

# $\alpha$ -Galacto-oligosaccharides Dose-Dependently Reduce Appetite and Decrease Inflammation in Overweight Adults<sup>1–3</sup>

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## Abstract

**Background:** Dietary fibers have been associated with a reduction in appetite and energy intake. However, although a few studies suggest that nonviscous fibers can exert such effects, likely through colonic fermentation, limited data are available.

**Objective:** This study aimed to determine whether  $\alpha$ -galacto-oligosaccharides ( $\alpha$ -GOSs), fermentable soluble fibers extracted from legumes, could reduce appetite, food intake, and inflammation in overweight subjects.

**Methods:** In 2 single-center, double-blinded, randomized, placebo-controlled trials, 88 overweight adults [50% men and 50% women; 18–60 y old; body mass index (in kg/m<sup>2</sup>): 25–28] were supplemented for 14 d with tea that contained  $\alpha$ -GOSs with different  $\alpha$ -GOS dosages (6, 12, or 18 g  $\alpha$ -GOSs/d), formulas (12 g  $\alpha$ -GOSs/d with >80% of molecules with a degree of polymerization of 2, 3, or 4), or a control substance (glucose syrup). Appetite scores (5 appetite dimensions were assessed on visual analog scales during a preload test meal), food intake (test meal and 24-h food recall), and inflammatory markers [plasma lipopolysaccharide (LPS) and C-reactive protein (CRP)] were evaluated at day 0 (baseline) and day 15.

**Results:** Changes in appetite scores from day 0 to day 15 were significantly higher after  $\alpha$ -GOS intake, with areas under the curve for the satiety score of +121  $\pm$  108, +218  $\pm$  218, and +306  $\pm$  205 score  $\cdot$  min for 6, 12, and 18 g  $\alpha$ -GOSs/d, respectively, and  $-5 \pm 64$  score  $\cdot$  min for the control group. We observed dose-dependent effects that did not vary by  $\alpha$ -GOS composition. The administration of 6, 12, or 18 g  $\alpha$ -GOSs/d significantly and dose-dependently increased the change in energy intake from day 0 to day 15 during a test meal ( $-13 \pm 19$ ,  $-26 \pm 22$ , and  $-32 \pm 22$  kcal, respectively;  $+6 \pm 21$  kcal for the control group). Reductions in energy intake during lunch and dinner were also higher in the  $\alpha$ -GOS groups in the dose-effect study. At day 15, LPS was dose-dependently reduced without an association with  $\alpha$ -GOS composition (0.16  $\pm$  0.02, 0.12  $\pm$  0.08, and 0.08  $\pm$  0.05 EU/mL for 6, 12, and 18 g  $\alpha$ -GOSs/d, respectively, and 0.06  $\pm$  0.04 EU/mL for the control group) and CRP was significantly lower in the  $\alpha$ -GOS groups than in the control group in the formulation-effect study.

**Conclusions:** Consumption of  $\alpha$ -GOSs over 14 d dose-dependently reduced appetite, food intake, and inflammation in overweight adults with no impact of  $\alpha$ -GOS composition. Consequently,  $\alpha$ -GOSs appeared to promote long-term weight loss and mitigate metabolic disorders. *J Nutr* doi: 10.3945/jn.114.204909.

**Keywords:** alpha-galacto-oligosaccharides, fibers, appetite, food intake, inflammation

## Introduction

Obesity has reached epidemic proportions globally; currently >1.9 billion adults are overweight and >0.9 billion individuals

are clinically obese (1). A high BMI is associated with a cluster of abnormalities, including chronic low-grade inflammation, that constitute metabolic syndrome and with diseases that reduce life expectancy, such as type 2 diabetes, cardiovascular diseases, and hepatic steatosis (2). Weight reduction results in significant improvements in both inflammation and metabolic abnormalities. Consequently, identifying strategies that can reduce appetite and subsequent food intake to promote weight loss would aid and inform public health efforts to combat obesity.

During a meal, fiber consumption has been associated with increased satiety and reduced energy intake (3, 4). Several

<sup>1</sup> Supported by Olygose S.A.S.

<sup>2</sup> Author disclosures: Q Dai, J Ni, D Thomas, and P Parnet, no conflicts of interest. FB Morel and P Fañça-Berthon are an employee and a former employee, respectively, of Olygose S.A.S.

<sup>3</sup> Supplemental Tables 1–3 and Supplemental Figure 1 are available from the “Online Supporting Material” link in the online posting of the article and from the same link in the online table of contents at <http://jn.nutrition.org>.

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**TABLE 1** Baseline characteristics of the overweight adults who participated in the studies<sup>1</sup>

