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Obesity

Oligofructose Decreases Serum Lipopolysaccharide and Plasminogen Activator Inhibitor-1 in Adults with Overweight/Obesity

Jill A. Parnell[1], Teja Klancic[2], and Raylene A. Reimer[2,3]

Objective: To determine the effect of prebiotic supplementation on metabolic endotoxemia and systemic inflammation in adults with overweight and obesity.

Methods: Samples from a previously conducted randomized, double-blind, placebo-controlled trial were used for analysis. Participants were randomized to 21 g of oligofructose ($n = 20$; BMI 30.4 kg/m^2) or a maltodextrin placebo ($n = 17$; BMI 29.5 kg/m^2) for 12 weeks. A total of 37 participants had samples available for the current analysis. Resistin, adiponectin, plasminogen activator inhibitor-1 (PAI-1), interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and macrophage chemoattractant protein-1 (MCP-1) were quantified using MILLIPLEX® assays. Lipopolysaccharide (LPS) was measured using PyroGene™ Recombinant Factor C Assay.

Results: Plasma LPS concentrations were reduced by 40% in the oligofructose group over 12 weeks compared to a 48% increase in the placebo group ($P = 0.04$). PAI-1, a risk factor for thrombosis, was reduced to a greater extent in the oligofructose group (-17.3 ± 2.6 ng/ml) compared to the placebo group (-9.7 ± 1.8 ng/ml; $P = 0.03$). Oligofructose did not affect IL-6, TNF-α, MCP-1, adiponectin, or resistin.

Conclusions: Oligofructose reduces metabolic endotoxemia and PAI-1. Incorporating prebiotics into the diet through supplements or functional foods may help mitigate some markers of obesity-associated inflammation.

Obesity (2017) **25**, 510-513. doi:10.1002/oby.21763

Introduction

The complex interactions between host and resident gut microbiota are involved in the pathogenesis of obesity and its comorbidities. Based on the dysbiosis, or imbalance in gut microbial communities, that occurs in obesity, there is growing interest in dietary manipulation of the gut microbiota for preventive and therapeutic interventions in obesity. Prebiotics are nondigestible food ingredients that shift the composition of the gut microbiota and confer a health benefit for the host. A variety of prebiotics, including inulin, oligofructose, and galacto-oligosaccharides, has been examined in the context of obesity, type 2 diabetes, fatty liver disease, digestive disorders (i.e., irritable bowel syndrome), and allergic diseases (1,2).

In a randomized controlled trial, we previously demonstrated that 12 weeks of oligofructose intake reduced food intake, improved satiety hormone profiles, and improved weight loss compared to a placebo (3). Of interest, however, is the ability of prebiotics to modulate other risk factors of the metabolic syndrome. Systemic inflammation has been identified as a common thread linking obesity to a host of other metabolic diseases, notably type 2 diabetes and cardiovascular disease. Dysbiosis of the gut microbiota promotes low-grade inflammation (metabolic endotoxemia) in mice via an increase in lipopolysaccharide (LPS), a component of the outer membrane of Gram-negative bacteria (4). The gut microbiota may also impact inflammation through their effects on gut barrier function (5). Although animal studies provide strong evidence to suggest prebiotics can

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Funding agencies: Funding for this project was provided by the Canadian Institutes of Health Research (MOP-136889) and the University of Calgary.

Disclosure: JAP and TK declared no conflict of interest. RAR previously held a research grant from the manufacturers of oligofructose for a project unrelated to the current study.

Author contributions: JAP and RAR conceived the experiments. JAP carried out the experiments. JAP, TK, and RAR performed data analysis and were involved in writing the paper. All authors approve of the submitted and published versions.

Clinical trial registration: Clinicaltrials.gov identifier NCT00522353.

