Effect of Chicory-derived Inulin on Abdominal Sensations and Bowel Motor Function

Fernando Azpiroz, MD,†‡ Laura Molne, RN,*†‡ Sara Mendez, RN,*†‡ Adoración Nieto, RN,*†‡ Chaysavanh Manichanh, PhD,*†‡ Marianela Mego, MD,*†‡ Anna Accarino, MD,*†‡ Javier Santos, MD,*†‡ Manuela Sailer, PhD,§ Stephan Theis, PhD,§ and Francisco Guarner, MD*†‡*

Goal: To determine the effect of a prebiotic chicory-derived inulin-type fructan on the tolerance of intestinal gas.

Background: Subjects with gas-related complaints exhibit impaired handling of intestinal gas loads and we hypothesized that inulin would have a beneficial effect.

Study: Placebo-controlled, parallel, randomized, double-blind trial. Subjects with abdominal symptoms and reduced tolerance of intestinal gas (selected by a pretest) received either inulin (8 g/d, n = 18) or maltodextrin as a placebo (8 g/d, n = 18) for 4 weeks. A gas challenge test (4 h jejunal gas infusion at 12 mL/min while measuring abdominal symptoms and gas retention for 3 h) was performed before and at the end of the intervention phase. Gastrointestinal symptoms and bowel habits (using daily questionnaires for 1 wk) and fecal bifidobacteria counts were measured before and at the end of the intervention.

Results: Inulin decreased gas retention during the gas challenge test (by 22%; $P = 0.035$ *vs.* baseline), while the placebo did not, but the intergroup difference was not statistically significant ($P = 0.343$). Inulin and placebo reduced the perception of abdominal sensations in the gas challenge test to a similar extent (by 52% and 43%, respectively). Participants reported moderate gastrointestinal symptoms and normal bowel habits during baseline examination, and these findings remained unchanged in both groups during the intervention. Inulin led to a higher relative abundance of bifidobacteria counts ($P = 0.01$ vs. placebo).

Conclusions: A daily dose of inulin that promotes bifidobacteria growth and may improve gut function, is well tolerated by subjects with gastrointestinal complaints.

Key Words: intestinal motility, intestinal sensitivity, intestinal microbiota, intestinal gas, functional gut symptoms

(*J Clin Gastroenterol* 2017;51:619–625)

Received for publication March 11, 2016; accepted August 16, 2016.

From the *Digestive System Research Unit, University Hospital Vall d'Hebron, Barcelona; †Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (Ciberehd) (Virtual Center for Biomedical Research Hepatic and Digestive Diseases), Madrid; ‡Department de Medicina, Universitat Autònoma de Barcelona (Department of Medicine, Autonomous University of Barcelona), Bellaterra (Cerdanyola del Vallès), Spain; and §BENEO-Institute, Obrigheim, Germany.

Supported by a grant from Beneo-Institute, Germany, and by the Spanish Ministry of Economy and Competitiveness (Dirección General de Investigación Científica y Técnica, SAF 2013-43677-R); Ciberehd is funded by the Instituto de Salud Carlos III.

M.S. and S.T. are employees of Beneo Institute. The remaining authors declare that they have nothing to disclose.

Address correspondence to: Fernando Azpiroz, MD, Digestive System Research Unit, Hospital General Vall d'Hebron, 08035-Barcelona, Spain (e-mail: azpiroz.fernando@gmail.com).

DOI: 10.1097/MCG.0000000000000723

A large proportion of patients in clinical practice complain of functional digestive symptoms without any detectable cause. These symptoms are related to a poor tolerance of gut contents, which involves an impaired reflex control and hypersensitivity of the gastrointestinal tract. Recent data suggest that intestinal microbiota may play a role; indeed, microbiota has been shown to influence intraluminal content as well as both gut reflex activity and sensitivity.[1]

Prebiotics serve as substrate for gut microbiota, thereby influencing gut microbiota activity and composition and exerting beneficial effects for the host. In particular, inulin-type fructans are storage carbohydrates that are found in many plants, including chicory, leek, onion, wheat, garlic, and artichoke, which are part of the normal human diet. Orafti HSI inulin is a highly soluble inulin and is an ingredient in food derived from chicory. Inulin is a mixture of oligosaccharides and polysaccharides composed of fructose units connected by β (2→1) links.[2] The total number of fructose and glucose units of chicory inulin ranges mainly between 2 and 70. It is a nondigestible carbohydrate, is a dietary fiber that reaches the colon intact and serves as a substrate for microbiota metabolism. The main characteristics of inulin are its prebiotic properties because it selectively stimulates beneficial bacteria, particularly bifidobacteria.[2] Because of these properties, inulin is thought to have a stabilizing effect on the normal gastrointestinal function.[3–5]

