



NUTRITION / DETOXIFICATION

Why You Should Care About Prebiotics (Pt. 2)

Peter Swann, MD, FAAFP, FACOEM

In my last article [[January 2017](#)], I discussed the concept of prebiotics (also known as *microfood*, as a way to avoid the consumer confusion that can occur between the terms *probiotic* and *prebiotic*) and began exploring the literature supporting the health benefits of prebiotic soluble fiber. Let's continue that conversation in this article by outlining some additional benefits.

Improvement in GERD Symptoms

Our understanding of how [gastro-esophageal reflux disorder](#) (GERD) develops has evolved. Along with esophageal exposure to gastric acid, other factors involved in the pathophysiology include dysfunction of the lower esophageal sphincter (LES)¹ and variables that increase intragastric pressure, such as gastric dysmotility,² hiatal hernia³ and body habitus.⁴

It is increasingly recognized that bacteria also play a role in the pathogenesis of GERD. Throughout the gastrointestinal tract, there is a mucosal barrier that defends the local epithelium against ambient aggressive factors. The nature of this barrier is, in part, a product of the local microbiome.⁵ Nearly 100 commensal species of bacteria reside in the distal esophagus.⁶

A contemporary proposed pathophysiology for GERD involves alteration of the microbiome local to the distal esophagus and LES. Factors contributing to this alteration may include inappropriate diet, antibiotics, infection, toxins, etc. Once disrupted, the advantageous symbiotic relationship of the local microbiome becomes a pathogenic one. This dysbiotic state has been grossly characterized as a change in the esophageal microbiome from predominantly gram-positive to predominantly gram-negative organisms.⁷



This change alters the nature of the bacterial biofilm,⁸ altering, among other things, permeability. This, in turn, can negatively affect the maintenance of a robust mucosal barrier, exposing the esophageal epithelium to pathogenic bacteria, gastric refluxate, and bacterially produced toxins.

Endotoxins, including lipopolysaccharides (LPS), are located on the outer membrane of gram-negative microorganisms. LPS are known to upregulate gene expression of proinflammatory cytokines.⁹ These LPS are also capable of triggering relaxation of the LES,¹⁰ which decreases resistance to gastric pressure and can lead to delayed gastric emptying.¹¹ These changes in motility promote acid-induced injury to the LES, which has been shown in animals to further decrease LES pressure.¹²

The action of a prebiotic soluble fiber may be twofold. First, the proliferation of bacterial cells should be increased, leading to a higher ratio of species producing exopolysaccharides (EPS).¹³ These EPS are responsible for the creation of biofilm,¹⁴ which can contribute to the defensive mucosal barrier.

Second, once established in a biofilm, the presence of certain gram-positive species, such as *L. salivarius*, *L. gasseri*, or *Lactococcus (Lc) lactis*, known to metabolize MIMO, coincides with the production of antibacterial peptides known as bacteriocins.¹⁵⁻¹⁷ These bacteriocins curate the attendant species by selectively killing competing species, restoring the distal esophageal microbiome to a healthier state. This results in improvement of GERD symptoms.

This is significantly different from studies on plant-derived soluble fiber such as fructooligosaccharides (FOS), which has been shown to increase GERD symptoms.¹⁸

Improvement in Mineral Absorption & Bone Density

When prebiotic soluble fiber arrives in the colon, it is fermented by certain bacteria, which then produce short-chain fatty acids (SCFA),¹⁹⁻²⁰ lowering the colonic luminal pH. This, in turn, improves calcium and magnesium speciation and solubility so that passive diffusion is improved.²¹⁻²⁴

Additionally, SCFA and other organic acids produced via bacterial fermentation enhance calcium absorption via both cation exchange²⁵ and active calcium transport.²⁶⁻²⁷ Finally, ingestion of prebiotic soluble fiber leads to colon-wall cell growth and functional enhancement of absorptive area,²⁸ further increasing calcium, magnesium and other mineral absorption.