	Dose-effect study				Formulation-effect study			
	Control	Mix of $\alpha$ -GOSs			Control	Mix of $\alpha$ -GOSs with high DP, 12 g/d		
		6 g/d	12 g/d	18 g/d		High DP2	High DP3	High DP4
Subjects (M/F), <i>n</i>	11/11	11/11	11/11	11/11	11/11	11/11	11/11	11/11
Age, y	30 $\pm$ 9	32 $\pm$ 8	32 $\pm$ 9	31 $\pm$ 7	35 $\pm$ 10	39 $\pm$ 9	38 $\pm$ 11	34 $\pm$ 10
Weight, kg	71.6 $\pm$ 8.3	71.6 $\pm$ 6.6	71.7 $\pm$ 9.0	71.8 $\pm$ 7.4	73.0 $\pm$ 8.0	73.6 $\pm$ 8.4	72.4 $\pm$ 8.7	74.8 $\pm$ 6.8
Height, cm	164 $\pm$ 9	165 $\pm$ 8	165 $\pm$ 9	164 $\pm$ 7	166 $\pm$ 7	166 $\pm$ 8	164 $\pm$ 8	167 $\pm$ 7
BMI, kg/m <sup>2</sup>	26.4 $\pm$ 0.7	26.4 $\pm$ 0.7	26.3 $\pm$ 0.9	26.6 $\pm$ 0.7	26.3 $\pm$ 0.9	26.5 $\pm$ 1.1	26.7 $\pm$ 1.3	26.8 $\pm$ 1.2
Waist circumference, cm	90.4 $\pm$ 5.2	90.5 $\pm$ 5.3	90.4 $\pm$ 6.4	90.6 $\pm$ 5.4	86.7 $\pm$ 6.2	89.1 $\pm$ 8.0	87.6 $\pm$ 7.4	88.0 $\pm$ 7.8
Hip circumference, cm	96.7 $\pm$ 4.9	96.6 $\pm$ 5.8	96.8 $\pm$ 4.8	96.8 $\pm$ 5.4	92.2 $\pm$ 8.8	93.3 $\pm$ 8.8	92.1 $\pm$ 10.3	93.9 $\pm$ 11.2
Waist-to-hip ratio	0.94 $\pm$ 0.05	0.94 $\pm$ 0.05	0.93 $\pm$ 0.04	0.94 $\pm$ 0.05	0.94 $\pm$ 0.06	0.96 $\pm$ 0.06	0.96 $\pm$ 0.06	0.94 $\pm$ 0.05
Body fat, %	27.2 $\pm$ 2.2	27.2 $\pm$ 2.4	27.3 $\pm$ 2.4	27.1 $\pm$ 2.0	26.4 $\pm$ 4.3	26.8 $\pm$ 3.9	27.8 $\pm$ 4.1	28.8 $\pm$ 3.4
Body fat mass, kg	19.4 $\pm$ 2.1	19.4 $\pm$ 1.5	19.5 $\pm$ 2.3	19.4 $\pm$ 2.0	19.3 $\pm$ 4.2	19.6 $\pm$ 3.0	20.2 $\pm$ 4.2	21.5 $\pm$ 3.0
Fat-free mass, kg	52.2 $\pm$ 6.8	52.2 $\pm$ 6.1	52.1 $\pm$ 7.4	52.4 $\pm$ 6.1	53.7 $\pm$ 6.0	53.9 $\pm$ 7.6	52.2 $\pm$ 6.4	53.3 $\pm$ 5.7
Daily energy intake, kcal	3062 $\pm$ 457	3036 $\pm$ 429	3014 $\pm$ 511	3009 $\pm$ 418	2887 $\pm$ 351	2682 $\pm$ 350	2639 $\pm$ 416	2683 $\pm$ 451
Daily fiber intake, g	31.6 $\pm$ 3.1	31.6 $\pm$ 3.7	31.2 $\pm$ 3.4	31.6 $\pm$ 2.3	30.4 $\pm$ 2.7	29.1 $\pm$ 2.6	29.0 $\pm$ 3.0	29.4 $\pm$ 2.8

<sup>1</sup> Values are means  $\pm$  SDs unless otherwise indicated, *n* = 22. DP, degree of polymerization; High DP2,  $\alpha$ -GOSs with >98% melibiose in  $\alpha$ -GOS content; High DP3,  $\alpha$ -GOSs with >90% manninotriose in  $\alpha$ -GOS content; High DP4,  $\alpha$ -GOSs with >80% verbascotetraose in  $\alpha$ -GOS content;  $\alpha$ -GOS,  $\alpha$ -galacto-oligosaccharide.

mechanisms linked to fiber viscosity have been proposed to explain this effect, which include the following: 1) the lower energy density of fiber-containing foods; 2) the need to chew high-fiber foods longer and their greater induction of gastric distention, which can promote satiety; and 3) the delayed gastric-emptying resulting from fiber viscosity, which has been associated with a prolonged absorption time that can also promote satiety [see (3) for review]. However, the consumption of nonviscous fibers, which can also regulate appetite (5–9), reduce food intake (6, 9, 10), and induce weight loss in overweight and obese subjects (6), could not be explained by the above mechanisms. A recent hypothesis, now bolstered by several studies aimed at showing a causative role for gut microbiota in obesity, could explain the impact of nonviscous fibers on the appetite of the consumer. Nonviscous fibers may induce changes in gut microbiota that could be involved in the regulation of appetite and food intake (5). Indeed, increased SCFAs, which are bacterial end products that result from fiber fermentation, promote gut peptide secretion (11, 12), thereby contributing to appetite and food intake control (5–7). Fiber consumption could also affect body weight, independently of its role in appetite regulation. Indeed, the modulation of intestinal microbiota could alter how energy is harvested from food, could modify the activity of lipoprotein lipase interfering with TG accumulation in adipose tissue, or could perturb intestinal permeability, thereby affecting systemic inflammation [see (13) for review].

The satietogenic effect of nonviscous fibers has mainly been obtained with fructans, whereas data on other soluble nonviscous fibers are sparse. Derived from legumes,  $\alpha$ -galacto-oligosaccharides ( $\alpha$ -GOSs)<sup>9</sup> are soluble fibers that have prebiotic activity that has been established in vitro (14, 15), in rodents (16), and in humans (17–19). They represent new candidates for appetite regulation. Because both the dose (20) and degree of polymerization (DP) of nondigestible oligosaccharides can influence their impact on intestinal microbiota composition (21, 22) and activity (23), as well as the associated physiologic

effects (24, 25), we tested 3 doses (6, 12, and 18 g/d) of a mixture of  $\alpha$ -GOSs with a DP of 2, 3, and 4 (DP2, DP3, and DP4) and 3 formulations of  $\alpha$ -GOSs with a high content of DP2 (melibiose), DP3 (manninotriose), or DP4 (verbascotetraose). We aimed to determine the impact of  $\alpha$ -GOS consumption on appetite and subsequent energy intake.

