Management of Obesity by Modulating the Gut Microbiota

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INTRODUCTION

Obesity, once an uncommon phenomenon, is now pandemic. The World Health Organization currently estimates 1.4 billion adults worldwide are overweight.[1] Of these, an alarming 200 million men and 300 million women are obese. Once a condition primarily affecting developed countries, obesity is increasingly prevalent in developing countries. Obesity is an inflammatory disease associated with a constellation of physiological disorders such as insulin resistance, type 2 diabetes mellitus, hypertension, dyslipidemia, cardiovascular disease, and metabolic syndrome.[2] The link between obesity and type 2 diabetes is so inextricable the term "diabesity" has been coined.[3] Once simplistically considered a disorder caused by an imbalance of energy intake (caloric consumption) vs energy expenditure (physical activity/exercise), obesity is now viewed as a complex, multifactorial disorder. One factor recently revealed to play a role in weight homeostasis and risk for obesity is the composition of the intestinal microbiota.[4,5] The bacterial residents of the intestinal tract generate an enormous amount of metabolic activity and perform such a wide variety of physiological functions they can collectively be considered an accessory organ. Observations linking dysbiosis of the intestinal microflora to caloric regulation and the pathogenesis of obesity raise the exciting potential that probiotic and prebiotic nutritional supplements can be used to promote weight loss and reduce the risk of metabolic disorders.

THE GUT MICROBIOTA & OBESITY

With its tens of trillions of microorganisms and a collective microbial genome (microbiome) 150 times the size of the human genome,[6] the gut microbiota profoundly impacts human physiology and appears to govern energy regulatory and inflammatory processes in ways that mitigate or enhance the risk of developing obesity, type 2 diabetes, and metabolic syndrome. It has long been known that the gut microbiota extracts energy from dietary substances indigestible by the host. Germ-free animals fail to gain weight normally.[7] The metabolic activities of gastrointestinal microorganisms contribute an estimated 30% of our daily caloric energy.[8] However, the metabolic activities of the gut microbiota extend far beyond normal weight gain. The finding by Washington University researchers that intestinal microorganisms transplanted from normal mice into germ-free mice not only result in weight gain, but could cause increased body fat and insulin resistance even in the setting of calorie restriction[7] signaled that the microbiota may contribute to obesity and obesity-related disorders such as type 2 diabetes and metabolic syndrome. Subsequent human studies found that the gut microbiota of obese subjects contained greater numbers of microbes in the phylum Firmicutes and fewer in the phylum Bacteroidetes than did matched lean controls.[9] Interestingly, after 52 weeks of either a carbohydrate- or fat-restricted low-calorie diet, the ratio of Firmicutes to Bacteroidetes in obese individuals approached that found in lean subjects. These results raised the question as to whether changes in the microbiota are a cause or a consequence of obesity. Animal studies show transplantation of gut microbes from genetically obese mice into germ-free mice leads to significantly greater weight gain than does microbiota transplantation from lean mice.[10] These results suggest microfloral changes play a contributory role in obesity. Other animal studies, however, have found high-fat diets produce a marked expansion of intestinal Firmicutes populations and a corresponding decrease in Bacteroidetes suggesting the altered bacterial ratios are a secondary phenomenon.[11] The likely reality is there is a complex interplay between microbiota and the diet where microfloral imbalances can both predispose to adiposity and be caused, or exacerbated, by adipogenic high-fat or high-sugar diets.

THE NATURE OF OBESITY-ASSOCIATED DYSBIOSIS

The role of diminished Bacteroidetes numbers in obesity is controversial. While some researchers confirm finding reduced gut Bacteroidetes numbers in obese humans,[10] others actually report *decreased* numbers of Bacteroidetes in obese test subjects.[12] Yet others have failed to find any association between Bacteroidetes levels and adiposity.[13,14] A difference in methodologies may explain the diversity of observations. The focus on phylum level ratios in obesity has also been contentious. Phyla are very large taxonomic designations that may not adequately reflect dysbiotic alterations in the gut microbiota. Some investigators have described high numbers of *Prevotellaceae*, a member of the phylum Bacteroidetes, in obese people.[15] Weight loss after bariatric surgery has been associated with reduced numbers of Firmicutes[15,16] and increased numbers of *Gammaproteobacteria*,[15,17] members of the *Enterobacteriaceae* family in the phylum Proteobacteria. The focus on the phyla Bacteroidetes and Firmicutes ignores the potentially important role of other microbes such as *Bifidobacterium* in the phylum Actinobacteria. Finnish investigators have found that *Bifidobacterium* numbers are much higher during infancy in children who have a normal weight in later childhood than they are in obese children.[18] Obese children were also found to have higher fecal numbers of *Staphylococcus aureus* (Firmicutes) during infancy than did lean children.[18] *S. aureus* may trigger intestinal inflammation that contributes to obesity.