In clinical trials of prebiotic soluble fiber supplementation in infants, magnesium and iron absorption and retention were increased.²⁹ In adolescents, calcium absorption increased by 10 percent in boys³⁰ and 30 percent in girls.³¹ A one-year longitudinal clinical trial in adolescent boys and girls showed significantly increased calcium absorption and improved bone density.³²

In adults, a 28-day clinical trial of prebiotic soluble fiber supplementation demonstrated significantly improved calcium balance,³³ while postmenopausal women supplemented for five weeks experienced a significant increase in calcium absorption,³⁴ magnesium absorption or both.³⁵⁻³⁶ Other studies in postmenopausal women have shown similar results.³⁷⁻⁴⁰

Improved Weight Management, Decreased Appetite

Numerous animal studies on [soluble fiber](#) supplementation have shown decreases in fat mass in animal models, with and without changes in body weight, affecting all types of adipose tissue, and often accompanied by *ad libitum* decrease in food / energy intake⁴¹⁻⁴⁷ which, if sustained in humans, would produce up to a three-fourth-pound weight loss per week.⁴⁸ Decreases in fat mass as shown in these studies, with or without weight loss, would be beneficial from a health perspective.

The mechanism for these effects is believed to be microbiome-induced changes in the activity of intestinal endocrine cells that secrete peptides involved in the regulation of energy homeostasis, such as ghrelin, glucagon-like peptide (GLP-1) and peptide YY (PYY).⁴⁹⁻⁵²

For instance, several studies in rats and mice fed prebiotic soluble fiber have shown reductions in food intake, body weight and fat mass, associated with a significant increase in portal peptides that stimulate satiety (GLP-1 and PYY), and a decrease in a hunger-inducing peptide (ghrelin).⁵³⁻⁵⁸

In healthy-human trials, supplementation with soluble fiber has been shown to promote satiety, reduce hunger and decrease food intake, leading to 10 percent lower total energy intake.⁵⁹ Based on a 2,000 kcal/day diet, that would equate to about 0.5 lb./week of fat loss.

Additionally, it has been shown that fermentation of soluble fiber by gut bacteria is associated with lower energy intake, correlated with an increase in plasma peptides GLP-1⁶⁰ and PYY, which stimulate satiety.⁶¹ Similarly, studies in obese subjects show a decrease in food intake, body weight gain and fat mass development, correlated with a decrease in hunger peptide ghrelin following a meal.⁶²

Improved Glucose and Lipid Homeostasis

In studies with diabetic rats, soluble fiber supplementation improved glucose homeostasis with improvement in insulin secretion or insulin sensitivity,⁶³⁻⁶⁶ and in obese rats, improved hepatic insulin sensitivity and plasma insulin.⁶⁷ Studies in humans have shown decreased hepatic glucose production⁶⁸ and increased GLP-1 production, with a slower rise in blood glucose after a meal.⁶⁹

As for lipids, soluble fiber supplementation in rats, hamsters or mice has led to decreased serum lipids, including cholesterol and/or triglycerides.⁷⁰⁻⁷⁵ The mechanism for these results is believed to be decreased glycaemia, a driver of lipogenesis, or the effect of SCFA produced by colonic fermentation, lowering hepatic lipid synthesis.⁷⁶⁻⁷⁷ Modulation of intestinal metabolism of bile acids may also play a role, independent of fermentation.⁷⁸⁻⁷⁹ Similarly, in humans, prebiotic soluble fiber supplementation may result in decreased hepatic lipid production.⁸⁰

That completes our walk through the scientific literature on prebiotic soluble fiber. Given the voluminous literature cited above, I think it is clear how important it is to have adequate soluble fiber in the diet, either through daily consumption of both plants and fermented foods at each meal, or through a daily prebiotic soluble fiber supplement.