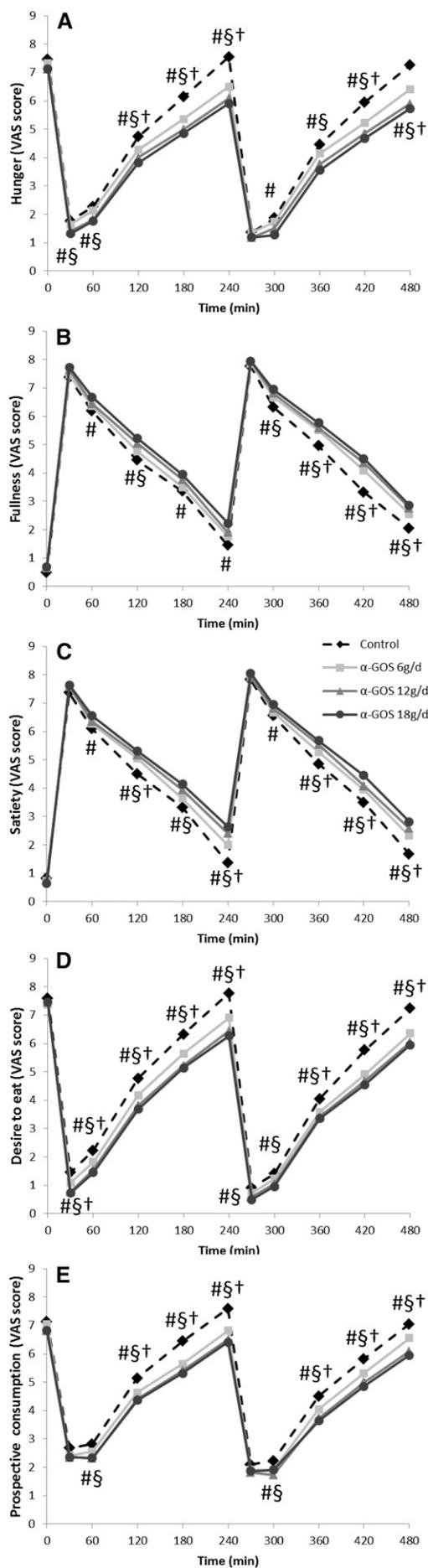
## Methods

**Study designs.** At the Institute of Nutrition and Health Food (Tongji University, Shanghai, China), 2 single-center, double-blinded, randomized, placebo-controlled, parallel 4-arm studies were conducted separately. Both studies were performed in accordance with the Declaration of Helsinki as revised in 1983, the guidelines of Good Clinical Practice (guidelines E6 from The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Care), and local regulations. These studies were granted approval by the Shanghai Nutrition Society Ethics Committee. All participants provided written informed consent before any research activities were initiated.

**Participants.** The 2 studies were conducted separately, with distinct patient cohorts. In both studies, 88 healthy, free-living men and women, aged 18–45 y, with a BMI (in kg/m<sup>2</sup>) between 25 and 28, and with a stable weight ( $\pm$ 3 kg) for at least 3 mo were included. Exclusion criteria were as follows: having participated in another trial within the 2 previous months, having attempted to lose weight in the past 3 mo, having taken medication or dietary supplements that could influence study outcomes within the 3 mo before the study, having a contraindication to dietary fiber supplementation, having a previous known allergic reaction to wheat products (gluten intolerance or celiac disease), having endocrine or gastrointestinal disease(s), being pregnant or lactating, exhibiting alcohol or drug dependence, consuming >3 drinks of alcohol/d, and smoking. Subjects had to report any medication/treatment that they were taking to the investigator during the study. Each medication/treatment, except for paracetamol up to a maximum dose of 1 g/d, was discussed between the investigator and study monitor to decide whether or not to keep the subject in the study.

**Intervention.** In each study, qualified subjects were randomly assigned to 1 of 4 groups. In the dose-effect study, subjects drank 250 mL bottled oolong tea (water, oolong tea leaves, vitamin C, sodium hydrogen carbonate; 0 kcal) twice a day to which either 3, 6, or 9 g  $\alpha$ -GOSs [with >98% polymers of D-galactose residues linked by  $\alpha$ (1 $\rightarrow$ 6) bonds with a

<sup>9</sup> Abbreviations used: CRP, C-reactive protein; DP, degree of polymerization; VAS, visual analog scale;  $\alpha$ -GOS,  $\alpha$ -galacto-oligosaccharide.



terminal  $\alpha(1 \rightarrow 6)$ -linked D-glucose; Cravingz'Gone; Olygose] or a control (dried glucose syrup C\*DRY 01934; Cargill) were added. Study groups were as follows: 6 g  $\alpha$ -GOSs/d (3 g  $\alpha$ -GOSs twice per day), 12 g  $\alpha$ -GOSs/d (6 g  $\alpha$ -GOSs twice per day), and 18 g  $\alpha$ -GOSs/d (9 g  $\alpha$ -GOSs twice per day).

In the formulation-effect study, subjects drank 250 mL bottled oolong tea twice per day to which 1 of the following was added: 6 g  $\alpha$ -GOSs (with >98%  $\alpha$ -GOS dry matter) with a high content of DP2 (high DP2; including >98% melibiose  $\alpha$ -GOS content), DP3 (high DP3; including >90% mannanotriose  $\alpha$ -GOS content), or DP4 (high DP4; including >80% verbascotetraose  $\alpha$ -GOS content) or a control (dried glucose syrup, C\*DRY 01934).

In each study, participants consumed 1 bottle in the morning during breakfast (~0800 h) and 1 during the afternoon (between 1500 and 1600 h). All subjects consumed the control drink during the first day of the study (day 0) and consumed the tested products or control daily from days 1 to 15 (i.e., an intervention period of 14 d). No follow-up was conducted after the end of the intervention.

**Outcomes.** The primary endpoint of both studies was an appetite rating evaluated on 5 appetite dimensions (hunger, fullness, satiety, desire to eat, and prospective consumption) according to a preload and test meal design. The preload meal was a standardized breakfast consumed in 15 min. All participants consumed the entire breakfast. The test meal was an ad libitum lunch during which participants were informed that they could eat as much or as little food as they desired. The compositions of both meals are described in Supplemental Table 1. Appetite ratings during the preload test meal were assessed on day 0 (before the intervention) and day 15 (after the intervention) with the use of visual analog scales (VASs) just before the start of a preload meal (consumed at 0800 h); 30, 60, 120, 180, and 240 min after the preload meal; and 30, 60, 120, 180, and 240 min after the test meal (consumed at 1200 h). A 9-point numerical scale ranging from 0 (not at all) to 9 (extremely) was used for evaluating subject feelings on the 5 appetite dimensions. The AUC from the start of the preload meal to 240 min after the test meal was calculated for each of the appetite categories.

Secondary endpoints in both studies included food intake and anthropometric measurements. Food and beverage intakes during the test meal were determined by weighing food and drinks before and after the meal. In addition, a 24-h dietary recall (after a training session) was used to calculate the daily intakes of calories, protein, fat, carbohydrate, and fiber at days 0 and 15. Anthropometric variables, including height, weight, BMI, waist and hip circumferences (measured in centimeters as the minimum value between iliac crest and the lateral costal margin and the maximum value over the buttocks, respectively, with each variable measured twice), and body fat percentage (measured by impedancemetry by using an Omron Karada Scan Body Composition Monitor HBF-306), were measured on days 0 and 15.

