

Review Article

Inulin-Type Prebiotics: A Review (Part 2)

Greg Kelly, ND

Abstract

This is part 2 of a two-part review of inulin-type prebiotics. This article discusses the clinical research on inulin-type prebiotics, including effects on infant nutrition, gastrointestinal health, colon cancer prevention, blood sugar and lipid metabolism, bone mineralization, fatty liver disease, obesity, and immunity. Gastrointestinal side effects and dosage recommendations are also considered.

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Introduction

This article is part 2 of a two-part review of inulin-type prebiotics. In part 1, inulin-type prebiotics were defined and food applications were explored. Evidence of ability to modulate gut microflora was also examined. Part 2 discusses the clinical research on inulin-type prebiotics.

Prebiotics are a category of nutritional compounds grouped together based on ability to promote growth of specific beneficial (probiotic) gut bacteria. According to Roberfroid's definition, a prebiotic is "a selectively fermented ingredient that allows specific changes, both in the composition and/or activity of the gastrointestinal microflora that confers benefits upon host well-being and health."¹ Many dietary fibers, especially soluble fibers, exhibit some prebiotic activity; however, Roberfroid only identifies two groupings of nutritional compounds that meet his definition. These two groupings or sub-categories can be described as inulin-type prebiotics and galactooligosaccharides (GOS).¹

Part 1 focused on inulin-type prebiotics, which include fructooligosaccharides (FOS), oligofructose, and inulin. These inulin-type prebiotics are oligo- or polysaccharide chains comprised primarily of linked fructose molecules. They are considered to be bifidogenic (stimulating the growth of *Bifidobacteria* species). This grouping of prebiotics was selected for review because they represent the most widely commercially available and the most researched prebiotic compounds.

In prebiotic clinical studies, inulin-type prebiotics have been studied as an isolated intervention or combined with other types of prebiotics (primarily GOS) as part of "prebiotic mixtures." This review focuses on the former; however, a summary of mixed prebiotic research is provided.

Nomenclature

Within the category of inulin-type prebiotics, there are no uniformly accepted and used standards for nomenclature. To provide consistency, the nomenclature outlined in Table 1 will be used within this review. In instances where authors of a research paper specify what they used, the nomenclature outlined in Table 1 will be used even if the authors of the original paper used different terminology. Table 2 reviews the abbreviations originally defined in part 1.

Gregory Kelly, ND – Founding partner of Direct Access eHealth; contributing editor, *Alternative Medicine Review*; past instructor at the University of Bridgeport in the College of Naturopathic Medicine; published articles on various aspects of natural medicine and contributed three chapters to the *Textbook of Natural Medicine*, 2nd edition; teaches courses on weight management, the role of stress in health and disease, chronobiology of performance and health, and mind-body medicine.

E-mail: greghealthcoach@netscape.net
Phone: 888-888-8565

Table 1. Prebiotic Nomenclature

FOS	This term will be used to describe short-chain, inulin-type fructan mixes synthesized from sucrose.
Oligofructose	This term will be used to describe inulin-type fructan mixes with a DPmax <10 that have been produced by partial hydrolysis of inulin and then undergone physical separation to remove all long chain (DP ≥10) inulin-type fructans.
Inulin	This term will be used to describe the hot water extracts that result in inulin fructans that have not undergone further processing.
Inulin HP	This term will be used to describe the exclusively long-chain, high-molecular weight mixes of inulin-type fructans (fructans with a DP <10 physically removed).
FOS-enriched inulin	This term will be used to describe proprietary mixes that enrich inulin with FOS.
FOS-enriched inulin HP	This term will be used to describe proprietary mixes that enrich inulin HP with FOS.
Oligofructose-enriched inulin	This term will be used to describe proprietary mixes that enrich inulin with oligofructose.
Oligofructose-enriched inulin HP	This term will be used to describe proprietary mixes that enrich inulin HP with oligofructose.
GOS	This term will be used to describe galactose-based prebiotics.

Mixed Prebiotics Overview and Research Summary

The clinical research that has investigated “prebiotic mixtures” has primarily used inulin-type prebiotics combined with galactooligosaccharide prebiotics. GOS, which are oligo- or polysaccharide chains comprised primarily of linked galactose units, are one of the two categories of compounds that meet Roberfroid’s definition of a prebiotic.¹ Similar to inulin-type prebiotics, GOS are selectively fermented in the colon and promote specific changes in the composition of the gastrointestinal microflora. Specifically, they stimulate the growth of Bifidobacteria and Lactobacilli species.²⁻⁵

Table 2. Degree of Polymerization: Definitions

Abbreviation	Definition
DP	Degree of polymerization; the number of repeat units in an oligomer or polymer chain
DPav	Average degree of polymerization; used to describe mixtures with varying DP values
DPmax	Maximum degree of polymerization; represents the longest chain in a mixture

A specific GOS/inulin-type prebiotic mixture has been extensively investigated. It is comprised of short-chain GOS combined with long-chain inulin (inulin HP) in a 9:1 ratio. This mixture has been researched for infant nutrition applications and is typically added to standard formulas in these trials. The GOS/inulin HP mixture was designed to more closely mimic the oligosaccharide portfolios found in human breast milk than inulin-type prebiotics alone, since the oligosaccharides in breast milk contain relatively high amounts of galactose polymers.⁶ Studies in preterm and term infants have shown a formula supplemented with this GOS/inulin HP prebiotic mixture results in an intestinal microbiota similar to that found in breast-fed infants.^{3,7}

In infants, this GOS/inulin HP combination has been reported to: (1) reduce the incidence of atopic disease, recurrent wheezing, and allergic urticaria in infants with a parental history of atopic disease;^{5,8,9} (2) result in fewer episodes of upper respiratory tract infections, fever, and antibiotic prescriptions;^{8,10,11} (3) reduce the incidence of acute diarrhea;¹¹ (4) improve stool consistency, increase stool frequency, and accelerate gastrointestinal transport time;^{3,12-14} (5) increase fecal secretory IgA;^{15,16} and (6) significantly lower bilirubin levels during the first 72 hours of life in formula-fed infants.¹⁷

Table 3. Summary of Inulin HP Research Findings

Clinical Application	Subjects	Dose/Duration	Results
Blood sugar regulation	8 healthy adults	10 g daily for 6 weeks	No statistically significant changes in plasma glucose or insulin levels were observed. ¹⁹
Lipid management	8 healthy adults	10 g daily for 6 weeks	No statistically significant differences in lipids, except triglycerides that decreased significantly. ¹⁹

Since GOS has prebiotic activity in isolation, and hence presumably some ability to influence physiological responses to supplementation, it is not possible to determine which aspects of the clinical response in the infant nutritional studies of the GOS/inulin HP prebiotic mixture are due to inulin-type prebiotics and which are due to the GOS component of the prebiotic.

Therapeutic Uses of Inulin-type Prebiotics

This section discusses clinical research on inulin-type prebiotics used as stand-alone clinical interventions.

Blood Sugar Regulation

Several investigators have attempted to determine whether supplementing the diet with inulin-type prebiotics has an effect on blood sugar regulation. Studies in both normoglycemic and hyperglycemic subjects have largely reported no statistically observable differences between inulin-type prebiotics and placebo interventions.

van Dokkum et al recruited 12 healthy male subjects for a trial lasting 84 days during which time the participants received a constant and controlled diet. The trial was divided into four distinct experimental periods in which the same diet was supplemented with: (1) 15 g/day inulin, (2) 15 g/day FOS, (3) 15 g/day GOS, or (4) no added prebiotic. No statistically significant differences in glucose tolerance tests and insulin responses to these tests were observed among four experimental periods.¹⁸

Letexier et al gave inulin HP or placebo (maltodextrin) to eight healthy subjects in a double-blind, randomized, placebo-controlled (RCT) crossover study for six weeks. The daily dose and duration was 10 g given

in two divided doses at breakfast and dinner. No statistically significant changes in plasma glucose or insulin levels were observed.¹⁹ Table 3 summarizes this and other inulin HP research.