References

1. Dent J, Dodds WJ, Friedman RH, et al. Mechanism of gastroesophageal reflux in recumbent asymptomatic human subjects. *J Clin Invest*, 1980;Feb; 65(2):256-267.
2. Diamant NE. Pathophysiology of gastroesophageal reflux disease. GI Motility online. DOI: 10.1038/gimo21. [url=<http://www.nature.com/gimo/contents/pt1/full/gimo21.html>]http://www.nature.com/gimo/contents/pt1/full/gimo21.html[url]. Published May 16, 2006. Accessed Feb 7, 2017.
3. De Giorgi F, Palmiero M, Esposito I, et al. Pathophysiology of gastro-oesophageal reflux disease. *Acta Otorhinolaryngol Ital*, 2006;Oct;26(5):241-246.
4. Fass R, Quan SF, O'Connor GT, et al. Predictors of heartburn during sleep in a large prospective cohort study. *Chest*, 2005;May;127(5):1658-66.
5. Harris JK, Fang R, Wagner BD, et al. Esophageal microbiome in eosinophilic esophagitis. *PLoS ONE*, 2015;10(5):e0128346.
6. Yang L, Chaudhary N, Baghdadi J, Pei Z. Microbiome in reflux disorders and esophageal adenocarcinoma. *Cancer J*, 2014;20(3):207-210.
7. Yang L, Lu X, Nossa CW, et al. Inflammation and intestinal metaplasia of the distal esophagus are associated with alterations in the microbiome. *Gastroenterology*, 2009;Aug;137(2):588-97.
8. Mathias A, Corthesy B. N-Glycans on secretory component: mediators of the interaction between secretory IgA and gram-positive commensals sustaining intestinal homeostasis. *Gut Microbes*, 2011;Sep 1;2(5):287-93.
9. Yang L, Francois F, Pei Z. Molecular pathways: pathogenesis and clinical implications of

- microbiome alteration in esophagitis and Barrett's esophagus. *Clin Cancer Res*, 2012 Feb 16.
10. Fan YP, Chakder S, Rattan S. Inducible and neuronal nitric acid synthase involvement in lipopolysaccharide-induced sphincteric dysfunction. *Am J Physiol Gastrointest Liver Physiol*, 2001;Jan;280(1):G32-42.
 11. Calatayud S, Garc a-Zaragoz a E, Hern andez C, et al. Downregulation of nNOS and synthesis of PGs associated with endotoxin-induced delay in gastric emptying. *Am Journal Physiol - Gastrointestinal and Liver Physiol*, 2002;283(6): G1360-G1367.
 12. Biancani, P, Barwick, K, Selling, J, McCallum, R. Effects of acute experimental esophagitis on the lower esophageal sphincter. *Gastroenterology*,1984;Jul;87:8-16.
 13. Salazar N, Prieto A, Leal JA, et al. Production of exopolysaccharides by *Lactobacillus* and *Bifidobacterium* strains of human origin, and metabolic activity of the producing bacteria in milk. *J Dairy Sci*, 2009;92(9):4158-4168.
 14. Slizova M, Nemcova R, Madar M, et al. Analysis of biofilm formation by intestinal lactobacilli. *Can J Microbiol*, 2015;Jun;61(6):437-46.
 15. Messaoudi S, Manai M, Kergourlay G, et al. *Lactobacillus salivarius*: bacteriocin and probiotic activity. *Food Microbiol*, 2013;36(2):296-304.
 16. Pandey N, Malik RK, Kaushik JK, Singroha G. Gassericin A: a circular bacteriocin produced by lactic acid bacteria *Lactobacillus gasseri*. *World J Microbiol Biotechnol*, 2013;29(11):1977-1987.
 17. Alegria A, Delgado S, Roces C, et al. Bacteriocins produced by wild *Lactococcus lactis* strains isolated from traditional starter-free cheeses made of raw milk. *Int J Food Microbiol*, 2010;143(1-2):61-66.
 18. Piche T, et al. Colonic fermentation influences lower esophageal sphincter function in gastroesophageal reflux disease. *Gastroenterology*, 2003 April;124(4):894-902.
 19. Roberfroid M. Dietary fiber, inulin, and oligofructose: a review comparing their physiological effects. *Critical Reviews in Food Science and Nutrition*, 1993 Jan;33(2):103-48.
 20. Roberfroid MB. Prebiotics and synbiotics: concepts and nutritional properties. *British J Nutrition*, 1998 Oct;80(4):S197-202.
 21. R m syc C, et al. Cecal fermentations in rats fed oligosaccharides (inulin) are modulated by dietary calcium level. *American J Physiology*, 1993;264(5, Pt 1):G855-62.
 22. Ohta A, et al. Calcium and magnesium absorption from the colon and rectum are increased in rats fed fructooligosaccharides. *J Nutrition*, 1995 Sep;125(9):2417-24.
 23. Lopez HW, et al. Fructooligosaccharides enhance mineral apparent absorption and counteract the deleterious effects of phytic acid on mineral homeostasis in rats. *J Nutritional Biochemistry*, 2000 Oct;11(10):500-508.
 24. Heijnen AM, et al. Ileal pH and apparent absorption of magnesium in rats fed on diets containing either lactose or lactulose. *British J Nutrition*, 1993 Nov;70(3):747-56.
 25. Lutz T, et al. Effect of short-chain fatty acids on calcium absorption by the rat colon. *Experimental Physiology*, 1991 July;76(4):615-18.
 26. Ohta A, et al. Dietary fructooligosaccharides increase calcium absorption and levels of mucosal calbindin-D9k in the large intestine of gastrectomized rats. *Scandinavian J Gastroenterology*, 1998 Oct;33(10):1062-68.
 27. Takasaki M, et al. Dietary short-chain fructooligosaccharides increase calbindin-D9k levels only in the large intestine in rats independent of dietary calcium deficiency or serum 1,25 dihydroxy vitamin D levels. *Int J Vitamin Nutrition Research*, 2000 Sept;70(5):206-13.
 28. Raschka L, Daniel H. Mechanisms underlying the effects of inulin-type fructans on calcium absorption in the large intestine of rats. *Bone*, 2005 Nov;37(5):728-35.
 29. Yap KW, et al. Dose-response effects of inulin on the faecal short-chain fatty acids content and mineral absorption of formula-fed infants. *Nutrition & Food Science*, 2005 Aug;35(4):208-19.
 30. van den Heuvel EG, et al. Oligofructose stimulates calcium absorption in adolescents. *American J Clinical Nutrition*, 1999 March;69(3):544-48.