Fasting blood samples were drawn on days 0 and 15 and collected into depyrogenated tubes (Becton Dickinson) containing EDTA. Plasma LPS was measured in samples stored at  $-70^{\circ}\text{C}$  with the Limulus Amebocyte Lysate chromogenic endpoint assay HIT302 kit from Hycult. Plasma high-sensitivity C-reactive protein (CRP) was measured for samples stored at  $-20^{\circ}\text{C}$  with ELISA kits from R&D Systems. Fecal bifidobacteria and total bacteria were quantified in the formulation-effect study according to the method described by Faca-Berthon et al. (26). Gastrointestinal tolerance was self-monitored at days 0 and 15 with a VAS rating ranging from 0 to 9 for flatulence, borborygmi, bloating, abdominal pain, stool frequency, and stool consistency.

**Sample size and power consideration.** Sample size calculations were based on the primary endpoint criterion of these studies, appetite scores.

**FIGURE 1** Appetite VAS scores for hunger (A), fullness (B), satiety (C), desire to eat (D), and prospective consumption (E) after meals in overweight adults who consumed a mix of 6, 12, or 18 g  $\alpha$ -GOSs/d for 14 d. Values are means  $\pm$  SEMs,  $n = 22$ . # $P < 0.05$  between the 18-g/d  $\alpha$ -GOS and control groups; ‡ $P < 0.05$  between 12-g/d  $\alpha$ -GOS and control groups; † $P < 0.05$  between 6-g/d  $\alpha$ -GOS and control groups. VAS, visual analog scale;  $\alpha$ -GOS,  $\alpha$ -galacto-oligosaccharide.

These calculations revealed that requiring the detection of a minimum difference of 10% in the AUC for each VAS rating (27) with a patient cohort of 22 individuals (allocation ratio of 1:1:1:1, 10% attrition rate) would show 80% power.

**Randomization.** For both studies, 88 subjects were randomly assigned to 1 of the 3 treatment groups ( $n = 22$ ) or to the control group ( $n = 22$ ). Subjects were stratified by age (18–30 or 31–45 y) and sex and assigned by using a permuted block design.

**Statistical analyses.** Continuous variables were statistically assessed for verisimilitude of the normal distribution assumption by using the Shapiro-Wilk test. Continuous outcome variables are reported as means  $\pm$  SDs. One-factor ANOVA was used to evaluate between-group differences for baseline and postintervention subject characteristics. When a significant difference was detected with ANOVA, multiple tests with the use of Fisher's least significant difference technique were performed without correction of the significance level. Comparisons across all groups were performed in both studies. Repeated-measures ANOVA was used to evaluate between-group changes in appetite scores. Spearman rank correlation coefficients ( $r$ ) were calculated to assess correlations between changes in the AUC for appetite VAS scores in response to the test meal or plasma LPS and either doses or formulation. Data related to anthropometric variables and energy intake are presented as changes rather than as endpoints to limit interindividual variability. All analyses were conducted according to the intent-to-treat principle. The last observation carried forward method was used to impute missing outcome data. A significance threshold for statistical tests was set at  $P < 0.05$  (2-sided). All analyses were performed by using SAS 9.3 for Windows (SAS Institute).

## Results

**Baseline patient characteristics.** A total of 88 subjects (22/group) participated in both studies. No patients dropped out of the dose-effect study, whereas 2 individuals (1 in the control group and 1 in the high-DP3-formula group) withdrew in the middle of the formulation-effect study for personal reasons. Patient baseline characteristics were well matched across study groups (Table 1). No significant differences were detected between groups within each study.

**Appetite.** There were no significant differences between study groups at baseline for all appetite dimensions. In the dose-effect study, after 14 d of intervention, a significant effect of 3 doses of

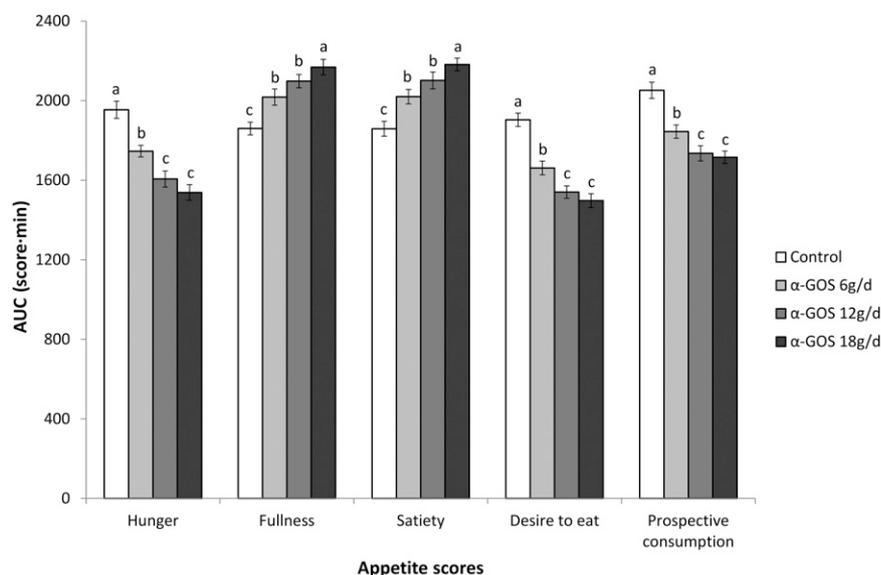
$\alpha$ -GOSs was observed on mean appetite scores over the 240 min after preload meal consumption (except for the fullness score in the group who received 6 g  $\alpha$ -GOSs/d) and over the 240 min after the test meal. We found that mean scores for hunger, desire to eat, and prospective consumption were lower in the 3  $\alpha$ -GOS groups than in control group, whereas mean fullness and satiety scores were higher in the 3  $\alpha$ -GOS groups than in the control group for both periods. All appetite dimension profiles are shown in Figure 1. The AUCs calculated for all appetite dimensions during the preload test meal experiment were significantly different between groups (Figure 2). Significant positive correlations were detected between  $\alpha$ -GOS doses and changes in the AUC for fullness ( $\rho = +0.55$ ,  $P < 0.001$ ) and satiety ( $\rho = +0.68$ ,  $P < 0.001$ ), whereas negative correlations were found between changes in AUC for hunger ( $\rho = -0.69$ ,  $P < 0.001$ ), desire to eat ( $\rho = -0.65$ ,  $P < 0.001$ ), and prospective consumption ( $\rho = -0.63$ ,  $P < 0.001$ ) in response to the preload test meal period. This finding indicated a dose-response effect of  $\alpha$ -GOSs on appetite scores.