We hypothesized that Orafti HSI inulin would improve functional digestive symptoms by influencing the key pathophysiological factors described above: gut content, reflex dysfunction, and hypersensitivity. The problem of investigating the effect of a treatment on clinical complaints related to gut function is the heterogeneity in pathophysiology, the intraindividual day-to-day variability of symptoms, and the high placebo response. To overcome these problems, our study applied very precise selection criteria through a comprehensive preentry selection process and measured symptoms during standard conditions and in response to a challenge test. Previous studies using the gas challenge test showed that patients with functional gut symptoms have impaired transit and poor tolerance to intestinal gas loads.[6–9]

MATERIALS AND METHODS

Dietary Intervention and Experimental Design

This was a single-center, placebo-controlled, parallel (n = 18 per group), randomized and double-blind study conducted at the University Hospital Vall dHebron. Orafti

HSI inulin (8 g/d; Beneo-Orafti, Tienen, Belgium) was tested against a placebo (maltodextrine 8 g/d) during a 4-week intervention period (Fig. 1). After a preliminary visit, potential participants entered a 1-week basal period. Those who fulfilled specific inclusion criteria (see below) were then randomized into inulin and placebo groups through a computer-generated randomization list and entered a 4-week intervention period. During the intervention period, either inulin or placebo was administered in 4-g sachets and was taken in 200 mL liquid (water, juice, milk, coffee, or tea) during breakfast and dinner. During the first 3 days of the intervention period, only half of the dose was administered for adaptation.

Participants

Patients (20 to 70 y of age) who presented in the gastroenterology outpatient clinic complaining of moderate abdominal discomfort without diarrhea followed a work-up by their attending physician, including blood test, endoscopy, and ultrasonography as indicated. Once organic disorders were ruled out, patients willing to participate in the study entered a 1-week basal evaluation period. At the end of the basal period, only the participants fulfilling the following inclusion criteria continued in the study and entered the intervention period: (a) a negative sensation of digestive well-being (score ≤ 1 on at least 2 of the 6 evaluation days, scored on a $-5/+5$ scale; see "Clinical evaluation" below); (b) poor tolerance of a gas challenge test (abdominal perception score ≥ 3, on a 0 to 6 scale, for at least three 15-minute time points over the last 90 minutes of the 180-minute long intestinal gas infusion test; see below). Over the preceding month antibiotic intake, exceptional diets, changes in dietary habits or intake of Ca supplements were not allowed. Medications that could interfere with intestinal motility or sensitivity as well as prebiotics and probiotics were discontinued before entering the study. Subjects gave written informed consent to participate in the study.

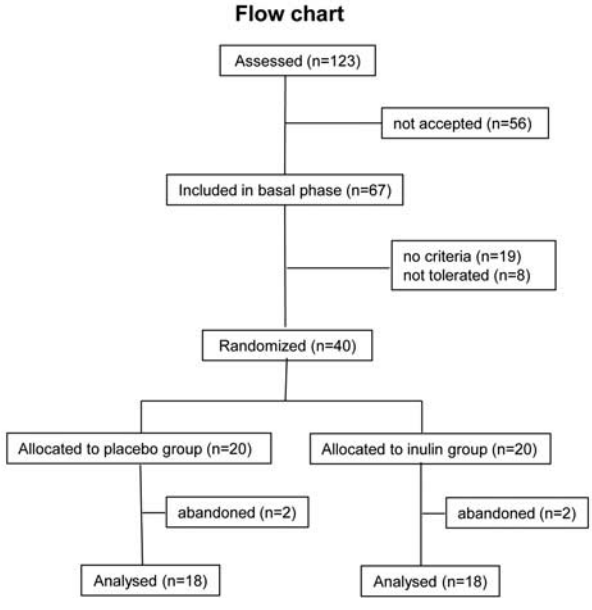

FIGURE 1. Flow chart.

Dietary and Lifestyle Instructions

During the study (basal and intervention periods), the participants were instructed to consume at least 2 glasses of milk, 40 g of hard cheese, 80 g of soft cheese or 100 g of cream cheese per day, because colonic fermentation of inulin in individuals with low Ca intake may damage the epithelium and facilitate bacterial translocation.[10,11] Participants were also told not to consume food labeled as "prebiotic," "probiotic," or "rich in fiber" to prevent confounding effects on microbiota activity, and were to avoid the excessive consumption of alcohol or coffee as well as changes in their physical activity or diet to standardize the testing conditions.

Procedures

At the end of the basal and intervention periods, the following procedures were performed: (a) clinical evaluation, (b) measurement of colonic transit time, (c) fecal sampling, and (d) measurement of intestinal gas transit and tolerance using a gas challenge test on the last day of each period.

Clinical Evaluation

Participants were instructed to fill out daily questionnaires on each of the last 6 days of the basal and intervention periods. The questionnaires evaluated digestive well-being using a scale graded from $+5$ to -5; digestive symptoms (eg, abdominal bloating, distension, borborygmi, flatulence, and abdominal discomfort/pain) on a 0 to 10 score scale; and bowel habits (the number and form of stools using the Bristol scale).[12]

Measurement of Colonic Transit

Colonic transit was measured by a standard technique using radioopaque markers. Markers were administered in a capsule for 3 consecutive days (20 markers per day), and a plain x-ray film of the abdomen was taken on the fourth day. The number of markers localized in the right, transverse, left and pelvic colonic segments was counted (using bone references) to calculate the total and segmental colonic transit times.[13,14]

Fecal Sampling and Analysis

Fecal samples were collected at home, kept immediately at -20°C in the home freezer and delivered frozen to the laboratory using a freezer pack. They were stored at -80°C for later analysis. Subjects were instructed to collect fecal samples on the 2 days before their scheduled visit at the end of each study period (basal and intervention), and the last sample was used.