31. Griffin IJ, Davila PM, Abrams SA. Non-digestible oligosaccharides and calcium absorption in girls with adequate calcium intakes. *British J Nutrition*, 2002 May;87(Suppl 2):S187-91.
32. Cashman KD. A prebiotic substance persistently enhances intestinal calcium absorption and increases bone mineralization in young adolescents. *Nutrition Reviews*, 2006 April;64(4):189-96.
33. Coudray C, et al. Effect of soluble or partly soluble dietary fibres supplementation on absorption and balance of calcium, magnesium, iron and zinc in healthy young men. *European J Clinical Nutrition*, 1997 June;51(6):375-80.
34. Ducros V, et al. Influence of Short-chain fructo-oligosaccharides (Sc-FOS) on absorption of Cu, Zn, and Se in healthy postmenopausal women. *J American College of Nutrition*, 2005 Feb;24(1):30-37.
35. Tahiri M, et al. Five-week intake of short-chain fructo-oligosaccharides increases intestinal absorption and status of magnesium in postmenopausal women. *J Bone and Mineral Research*, 2001 Nov;16(11):2152-60.
36. Tahiri M, et al. Effect of short-chain fructooligosaccharides on intestinal calcium absorption and calcium status in postmenopausal women: a stable-isotope study. *American J Clinical Nutrition*, 2003 Feb;77(2):449-57.
37. van den Heuvel EG, et al. Lactulose stimulates calcium absorption in postmenopausal women. *J Bone and Mineral Research*, 1999 July;14(7):1211-16.
38. van den Heuvel EG, Schoterman MH, Muijs T. Transgalactooligosaccharides stimulate calcium absorption in postmenopausal women. *J Nutrition*, 2000 Dec;130(12):2938-42.
39. Adolphi B, et al. Short-term effect of bedtime consumption of fermented milk supplemented with calcium, inulin-type fructans and caseinphosphopeptides on bone metabolism in healthy, postmenopausal women. *European J Nutrition*, 2009 Feb;48(1):45-53.
40. Holloway L, et al. Effects of oligofructose-enriched inulin on intestinal absorption of calcium and magnesium and bone turnover markers in postmenopausal women. *British J Nutrition*, 2007 Feb;97(2):365.
41. Daubioul CA, Taper HS, De Wispelaere LD, et al. Dietary oligofructose lessens hepatic steatosis, but does not prevent hypertriglyceridemia in obese Zucker rats. *J Nutr*, 2000;130:1314-1319.
42. Daubioul C, Rousseau N, Demeure R, et al. Dietary fructans, but not cellulose, decrease triglyceride accumulation in the liver of obese Zucker fa/fa rats. *J Nutr*, 2002;132:967-973.
43. Cani PD, Neyrinck AM, Maton N, et al. Oligofructose promotes satiety in rats fed a high-fat diet: involvement of glucagon-like peptide-1. *Obes Res*, 2005;13:1000-1007.
44. Cani PD, Knauf C, Iglesias MA, et al. Improvement of glucose tolerance and hepatic insulin sensitivity by oligofructose requires a functional glucagon-like peptide 1 receptor. *Diabetes*, 2006;55:1484-1490.
45. Cani PD, Hoste S, Guiot Y, et al. Dietary non-digestible carbohydrates promote L-cell differentiation in the proximal colon of rats. *Br J Nutr*, 2007;98:32-37.
46. Cani PD, Possemiers S, van de WT, et al. Changes in gut microbiota control inflammation in obese mice through a mechanism involving GLP-2-driven improvement of gut permeability. *Gut*, 2009;58:1091-1103.
47. Urias-Silvas JE, Cani PD, Delmee E, et al. Physiological effects of dietary fructans extracted from Agave tequilana Gto. and Dasyliirion spp. *Br J Nutr*, 2008;99:254-261.
48. Mayo Clinic Staff. "Counting Calories: Get back to Weight-Loss Basics," 2015: www.mayoclinic.org/healthy-lifestyle/weight-loss/in-depth/calories/art-20048065.
49. Chaudhri OB, Salem V, Murphy KG, et al. Gastrointestinal satiety signals. *Annu Rev Physiol*, 2008;70:239-255.
50. Druce MR, Small CJ, Bloom SR. Minireview: gut peptides regulating satiety. *Endocrinology*, 2004;145:2660-2665.
51. Wynne K, Stanley S, McGowan B, et al. Appetite control. *J Endocrinol*, 2005;184:291-318.
52. Knauf C, Cani PD, Perrin C, et al. Brain glucagon-like peptide-1 increases insulin secretion