In the formulation-effect study, the mean scores for hunger, desire to eat, and prospective consumption were lower in the 3 groups with different  $\alpha$ -GOS formulas than in the control group and the mean scores for fullness and satiety were higher in the 3 groups with different  $\alpha$ -GOS formulas than in the control group over the 240 min after the preload meal and over the 240 min after the test meal. Moreover, the AUC for appetite scores was significantly affected in those groups who received formula with a high content of DP2, DP3, or DP4 compared with the control group. Specifically, hunger, desire to eat, and prospective consumption were significantly lower in the 3 groups who received different  $\alpha$ -GOS formulas than in the control group, whereas fullness and satiety were significantly higher (Supplemental Figure 1). However, there was no significant difference between the 3 formulas.

**Food intake.** In the dose-effect study, the change from day 0 to 15 in food and nutrient (except for fat) intake during the test meal was significantly increased by  $\alpha$ -GOS intake, with greater differences in groups who received higher doses of  $\alpha$ -GOSs (Table 2).

The change from day 0 to day 15 in 24-h recall of energy intake during lunch and dinner was significantly increased by

**FIGURE 2** Change from day 0 to day 15 in AUCs for appetite scores (assessed with visual analog scales) in overweight adults who consumed a mix of 6, 12 or 18 g  $\alpha$ -GOSs/d. Values are means  $\pm$  SEMs,  $n = 22$ . Labeled means without a common letter differ,  $P < 0.05$ .  $\alpha$ -GOS,  $\alpha$ -galacto-oligosaccharide.



**TABLE 2** Changes in food intake during a test meal (consumed 4 h after a preload meal) of overweight adults after 14 d of consumption of 6, 12, or 18 g  $\alpha$ -GOSs/d<sup>1</sup>

	Food intake during test meal, $\Delta$ day 15 – day 0			
	Control	Mix of $\alpha$ -GOSs		
		6 g/d	12 g/d	18 g/d
Weight, g	4.7 $\pm$ 19.2 <sup>a</sup>	-11.4 $\pm$ 16.9 <sup>b</sup>	-22.5 $\pm$ 19.1 <sup>b</sup>	-28.8 $\pm$ 18.6 <sup>c</sup>
Energy, kcal	6.1 $\pm$ 20.8 <sup>a</sup>	-12.6 $\pm$ 18.6 <sup>b</sup>	-25.7 $\pm$ 21.6 <sup>c</sup>	-32.1 $\pm$ 22.0 <sup>c</sup>
Protein, g	0.2 $\pm$ 0.6 <sup>a</sup>	-0.3 $\pm$ 0.5 <sup>b</sup>	-0.7 $\pm$ 0.6 <sup>c</sup>	-0.9 $\pm$ 0.6 <sup>c</sup>
Fat, g	-0.02 $\pm$ 0.29	-0.06 $\pm$ 0.18	-0.07 $\pm$ 0.10	-0.14 $\pm$ 0.3
Carbohydrates, g	1.5 $\pm$ 4.9 <sup>a</sup>	-2.9 $\pm$ 4.3 <sup>b</sup>	-6.0 $\pm$ 5.0 <sup>c</sup>	-7.4 $\pm$ 5.3 <sup>c</sup>
Dietary fiber, g	0.1 $\pm$ 0.4 <sup>a</sup>	-0.2 $\pm$ 0.3 <sup>b</sup>	-0.4 $\pm$ 0.4 <sup>b</sup>	-0.6 $\pm$ 0.4 <sup>c</sup>

<sup>1</sup> Values are means  $\pm$  SDs,  $n = 22$ . Labeled means without a common letter differ,  $P < 0.05$ .  $\alpha$ -GOS,  $\alpha$ -galacto-oligosaccharide;  $\Delta$ , change.

$\alpha$ -GOS intake, with greater differences in the groups who received higher doses of  $\alpha$ -GOSs (Table 3).

In the formulation-effect study, changes from day 0 to day 15 in food weight and carbohydrate and dietary fiber intake during the test meal were greater for all 3  $\alpha$ -GOS formula groups than for the control group (Supplemental Table 2). The reduction in energy and protein intake from day 0 to day 15 was significantly higher in the group who received the high-DP4 formula than in the control group. However, no significant difference was observed for changes in energy intake between the 3  $\alpha$ -GOS formula groups (high DP2, DP3, or DP4 content) during the test meal.

The 24-h recall of energy intake indicated that the reduction in energy intake during lunch was higher in the high-DP3 and -DP4 groups ( $-25 \pm 54$  and  $-29 \pm 46$  kcal, respectively) than in the control group ( $+20 \pm 71$  kcal;  $P < 0.05$ ). There were no significant differences detected between the 3  $\alpha$ -GOS formula groups.

In both studies, change in daily energy intake measured for the 24-h recall did not differ between groups, with the exception of the high-DP3 group in the formulation-effect study ( $-233 \pm 559$  kcal), which was significantly lower than that in the controls ( $-85 \pm 647$  kcal).

**Inflammatory markers.** In both studies, there were no significant between-group differences in the concentration of plasma endotoxin (LPS) at baseline. Plasma LPS at day 15 was significantly lower after  $\alpha$ -GOS intake (Figure 3). A significant negative correlation was observed between dose and changes in plasma LPS ( $\rho = -0.57$ ,  $P < 0.001$ ). Plasma LPS did not differ between the 3  $\alpha$ -GOS formula groups (high content in DP2, DP3, or DP4).

In the formulation-effect study, there were no significant between-group differences in the concentration of plasma CRP at baseline. The plasma CRP concentration was significantly lower in all  $\alpha$ -GOS formula groups than in the control group after the study period (Figure 4); however, there was no significant difference between the groups who consumed high-DP2, -DP3, or -DP4 formulas.