Boutron-Ruault et al conducted an open multicenter pilot study of adenoma and adenoma-free subjects. All participants received 10 g FOS daily in two divided doses for three months; 74 subjects completed the study. No statistically significant differences were observed in blood glucose or insulin following supplementation with FOS.²⁰

Giacco et al conducted a crossover RCT in 30 subjects with mild hyperlipidemia. Participants received either 10.6 g FOS or 15 g placebo (maltodextrin plus aspartame) as powder in packets and were instructed to add it daily to coffee or tea for two months, after which time they were switched to the other intervention for an additional two months. No statistically significant differences were observed in fasting blood glucose or insulin levels. Although postprandial plasma glucose levels were similar after FOS and placebo at every time point, postprandial insulin response was significantly reduced after FOS compared to placebo.²¹

Daubioul et al investigated the effects of 16 g oligofructose daily on blood glucose and insulin in seven subjects with biopsy-confirmed nonalcoholic steatohepatitis (NASH) – (methodology described under section on fatty liver disease). No statistically significant differences were observed for glucose or insulin levels during the oligofructose versus placebo periods.²²

Luo et al gave 12 healthy, normoglycemic males 20 g FOS or placebo (sucrose) daily for two four-week periods, separated by a two-week washout interval. In this crossover RCT, the intervention was incorporated into cookies that were eaten throughout the day to reach the target intervention levels of active and placebo

compounds. No statistically significant differences were observed for insulin-stimulated glucose metabolism. A decrease in basal hepatic glucose production was observed in the group receiving FOS.²³

Luo et al subsequently investigated the effects of FOS in 12 persons with type 2 diabetes. Subjects were maintained on their existing medical therapies (10 on oral hypoglycemic agents and two on antidiabetic dietary management) throughout the study. The study design was identical to that described above as was the daily dose of FOS or placebo (sucrose). The FOS or sucrose was supplied as powder in packets and participants were instructed to add these as sweeteners to food or beverages several times daily to complete a daily dose of 20 g; 10 subjects completed the study period. No statistically significant differences were observed for fasting plasma glucose concentrations. Levels of hemoglobin A1c and fructosamine (markers of long-term blood sugar control) also did not differ during the active and placebo periods. No significant differences were observed for fasting insulin, insulin binding to erythrocytes, and insulin-mediated glucose disposal for the two interventions. Basal hepatic glucose production also did not differ during the FOS and sucrose periods.²⁴

Yamashita et al conducted a 14-day uncontrolled study on poorly controlled type 2 diabetics with high glucose levels. Subjects received 8 g FOS daily for 14 days. The intervention resulted in an eight-percent decrease in fasting blood glucose concentrations.²⁵

Alles et al investigated the effects of oligofructose on blood glucose in 20 patients with type 2 diabetes. Seventeen of the participants were using oral hypoglycemic medications to assist with blood sugar control. The study was a randomized, single-blind, crossover design with subjects consuming either a placebo (4 g/day glucose) or oligofructose (15 g/day) for 20 days in two divided doses. The dose of oligofructose was gradually increased during the first three days by 5 g/day in an attempt to prevent gastrointestinal side effects. Compared to placebo, oligofructose did not significantly affect fasting blood glucose levels.²⁶

Existing evidence, taken as a whole, suggests supplementation with inulin-type prebiotics is unlikely to have a positive effect on blood sugar in normoglycemic individuals or have a clinically relevant benefit in terms of improving metabolic control in hyperglycemic individuals.

Table 4 summarizes the clinical studies of FOS for blood sugar management and other conditions.

Colon Cancer

In multiple experimental animal models inulin-type prebiotics have demonstrated anticarcinogenic properties. In studies that have examined the effects of inulin-type prebiotics on chemically induced pre-neoplastic lesions or tumors in the colon of rats and mice, the most consistent findings have been reductions in aberrant crypt foci, tumor incidence, and metastasis of implanted tumor cells.²⁷ Only a single preliminary study in humans exists.

Boutron-Ruault et al conducted an open multicenter pilot study of colon adenoma and adenoma-free subjects. All participants received 5 g FOS twice daily for three months; 74 subjects completed the study. Cell proliferation at the rectal crypts was not significantly modified by FOS ingestion in either group.²⁰

While the results observed in animal studies have been promising, human intervention evidence is very limited and currently not very compelling. The question of whether inulin-type prebiotics have an ability to prevent or alter the clinical progression of colon cancer in humans is unanswered and requires future research.

Fatty Liver Disease

One study has been conducted of the effects of inulin-type prebiotics on the clinical course of fatty liver disease. A beneficial effect was observed on serum aspartate aminotransferase (AST) but not on serum alanine aminotransferase (ALT).

Daubioul et al investigated the effects of oligofructose on liver enzymes in seven subjects with biopsy-confirmed NASH. Each subject received 16 g oligofructose or placebo (maltodextrin) daily in a crossover RCT. Observations were made over two eight-week periods of supplementation with the active or placebo treatments and separated by a washout period of minimum five weeks. Oligofructose decreased AST after eight weeks; however, no statistically significant differences were observed for ALT. Analysis of liver ultrasonography did not reveal any difference in liver size.²²

While larger and longer studies might produce more positive results, based on this one small study it does not appear inulin-type prebiotics alter the course of fatty liver disease in a clinically significant manner.

Table 4. Summary of FOS Research Findings

Clinical Application	Subjects	Dose/Duration	Results
Blood sugar regulation	12 healthy males	15 g daily for 21 days	No statistically significant differences in glucose tolerance tests and insulin responses. ¹⁸
Blood sugar regulation	74 adenoma and adenoma-free adults	10 g daily for 3 months	No statistically significant differences in blood glucose or insulin. ²⁰
Blood sugar regulation	30 subjects with mild hyperlipidemia	10.6 g daily for 2 months	No statistically significant differences in fasting blood glucose or insulin levels. Postprandial plasma glucose levels were unchanged but postprandial insulin response was reduced. ²¹
Blood sugar regulation	12 healthy, normoglycemic males	20 g daily for 4 weeks	No statistically significant differences in insulin-stimulated glucose metabolism. A decrease in basal hepatic glucose production. ²³
Blood sugar regulation	12 adults with type 2 diabetes	20 g daily for 4 weeks	No statistically significant differences in fasting plasma glucose concentrations, levels of hemoglobin A1c, fructosamine, fasting insulin, insulin binding to erythrocytes, insulin-mediated glucose disposal, and basal hepatic glucose production. ²⁴
Colon cancer prevention	74 adenoma and adenoma-free adults	10 g daily for 3 months	Cell proliferation at the rectal crypts was not significantly modified. ²⁰
GI: bowel transit, stool consistency and stool frequency	56 infants ages 16.2-46.2 months	0.74 g daily for 28 days	Softer stools, significant increase in the mean number of stools per day and fewer days with skipped stools. ²⁹
GI: bowel transit, stool consistency and stool frequency	12 healthy males	15 g daily for 21 days	No statistically significant differences in fecal wet weight, dry weight, or bowel transit times. ¹⁸
GI: bowel transit, stool consistency and stool frequency	6 healthy elderly adults	8 g daily for 4 weeks	Stool weight, water percentage, and bowel transit time were unchanged. ³¹
GI: IBS	105 subjects with functional bowel disorder	5 g daily for 6 weeks	Statistically significant decrease in symptom scores. ³⁹
Lipid management	12 adult normo-lipidemic males	20 g daily for 4 weeks	No statistically significant differences in lipids. ²³
Lipid management	12 adult normo-lipidemic males	15 g daily for 21 days	No statistically significant differences in lipids. ¹⁸
Lipid management	74 adenoma and adenoma-free adults	10 g daily for 3 months	No statistically significant differences in lipids. ²⁰
Lipid management	30 subjects with mild hyperlipidemia	10.6 g daily for 2 months	Only statistically significant difference in lipids was an increase in fasting plasma lipoprotein(a). ²¹
Lipid management	12 adults with type 2 diabetes	20 g daily for 4 weeks	No statistically significant differences in lipids. ²⁴
Mineral metabolism & bone remodeling	12 postmenopausal women	10 g daily for 5 weeks	No statistically significant differences in mean intestinal calcium absorption, plasma parathyroid hormone, 1,25-dihydroxyvitamin D concentrations, plasma osteocalcin concentration, and urinary deoxypyridinoline excretion. ⁵³
Mineral metabolism & bone remodeling	11 postmenopausal women	10 g daily for 5 weeks	Increase in magnesium absorption. ⁵⁴
Mineral metabolism & bone remodeling	11 postmenopausal women	10 g daily for 5 weeks	Increase in copper absorption, but no effects on selenium or zinc absorption. ⁵⁵