- and muscle insulin resistance to favor hepatic glycogen storage. *J Clin Invest*, 2005;115:3554-3563.
53. Cani PD, Dewever C & Delzenne NM. Inulin-type fructans modulate gastrointestinal peptides involved in appetite regulation (glucagon-like peptide-1 and ghrelin) in rats. *Br J Nutr*, 2004;92:521-526.
 54. Delzenne NM, Cani PD, Daubioul C, et al. Impact of inulin and oligofructose on gastrointestinal peptides. *Br J Nutr*, 2005;93(Suppl. 1):S157-S161.
 55. Urias-Silvas JE, Cani PD, Delmee E, et al. Physiological effects of dietary fructans extracted from *Agave tequilana* Gto. and *Dasyliroton* spp. *Br J Nutr*, 2008;99:254-261.
 56. Cani PD, Knauf C, Iglesias MA, et al. Improvement of glucose tolerance and hepatic insulin sensitivity by oligofructose requires a functional glucagon-like peptide 1 receptor. *Diabetes*, 2006; 55:1484-1490.
 57. Reimer RA, Russell JC. Glucose tolerance, lipids, and GLP-1 secretion in JCR:LA-cp rats fed a high protein fiber diet. *Obesity*, 2008;16:40-46.
 58. Maurer AD, Chen Q, McPherson C, et al. Changes in satiety hormones and expression of genes involved in glucose and lipid metabolism in rats weaned onto diets high in fibre or protein reflect susceptibility to increased fat mass in adulthood. *J Physiol*, 2009;587:679-691.
 59. Cani PD, Joly E, Horsmans Y, et al. Oligofructose promotes satiety in healthy human: a pilot study. *Eur J Clin Nutr*, 2006;60:567-572.
 60. Piche T, desVarannes SB, Sacher-Huvelin S, et al. Colonic fermentation influences lower esophageal sphincter function in gastroesophageal reflux disease. *Gastroenterology*, 2003;124:894-902.
 61. Cani PD, Lecourt E, Dewulf EM, et al. Gut microbiota fermentation of prebiotics increases satietogenic and incretin gut peptide production with consequences for appetite sensation and glucose response after a meal. *Am J Clin Nutr*, 2009;90:1236-1243.
 62. Parnell JA, Reimer RA. Weight loss during oligofructose supplementation is associated with decreased ghrelin and increased peptide YY in overweight and obese adults. *Am J Clin Nutr*, 2009;89:1751-1759.
 63. Cani PD, Knauf C, Iglesias MA, et al. Improvement of glucose tolerance and hepatic insulin sensitivity by oligofructose requires a functional glucagon-like peptide 1 receptor. *Diabetes*, 2006;55:1484-1490.
 64. Kok NN, Taper HS, Delzenne NM. Oligofructose modulates lipid metabolism alterations induced by a fat-rich diet in rats. *J Appl Toxicol*, 1998;18:47-53.
 65. Cani PD, Neyrinck AM, Maton N, et al. Oligofructose promotes satiety in rats fed a high-fat diet: involvement of glucagon-like peptide-1. *Obes Res*, 2005;13:1000-1007.
 66. Delmee E, Cani PD, Gual G, et al. Relation between colonic proglucagon expression and metabolic response to oligofructose in high fat diet-fed mice. *Life Sci*, 2006;79:1007-1013.
 67. Cani PD, Knauf C, Iglesias MA, et al. Improvement of glucose tolerance and hepatic insulin sensitivity by oligofructose requires a functional glucagon-like peptide 1 receptor. *Diabetes*, 2006;55:1484-1490.
 68. Luo J, Rizkalla SW, Alamowitch C, et al. Chronic consumption of short-chain fructooligosaccharides by healthy subjects decreased basal hepatic glucose production but had no effect on insulin-stimulated glucose metabolism. *Am J Clin Nutr*, 1996;63:939-945.
 69. Cani PD, Lecourt E, Dewulf EM, et al. Gut microbiota fermentation of prebiotics increases satietogenic and incretin gut peptide production with consequences for appetite sensation and glucose response after a meal. *Am J Clin Nutr*, 2009;90:1236-1243.
 70. Delzenne NM, Cani PD. Gut microflora is a key player in host energy homeostasis. *Med Sci*, 2008;24:505-510.
 71. Delzenne NM, Williams CM. Prebiotics and lipid metabolism. *Curr Opin Lipidol*, 2002;13:61-67.
 72. Levrat MA, Favier ML, Moundras C, et al. Role of dietary propionic acid and bile acid excretion