**Anthropometric variables.** In both studies, there was no significant difference between groups in anthropometric measurements at baseline and postintervention. However, in the dose-effect study, changes in body weight, BMI, and body fat mass from baseline showed significant pairwise differences between  $\alpha$ -GOS supplementation in the 12- and 18-g/d groups

vs. the control group (Table 4). Significant pairwise differences were also observed for changes in the waist-to-hip ratio between the group who consumed 18 g  $\alpha$ -GOSs/d and the control group. A significant negative correlation was detected between changes in body weight, BMI, waist-to-hip ratio, body fat percentage, and body fat mass from baseline and dose amounts (all  $P < 0.05$ ).

In the formulation-effect study, the  $\alpha$ -GOS formulas with high DP2, DP3, or DP4 did not significantly affect anthropometric variables (body weight change:  $0.02 \pm 1.15$ ,  $0.07 \pm 1.22$ , and  $-0.06 \pm 1.17$  kg for the high-DP2, -DP3, and -DP4 groups, respectively, vs.  $0.35 \pm 1.14$  kg for the control group;  $P > 0.05$ ).

**Gut microbiota.** There was no significant difference between groups in the amount of fecal bifidobacteria at day 0. After intervention, fecal bifidobacteria amounts were significantly higher for all  $\alpha$ -GOS formulas vs. the control group, whereas there were no differences detected between  $\alpha$ -GOS formula groups (Figure 5A). Moreover, no significant difference was observed for total fecal bacteria between the 3  $\alpha$ -GOS formulation groups and controls at baseline and postintervention (Figure 5B).

**Tolerance.** None of the subjects experienced abdominal pain throughout the studies. Borborygmi, bloating scores, and stool consistency did not significantly differ between days 0 and 15 in either of the studies. In the high-DP3 and -DP4 groups, the flatulence score was slightly increased compared with that in the control group (Supplemental Table 3). In the formulation-effect study, stool frequency was increased in all  $\alpha$ -GOS groups compared with that in the control group.

## Discussion

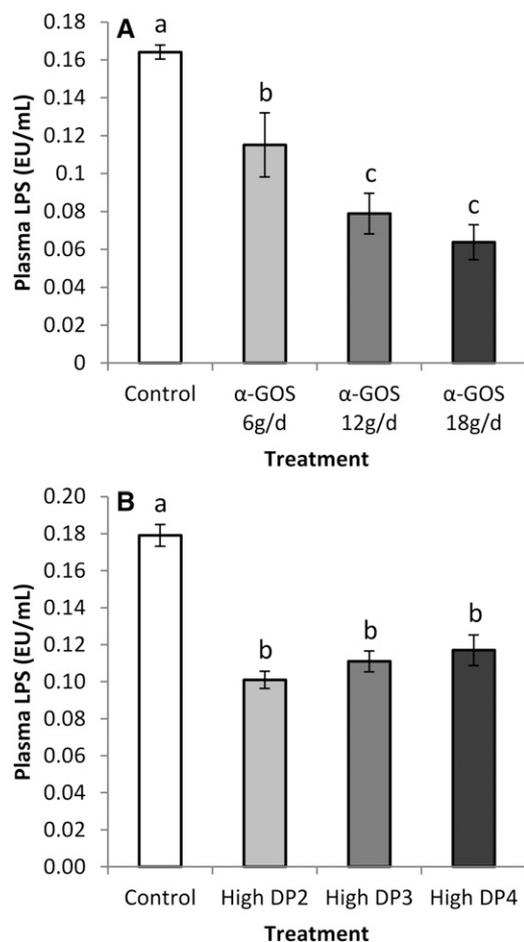
The present studies were designed to investigate the impact of dietary supplementation for 14 d with soluble nonviscous fibers on appetite and subsequent food intake in overweight participants. A dose-dependent reduction in appetite was shown after 14 d of  $\alpha$ -GOS consumption, which was associated with a reduction in food intake during meals. Moreover,  $\alpha$ -GOS consumption was associated with a noticeable reduction in 2 inflammatory markers, LPS and CRP.

The impact of  $\alpha$ -GOS consumption on appetite was shown by using a reference experimental technique—a preload test meal—that included the widely used multiple scale analysis approach (27). In the experiments, hunger, desire to eat, and prospective consumption were reduced, whereas greater satiety and fullness were observed in subjects supplemented with

**TABLE 3** Changes in energy intake (assessed by a 24-h recall) of overweight adults after consumption of 6, 12, or 18 g  $\alpha$ -GOSs/d for 14 d<sup>1</sup>

	Energy intake, $\Delta$ day 15 – day 0			
	Control	Mix of $\alpha$ -GOSs		
		6 g/d	12 g/d	18 g/d
Lunch, kcal	4.2 $\pm$ 30.9 <sup>a</sup>	-23.2 $\pm$ 29.5 <sup>b</sup>	-36.8 $\pm$ 33.0 <sup>b</sup>	-40.8 $\pm$ 29.7 <sup>b</sup>
Dinner, kcal	2.2 $\pm$ 24.3 <sup>a</sup>	-25.0 $\pm$ 45.6 <sup>b</sup>	-32.3 $\pm$ 46.2 <sup>b</sup>	-38.0 $\pm$ 57.1 <sup>b</sup>
Daily total, kcal	-117 $\pm$ 436	-92.0 $\pm$ 432	-208 $\pm$ 372	-196 $\pm$ 401

<sup>1</sup> Values are means  $\pm$  SDs,  $n = 22$ . Labeled means without a common letter differ,  $P < 0.05$ .  $\alpha$ -GOS,  $\alpha$ -galacto-oligosaccharide;  $\Delta$ , change.



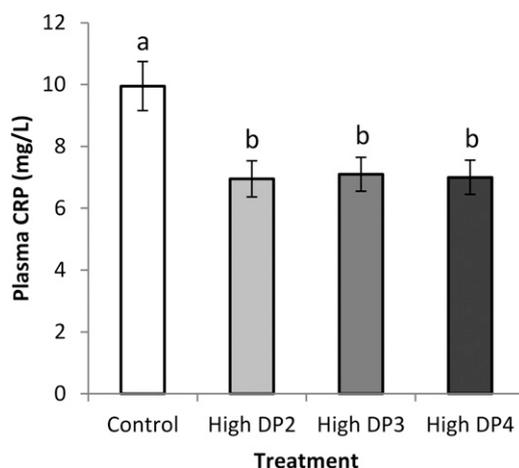
**FIGURE 3** Plasma LPS concentrations in overweight adults after 14 d of  $\alpha$ -GOS consumption. (A) Dose effect. (B) Formulation effect. Groups consumed 6, 12, or 18 g/d of a mix of  $\alpha$ -GOSs and 12 g  $\alpha$ -GOSs/d with >98% melbiose (High DP2), >90% mannanotriose (High DP3), or >80% verbascotetraose (High DP4) in  $\alpha$ -GOS content. Values are means  $\pm$  SEMs,  $n = 21$ – $22$ . Labeled means without a common letter differ,  $P < 0.05$ . DP, degree of polymerization;  $\alpha$ -GOS,  $\alpha$ -galacto-oligosaccharide.