Gastrointestinal Health

Because inulin-type prebiotics are thought to exert therapeutic effect in the gastrointestinal tract, they have been investigated for a wide variety of gastrointestinal conditions.

Bowel Transit, Stool Consistency, and Stool Frequency

Several studies have investigated the effects of inulin-type prebiotics on aspects of bowel transit time, stool consistency, or stool frequency in infants and adults. More research is required before definitive conclusions can be reached; however, existing evidence supports an effect in infants but does not support a significant effect in adults who have no pre-existing functional gastrointestinal problems.

Kapiki et al conducted an RCT in preterm infants. Starting within the first two weeks after birth, 56 bottle-fed preterm infants were randomized to receive a formula supplemented with oligofructose or maltodextrin for 14 days. Supplementation with oligofructose increased daily stool frequency. Stool consistency also differed between the two groups, with infants fed the oligofructose having softer stools.²⁸

In an RCT of 56 healthy children ages 16-46 weeks, Moore et al supplemented cereals with either FOS or placebo for 28 days. Average daily FOS consumption was 0.74 g/day. FOS supplementation resulted in softer stools and significant increase in the mean number of stools per day compared with placebo. There were also fewer days with skipped stools in the infant group receiving FOS.²⁹

In a crossover RCT, Euler et al gave formula-fed, full-term infants (ages 2-6 weeks) a cow's milk formula with or without oligofructose at a dose of both 1.5 and 3 g/liter; washout weeks preceded and followed a week of oligofructose-supplemented formula feeding. The frequency of stools was greater and the consistency of stools was looser during oligofructose supplementation. These observed differences were dose-dependent, with the higher dose of oligofructose producing a greater statistically significant effect.³⁰

In the study by van Dokkum et al (previously discussed in the blood sugar regulation section) aspects of general bowel function were assessed. In this study, 12 healthy male subjects had a control diet supplemented

with: (1) 15 g/day inulin, (2) 15 g/day FOS, (3) 15 g/day GOS, or (4) no added prebiotic. Fecal wet weight, dry weight, and bowel transit times were similar in all four study periods. After log transformation, periods of inulin and GOS supplementation produced statistically significantly greater fecal wet weight than what was observed during FOS supplementation.¹⁸

Bouhnik et al gave six elderly men and women 8 g FOS daily in two divided doses for four weeks. The subjects did not have any history of gastrointestinal issues. Stool weight, water percentage, and bowel transit time were unchanged following prebiotic supplementation.³¹

Constipation

In subjects with existing constipation, supplementation with inulin-type prebiotics might have a clinical role; however, placebo-controlled trials should be conducted before any definitive conclusions can be drawn.

Kleessen et al gave inulin to a group of 10 elderly females with constipation – defined as one or two bowel movements per week and hard stool consistency. The women received inulin for 19 days. An initial dose of 20 g daily was given from days 1 to 8 and the dose gradually increased to 40 g daily from days 9 to 11. Daily inulin supplementation remained at 40 g from days 12 to 19. Stool consistency was assessed as being softer with inulin supplementation. Inulin supplementation increased stool frequency in 7 of 10 patients from pre-intervention of 1-2 bowel movements per week to 8-9 bowel movements per week. This occurred independent of the total daily amount of inulin ingested. In the other three subjects, the results were mixed with responses in two cases appearing to differ based on the dose of inulin. One woman had an increase in stool frequency to five per week at a dose of 20 g inulin daily and an increase to seven bowel movements per week at the 40-g dose. Another woman had a slightly poorer outcome at the 40-g dose (four bowel movements weekly) compared with the 20-g daily dose (five bowel movements per week). The last woman had no distinct change in stool frequency following supplementation with inulin, but the stool was softer.³²

Review Article

Diarrhea Prevention

One study administered inulin-type prebiotics to infants to determine whether prebiotics might help prevent occurrences of acute diarrhea. The findings do not suggest a clinical role for reducing the incidence or severity of diarrhea in infants.

In an RCT Duggan et al compared the effect of cereal with or without added oligofructose (0.55 g/15 g cereal) on diarrhea incidence and severity in 282 infants, ages 6-12 months, for six months. The mean number of days with diarrhea was 10.3 in the non-supplemented cereal group and 9.8 in the oligofructose-supplemented cereal group, a difference not statistically significant.³³

Inflammatory Bowel Disease

Inulin-type prebiotics have shown therapeutic benefits in animal models of colitis.³⁴ The human studies on inflammatory bowel disease (IBD) have included small numbers of patients and interventions have been for only 2-3 weeks. All three studies reported some degree of functional change subsequent to supplementation with inulin-type prebiotics that suggest the potential to modulate inflammation in subjects with active IBD. Changes in disease activity have been mixed in persons with active disease. No trials have been conducted to determine whether chronic supplementation with inulin-type prebiotics might help prevent disease recurrence or sustain periods of clinical remission.

Casellas et al conducted an RCT of inulin-type prebiotics in patients with acute ulcerative colitis. Participants had been previously in remission and presented with a relapse of mild-to-moderate severity. Subjects were treated with the conventional medication mesalazine (at a dose of 3 g/day) and randomly allocated to receive either 12 g oligofructose-enriched inulin HP (in three divided doses) or placebo (maltodextrin) daily for two weeks; 15 subjects completed the trial. All participants except one (in the placebo group) demonstrated a decline in disease activity, assessed using the Rachmilewitz Index. Based on this index, all subjects in the active and six of eight subjects in the placebo group were considered to be in remission at the end of the two-week intervention period, demonstrating no significant difference in disease activity reduction scores between groups. Scores on a self-assessed dyspeptic symptoms questionnaire decreased

significantly with active treatment but not with placebo, suggesting at least a reduction of perceived dyspeptic symptoms with prebiotic supplementation. Concentrations of inflammatory markers interleukin-8 (IL-8) and prostaglandin-2 (PGE-2) in rectal fluid were measured before and after the intervention period. No differences were observed between groups. Concentrations of fecal calprotectin were assessed. Calprotectin is a calcium-binding protein found in neutrophilic granulocytes, which is used as a biomarker of intestinal inflammation and as a predictor of relapse in subjects with IBD. Although it was elevated in both groups at the start of the intervention period, a significant reduction in this marker was observed at the end of the study in the active group but not in the placebo group.³⁵