Quantification of the fecal bifidobacteria and the total bacterial population in the samples was performed on DNA extracts from fecal specimens by real-time polymerase chain reaction (PCR) analysis using the Applied Biosystems 7500 Fast Real-Time PCR System (Applied Biosystems, Foster City, CA) and a *Bifidobacterium* genus-specific PCR primer set (for Bifidobacterium: Forward: 5′ –TGG CTC AGG ATG AAC GCT G-3′; Reverse: 5′-TGA TAG GAC GCG ACC CCA T-3′; TaqMan probe: 5′-FAM-CAT CCG GCA TTA CCA-MGB-3′; for total bacteria: Forward: 5′-GCC AGC AGC CGC GGT AA-3′, Reverse: 5′-GAC TACC AGG GTA TCT AAT-3′).

Gas Challenge Test

Participants were instructed to follow a diet that excluded legumes, vegetables, garlic, onions, nuts, cereals, whole meal bread, and fizzy drinks during the day before each challenge test.[7–9] On the night before each test, participants had a light dinner (meat, fish, eggs, rice, pasta and/or white bread but avoided dairy products, salad, fruit, and alcoholic beverages). Studies were conducted in a quiet, isolated room. After an 8-hour fast, participants were orally intubated with a tube (1.6 mm internal diameter) that had multiple side holes scattered over the distal 2-cm segment; the tip of the tube was positioned under fluoroscopic control 5 cm caudal to the angle of Treitz. A rectal catheter (20 Fr Foley catheter, Bard, Barcelona, Spain) was introduced, and the subjects were then placed supine in a bed at an angle of 30° to the horizontal plane. The tubes were connected to infusion and collection systems (see below), and gas was perfused into the jejunum for 180 minutes while measuring anal gas evacuation, abdominal perception and changes in girth.

Jejunal gas infusion: Gas was continuously infused into the proximal jejunum at 12 mL/min using a modified volumetric pump (Asid Bonz PP 50-300; Lubratronics, Unterschleissheim, Germany). The gas mixture infused (88% nitrogen, 6.5% carbon dioxide, and 5.5% oxygen, bubbled into water for saturation) mimicked the partial pressures of venous blood gases to minimize diffusion across the intestinal-blood barrier.[15]

Anal gas evacuation: Intestinal gas evacuation was collected by an intrarectal catheter connected to a barostat, and the volume of evacuated gas was recorded continuously and measured at 30-minute intervals.

Perception measurements: The perception of abdominal sensations was measured at 15-minute intervals by using five graphic rating scales, each of which was graded from 0 (no perception) to 6 (maximum tolerable) and aimed to score 4 specific possible abdominal sensations: (a) pressure/bloating, (b) distension; (c) borborygmi/colicky sensations, (d) puncture/stingy sensations, and (e) other types of sensations (to be specified). Participants were asked to score any perceived sensations (one or more perceived simultaneously) on the scales.

Measurements of abdominal girth changes: Once the subjects were positioned in bed, a 48-mm-wide, nonstretch belt with a metric scale was adjusted around the abdomen by means of 2 elastic bands. Girth changes were measured at 15-minute intervals during the gas test while the subjects were breathing comfortably, and the changes were referenced to the mid-point of respiratory displacements.

Outcomes Measures

The primary outcome was the effect of inulin intake (change from baseline with inulin vs. placebo) on the tolerance of the gas challenge test, which was measured as the perception of digestive sensations during the gas challenge test. At each time point, the highest score instead of the mean or cumulative scores was computed for comparisons; these scores were averaged over the last 60 minutes of the test in each subject[16]; the differences between basal and intervention periods (inulin or placebo) were also calculated.

Secondary outcomes included the effects of inulin intake on (a) intestinal gas retention (volume infused minus evacuated), which was measured as the average value over the last 60 minutes of the test; (b) digestive well-being, digestive symptoms and bowel habits, which were measured as the average values of the 6 daily evaluations; and (c) colonic transit time.

Sample Size Calculation

Anticipating a positive response (defined as $\geq 30\%$ improvement in perception during gas infusion) in 10% of the placebo control and 57% of the inulin group, a sample size of 14 subjects per group was estimated to detect differences between the groups with a power of 80% and a significance level of 5% (2 sided). To detect differences in the secondary outcomes of daily symptoms, we anticipated an improvement of ≥ 1 in the score of the digestive well-being scale in 15% of the placebo group and 58% of the inulin group; thus, 18 subjects per group were recruited.

