food ingredient has triggered much research on their possible health effects. Because fructooligosaccharides are not hydrolyzed by enzymes in the small intestine of humans, they reach the colon intact. In a previous study we showed that fructooligosaccharides, added to the diet of young healthy subjects, are fully metabolized by the colonic microflora (3). End products of carbohydrate fermentation are gases, lactate, and short-chain fatty acids, such as acetate, propionate, and butyrate. Fermentation of fructooligosaccharides probably takes place in the proximal colon, leading to a rapid increase in breath hydrogen after consumption (3–5). The short-chain fatty acids that are produced during fermentation are thought to be readily absorbed by the colonic mucosa (6–8). It is known that butyrate serves as fuel for the mucosa, whereas acetate and propionate enter the portal blood and may influence systemic carbohydrate and lipid metabolism (7). Because acetate and propionate have dissimilar effects on glucose (9–14) and serum lipids (12, 15–17), the pattern of fermentation of fructooligosaccharides might be important when predicting their metabolic effects.

Yamashita et al (18) studied the systemic effects of adding 8 g fructooligosaccharides to the daily diet of patients with type 2 diabetes whose blood glucose and serum lipid concentrations were uncontrolled. They found an 8% decrease in fasting blood glucose concentrations, a 6% decrease in total cholesterol, and a 10% decrease in LDL cholesterol. Several experiments in rats have been conducted since, all showing that fructooligosaccharides lower serum triacylglycerol and total, LDL, and VLDL cholesterol (17, 19–21). Two recent intervention studies were done in healthy humans. A study by Luo et al (22) showed that chronic consumption of 20 g fructooligosaccharides/d increased basal hepatic glucose production but had no effect on insulin-stimulated glucose metabolism or serum lipids. Pedersen et al (23) studied the effect of inulin on blood lipids and did not find any changes in either total cholesterol, HDL cholesterol, LDL cholesterol, or triacylglycerol. Thus, the effects of fructooligosaccharides on blood glucose and serum lipids are not clear.

In the present study, we investigated in 20 patients with type 2 diabetes the effects of fructooligosaccharides on serum acetate

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concentrations, fasting glucose concentrations, free fatty acids, triacylglycerol, and total, LDL, and HDL cholesterol in a 6-wk placebo-controlled experiment with a crossover design.

SUBJECTS AND METHODS

Patients and experimental design

We recruited patients, who were diagnosed with type 2 diabetes on the basis of WHO diagnostic criteria (24), from 5 medical practices of general practitioners in the area of Nijmegen, Netherlands. All practices were connected to the Nijmegen Monitoring Project, the registration network of the Department of General Practice of the University of Nijmegen. Twenty patients with type 2 diabetes (9 men and 11 postmenopausal women) were selected. All patients had previous measures of fasting blood glucose concentrations exceeding 6.5 mmol/L and fasting serum cholesterol concentrations exceeding 6 mmol/L. Participants had no history of gastrointestinal disease and had not been treated with antibiotics or laxatives in the 3 mo before the experiment. All patients received dietary advice aimed at treating their diabetes and 17 patients used oral blood glucose–lowering medication. Patients were also treated for diabetes-related comorbidity with antihypertensive agents ($n = 9$) and lipid-lowering drugs ($n = 1$).

The study protocol was approved by the Medical Ethics Committee of the Division of Human Nutrition and Epidemiology. The protocol and aims of the study were fully explained to the patients, who gave their informed, written consent. After successfully completing the study, the patients received a small financial reward.

A single-blinded, placebo-controlled, crossover design with two 20-d treatment periods was used; there was no washout period between treatments. Each participant used each of 2 supplements in random order. Blood samples were collected at the end of each treatment period. Patients kept a diary in which they recorded time of supplement consumption, possible diseases or discomfort, medications used, and deviations in usual eating, drinking, or lifestyle behavior. Complaints of flatulence were rated on a 4-point scale (none, mild, moderate, or severe).

Supplements and food intake

Patients were instructed to maintain their habitual eating, drinking, and lifestyle behavior. They were asked to not eat probiotic dairy products that contain microorganisms able to survive passage through the upper gastrointestinal tract or to consume products containing large amounts of fructooligosaccharides, such as onions and leeks. Subjects were given a list of these probiotic and high-fructooligosaccharide–containing foods. Patients recorded their habitual dietary intakes for 2 d in each treatment period. These food records were coded and nutrient and energy intakes were calculated with use of the modified version of the 1993 release of The Netherlands Nutrient Data Bank (25).