- in the hypocholesterolemic effects of oligosaccharides in rats. *J Nutr*, 1994;124:531-538.
73. Fiordaliso M, Kok N, Desager JP, et al. Dietary oligofructose lowers triglycerides, phospholipids and cholesterol in serum and very low density lipoproteins of rats. *Lipids*, 1995;30:163-167.
 74. Rault-Nania MH, Gueux E, Demougeot C, et al. Inulin attenuates atherosclerosis in apolipoprotein E-deficient mice. *Br J Nutr*, 2006;96:840-844.
 75. Fava F, Lovegrove JA, Gitau R, et al. The gut microbiota and lipid metabolism: implications for human health and coronary heart disease. *Curr Med Chem*, 2006;13:3005-3021.
 76. Morand C, Remesy C, Demigne C. Fatty acids are potent modulators of lactate utilization in isolated hepatocytes from fed rats. *Am J Physiol*, 1993;264:E816-E823.
 77. Delzenne NM, Daubioul C, Neyrinck A, et al. Inulin and oligofructose modulate lipid metabolism in animals: review of biochemical events and future prospects. *Br J Nutr*, 2002;87:S255-S259.
 78. Delzenne NM, Cani PD. Gut microflora is a key player in host energy homeostasis. *Med Sci*, 2008;24:505-510.
 79. Adam A, Levrat-Verny MA, Lopez HW, et al. Whole wheat and triticale flours with differing viscosities stimulate cecal fermentations and lower plasma and hepatic lipids in rats. *J Nutr*, 2001;131:1770-1776.
 80. Diraison F, Moulin P, Beylot M. Contribution of hepatic de novo lipogenesis and reesterification of plasma non esterified fatty acids to plasma triglyceride synthesis during non-alcoholic fatty liver disease. *Diabet Metab*, 2003;29:478-485.

JUNE 2017