Statistical Analysis

Daily data during the 6-day evaluation period, as well as repeated measures during the last 60 minutes of the gas challenge test, were averaged in each subject, and the grand mean values (± SE) in each group of subjects were calculated. The Shapiro-Wilk test was used to check the normality of data distribution. All statistical tests were conducted with nonparametric tests: the Wilcoxon signed rank test was used for paired data, and the Mann-Whitney U test was used for unpaired data. Statistical significance was assumed for $P < 0.05$ (2 sided).

RESULTS

Demographics

One hundred twenty-three participants were assessed for eligibility; 67 participants were included in the basal phase, 40 were randomized, and 36 completed the study and were included in the analysis (18 per group) (Fig. 1).

Responses to the Gas Infusion Test

During the gas infusion test, part of the gas infused was retained within the gut (less gas evacuated than infused). At baseline, gas retention was not significantly different between the groups. However, a within-group comparison revealed that gas retention was significantly reduced by inulin intake but not by placebo (Figs. 2A, B). Because of the interindividual variability, the change in gas retention from baseline to intervention did not reach statistical significance between groups (-137 ± 87 mL inulin vs. 19 ± 128 mL placebo; $P = 0.343$).

During the basal infusion test, gas retention was associated with a moderate level of perception, which was similar in both groups. Both inulin and placebo significantly reduced the perception score to a similar extent (Figs. 2C, D).

Abdominal girth increased during the basal gas infusion test in both groups. After the intervention, the magnitude of the increase in abdominal girth during the gas test was less pronounced in both groups: 1.8 ± 0.4 cm basal to 1.2 ± 0.2 cm with inulin ($P = 0.081$) and 1.7 ± 0.3 cm basal to 0.5 ± 0.2 cm with placebo ($P = 0.001$).

Gastrointestinal Symptoms

As required by the inclusion criteria of the study, all participants reported a negative sensation of digestive well-being during the 6-day clinical evaluation period before the intervention (basal period), which was associated with a sensation of flatulence, abdominal bloating, distension, borborygmi and abdominal discomfort/pain (Fig. 3). No