On day 1 of the study, the patients were randomly assigned to daily treatment with 15 g fructooligosaccharides (Raftilose P95; ORAFTI, Tienen, Belgium) or 4 g glucose as a placebo (Cerestar Pur 01934; Cerestar Benelux BV, Sas van Gent, Netherlands). The supplements were aimed to be isoenergetic (≈70 kJ/d) (26) and of equal sweetness (A Franck-Frippiat, unpublished observations, 1995). Ten patients initially received fructooligosaccharides and 10 placebo. Patients consumed the supplements in a split dose—half of the supplement at breakfast and the other half at dinner. The supplements were mixed with yogurt. Because there was no adaptation period, the dose of fructooligosaccharides was gradually increased during the first 3 d, by 5 g/d, to prevent adverse gastrointestinal side effects.

Blood sampling and analyses

Blood samples were taken by medical assistants on days 1, 18, and 21 (period 1) and on days 39 and 42 (period 2) with subjects sitting after having fasted overnight (12 h). For glucose measurements, capillary blood samples were taken from a finger. A drop of blood was placed on a test strip and blood glucose was measured immediately with a blood glucose meter. The participating medical practices used different glucose meters, but standard procedures were used for each glucose meter and repeat measurements were made with the same equipment. All glucose meters were gauged before the experiment.

For the lipid analyses, blood was obtained by venipuncture according to a standardized protocol. After the blood samples had been allowed to clot (15–30 min), the tubes were put on ice and transported to the laboratory, where serum was obtained by low-speed centrifugation at 1500 × g for 10 min at 4°C (Sigma 4K10; Salm en Kipp BV, Breukelen, Netherlands). Within 2 h after the samples were taken, serum was stored at −80°C until analyzed.

Lipids were analyzed enzymatically for total cholesterol (27), HDL cholesterol (28), and triacylglycerol (29) with a Spectrum Analyzer (Abbott Laboratories, Chicago). The CV within runs was 1.0% for total cholesterol, 1.4% for HDL cholesterol, and 0.5% for triacylglycerol. The mean bias with regard to the target values from serum pools provided by the Centers for Disease Control and Prevention, Atlanta, was −1.4% for total cholesterol, 0.8% for HDL cholesterol, and 9.7% for triacylglycerol. LDL cholesterol was calculated by using the equation of Friedewald et al (30). Free fatty acids in serum were measured enzymatically (catalog no. 1383 175; Boehringer Mannheim GmbH, Mannheim, Germany). The mean recovery of the standard (palmitic acid) was 69% and a correction factor of 1.44 was used for all data.

Serum acetate was measured after deproteinizing the samples. Perchloric acid (0.5 mL, 1 mol/L) was added to the serum samples (0.5 mL). After centrifugation (1500 × g for 15 min at 4°C), potassium hydroxide (45 mL, 4 mol/L) was added to the supernate (0.6 mL), and, after a second centrifugation step (1500 × g for 10 min at 4°C), acetate was measured enzymatically in the supernate (catalog no. 148 261; Boehringer Mannheim). Values were corrected for volumes, for specific gravity, and for the liquid fraction of serum. The mean recovery of the standard was 100%. For all blood variables, samples from one particular patient were analyzed in one run.

Statistical analyses

The statistical analysis package SAS, version 6.09 (Statistical Analysis Systems Institute, Inc, Cary, NC), was used to perform the statistical analyses. The concentrations of lipids, glucose, and acetate in 2 blood samples per person, taken at the end of each period, were averaged. Complaints of flatulence were averaged over the last 2 wk of each supplement period. The differences between the 2 treatments were normally distributed as judged by visual inspection of the normal probability plots (univariate procedure). We used an analysis of variance model

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TABLE 1
Patient characteristics and baseline blood values[1]

	Men (n = 9)	Women (n = 11)
Characteristics		
Age (y)	56 ± 5.2	62 ± 4.1
Height (m)	1.76 ± 0.07	1.65 ± 0.07
Weight (kg)	91.1 ± 14.4	74.3 ± 9.05
Body mass index (kg/m^2)	29.4 ± 4.22	27.4 ± 2.72
Baseline blood values		
Total serum cholesterol (mmol/L)	5.61 ± 1.34	6.26 ± 0.89
Serum triacylglycerol (mmol/L)	2.66 ± 1.46	2.95 ± 1.53
Blood glucose (mmol/L)	8.83 ± 2.30	8.06 ± 1.75

including patient and treatment. When period was added to this model, the significance of the differences did not change, indicating that there were no significant effects of time or sequence of the treatments (SAS, general linear models procedure). We then used paired t tests to test for differences between the placebo and fructooligosaccharide treatments. One-sided P values <0.05 were considered significant. SDs of the effects were calculated and used to estimate the detectable effect of the treatment with a given probability (31).