Received: 11 October 2016; **Accepted:** 8 December 2016; **Published online 23 February 2017. doi:10.1002/oby.21763**

TABLE 1 Metabolic and inflammatory markers in adults with overweight and obesity consuming oligofructose or placebo for 12 weeks

Risk factor	CTRL, baseline ($n = 17$)	CTRL, final ($n = 17$)	OFS, baseline ($n = 20$)	OFS, final ($n = 20$)	Time, *P* value	Diet, *P* value	Time × Diet, *P* value
BW (kg)	80.2 ± 3.0	80.7 ± 3.1	83.4 ± 2.8	82.3 ± 2.6	0.781	0.730	0.007
Fat mass (kg)	29.8 ± 1.6	29.4 ± 2.0	30.3 ± 1.7	29.6 ± 1.8	0.023	0.798	0.028
IL-6 (pg/ml)	1.20 ± 0.28	0.97 ± 0.12	1.19 ± 0.15	1.09 ± 0.12	0.197	0.792	0.622
TNF-α (pg/ml)	2.34 ± 0.2	3.20 ± 0.2	2.36 ± 0.2	3.37 ± 0.3	<0.001	0.807	0.550
MCP-1 (pg/ml)	166.6 ± 23.3	194.3 ± 29.3	158.9 ± 14.3	173.7 ± 17.2	0.207	0.572	0.698
Adiponectin (μg/ml)	218.2 ± 5.7	190.7 ± 15.3	226.9 ± 6.6	196.3 ± 9.3	0.001	0.532	0.845
Resistin (ng/ml)	32.2 ± 2.0	14.6 ± 1.7	29.8 ± 2.4	12.0 ± 1.0	<0.001	0.254	0.930
PAI-1 (ng/ml)	22.5 ± 2.8	12.8 ± 2.0	32.3 ± 3.8	15.0 ± 2.1	<0.001	0.113	0.026
LPS (EU/ml)	1.6 ± 0.2	2.4 ± 0.7	2.3 ± 0.5	1.3 ± 0.2	0.846	0.717	0.042

Data is mean ± SEM; n = participants per group. Differences between groups determined by repeated-measures ANOVA.
OFS, oligofructose; CTRL, control; BW, body weight; IL-6, interleukin-6; TNF-α, tumor necrosis factor-α; MCP-1, macrophage chemoattractant protein-1; PAI-1, plasminogen activator inhibitor-1; LPS, lipopolysaccharide.

modulate the gut microbiota to reduce metabolic endoxemia and inflammation, there remains a lack of human clinical data (1).

The objective of this analysis was to extend the findings from our 12-week, double-blind, randomized controlled trial with oligofructose and placebo supplementation in adults with overweight and obesity. The outcomes of interest included plasma levels of inflammatory and metabolic markers of disease and their correlation to previously published body fat mass, glycemia, and food intake data.

Methods

The randomized controlled trial design has been previously described (3). Briefly, 48 participants began the study and 37 participants completed the study, with new analysis of stored blood samples presented here. Participants were randomized to either oligofructose 7 g three times per day ($n = 20$; BMI 30.4 kg/m^2) or an equicaloric maltodextrin placebo group ($n = 17$; BMI 29.5 kg/m^2) for 12 weeks. In order to examine the effects of oligofructose independent of other lifestyle changes, the participants, who were weight stable upon enrollment, were instructed to maintain their usual lifestyle, eat until comfortably full, and not change their physical activity. Testing at baseline (week 0) and completion (week 12) included a dual-energy x-ray absorptiometry scan, 3-day food records, 4-hour meal tolerance test (MTT), and blood sampling for satiety hormones, lipids, glucose, and insulin. All participants provided informed, written consent, and the procedures were approved by the Conjoint Health Research Ethics Board of the University of Calgary.

Analysis of stored plasma samples, taken at fasting during the MTT, was conducted to measure metabolic and inflammatory markers. Plasma adiponectin, resistin, plasminogen activator inhibitor-1 (PAI-1), interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and macrophage chemoattractant protein-1 (MCP-1) were quantified in duplicate using MILLIPLEX® human cytokine and adipokine kits (Millipore, Billerica, MA) and Luminex® instruments at Eve Technologies (Calgary, Canada). Plasma LPS was quantified using PyroGene™ Recombinant Factor C Assay (Lonza, Walkersville, MD).

Differences between baseline and week 12 samples were analyzed by a repeated-measures ANOVA using time and diet as factors. Change between baseline and week 12 (delta value) was calculated by subtracting the week 0 value from the week 12 value, and differences between groups were analyzed using a one-way ANOVA. Relationships between plasma markers and previously published body fat data, glycemia during the MTT, and energy/macronutrient intake were analyzed using Pearson's correlation. All analysis was performed using SPSS® version 22 (IBM Corporation, Armonk, NY).