Lindsay et al gave 10 patients with active ileo-colonic or colonic Crohn's disease 15 g oligofructose-enriched inulin daily for three weeks. Supplementation resulted in a statistically significant reduction in the Harvey Bradshaw Index (HBI) from 9.8 to 6.9. Four patients were categorized as achieving clinical remission based on reductions in HBI (with clinical remission defined as a fall in HBI to 5 or less). Mean Crohn's Disease Activity Index (CDAI) fell from 250.9 to 220.6, although this change was not statistically significant. The researchers used HBI rather than CDAI as the disease activity index, since the HBI places less weight on subjective criteria such as abdominal symptoms and supplementation was expected to and did induce an increase in the severity of flatulence. A statistically significant increase in the percentage of anti-inflammatory interleukin-10 positive CD11c+ dendritic cells was observed following supplementation. Supplementation with the oligofructose-enriched inulin also resulted in statistically significant increases in toll-like receptor 2 (TLR2) and TLR4 expression. These changes suggest some degree of immunomodulatory activity and possibly the initiation of cytoprotective mechanisms in colonic cells.³⁶

Welters et al gave 20 patients with an ileal pouch-anal anastomosis 24 g inulin (in two divided doses) or placebo daily for three weeks in a crossover RCT. There were no differences in observed clinical symptoms between the inulin and placebo periods. However, compared with the placebo, inulin supplementation did increase butyrate concentrations (beneficial fatty acid and the main fuel of colonocytes), lower

Table 5. Summary of Oligofructose Research Findings

Clinical Application	Subjects	Dose/Duration	Results
Blood sugar regulation	7 adults with nonalcoholic steatohepatitis	16 g daily for 8 weeks	No statistically significant differences in glucose or insulin levels. ²²
Blood sugar regulation	20 adults with type 2 diabetes	15 g daily for 20 days	No statistically significant differences in fasting blood glucose. ²⁶
Fatty liver disease	7 adults with nonalcoholic steatohepatitis	16 g daily for 8 weeks	Decrease in AST but no statistically significant differences in ALT; imaging did not reveal any difference in liver size. ²²
GI: bowel transit, stool consistency, and stool frequency	56 preterm infants	0.4 g/100 mL of formula for 14 days	Increased stool frequency and softer stool consistency. ²⁸
GI: bowel transit, stool consistency, and stool frequency	72 infants ages 2-6 weeks	1.5 and 3 g/L of formula	Increased stool frequency and softer stool consistency. ³⁰
GI: diarrhea prevention	282 infants ages 6-12 months	0.55 g/15 g cereal daily for 6 months	No statistically significant difference in the mean number of days with diarrhea. ³³
GI: IBS	75 subjects with IBS	10 g for the first 2 weeks and 20 g daily for following 10 weeks	No significant differences in symptom scores; statistically significant increase in defecation frequency at weeks 4 and 6, which was not maintained at week 12. ³⁸
Lipid management	75 subjects with IBS	10 g for the first 2 weeks and 20 g daily for following 10 weeks	No statistically significant differences in lipids. ³⁸
Lipid management	7 adults with nonalcoholic steatohepatitis	16 g daily for 8 weeks	No statistically significant differences in lipids. ²²
Lipid management	20 subjects with type 2 diabetes (and mild hyperlipidemia)	15 g daily for 20 days	No statistically significant differences in lipids. ²⁶
Mineral metabolism & bone remodeling	12 adult males	15 g daily for 21 days	No significant effect on calcium or iron absorption. ⁴⁷
Mineral metabolism & bone remodeling	14- to 16-year-old boys	15 g daily for 9 days	Significant increase in fractional calcium absorption. ⁴⁸
Mineral metabolism & bone remodeling	59 adolescent girls near menarche	8 g daily for 3 weeks	No statistically significant change in calcium absorption. ⁴⁹

Review Article

colonic pH, decrease numbers of *Bacteroides fragilis*, and diminish concentrations of secondary bile acids in feces. These changes were accompanied by endoscopically and histologically verified reductions in inflammation of the mucosa of the ileal reservoir.³⁷

Given the small numbers of subjects in the studies conducted to date, and the mixed results reported, it is not possible to determine whether inulin-type prebiotics can reduce disease activity in individuals with acute inflammation. Larger trials are required before definitive conclusions can be drawn. Whether inulin-type prebiotics would have a role in keeping patients with IBD in remission between bouts of active disease has not been explored.

Irritable Bowel Syndrome

Two studies have investigated whether inulin-type prebiotics have a role in irritable bowel syndrome (IBS). One study observed no statistical benefit while the other reported an improvement in symptom scores following supplementation with an inulin-type prebiotic.

Olesen et al conducted a parallel group RCT. The study consisted of a two-week, single-blind run-in phase and a 12-week, double-blind comparative phase. Participants were randomly assigned to receive oligofructose or a placebo (dried and powdered glucose syrup). The dose used was 10 g/day for the first two weeks and 20 g/day for the following 10 weeks. Seventy-five patients (38 in the oligofructose group and 37 in the placebo group) completed the trial. In terms of clinical changes (as assessed by changes in symptom scores), no significant differences were observed between the two groups after 12 weeks of supplementation. IBS symptoms improved in 58 percent and worsened in eight percent of the participants receiving oligofructose, while among participants receiving the placebo 65 percent improved and 13 percent worsened. A statistically significant increase in defecation frequency was observed in participants receiving the oligofructose compared to placebo at weeks 4 and 6; however, no statistically significant difference persisted by the end of the 12-week intervention.³⁸

Paineau et al investigated the use of FOS in 105 patients diagnosed by Rome II criteria with a minor degree of functional bowel disorder (FBD). As defined in the article, FBD includes symptoms of abdominal bloating, rumbling, transit disorders (occasional constipation

and/or diarrhea, possibly alternating), abdominal pains, and flatulence. Thus, FBD is symptomatically the same as IBS. Participants were randomized to receive either 5 g FOS or placebo (50% sucrose and 50% maltodextrins) daily in divided doses for six weeks; 97 participants completed the study. At baseline, overall scores on the Functional Digestive Disorders Quality of Life questionnaire were similar between groups. Following six weeks of supplementation a statistically significant decrease in symptom scores was observed in the group taking FOS compared to placebo.³⁹

The response to inulin-type prebiotics in persons with IBS-like symptoms has been mixed. This might be due to the differences in what was supplemented (FOS in one case and oligofructose in the other), differences in the length of the supplementation periods, or other factors. Additional research might determine whether inulin-type prebiotics have any clinical role in managing IBS symptoms; however, since, in the longer study, some of the benefits observed early (an increase in stool frequency at 4 and 6 weeks) did not appear to persist, future studies should be of sufficient duration to determine occurrence and persistence of benefits.

Table 5 summarizes the clinical research of oligofructose for gastrointestinal health and other clinical situations.

Immunity

One study investigated the immune effects of inulin-type prebiotics in infants. In this RCT, Firman-syah et al supplemented the diet of 50 infants (ages 7-9 months) with oligofructose-enriched inulin or placebo for four weeks prior to measles vaccination. The average daily intake of the inulin-type prebiotic was 0.2 g/kg body weight. A significantly greater rise in post-vaccination antimeasles IgG was observed in infants supplemented with the oligofructose-enriched inulin.⁴⁰

While this study suggests the potential for inulin-type prebiotics to influence aspects of immune response in infants, more research is required to determine to what extent supplementation influences other populations and other aspects of immunity.