RESULTS

Characteristics of the study population are given in **Table 1**. Cholesterol concentrations were lower than we had anticipated based on the patients' records; half of the baseline values were <6 mmol/L. Two participants had blood glucose concentrations <6.5 mmol/L at baseline. All participants completed the study successfully. Complaints of flatulence were significantly higher (P = 0.008) during fructooligosaccharide supplementation than during the placebo treatment. No other gastrointestinal complaints were reported.

Compliance, expressed as the proportion of supplements not returned, was 100% during both treatments. The food diaries did not indicate relevant differences in physical activity patterns, medications used, or eating, drinking, and lifestyle behavior between the 2 treatment groups. Body weight decreased significantly over time and was 0.6 kg lower at the end of the study than at baseline (P = 0.008). However, there were no significant differences in mean (±SD) body weight between the treatment groups: 81.7 ± 14.0 kg in the placebo group and 81.9 ± 14.4 in the fructooligosaccharide group. There were no significant differences in the average daily intakes of energy, protein, fat, carbohydrates, or dietary fiber between the 2 groups (**Table 2**).

Blood indexes

Average fasting concentrations of blood glucose, serum acetate, serum total cholesterol, HDL and LDL cholesterol, and triacylglycerol did not differ significantly between treatment groups (**Table 3**). Mean differences and 95% CIs are shown in **Figure 1**. Eight patients had higher total cholesterol concentrations after the placebo treatment than after fructooligosaccharide supplementation, 1 patient showed no differences, and 11 patients had lower values after the placebo. Eleven patients had higher blood glucose concentrations after the placebo treatment than after fructooligosaccharide supplementation, 1 patient showed no differences, and 8 patients had lower concentrations after the placebo. Data analyses for men and women separately did not show any differences between the sexes by treatment (data not shown). The sample size was too small to perform analyses in smaller subgroups, eg, in patients who took similar medications.

TABLE 2
Reported dietary intake of 20 diabetic patients after supplementation with glucose (placebo) or fructooligosaccharides[1]

	Glucose (placebo)	Fructooligosaccharides
Energy intake (MJ)	6.6 ± 3.2	6.1 ± 2.1
Carbohydrate intake (% of energy)	38.5 ± 7.5	39.4 ± 7.2
Fat intake (% of energy)	39.9 ± 9.0	36.7 ± 9.6
Protein intake (% of energy)	21.5 ± 6.2	23.2 ± 6.1
Dietary fiber (g/MJ)	2.1 ± 0.9	2.1 ± 0.8

[1] $\bar{x}$ ± SD; supplements were not included.

DISCUSSION

Our findings showed that consumption of 15 g fructooligosaccharides/d did not significantly affect blood glucose or serum lipid concentrations in patients with type 2 diabetes.

Patient compliance, statistical power of the experiment, and dietary intakes

We believe that the lack of effect in our study could not be explained by insufficient compliance of the participants, by low statistical power, by changes in intakes of other nutrients, or by the fact that we studied both men and women. Both reported compliance and compliance judged on the basis of supplements that were not returned were near 100% and did not differ between treatment groups. Furthermore, consumption of the fructooligosaccharide supplements was confirmed by the anticipated increase in flatulence during this treatment.

On the basis of studies with soluble dietary fibers, such as pectin and guar gum, we hypothesized that 15 g fructooligosaccharides would decrease serum cholesterol by 10%. In our study, we were able to detect a decrease of 6.1% with 80% confidence and a decrease of 7.2% with 90% confidence. We we were able to detect changes of <10% in 3 of 6 of the other indexes. Because the variation in response was high for the variables acetate, free fatty acids, and triacylglycerol, the detectable effects were also higher (15–21% with 90% confidence). We conclude that the study design was powerful enough to detect biologically relevant changes in our main outcome variables.

TABLE 3
Fasting serum lipids, serum acetate, and blood glucose in 20 diabetic patients after 20 d of daily supplementation with glucose (placebo) or fructooligosaccharides[1]

	Glucose (placebo)	Fructooligosaccharides
	mmol/L	
Total cholesterol	6.01 ± 1.18	6.21 ± 1.29
HDL cholesterol	1.09 ± 0.25	1.12 ± 0.23
LDL cholesterol	3.80 ± 1.04	3.99 ± 0.91
Triacylglycerol	2.44 ± 0.79	2.56 ± 1.22
Free fatty acids	0.83 ± 0.28	0.75 ± 0.26
Acetate	0.11 ± 0.02	0.11 ± 0.02
Glucose	8.59 ± 2.66	8.61 ± 2.61

[1] $\bar{x}$ ± SD.