Results

We previously reported that the oligofructose group lost 1.03 ± 0.43 kg, which was primarily fat (3), whereas the placebo group gained 0.45 ± 0.31 kg (Table 1). Energy intake, glycemia, lipid, and satiety hormone responses were described previously (3).

New analyses related to inflammatory and metabolic markers at baseline and 12 weeks are described in Table 1. PAI-1 decreased in both groups, but the decrease was significantly greater in the oligofructose group ($P = 0.026$). LPS increased 48% in the placebo group and decreased 40% in the oligofructose group ($P = 0.042$). There were no changes in IL-6, TNF-α, MCP-1, adiponectin, or resistin.

Analysis of placebo and control groups combined showed that final fat mass was positively correlated with final PAI-1 ($r = 0.619$; $P = 0.001$) and final leptin ($r = 0.714$; $P = 0.001$). MCP-1 correlated with TNF-α ($r = 0.470$; $P = 0.003$) and insulin ($r = 0.465$; $P = 0.004$). PAI-1 and resistin were associated with dietary intake (Table 2); most notably, the change in PAI-1 was positively correlated with energy and carbohydrate intake.

Within the oligofructose group, the change in body fat was positively correlated with the change in plasma resistin (Figure 1A). Glucose area under the curve (AUC) at the final MTT was positively associated with final PAI-1 (Figure 1B). Resistin at week 12 was positively associated with carbohydrate intake at week 12 and adiponectin with fiber intake (Table 2).

TABLE 2 Pearson's correlation between blood parameters and dietary intake in participants with overweight and obesity consuming oligofructose for 12 weeks

Blood parameter	Dietary parameter	Pearson correlation coefficient	*P* value
All subjects			
Delta PAI-1 (ng/ml)	Energy intake (kcal) week 6	0.410	0.022
Delta PAI-1 (ng/ml)	Carbohydrate intake (g) week 6	0.494	0.005
Delta PAI-1 (ng/ml)	Carbohydrate intake (g) week 9	0.523	0.007
Oligofructose subjects			
Resistin (ng/ml) week 12	Carbohydrate intake (g) week 12	0.543	0.016
Delta adiponectin (μg/ml)	Dietary fiber intake (g) week 12	0.492	0.032

Dietary intake data was derived from weighed 3-day food records collected at weeks 0, 3, 6, 9, and 12. "Delta" represents the change in blood parameter from baseline to week 12.

Discussion

Obesity and associated metabolic disorders are linked to chronic, low-grade inflammation demonstrated by elevated proinflammatory markers such as TNF-α, MCP-1, IL-6, and LPS and a decrease in anti-inflammatory factors such as adiponectin (1,6,7). Nutrition, in the form of a high-fat diet, has been shown to promote inflammation, whereas prebiotics have the potential to reduce inflammation (1).

In our randomized controlled trial, oligofructose reduced plasma LPS, a finding initially shown in mice by Cani et al. (4). Further studies in obese mice have shown that prebiotics alter gut microbiota (increases in *Bifidobacterium* spp.) and thereby reduce intestinal permeability and plasma LPS (5). In human clinical trials, there are a limited number of studies with three different prebiotics tested. Dehghan et al. (8) administered 10 g/d of oligofructose-enriched inulin to 52 women with type 2 diabetes for 8 weeks and observed a significant reduction in LPS, IL-6, and TNF-α compared to maltodextrin control. In contrast, Dewulf et al. (9) provided 16 g/d of oligofructose-enriched inulin to 30 otherwise healthy women with obesity for 90 days and did not see changes in LPS or C-reactive protein. The greater metabolic dysfunction in subjects in the Dehghan study may explain the difference in ability to detect reductions in LPS between studies. Similar to Dewulf et al. (9), we also enrolled otherwise healthy adults with overweight/obesity but administered a higher dose (21 g/d) which may explain the significant reduction in LPS we observed. Another prebiotic, galacto-oligosaccharides, was shown to dose-dependently (6, 12, 18 g/d) decrease LPS in overweight adults after 14 days compared to control (10). Finally, in patients with nonalcoholic steatohepatitis, 168 days of 2.5 g/d of fructo-oligosaccharide in combination with the probiotic *Bifidobacterium longum* W11 reduced LPS, TNF-α and C-reactive protein compared to placebo (11).