Lipids

The effect of inulin-type prebiotics on lipid levels has been investigated in a variety of studies. In individuals with normal lipid levels, the most consistent observation is that inulin-type prebiotics have no statistically significant effect on lipid levels. In persons with elevated lipid levels findings have been mixed, with some studies reporting improvements in lipid levels subsequent to supplementation and other studies reporting no effect of supplementation.

Luo et al reported that 20 g FOS daily had no effect on lipids in healthy, normoglycemic males (methodology described in the section on blood sugar regulation).²³ Similarly, in the study van Dokkum et al conducted for 84 days in 12 healthy male subjects (methodology described in the section on blood sugar regulation) neither inulin nor FOS produced statistically significant differences in total cholesterol, LDL-cholesterol, total HDL-cholesterol, HDL-2 and HDL-3 concentrations, apolipoprotein A-1 and B, or triglycerides.¹⁸

In the study by Letexier et al in which eight healthy subjects were given 10 g inulin HP or placebo daily (methodology described in the section on blood sugar regulation), total cholesterol, HDL-cholesterol, and LDL-cholesterol concentrations did not change significantly. However, a statistically significant decrease in plasma triglyceride concentrations was observed after inulin HP ingestion.¹⁹

Pedersen et al also studied the effect of 14 g inulin daily on blood lipids in 64 healthy, normolipidemic females in a crossover RCT. Inulin produced no statistically significant changes in total cholesterol, HDL-cholesterol, LDL-cholesterol, or triglycerides.⁴¹

In the study by Olesen et al (methodology described in the section on IBS) of individuals with IBS, lipids were also assessed. Oligofructose produced no significant changes compared to placebo in these normolipidemic individuals.³⁸

In the study by Boutron-Ruault et al (described in the colon cancer section) lipid levels were assessed before and after three months of FOS supplementation. No statistically significant differences were observed in total cholesterol or HDL-cholesterol following supplementation with FOS in these normolipidemic individuals.²⁰

Daubioul et al investigated the effect of 16 g oligofructose daily on blood glucose, insulin, and lipids in seven subjects with biopsy confirmed NASH (methodology described in fatty liver disease section). As a group, baseline total cholesterol was below 200 mg/dL and triglycerides values were in the normal range. No statistically significant differences were observed for total cholesterol, HDL- or LDL-cholesterol, or triglycerides between the oligofructose and placebo periods.²²

Yamashita et al conducted an uncontrolled 14-day clinical study in type 2 diabetics with elevated lipid levels. FOS was given at a daily dose of 8 g. A six-percent decrease in total cholesterol and a 10-percent decrease in LDL-cholesterol were reported.²⁵

Balcazar-Munoz et al conducted an RCT in 12 obese individuals with high triglycerides and cholesterol. Subjects were randomized to receive 7 g/day inulin or placebo for four weeks. Inulin administration produced a significant reduction in total cholesterol (248.7 to 194.3 mg/dL), LDL-cholesterol (136.0 to 113.0 mg/dL), VLDL-cholesterol (45.9 to 31.6 mg/dL), and triglyceride (235.5 to 171.1 mg/dL) concentrations.⁴²

Alles et al investigated the effects of 15 g/day oligofructose on lipids in 20 patients with type 2 diabetes (methodology described in the section on blood sugar regulation). Subjects had mild hyperlipidemia, with baseline total cholesterol of 216 mg/dL for men and 242 mg/dL for women. Baseline serum triglycerides were 235 mg/dL for men and 261 mg/dL for women. Compared to placebo, oligofructose had no significant effect on total cholesterol, HDL-cholesterol, LDL-cholesterol, or triglycerides.²⁶

Giacco et al conducted a crossover RCT in 30 subjects with mild hyperlipidemia (methodology described in the section on blood sugar regulation). To be eligible for inclusion subjects had to have plasma cholesterol greater than 200 and less than 300 mg/dL and plasma triglycerides less than 305 mg/dL. A daily dose of 10.6 g FOS or placebo (maltodextrin plus aspartame) was given for two months. No statistically significant differences were observed in fasting total cholesterol, VLDL-cholesterol, LDL-cholesterol, HDL-cholesterol, apolipoprotein A-1, or triglycerides. A statistically significant increase in fasting plasma lipoprotein(a) (a cardiac risk factor) was observed with FOS (an increase from 33 to 37 mg/dL).²¹



Review Article

Luo et al investigated the effect on lipids of 20 g FOS or placebo daily in 10 subjects with type 2 diabetes (methodology described in the section on blood sugar regulation). At baseline average triglyceride levels, total cholesterol, and HDL-cholesterol were 133, 207, and 38 mg/dL, respectively. No statistically significant differences were observed subsequent to the interventions for fasting levels of triglycerides, total or HDL-cholesterol, apolipoproteins A-1 or B, or lipoprotein(a).²⁴

In normolipidemic subjects, inulin-type prebiotics do not appear to positively modify lipid levels. The one positive reported result was a reduction in triglycerides with inulin HP (studies with FOS, oligofructose, and inulin demonstrated no statistically significant changes). More research is required before conclusions can be drawn based on this preliminary finding; however, it is theoretically possible a long-chain inulin-type prebiotic (inulin HP) might produce different responses than inulin-type prebiotics with short-chain fructans.

In individuals with elevated lipids the results have been mixed, although the preponderance of studies report no benefit with supplementation. The differences in reported outcomes might be due to differences in the study populations, the duration of the studies (although all have been relatively short-term – lasting for one month or less), or differences in the type of inulin-type prebiotic used. The one positive trial using FOS was not placebo-controlled and lasted only two weeks. In the placebo-controlled trials of FOS, which were also short-term in nature, no significant differences were observed. In the trial that administered oligofructose, no statistically significant benefits were reported. In the single inulin trial positive results were reported. Whether this was because inulin was used rather than exclusively short-chain inulin-type prebiotic supplements (FOS and oligofructose), differences in the study population (obese subjects with high cholesterol and triglycerides), or some other factor cannot be determined. While it is possible that some forms of inulin-type prebiotics might positively influence lipids in some subsets of the population, until more definitive research is available and longer-term studies are conducted, these prebiotics should not be expected to significantly modify lipid levels.

Mineral Metabolism and Bone Remodeling

In animals, inulin-type prebiotics have consistently shown a positive impact on aspects of calcium and magnesium absorption. In humans the effects have been somewhat less consistent for absorption of these and other minerals. In a review of this subject, Scholz-Ahrens et al suggested the inconsistent results might be caused by differences in experimental design.⁴³ Experimental design differences have included: (1) study populations, (2) minerals assessed, (3) assessment techniques used to gauge changes in mineral metabolism, and (4) dose, type of prebiotic, and duration of intervention.

The effect of inulin-type prebiotics on calcium absorption has been the most researched, while the absorption of copper, iron, magnesium, selenium, and zinc has been studied less intensively. Although some studies have been long-term, most have been short-term. Several of the studies have reported inulin-type prebiotics enhance intestinal calcium absorption. Roberfroid notes the most convincing data has been with oligofructose-enriched inulin HP in adolescents and postmenopausal women.¹ The studies on other minerals have been inconsistent.