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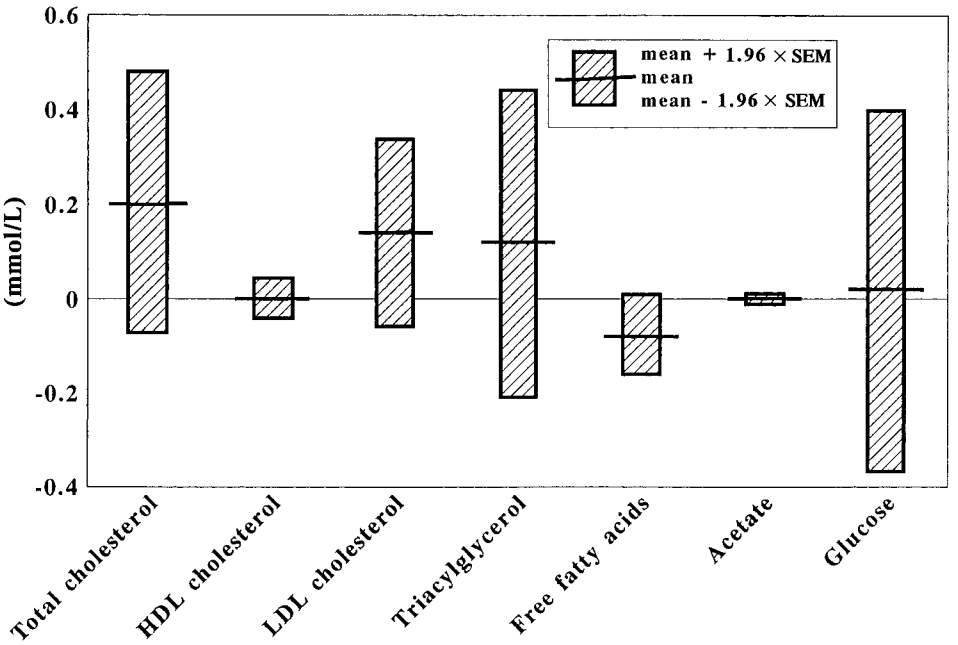

FIGURE 1. Mean (and 95% CIs) of differences in fasting concentrations of serum lipids, serum acetate, and blood glucose in 20 patients with type 2 diabetes, calculated as the effect of fructooligosaccharide supplementation for 20 d minus the effect of a placebo (glucose).

Contrary to our expectations, we observed small, nonsignificant increases in all variables studied, except free fatty acids. The 9.2% decrease in free fatty acids might have been a true change, but was not detectable with the study design we used.

We assessed the dietary intakes of the patients by analyzing 2-d food records completed during both treatment periods. Reported energy intakes were low in both men (8 MJ/d) and women (5 MJ/d) compared with the mean intake of Dutch men (10.5 MJ/d) and women (7.9 MJ/d) (32), probably because of underreporting. The results, however, showed no significant differences in the average intakes of energy, macronutrients, or dietary fiber between treatments. There were also no significant differences in body weight between treatments. It is thus unlikely that the participants adjusted their dietary habits in response to the treatment.

Both men and women were included in our study population. It is often believed that women are less suitable patients for studying dietary effects on colonic fermentation or serum lipids because of confounding effects of the menstrual cycle (33, 34) or of the use of oral contraceptives (35). However, all women were postmenopausal and none used oral contraceptives.

Dose and duration of the treatment

The study tested the effects of daily supplementation with 15 g fructooligosaccharides for 20 d. This dosage and duration of the treatment may have influenced the results. In our experience, a dose of 15 g results in gastrointestinal complaints, particularly flatulence, but is still acceptable to healthy humans (3). By supplementing the diet with 15 g fructooligosaccharides, we at least doubled the average daily intake of inulin plus fructooligosaccharides, which is estimated to be 1–10 g/d, depending on the population and the method of food analysis used (1). It is thus unlikely that effects of the fructooligosaccharide supplements were masked by effects of naturally occurring fructooligosaccharides.