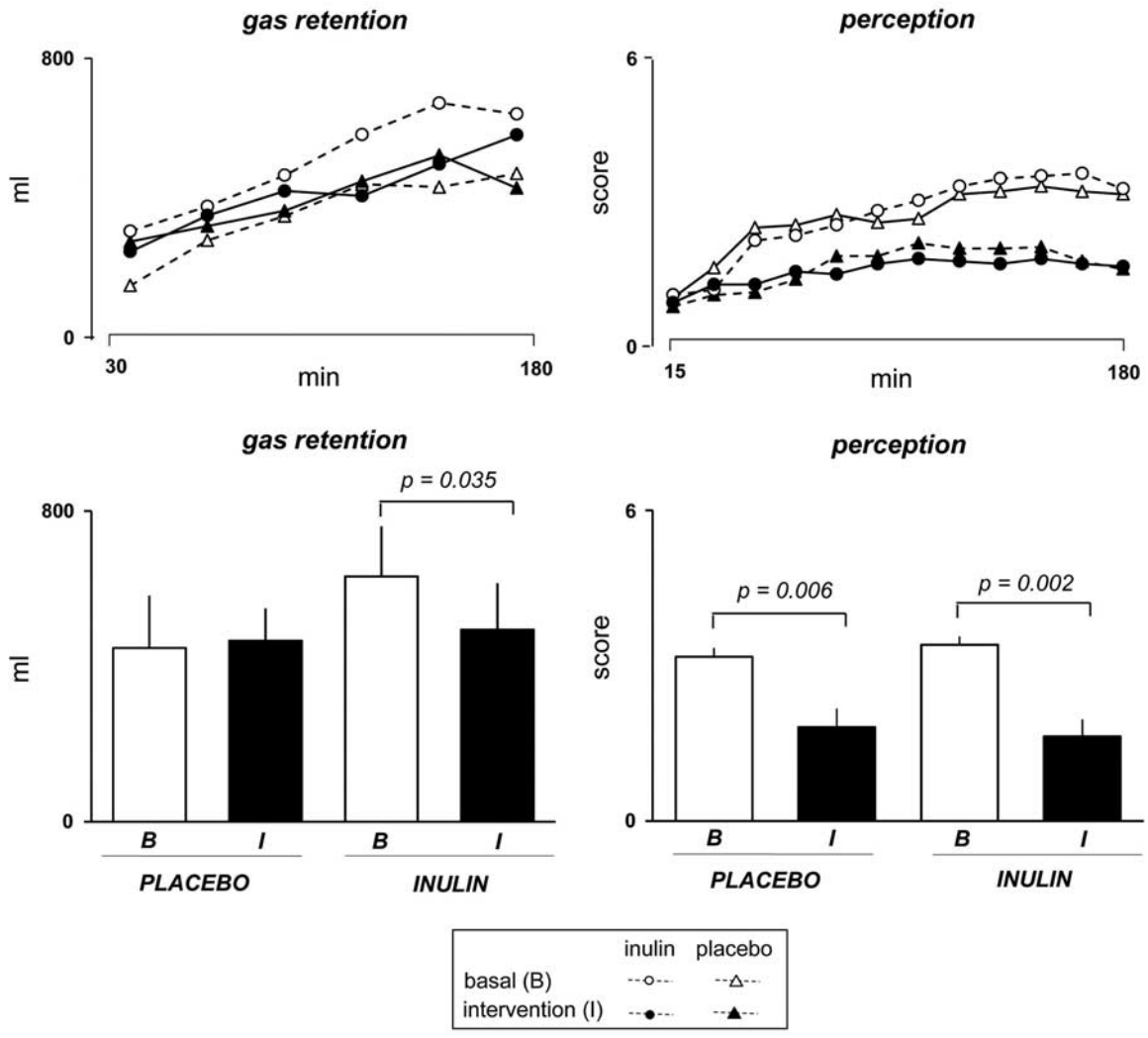

FIGURE 2. Responses to gas infusion test. Upper panels: time courses for retained gas and perception scores; data are mean ± SE. Lower panels: bar plots for retained gas and perception scores; data are grand mean ± SE calculated from the last 60 minutes of the gas test before (white) and during intervention (black) (n = 18 per group).

group differences and no modification during the intake of either inulin or placebo were observed (Fig. 3).

Bowel Habits and Colonic Transit Time

During the basal period, the stool frequency and consistency and the total colonic transit time were similar in both groups. Of note, the stool frequency, stool consistency and colonic transit times were within the normal range and did not change during the intervention period in either group (Fig. 4).

Microbiota

Fecal collection during the basal period showed a similar abundance of bifidobacteria in both groups. Inulin significantly increased the abundance of bifidobacteria, whereas the placebo did not (Fig. 5), and the effect of inulin was significantly greater than that of the placebo ($P = 0.011$).

DISCUSSION

Previous studies showed that in patients with functional gut disorders clinical complaints are influenced by the diet: symptoms worsen with high-residue diets and improve with low-residue diets. In this context, our study shows that inulin at a dose that induces significant proliferation of colonic bifidobacteria, is well tolerated by patients with digestive symptoms in daily life. The primary aim of our study was to prove the effect of inulin in improving the tolerance to a standard intestinal gas load. Inulin significantly reduced perception as compared with baseline. However, the effect was not significantly different than that of placebo, and hence, the primary outcome was not met.

Characteristically, clinical symptoms in patients with functional gut disorders markedly improve in response to placebo.[17] Since our primary aim was to measure perception in response to a standard challenge test in a selected population of patients, we assumed a smaller placebo