Yap et al investigated the effect of inulin on mineral absorption in 36 healthy, formula-fed infants. Significant increases in iron absorption and retention, magnesium retention, and zinc absorption and retention were observed in infants supplemented with inulin. Calcium and copper absorption and retention were not influenced by supplementation with inulin.⁴⁴

Teuri et al investigated the effect of inulin on calcium metabolism using a randomized, two-period crossover design (each period consisting of one test day) in 15 young healthy women (mean age 23.7). The volunteers were given cheese containing 210 mg of calcium with or without added inulin (15 g/dose). The authors conclude that inulin did not acutely affect markers of calcium metabolism compared to a corresponding breakfast without inulin.⁴⁵

In a crossover study, Coudray et al investigated the effect of inulin on absorption and balance of calcium, magnesium, iron, and zinc in nine healthy young men (mean age 25.5). Active treatment lasted 26 days and participants received up to 40 g inulin daily. The authors reported inulin increased calcium absorption and calcium balance but had no effect on the other minerals.⁴⁶

van den Heuvel et al investigated the effect of inulin or oligofructose on calcium and iron absorption in 12 healthy males (ages 20-30) using a randomized, crossover design. The dose studied was 15 g daily for 21 days and the effects on calcium absorption were compared to a control period with no supplementation. No significant effect on calcium or iron absorption was observed.⁴⁷

In a second study, the same authors investigated the effect of 15 g/day oligofructose compared with placebo (sucrose) on calcium absorption in a crossover experiment in a younger study group – 12 healthy, 14- to 16-year-old boys for nine days per treatment period. The authors reported oligofructose significantly increased fractional calcium absorption compared to the placebo periods.⁴⁸

Griffin et al reported an oligofructose-enriched inulin HP prebiotic significantly increased calcium absorption in girls. A group of 59 adolescent girls at or near menarche was supplemented with either 8 g oligofructose, oligofructose-enriched inulin HP, or placebo (sucrose) daily in a randomized, crossover design. Each intervention was given for three weeks with two-week washout periods between interventions. Throughout the study, subjects consumed approximately 1,500 mg/day dietary calcium. The authors reported calcium absorption was significantly higher in the group receiving the oligofructose-enriched inulin HP compared to the placebo group. Unlike the study by van den Heuvel et al of adolescent boys, in this study oligofructose, compared to placebo, did not produce a statistically significant change in calcium absorption.⁴⁹

Abrams et al conducted the first long-term study of inulin-type prebiotics and mineral absorption. The objective was to assess the effect on calcium absorption and bone mineral accretion after eight weeks and one year of supplementation in adolescents ages 9-13. One hundred subjects were randomly assigned to receive 8 g/day oligofructose-enriched inulin HP or a placebo (maltodextrin). At the end of the study, 92 subjects were available for calcium absorption measurement, which was significantly greater in the active group than in the control group at both eight weeks and one year.⁵⁰

Holloway et al investigated the effects of an oligofructose-enriched inulin HP prebiotic in 15 postmenopausal women in a six-week RCT. Fractional

absorption of calcium and magnesium increased following active treatment compared to placebo.⁵¹

In a three-month study, Kim et al reported that inulin (8 g/day) compared to placebo (maltodextrin/sucrose mixture) increased calcium absorption in postmenopausal women (mean age 60-61) who were not receiving hormonal replacement therapy.⁵²

Tahiri et al gave 12 postmenopausal women a daily dose of 10 g FOS or placebo (sucrose) for five weeks using a crossover design. Mean intestinal calcium absorption was not significantly different between the two interventions nor were plasma parathyroid hormone or 1,25-dihydroxyvitamin D concentrations.⁵³

Tahiri et al also investigated the effect of FOS supplementation on magnesium absorption in 11 postmenopausal women. Participants received 10 g FOS or placebo for five weeks in a crossover trial separated by a washout period of three weeks. Magnesium absorption increased with FOS supplementation.⁵⁴

Ducros et al investigated the effect of FOS on copper, selenium, and zinc absorption in 11 postmenopausal women. Participants were given either 10 g/day FOS or placebo for five weeks in random order, followed by a washout period of three weeks. Copper absorption was significantly enhanced with FOS supplementation; however, no differences in selenium or zinc absorption were observed.⁵⁵

Several studies have looked beyond mineral absorption to investigate the effect of inulin-type prebiotics on biomarkers of bone remodeling. The results have been inconsistent for the entire category of inulin-type prebiotics; however, the studies using an oligofructose-enriched inulin HP prebiotic mixture have reported positive results.

Tahiri et al (described above) reported that 10 g FOS daily for five weeks had no effect on bone turnover biomarkers in postmenopausal women. Plasma osteocalcin concentrations and urinary deoxypyridinoline excretion were monitored, and no significant differences were observed when active and placebo periods were compared.⁵³

In the Kim et al study (described above) the effect of inulin on serum bone parameters related to bone turnover and bone mineral density was assessed. After three months of supplementation, the level of serum alkaline phosphatase was significantly lower in the inulin

Review Article

group compared to placebo, and a non-significant trend toward a slight reduction in urinary deoxypyridinoline was also observed, both indicating reductions in bone turnover. No significant effect on bone mineral density was observed.⁵²

Dahl et al gave institutionalized adults thickened beverages fortified with inulin (13 g/day) or isocaloric standard modified starch-thickened beverages. The three-week trial was double-blind and crossover in design. The authors reported the inulin-fortified beverage failed to induce any change in bone resorption rate, as assessed by the measurement of cross-linked N-telopeptides.⁵⁶

While these three studies reported no positive effects, studies using oligofructose-enriched inulin HP have reported positive results. Holloway et al (described above) reported that, compared to placebo, bone resorption (assessed by urinary deoxypyridinoline crosslinks) was greater and bone formation (assessed by serum osteocalcin) showed an increase after six weeks of treatment. A greater response in bone turnover biomarkers was observed in postmenopausal women with lower initial spine bone mineral density. Positive changes in these parameters occurred only in volunteers who increased mineral absorption in response to supplementation with oligofructose-enriched inulin HP.⁵⁵

Abrams et al (described above) assessed whole-body bone mineral content and whole-body bone mineral density after one year of supplementation with 8 g/day oligofructose-enriched inulin HP. Of 100 adolescents who began the study, 95 were available for the bone mineral measurements. Compared to placebo, whole-body bone mineral content and whole-body bone mineral density were significantly greater in the active group.⁵⁰

A few studies have attempted to determine whether predictable factors might impact the effect inulin-type prebiotics have on calcium absorption. Griffin et al conducted a study on 54 adolescent subjects to determine which subject characteristics were associated with a beneficial effect of oligofructose-enriched inulin HP. In a crossover trial, subjects were given 8 g oligofructose-enriched inulin HP or placebo (sucrose) daily for three weeks. In the group as a whole the active treatment increased calcium absorption. The most consistent identifiable determinant of a beneficial response to the prebiotic was the fractional calcium absorption during

the placebo period. Individuals with lower calcium absorption during the placebo period showed the greatest benefit in terms of improved calcium absorption when given oligofructose-enriched inulin HP.⁵⁷

Roberfroid commented on these findings: "An interesting conclusion of the studies in adolescence is the inverse correlation between the relative increase in absorption caused by inulin-type fructans and the basal absorption capacity as measured before the intervention. The same correlation was demonstrated in analyses of the animal data. That would indicate that, with regard to mineral absorption, consuming inulin-type fructans would benefit more the adolescents who have a low basal level."¹

In the study of 100 adolescents (described above) by Abrams et al, polymorphisms of the Fok1 vitamin D receptor gene were determined. A significant interaction of genotype with prebiotic supplementation was observed following eight weeks of supplementation but not at one year. Participants with the ff genotype had the least initial response to prebiotic supplementation, while the FF and Ff genotypes were associated with higher calcium absorption. In the active treatment group, the percentage of children with an increase in calcium absorption of greater than or equal to three percent after eight weeks of inulin-type prebiotic supplementation were 92 percent, 62 percent, and 50 percent for FF, Ff and ff subjects, respectively. The authors suggested that, "...at least initially, the magnitude of the benefit was affected by genetic modifiers of calcium absorption, including polymorphisms of the Fok1 gene."⁵⁰