Our results do not agree with those of several studies in rats (17, 19–21). However, this discrepancy can be explained by species differences or incomparable doses. In all rat studies, animals were fed a diet consisting of 10% fructooligosaccharides and providing a mean food intake of 23 g/d, resulting in an average body weight of 300 g at the end of the study. For rats, the intake of fructooligosaccharides per kilogram of metabolic weight (body weight$^{0.75}$) was thus 5.7 g/kg. For our diabetic patients, who had a mean body weight of 81 kg, the average intake was 0.6 g/kg metabolic weight. Thus, rats consumed a dose of fructooligosaccharides comparable with a dose of 150 g/d in humans, which is clearly not a feasible intake in humans.

In the study by Yamashita et al (18), 8 g fructooligosaccharides/d lowered fasting glucose concentrations and serum lipids in humans. The control group in their study consumed 5 g sucrose/d, which provides a somewhat higher energy content than does 8 g fructooligosaccharides, but this difference was too small to explain their results. Participants in the study of Yamashita et al had uncontrolled diabetes, with a mean blood glucose concentration of 11 mmol/L at baseline and a mean cholesterol concentration of 6.3 mmol/L at baseline. The greatest treatment effects were found in the most hypercholesterolemic patients. The participants in our study were under strict medical control for their diabetes. Their mean baseline blood glucose concentration was 8.4 mmol/L and that of total serum cholesterol was 5.95 mmol/L. We used patients' blood concentrations determined at their most recent medical check-up as a criterion for inclusion in the study. Baseline concentrations, however, were mostly lower, possibly because of differences in the analytic methods between the Human Nutrition Laboratory and the Nijmegen Hospital Laboratory or because our patients fasted overnight before blood was taken. The apparent effectiveness of medication in our patients may have masked a possible effect of the fructooligosaccharides.

It is possible that 20 d of supplementation may have been too short a time to induce differences in glucose and lipid metabolism. However, we think this was unlikely because serum lipid

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concentrations stabilize within 2 wk after a dietary change in healthy humans and hypercholesterolemic patients (36–38). Dietary effects on fasting glucose concentrations in patients with type 2 diabetes can be established within 2 wk (39).

Effects of short-chain fatty acids on glucose and lipid metabolism

The potential effect of fructooligosaccharides on glucose and lipid concentrations is based on the hypothetical effects of short-chain fatty acids produced during fermentation on glucose and lipid metabolism. Several researchers found increased serum concentrations of acetate after treatment with other types of nondigestible carbohydrates (6, 40–42). We did not observe this; however, we might have missed the effect because we measured fasting and not postprandial serum concentrations of acetate. Fructooligosaccharides are rapidly fermented and a peak concentration of serum acetate would be expected after a few hours, as is seen with lactulose (6, 42).

Acetate and propionate have dissimilar effects on glucose and lipid metabolism. Acetate is thought to facilitate the cellular uptake of glucose by suppressing lipolysis and thereby lowering the amount of free fatty acids in serum. Free fatty acids compete with glucose to enter the cell (9–11). The in vivo effect of propionate on fasting glucose concentrations seems to depend on the route of administration. Rectal infusion of propionate stimulates gluconeogenesis (12), whereas orally administered propionate tends to reduce glycemia (13, 14). Acetate may act as a precursor for cholesterol synthesis (12, 15), whereas propionate might decrease the use of acetate as a precursor of cholesterol synthesis (12, 15–17). Thus, acetate is thought to decrease glucose and increase cholesterol concentrations, whereas fermentation-derived propionate probably increases glucose production and decreases cholesterol concentrations.

The in vitro fermentation of both lactulose and fructooligosaccharides was tested by Luo et al (22). These authors concluded that the ratio of acetate to propionate is higher after lactulose fermentation (11.4) than after fructooligosaccharide fermentation (5.4), which was confirmed by Wang and Gibson (43). In vivo, acetate seems to dominate the net effects of lactulose. Jenkins et al (41) showed increased concentrations of total cholesterol after lactulose supplementation. With fructooligosaccharides, the net effect on glucose and lipid concentrations seems to be zero.

Conclusions

We conclude that fructooligosaccharides do not have important effects on blood glucose and serum lipid concentrations in patients with type 2 diabetes, who are under strict medical control. The lack of effect in our study could not be explained by changes in dietary intake, insufficient statistical power, or noncompliance of the patients. Thus, our findings do not suggest that fructooligosaccharides are an effective means to favorably affect serum lipids or glucose. However, it remains possible that other types of nondigestible oligosaccharides, with different fermentation patterns, do affect serum lipid or glucose concentrations.

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