$\alpha$ -GOSs (either with a mix of  $\alpha$ -GOSs of different degrees of polymerization or with a formula rich in DP2, DP3, or DP4) for 15 d vs. the control group. These results were consistent with previous studies that showed a satiating effect of nonviscous fibers (5–9). However, these studies are the first, to our knowledge, to demonstrate such an effect for  $\alpha$ -GOSs and highlight that the proportion of DP2, DP3, and DP4 did not influence the effect on appetite.

Because food consumption was also lower during the ad libitum meal after the consumption of a mix of  $\alpha$ -GOSs for 15 d than after placebo consumption, we conclude that  $\alpha$ -GOSs exerted both an impact on satiety (appetite between 2 meals) and satiation (fullness and appetite during a meal). This was also true for the high-DP4 formula. Daily patient reports of food intake indicated that energy intake during lunch and dinner was significantly lower in those groups who consumed 6, 12, or 18 g/d of a mix of  $\alpha$ -GOSs or 12 g/d of the high-DP3 (only true for lunch) or -DP4 formulas vs. the control group, whereas the reduction in daily intake did not significantly differ between groups. Notably, these studies were not designed (power calculation) to demonstrate an impact on daily intake but rather to detect an effect on the subsequent meal. Moreover, the high variability observed in self-reported food intake was a limitation

to testing for effects on daily food intake. Indeed, methodologic problems that limit the validity of self-reporting in free-living conditions have been previously discussed and include high errors in data collection, underreporting of energy intake, and differential misreporting of macronutrient intake (27). Notably, in our present studies, the reduction that we observed in daily food intake reached the extent of clinical relevance, although it did not reach the threshold for statistical significance. To explain this lack of significance between the  $\alpha$ -GOS groups and controls, we note that during the studies, participants consumed both their lunch and dinner in the investigation center and had access to the same menu, which could contribute to limiting interindividual variations. Because participants did not receive any nutritional recommendations and were not asked to follow a hypocaloric diet during the study, food consumption outside of mealtimes could be an important source of variation and might contribute to the lack of a significant difference between groups for total daily energy intake. Interestingly, in the dose-effect study, changes in body weight and body fat were significantly different between groups who consumed  $\geq 12$  g/d of a mix of  $\alpha$ -GOSs for 14 d and controls, although the lean mass was not different. This is an interesting finding that supports the physiologic relevance of consuming  $\alpha$ -GOSs to regulate satiation and caloric intake. In the formulation-effect study, consumption of the 12 g high-DP2, -DP3, or -DP4 formulation/d did not induce a significantly lower body weight vs. the control group. We again note that these studies were not powered to detect such an effect and the high variability observed in the formulation-effect study could explain why the body weight change did not significantly differ between groups, even though it was higher than the differences observed between the treated and control groups in the dose-effect study.

The extent of body weight and body fat loss was low in both studies, but this was expected because the duration of  $\alpha$ -GOS consumption was short and the volunteers were not subjected to any lifestyle intervention. Although a rather limited effect on weight loss was detected after  $\alpha$ -GOS consumption, this study clearly showed a link between appetite regulation and weight



**FIGURE 4** Plasma CRP concentrations in overweight adults after 14 d of consumption of 12 g/d of different formulations of  $\alpha$ -GOSs. Groups consumed 12 g  $\alpha$ -GOSs/d with >98% melbiose (High DP2), >90% mannanotriose (High DP3), or >80% verbascotetraose (High DP4) in  $\alpha$ -GOS content. Values are means  $\pm$  SEMs,  $n = 21$ – $22$ . Labeled means without a common letter differ,  $P < 0.05$ . CRP, C-reactive protein; DP, degree of polymerization;  $\alpha$ -GOS,  $\alpha$ -galacto-oligosaccharide.

**TABLE 4** Changes in anthropometric variables in overweight adults after consumption of 6, 12, or 18 g  $\alpha$ -GOSs/d for 14 d<sup>1</sup>

	Anthropometric variables, $\Delta$ day 15 – day 0			
	Control	Mix of $\alpha$ -GOSs		
		6 g/d	12 g/d	18 g/d
Weight, kg	0.04 $\pm$ 0.16 <sup>a</sup>	-0.06 $\pm$ 0.15 <sup>a,b</sup>	-0.11 $\pm$ 0.17 <sup>b,c</sup>	-0.21 $\pm$ 0.24 <sup>c</sup>
BMI, kg/m <sup>2</sup>	0.01 $\pm$ 0.38 <sup>a</sup>	-0.01 $\pm$ 0.06 <sup>a,b</sup>	-0.10 $\pm$ 0.27 <sup>b</sup>	-0.08 $\pm$ 0.09 <sup>b</sup>
Waist circumference, cm	0.05 $\pm$ 0.38	0.00 $\pm$ 0.44	-0.09 $\pm$ 0.29	-0.18 $\pm$ 0.50
Hip circumference, cm	-0.05 $\pm$ 0.2	0.00 $\pm$ 0.31	-0.05 $\pm$ 0.21	0.05 $\pm$ 0.21
Waist-to-hip ratio	0.0009 $\pm$ 0.004 <sup>a</sup>	-0.00001 $\pm$ 0.005 <sup>a,b</sup>	-0.0005 $\pm$ 0.002 <sup>a,b</sup>	-0.0023 $\pm$ 0.005 <sup>b</sup>
Body fat, %	0.10 $\pm$ 0.56	-0.06 $\pm$ 0.12	-0.07 $\pm$ 0.13	-0.08 $\pm$ 0.19
Body fat mass, kg	0.09 $\pm$ 0.43 <sup>a</sup>	-0.06 $\pm$ 0.10 <sup>a,b</sup>	-0.08 $\pm$ 0.11 <sup>b</sup>	-0.11 $\pm$ 0.16 <sup>b</sup>
Fat-free mass, kg	-0.05 $\pm$ 0.46	-0.01 $\pm$ 0.11	-0.04 $\pm$ 0.13	-0.10 $\pm$ 0.17

<sup>1</sup> Values are means  $\pm$  SDs,  $n = 22$ . Labeled means without a common letter differ,  $P < 0.05$ .  $\alpha$ -GOS,  $\alpha$ -galacto-oligosaccharide;  $\Delta$ , change.