Using the same group of adolescents, Abrams et al identified 32 of the 48 participants receiving the active treatment as "responders." To be identified as "responders," participants had a three-percent increase in calcium absorption after eight weeks of inulin-type prebiotic supplementation. Compared to the non-responder and placebo groups, the responders had significantly greater retention of calcium and accretion of this calcium in the skeleton over a year based on whole-body, dual-energy x-ray absorptiometry data and increases in whole-body bone mineral content.⁵⁸

In terms of a mechanism of action, it has been speculated that inulin-type prebiotics optimize passive calcium absorption and this optimization occurs primarily in the colon.⁵⁹ A study by Abrams et al lends support to this hypothesis. In the study, the authors

Table 6. Summary of Inulin Research Findings

Clinical Application	Subjects	Dose/Duration	Results
Blood sugar regulation	12 healthy males	15 g daily for 21 days	No statistically significant differences in glucose tolerance tests and insulin responses. ¹⁸
GI: bowel transit, stool consistency, and stool frequency	12 healthy males	15 g daily for 21 days	No statistically significant differences in fecal wet weight, dry weight, or bowel transit times. ¹⁸
GI: constipation	10 elderly females with constipation	Starting dose of 20 g increased to 40 g daily for 19 days	9 of 10 subjects had increased stool frequency and the remaining subject had no increased frequency but softer stools. ³²
GI: inflammatory bowel disease	20 subjects with ileal pouch-anal anastomosis	24 g daily for 3 weeks	No differences in clinical symptoms; increased butyrate concentrations, lower colonic pH, decreased numbers of <i>Bacteroides fragilis</i> , and diminished concentrations of secondary bile acids in feces; accompanied by endoscopically and histologically verified reductions in inflammation of the mucosa of the ileal reservoir. ³⁷
Lipid management	12 normolipidemic males	15 g daily for 21 days	No statistically significant differences in lipids. ¹⁸
Lipid management	64 normolipidemic females	14 g daily	No statistically significant differences in lipids. ⁴¹
Lipid management	12 obese subjects with high triglycerides and cholesterol	7 g daily for 4 weeks	Significant reduction in total cholesterol, LDL-cholesterol, VLDL-cholesterol, and triglycerides. ⁴²
Mineral metabolism & bone remodeling	36 healthy term infants ages 5-12 months	1.25 g daily	Significant increases in iron absorption and retention, magnesium retention, and zinc absorption and retention; calcium and copper absorption or retention was not influenced. ⁴⁴
Mineral metabolism & bone remodeling	15 adult females	15 g daily for 1 day	No acute effect on calcium metabolism. ⁴⁵
Mineral metabolism & bone remodeling	9 adult males	Up to 40 g daily for 26 days	Increased calcium absorption and calcium balance, but had no effect on the absorption of other minerals. ⁴⁶
Mineral metabolism & bone remodeling	12 adult males	15 g daily for 21 days	No significant effect on calcium or iron absorption. ⁴⁷
Mineral metabolism & bone remodeling	Postmenopausal women	8 g daily for 3 months	Increased calcium absorption; serum alkaline phosphatase was significantly lower and nonsignificant trend toward a slight reduction in urinary deoxypyridinoline; no significant effect on bone mineral density. ⁵²
Mineral metabolism & bone remodeling	Institutionalized adults	13 g daily for 3 weeks	No statistically significant change in bone resorption rate (cross-linked N-telopeptides). ⁵⁶

Table 7. Summary of Oligofructose-enriched Inulin/Inulin HP Findings

Clinical Application	Subjects	Dose/Duration	Results
GI: inflammatory bowel disease	15 subjects with acute ulcerative colitis	12 g daily oligofructose-enriched inulin HP for 2 weeks	While all participants except one demonstrated a decline in disease activity, there were no significant differences in disease activity reduction scores between active and placebo groups. Scores on a self-assessed dyspeptic symptoms questionnaire decreased significantly with active treatment; no statistically significant differences in IL-8 or PG-2; concentrations of fecal calprotectin decreased significantly with active treatment. ³⁵
GI: inflammatory bowel disease	10 subjects with active Crohn's disease	15 g daily oligofructose-enriched inulin for 3 weeks	Statistically significant reduction in the HBI; no statistically significant difference in CDAI; statistically significant increase in the percentage of anti-inflammatory IL-10 positive CD11c+ dendritic cells and in TLR2 and TLR4 expression. ³⁶
Mineral metabolism & bone remodeling	59 adolescent girls near menarche	8 g daily oligofructose-enriched inulin HP for 3 weeks	Calcium absorption was significantly greater. ⁴⁹
Mineral metabolism & bone remodeling	100 adolescents (ages 9-13)	8 g daily oligofructose-enriched inulin HP for 1 year	Calcium absorption was significantly greater; whole-body bone mineral content and whole-body bone mineral density were significantly greater. ⁵⁰
Mineral metabolism & bone remodeling	15 postmenopausal women	Oligofructose-enriched inulin HP for 6 weeks	Increase in fractional absorption of calcium and magnesium; urinary deoxypyridinoline crosslinks were greater and serum osteocalcin increased. ⁵¹
Mineral metabolism & bone remodeling	54 adolescents	8 g daily oligofructose-enriched inulin HP for 3 weeks	Increased calcium absorption. ⁵⁷
Mineral metabolism & bone remodeling	13 adults (ages 18-27)	8 g daily oligofructose-enriched inulin HP for 8 weeks	Increased calcium absorption. ⁶⁰
Weight management	97 adolescents (ages 9-13)	8 g daily oligofructose-enriched inulin HP for 1 year	A statistically significant smaller increase in BMI; increases in body fat mass were lower. ⁶¹

report the effects of inulin-type prebiotics on calcium absorption occur principally in the colon, with approximately 70 percent of the increase attributed to colonic absorption. This conclusion was based on a study with 13 participants, ages 18-27 years, who took 8 g oligofructose-enriched inulin HP daily for eight weeks.⁶⁰

As discussed in part 1, shorter-chain inulin polymers are believed to be primarily metabolized in

the proximal colon, while longer-chain polymers can reach the distal colon where they are metabolized. This might explain why shorter-chain polymers like FOS and oligofructose have had less consistent effects on calcium absorption than the oligofructose-enriched inulin HP (which contains a mix of short- and long-chain polymers) and why the latter are presumably better able to influence passive calcium absorption throughout the entirety of the colon.

While evidence on inulin-type prebiotics and mineral absorption is mixed, existing evidence suggests positive results are more likely to occur in adolescents and postmenopausal women. Even in these subsets of the population, there is a variable response to supplementation. The variability in response appears to be influenced by baseline calcium absorption – with lower baseline absorption expected to produce better response to inulin-type prebiotics – and possibly genetics. More research in this area is warranted.

In their review, Scholz-Ahrens concludes that, “Certain experimental or dietary conditions and the physiological characteristics of the target group studied might favor a positive outcome of a study.”⁴³ This conclusion appears to be correct. Rather than inulin-type prebiotics having a uniform effect on mineral absorption, the specific type of inulin-type prebiotic used, the duration of use, and individual characteristics (genetics, age, baseline calcium status, etc.) appear to play roles in terms of response.

With respect to improving calcium absorption and producing a long-term positive effect on bone health biomarkers, the best choice for supplementation appears to be oligofructose-enriched inulin HP. Current evidence suggests inulin-type prebiotics would not be expected to have a significant impact on absorption of iron, selenium, and zinc, and might have a positive effect on copper and magnesium in some population subsets.

Table 6 summarizes the clinical research on inulin for bone metabolism and other clinical applications. Table 7 summarizes the clinical research on inulin HP/oligofructose-enriched inulin on various clinical conditions.