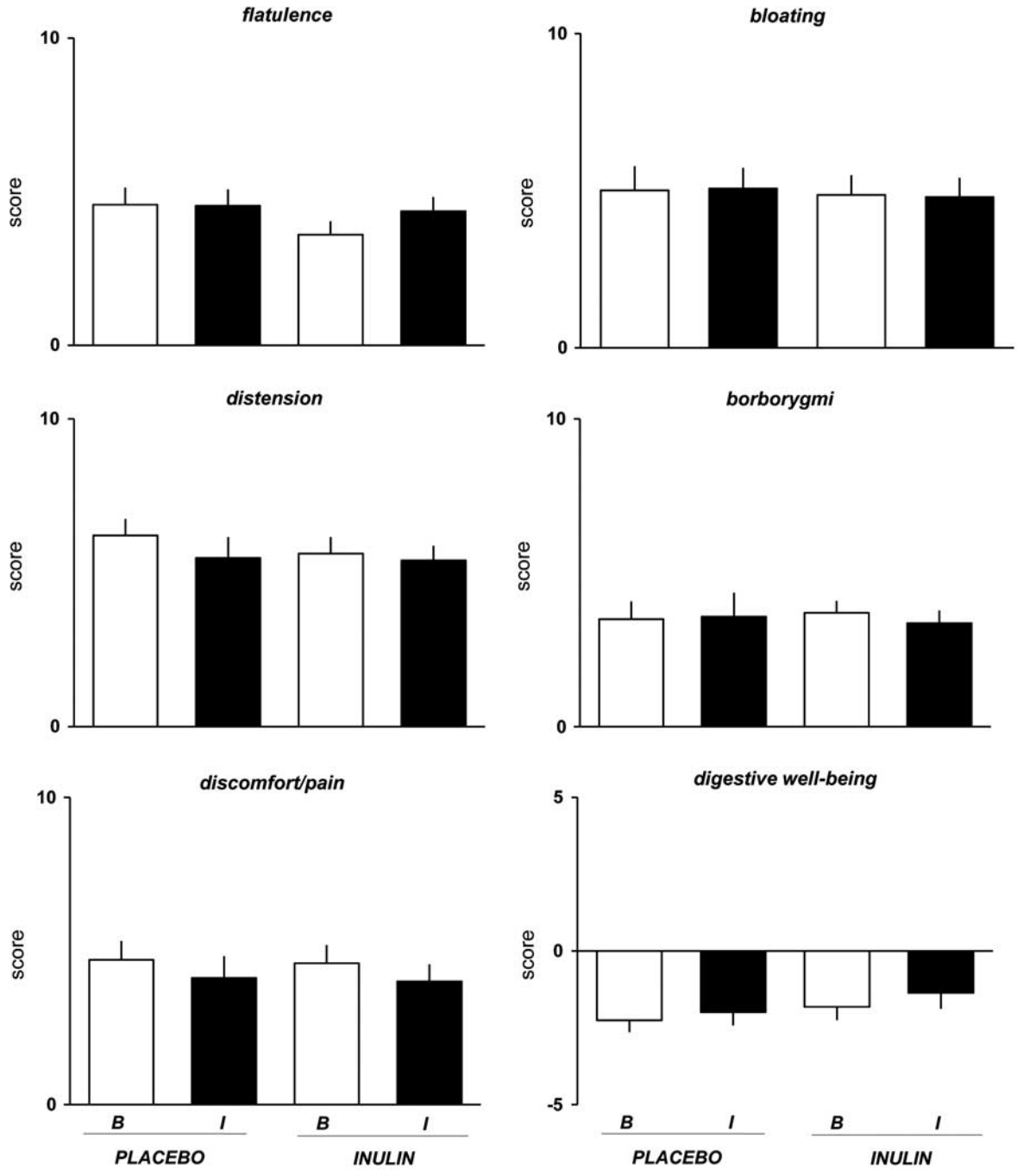

FIGURE 3. Clinical outcome. Data are average of 1 week daily measures before (white) and by the end of intervention (black) (n = 18 per group).

response, but still under these conditions the placebo group showed a high improvement rate. However, a type II error related to underestimation of the placebo effect seems unlikely, because individual effects in both groups were similar. In previous studies repeat experiments yielded reproducible results, but the order effect of baseline and intervention test could explain the reduced perception with both inulin and placebo as compared with the initial baseline test.

When measuring retention of the gas infused, as a physiological marker of intestinal function, inulin but not placebo, exhibited a significant effect versus the baseline tests. The difference between inulin and placebo did not reach statistical significance and this could be related to a type II error with the sample size calculation targeting perception.

Inulin has been characterized as a prebiotic that influences intestinal microbiota with beneficial effects on

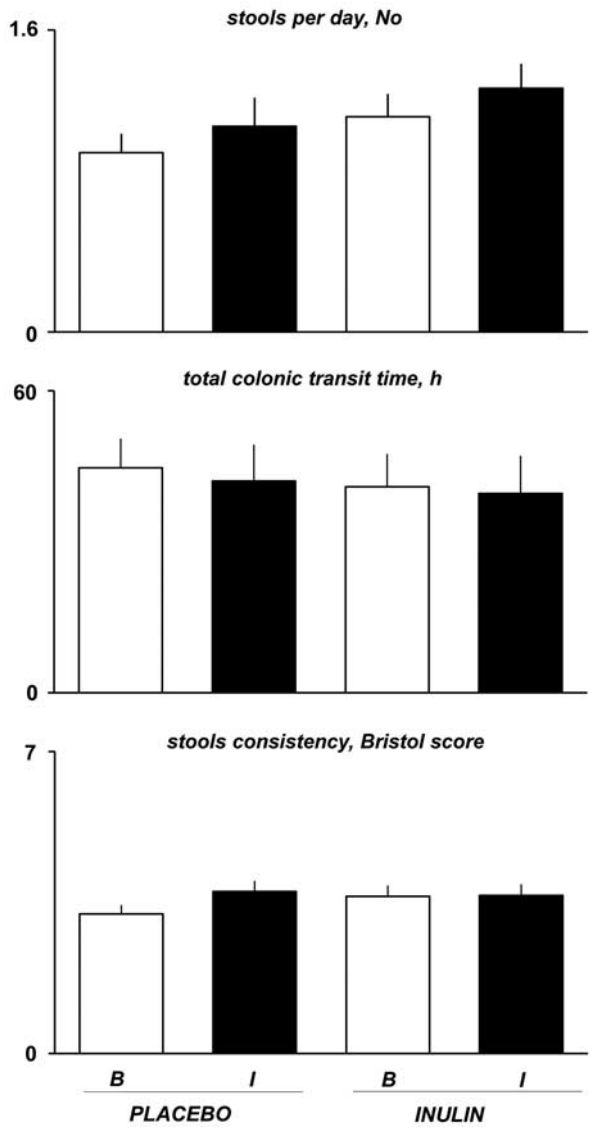

FIGURE 4. Bowel habit. Data are average of 1 week daily measures before (white) and by the end of intervention (black) (n = 18 per group).