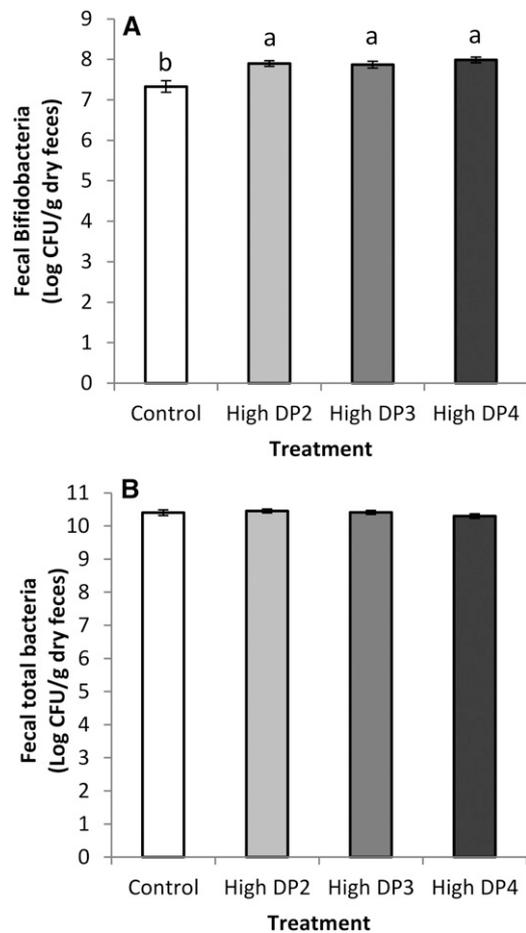
loss during the 14-d study period. To date, such a relation has been shown by using both pharmaceutical treatment and dietary interventions (e.g., low-energy or high-protein diets) but not with supplementation with soluble fibers, as in the present studies. Therefore, we consider that  $\alpha$ -GOS consumption could be a relevant tool for weight loss.

Notably, appetite regulation with specific foods might not only benefit consumers by acting directly on food intake but could also enhance dietary control to improve success in meeting active weight-management goals. A review by Hetherington et al. (28) comprehensively described multiple routes that link the consumption of more satiating foods with an improved quality of life and health. For a greater overall summed satiety effect for total diet, there was a greater food “reward,” improved acceptance of lower-energy foods, better control of (reduced) energy intakes, less stimulus for opportunistic eating, and reduced hunger dysphoria (28).

Supplementation with  $\alpha$ -GOSs was associated with a reduction in 2 inflammatory markers, LPS and CRP, which were significantly greater than reductions observed in the control group. This observation is consistent with an improvement in inflammatory markers associated with fiber supplementation in humans (29, 30) and with the reduction in endotoxemia measured in rodents that were supplemented with fibers (10). Two major mechanisms might underlie such an effect: a reduction in body fat induced by fiber consumption that could have resulted in a less inflammatory tone (31) and changes in intestinal microbiota induced by  $\alpha$ -GOS consumption, which could have improved intestinal permeability and consequently have reduced endotoxemia (10, 32). In the present studies, the extent of the reduction in body fat was low, so the involvement of fat loss in the reduction in inflammatory tone was unlikely. Our favored hypothesis is the involvement of intestinal microbiota in improving gut barrier function. Notably, we showed herein that  $\alpha$ -GOS components, independently of their degree of polymerization, could stimulate bifidobacteria growth. However, further studies designed to characterize the microbiota are needed to test this hypothesis. Whatever mechanisms are involved, the reductions in inflammatory tone represent a beneficial trait of  $\alpha$ -GOS consumption. Therefore, its 3 major effects—reductions in food intake and inflammation and weight loss—could be potentially exploited to help prevent or treat metabolic syndrome.

In conclusion, independently of any other intervention, the consumption of  $\alpha$ -GOSs for 14 d reduced both appetite and food intake. Although the impact of the DP on these outcomes

appeared to be mild, a strong impact of the dose of  $\alpha$ -GOSs was observed. Interestingly, the results of our formulation-effect study highlight that, although oligosaccharides of DP2 are not considered to be fibers, subjects who consumed DP2  $\alpha$ -GOSs (i.e., melibiose) exhibited physiologic effects (reduced appetite, an



**FIGURE 5** Change in fecal bifidobacteria (A) and total bacteria (B) from baseline after 15 d of consumption of 12 g/d of different formulations of  $\alpha$ -GOSs in overweight adults. Groups consumed 12 g  $\alpha$ -GOSs/d with >98% melibiose (High DP2), >90% manninotriose (High DP3), of >80% verbascotetraose (High DP4) in  $\alpha$ -GOS content. Values are means  $\pm$  SEMs,  $n = 22$ . Labeled means without a common letter differ,  $P < 0.05$ . DP, degree of polymerization;  $\alpha$ -GOS,  $\alpha$ -galacto-oligosaccharide.

increased fecal bifidobacteria population, and reduced plasma CRP) that were not different from those in subjects who consumed high-DP3  $\alpha$ -GOSs (i.e., manninotriose) or high-DP4  $\alpha$ -GOSs (i.e., verbascotetraose), which are considered to be fibers in many parts of the world (as defined by the Food Standard Australia New Zealand, the European Food Safety Authority and the European Commission, and the Institute of Medicine). This finding shows that DP2  $\alpha$ -GOSs behaved like a fiber. Moreover, our findings suggest that daily supplementation with at least 12 g  $\alpha$ -GOSs/d would be effective for regulating appetite and food intake. Reductions in inflammatory markers are also of interest for the prevention or treatment of metabolic syndrome. The therapeutic potential of such a nutritional strategy merits further study.

### Acknowledgments

PF-B designed the research; QD and JN conducted the research; JN performed statistical analyses; FBM, JN, DT, PP, and PF-B wrote the manuscript; and FBM had primary responsibility for the final content. All authors read and approved the final version of the manuscript.

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