Weight

Inulin-type fructans might have an influence on weight regulation; however, research in this area is very limited.

Abrams et al randomized 97 adolescents (ages 9-13) to receive 8 g oligofructose-enriched inulin HP or placebo (maltodextrin) daily for one year. Eighty-nine of the subjects who completed the one-year intervention were available for follow-up at two years. The subjects who received the prebiotic demonstrated a statistically significantly smaller increase in body mass index

(BMI) compared to the control group. The average difference in BMI increase between the two groups was 0.52 kg/m². Increases in body fat mass were also less in the group receiving the prebiotic at one year, the average gain in body fat being 0.84 kg greater in the placebo group. These observed differences tended to be maintained one year after supplementation was stopped.⁶¹

Safety/Toxicity

In 1992 a committee of U.S. experts declared inulin-type prebiotics as Generally Recognized as Safe (GRAS).⁶²

In animal experiments, the LD₅₀ for FOS is more than 9 g/kg for acute dosing. No treatment-related chronic toxicity has been reported for oral doses of 4.5 g/kg for six weeks. In animal experiments, FOS shows no toxicity compared with existing sugars commonly used in the food supply and no observable negative effects on pregnant rats or the development of fetuses and newborns.⁶² Presumably, these FOS results are applicable to all inulin-type prebiotics.

Potential Gastrointestinal Side Effects

The primary side effects of inulin-type prebiotics are gastrointestinal and can include osmotic diarrhea, abdominal rumbling, bloating, cramping, and excessive flatulence. These side effects are similar to the effects produced by lactose in people with lactose maldigestion.

Because of the configuration of the bond between fructose monomers (as described in part 1), inulin-type prebiotics are not broken down by intestinal enzymes, which is the probable cause of osmotic diarrhea. Although daily doses of 40-50 g can cause an osmotic effect, doses greater than 50 g would be expected to produce osmotic diarrhea in a large percent of the population.⁶³ While osmotic diarrhea is typically expected only with high doses, in one study abdominal distension was reported at daily doses of 10.6 g FOS.²¹

Although doses greater than 40 g/day are generally necessary to produce abdominal rumbling and bloating, and doses greater than 50 g/day to cause abdominal cramping,⁶³ bloating has been reported with daily doses as low as 2.5-5 g⁶⁴ and abdominal pain has been reported at doses as low as 10 g daily.³⁸

Review Article

Excessive flatulence is the most well-established side effect and can occur at daily doses as low as 1-2 g in sensitive individuals.^{63,64}

As noted in part 1, Rumessen and Gudmand-Hoyer concluded, after comparing the response to inulin-type prebiotics of different chain lengths, that chain length influences abdominal side effects; shorter-chain inulin-type prebiotics produce more abdominal side effects than longer-chain ones.⁶⁵ Other researchers suggest a similar correlation, with chain length influencing adverse responses.^{23,32,66-68}

Based on these observations, gastrointestinal tolerance to inulin-type prebiotics would be expected to decrease (and side effects increase) when FOS or oligofructose – both of which contain exclusively short-chain inulin polymers – are used as opposed to when inulin (a mix of short- and long-chain inulins) is supplemented. In theory, inulin HP – consisting entirely of long-chain inulin polymers – would be the best tolerated inulin-type prebiotic.

This differential response, in terms of gastrointestinal side effects, is theorized to be due to shorter-chain inulin polymers being metabolized primarily in the proximal colon; whereas, longer-chain polymers reach the distal colon before being fermented. The result is shorter-chain polymers are more rapidly fermented than longer-chain polymers, and thus seem to be more poorly tolerated.

Inulin-type prebiotics contain free sugars (fructose, glucose, and sucrose) unless removed by additional processing. The potential contribution of free sugar content of inulin-type prebiotics to the incidence of abdominal side effects has not been explored.

Dosing Prebiotics

For the promotion of healthy bacterial flora, the usual recommendation for supplementation of inulin-type prebiotics is a daily dose of 2.5-10 g. As detailed in part 1, 2.5-5 g daily is the low end for bifidogenic effects, which are typically dose-dependent. Bouhnik et al reported the optimal FOS dose for producing a bifidogenic effect, while remaining relatively well tolerated, is 10 g FOS daily.⁶⁹

In studies of inulin-type prebiotics, two supplementation approaches have been used to minimize gastrointestinal side effects: dose in two or more divided doses and start with a lower dose and increase after a

week or more of supplementation. One or both strategies were used in many of the studies and are potential approaches for lessening the likelihood of side effects.

In subjects who complain of side effects, several options exist. One option is to reduce the dose. A second option is to switch to a product consisting of either a lower percent of short-chain polymers or entirely of long-chain polymers (i.e., inulin or inulin HP instead of FOS or oligofructose).

In patients who complain of abdominal side effects it would be useful to inquire whether they are consuming foods or beverages that have added inulin-type prebiotics as ingredients. Since abdominal side effects tend to be dose dependent, dietary sources would be expected to contribute in an additive way to those prescribed as a supplement.

Conclusions

For infant nutritional applications, the majority of clinical evidence has been obtained from a combination of inulin HP and GOS. This specific mixture has been added to formulas for term and preterm infants.

For non-infant nutrition applications, inulin-type prebiotics have been investigated for a range of clinical uses, with the majority falling into four categories:

- Blood sugar regulation
- Blood lipids
- Gastrointestinal health
- Mineral absorption and biomarkers of bone health

A variety of studies have assessed biomarkers of blood sugar regulation in normo- and hyperglycemic subjects. To date, no form of inulin-type prebiotic has shown a consistent beneficial effect.

Lipids have been investigated in a variety of studies. In persons with normal lipid levels, the most consistent observation is inulin-type prebiotics have no statistically significant effect on lipid levels. In individuals with elevated lipids the results have been mixed, although the preponderance of studies report no benefit from supplementation. Positive results were reported in one trial of inulin. While definitive conclusions should wait for further research clarification, current evidence suggests that inulin, but not FOS or oligofructose, might positively influence lipids in hyperlipidemic individuals.

Because of a bifidogenic effect, the uses of inulin-type prebiotics for improvement of gastrointestinal function and as a potential therapy in gastrointestinal clinical conditions have been investigated. Several studies have investigated bowel transit time, stool consistency, and stool frequency. Existing evidence supports an effect in infants but not in adults without pre-existing functional problems. In subjects with existing constipation, one uncontrolled trial found supplementation with inulin improved stool frequency. In infants, inulin-type prebiotics as a stand-alone intervention do not appear to prevent diarrhea. Three studies report some degree of functional change subsequent to supplementation in persons with active inflammatory bowel disease. These studies were mixed with respect to the active intervention reducing disease activity compared to placebo. No trials have been conducted to determine whether chronic supplementation might help prevent disease recurrence or sustain periods of clinical remission. The two studies on IBS also had mixed findings.

Mineral absorption and biomarkers of bone health have received a significant degree of research attention. Current evidence suggests inulin-type prebiotics do not have a significant impact on absorption of iron, selenium, and zinc, but might have a positive effect on copper and magnesium in some population subsets.

There appears to be significant individual variability in response to inulin-type prebiotics and effects on calcium absorption. Adolescents and perimenopausal women have responded positively more consistently than young adults. However, even in these population subsets, some individuals respond better than others. Baseline calcium absorption and possibly genetics appear to influence response. The best choice for prebiotic supplementation to positively impact calcium absorption and bone health biomarkers appears to be oligo-fructose-enriched inulin HP, which has produced the most consistent results.

Based on available research, it appears inulin HP is the best prebiotic to reduce the likelihood of gastrointestinal side effects. FOS and oligofructose are considered the forms most likely to produce side effects.

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