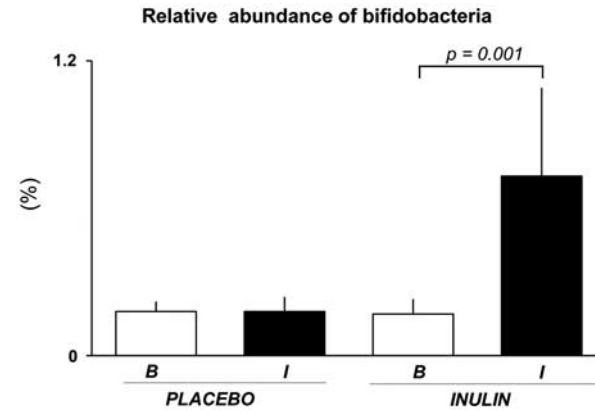

FIGURE 5. Effect of inulin on fecal bifidobacteria measured before (white) and by the end of intervention (black) (n = 18 per group).

the host. Indeed, as previously described,[2] inulin in our study, induced the proliferation of bifidobacteria. Prebiotics are metabolized by the intestinal microbiota, and in this fermentation process, short-chain fatty acids and a series of gasses are normally produced.[18] It has been shown that patients with functional gut disorders have intestinal hypersensitivity along with impaired gas handling.[7,16,19,20] Under these conditions, increased gas production due to the fermentation of residues may worsen their symptoms. However, inulin intake did not cause any increase in symptoms such as bloating and flatulence or other side effects. Conceivably, the good response to inulin is related to the adaptation of microbiota activity. Prebiotics promote the proliferation of more efficacious microbiota such as bifidobacteria, which are able to ferment residues using metabolic pathways with lower gas release.[21] Prebiotics may also stimulate the growth of gas-consuming microorganisms; thus, reduced gas production may also be associated with increased gas consumption, and this adaptation may take place a few days following treatment.[18,22]

Only patients with a negative sensation of digestive well-being were included in the study. Well-being was measured on a $-5/+5$ scale. This scale has been previously used in our laboratory and has been shown to provide a good discrimination between healthy subjects and patients with functional gut disorders and to detect changes in response to dietary interactions.[22–25]

In previous studies, the effects of inulin were investigated in a variety of gastrointestinal disorders, including constipation and irritable bowel syndrome. Chicory-derived inulin has been shown to improve bowel motor function in patients with functional constipation.[4,5,26,27] In our cohort, stool frequency increased slightly, yet non-significantly, during the 4-week intervention period, and stool consistency remained stable. Because the bowel habits in participants were within the normal range at study entry, we did not expect any improvements. The fact that inulin improved, clearance of the gas overload without affecting normal fecal transit or bowel habits in these patients, suggests that gas and the transport of solids are modulated by different mechanisms.

A recent trend involves advocating diets low in fermentable oligo-di- and monosaccharides and polyols (FODMAPs) to treat functional gut symptoms.[28] A low FODMAPs diet requires complex dietary advice, but a simple low-residue diet was proven to be effective in the short term[22] and was even equal to FODMAPs restriction.[29] However, a low FODMAPs diet may impoverish gut microbiota, which could be especially deleterious in patients who have been shown to harbor poor, less diverse and unstable microbiota.[25] Indeed, subjects who followed a low FODMAPs diet were shown to harbor reduced numbers of bifidobacteria, which are indicative of a healthy gut microbiota.[30] In this context, our study indicates that a daily dose of inulin, which promotes the proliferation of bifidobacteria, is well tolerated by hypersensitive subjects with gastrointestinal complaints and may have favorable effects on gut function. Hence, the current study would favor the use of inulin over restrictive dietary advice such as FODMAPs restriction to treat functional gastrointestinal symptoms, at least in patients with normal bowel habits or constipation.

ACKNOWLEDGMENTS

The authors thank American Journal Experts for English editing of the manuscript (Certificate Verification Key: AA4E-7997-6881-2599-204D) funded by SAF 2013-43677-R. The authors thank Gloria Santaliestra for secretarial assistance.