We believe we are the first to report a reduction in PAI-1 with oligofructose in humans. In mice, prebiotics increased bifidobacteria abundance, which was accompanied by a decrease in plasma endotoxin alongside decreased PAI-1 expression in visceral adipose tissue (5,12). PAI-1 is a procoagulant, and increased levels are associated with thrombosis. Weight loss lowers PAI-1 levels in patients with type 2 diabetes and coronary heart disease (13). Furthermore, elevations in glucose and insulin are among the factors that increase PAI-1 production (14), and we previously reported a decrease in glucose and insulin levels in the oligofructose group but not placebo

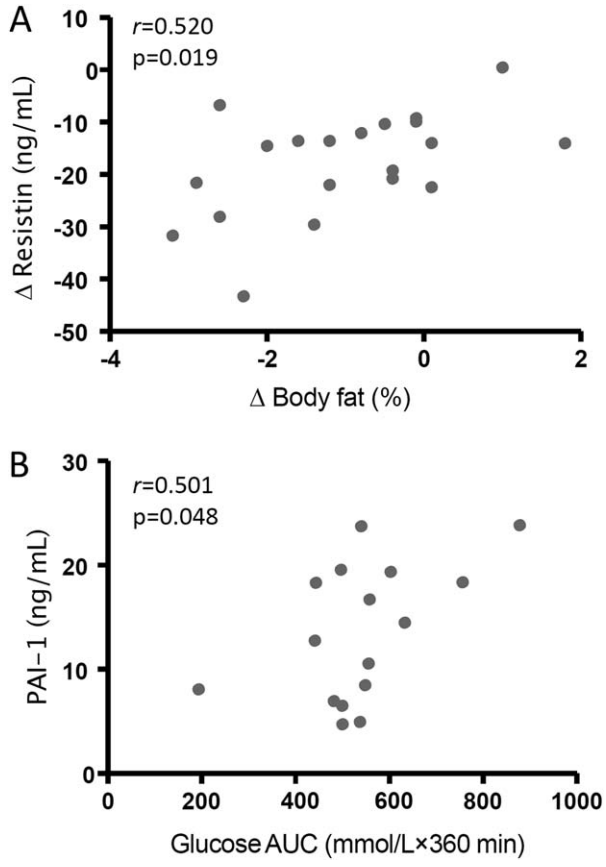

Figure 1 Pearson's correlation between the (**A**) change in body fat and change in plasma resistin and (**B**) final (12-week) glucose AUC during a 360-minute meal tolerance test and final plasma PAI-1 in participants with overweight and obesity consuming oligofructose for 12 weeks. Inset: Pearson's correlation coefficient (*r*) and the corresponding *P* value.

the group (3). Correlation analysis in the current study revealed that glucose AUC was positively correlated with PAI-1 at the end of the trial. Therefore, the lower PAI-1 we observed in our oligofructose group might be linked to reduced glucose and insulin levels and therefore reduced production of PAI-1. Because resistin encourages insulin resistance and inflammation (15), it is also consistent that the change in body fat in the oligofructose group was correlated with the change in plasma resistin. The significant correlation seen between PAI-1 and carbohydrate intake is consistent with similar findings in patients with nonalcoholic fatty liver disease (16). Furthermore, the positive correlation we observed between fiber intake and the change in adiponectin is consistent with the positive association between adiponectin and total and cereal fiber seen in women in the Nurses' Health Study (17).

The strength of the current research lies in the fully powered randomized controlled design as well as the array of inflammatory markers assessed. Our results are limited in that we did not quantify microbial changes and thus cannot make a direct link between the gut microbiota and the changes in inflammation presented here. Importantly, Dewulf et al. (9) did show an increase in *Bifidobacterium* and *Faecalibacterium prausnitzii* with oligofructose-enriched inulin, and both bacteria negatively correlated with serum LPS levels.

Conclusion

Supplementing the regular diet with 21 g/d of oligofructose has been previously shown to reduce body weight and body fat mass compared to placebo in adults with overweight/obesity (3). Furthermore, oligofructose supplementation, independent of any other lifestyle changes, reduced plasma levels of proinflammatory LPS and prothrombotic PAI-1. Because higher PAI-1 and LPS levels contribute to the complications of obesity (5), supplementing prebiotics in the diet may help delay or prevent comorbidities associated with obesity.O

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