REFERENCES

1. Simren M, Barbara G, Flint HJ, et al. Intestinal microbiota in functional bowel disorders: a Rome foundation report. *Gut*. 2013;62:159–176.
2. Roberfroid MB, Van Loo JA, Gibson GR. The bifidogenic nature of chicory inulin and its hydrolysis products. *J Nutr*. 1998;128:11–19.
3. Alexiou H, Franck A. Prebiotic inulin-type fructans: nutritional benefits beyond dietary fibre source. *Nutr Bulletin*. 2008;33:227–233.
4. Den Hond E, Geypens B, Ghoos Y. Effect of high performance chicory inulin on constipation. *Nutr Res*. 2000;20:731–736.
5. Kleessen B, Sykura B, Zunft HJ, et al. Effects of inulin and lactose on fecal microflora, microbial activity, and bowel habit in elderly constipated persons. *Am J Clin Nutr*. 1997;65:1397–1402.
6. Lobo B, Serra J, D'Amato M, et al. Effect of selective CCK1 receptor antagonism on accommodation and tolerance of intestinal gas in functional gut disorders. *J Gastroenterol Hepatol*. 2016;31:288–293.
7. Passos MC, Tremolaterra F, Serra J, et al. Impaired reflex control of intestinal gas transit in patients with abdominal bloating. *Gut*. 2005;54:344–348.
8. Serra J, Azpiroz F, Malagelada J-R. Impaired transit and tolerance of intestinal gas in the irritable bowel syndrome. *Gut*. 2001;48:14–19.
9. Serra J, Salvioli B, Azpiroz F, et al. Lipid-induced intestinal gas retention in the irritable bowel syndrome. *Gastroenterology*. 2002;123:700–706.
10. Ten Bruggencate SJ, Bovee-Oudenhoven IM, Lettink-Wissink ML, et al. Dietary fructo-oligosaccharides and inulin decrease resistance of rats to salmonella: protective role of calcium. *Gut*. 2004;53:530–535.
11. Ten Bruggencate SJ, Bovee-Oudenhoven IM, Lettink-Wissink ML, et al. Dietary fructooligosaccharides affect intestinal barrier function in healthy men. *J Nutr*. 2006;136:70–74.
12. Heaton KW, O'Donnell LJ. An office guide to whole-gut transit time. Patients' recollection of their stool form. *J Clin Gastroenterol*. 1994;19:28–30.
13. Chaussade S, Khyari A, Roche H, et al. Determination of total and segmental colonic transit time in constipated patients. Results in 91 patients with a new simplified method. *Dig Dis Sci*. 1989;34:1168–1172.
14. Fort JM, Azpiroz F, Casellas F, et al. Bowel habit after cholecystectomy: physiological changes and clinical implications. *Gastroenterology*. 1996;111:617–622.
15. Foster RE. Physiological basis of gas exchange in the gut. *Ann N YAcad Sci*. 1968;150:4–12.
16. Caldarella MP, Serra J, Azpiroz F, et al. Prokinetic effects in patients with intestinal gas retention. *Gastroenterology*. 2002;122:1748–1755.
17. Elsenbruch S, Enck P. Placebo effects and their determinants in gastrointestinal disorders. *Nat Rev Gastroenterol Hepatol*. 2015;12:472–485.
18. Azpiroz F. Intestinal gas. In: Feldman M, Friedman LS, Brand LJ, eds. *Pathophysiology, Diagnosis, Management*. Philadelphia, PA: Elsevier; 2015:242–250.
19. Kellow JE, Azpiroz F, Delvaux M, et al. Applied principles of neurogastroenterology: physiology/motility sensation. *Gastroenterology*. 2006;130:1412–1420.
20. Salvioli B, Serra J, Azpiroz F, et al. Origin of gas retention and symptoms in patients with bloating. *Gastroenterology*. 2005;128:574–579.
21. Azpiroz F, Barba E, Mego M, et al. Metabolic adaptation of colonic microbiota to diet. *United European Gastroenterol J*. 2014;2:A436.
22. Azpiroz F, Hernandez C, Guyonnet D, et al. Effect of a low-flatulogenic diet in patients with flatulence and functional digestive symptoms. *Neurogastroenterol Motil*. 2014;26:779–785.
23. Malagelada C, Barba I, Accarino A, et al. Cognitive and hedonic responses to meal ingestion correlate with changes in circulating metabolites. *Neurogastroenterol Motil*. 2016. [Epub ahead of print]. doi:10/111/nmo12879.
24. Malagelada C, Accarino A, Molne L, et al. Digestive, cognitive and hedonic responses to a meal. *Neurogastroenterol Motil*. 2015;27:389–396.
25. Manichanh C, Eck A, Varela E, et al. Anal gas evacuation and colonic microbiota in patients with flatulence: effect of diet. *Gut*. 2014;63:401–408.
26. EFSA Panel on Dietetics Products Nutrition and Allergies (NDA). Scientific opinion on the substantiation of health claims related to activated charcoal and reduction of excessive intestinal gas accumulation (ID 1938) and reduction of bloating (ID 1938) pursuant to Article 13(1) of Regulation (EC) No 1924/2006. *EFSA J*. 2011;9:2049 (1–15).
27. Isakov V, Pilipenko V, Shakhovskaya A, et al. Efficacy of inulin enriched yogurt on bowel habits in patients with irritable bowel syndrome with constipation. A pilot study. *FASEB J*. 2013;27:Ib426.
28. Halmos EP, Power VA, Shepherd SJ, et al. A diet low in FODMAPs reduces symptoms of irritable bowel syndrome. *Gastroenterology*. 2014;146:67–75.
29. Bohn L, Storsrud S, Liljebo T, et al. Diet low in FODMAPs reduces symptoms of irritable bowel syndrome as well as traditional dietary advice: a randomized controlled trial. *Gastroenterology*. 2015;149:1399–1407.
30. Staudacher HM, Lomer MC, Anderson JL, et al. Fermentable carbohydrate restriction reduces luminal bifidobacteria and gastrointestinal symptoms in patients with irritable bowel syndrome. *J Nutr*. 2012;142:1510–1518.