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Low numbers of bifidobacteria have also been described in overweight women compared to lean women. Low gut *Bifidobacterium* populations have been associated with excessive weight gain during pregnancy[19] and are depressed in people with type 2 diabetes.[20] Studies of weight gain with pregnancy correlate high intestinal numbers of *Bacteroides* (Bacteroidetes), *Clostridium* (Firmicutes), and *Staphylococcus* with being overweight before pregnancy and excessive weight gain during pregnancy.[19] Another feature common to both obesity and pregnancy is reduced overall microbial diversity.[10,21] Weight loss following a diet and exercise program has been associated with increased levels of *Bacteroides fragilis* and total lactobacilli and decreased numbers of *Bifidobacterium longum* and *Clostridium coccoides*.[22] A subgroup of Firmicutes, the *Erysipelotrichaceae*, is significantly elevated in obese persons while another Firmicutes subgroup, the *Lachnospira*, is significantly depleted.[15] Low numbers of the species *Faecalibacterium prausnitzii* (Firmicutes) have been associated with type 2 diabetes in obesity while higher numbers are found in obese individuals without diabetes.[23] In obesity, robust populations of *F. prausnitzii* appear to correlate with lower levels of inflammatory markers. The *Lactobacillus* genus is part of the phylum Firmicutes. Lactobacilli numbers have been observed to be higher in 8 of

20 obese adolescents compared to lean controls.[24] In contrast, weight loss induced by diet and exercise has been associated with an increased population of *Lactobacillus*.[22] Furthermore, *Lactobacillus* probiotics have been among the interventions shown to be associated with weight loss and improved glucose metabolism in both animal and human studies.[25-28] While it is clear that obesity, type 2 diabetes, and metabolic syndrome are associated with gastrointestinal dysbiosis, the microbiological disturbances are complex. The published studies so far fail to demonstrate a definitive link between obesity and relative proportions of Bacteroidetes and Firmicutes in the intestinal flora. The important microbiota disturbances appear to be at the genus and species levels. These are also the levels at which probiotic and prebiotic interventions may be useful.

MECHANISMS FOR MICROBIOTA REGULATION OF WEIGHT AND METABOLIC STATUS

Several plausible mechanisms whereby the intestinal microbiota can influence weight gain or loss have been posited, including modulation of caloric extraction from foods. Certain populations of intestinal flora, such as the Firmicutes, have been found to possess a greater array of genes encoding for enzymes involved in the degradation of digestion-resistant dietary polysaccharides.[4] By increasing the energy harvest from otherwise indigestible foods, some microfloral organisms could conceivably contribute to weight gain. Despite an association between Firmicutes levels and obesity in animals, human studies do not provide compelling evidence of a link between particular bacterial phyla and weight or metabolic status. Studies of mono- and dizygotic twins reveal that core microbiome characteristics are shared within families and that expression of obesity-related genes can exist across a diversity of organismal assemblages.[29] Obese phenotypic traits in humans thus appear more related to gene-level, functional characteristics of the microflora than to any identifiable taxonomic profile.[29,30]

Another means by which probiotic organisms may influence body weight involves production of the bioactive fatty acid, conjugated linoleic acid (CLA). CLA is an umbrella term for a family of linoleic acid (LA) isomers containing conjugated double bonds. The most bioactive CLA isomers, *cis*-9, *trans*-11, *trans*-10, and *cis*-12, have been associated with a number of health-promoting effects including favorable modulation of blood pressure, serum lipids, immune activity, inflammation, cell proliferation, bone formation, and body composition.[31] Nutritional supplementation with CLA has been shown to reduce adiposity in both animal and human experiments.[32-34] Mechanisms postulated for the antiobesity effects of CLA include regulation of energy expenditure, adipocyte proliferation, fatty acid oxidation, lipogenesis, and lipolysis.[35,36]

One of the likeliest mechanisms by which bifidobacteria and lactobacilli exert a regulatory effect on weight gain is by modulating inflammatory processes.

Various probiotic organisms, including lactobacilli and bifidobacteria, are capable of synthesizing CLA.[25,37,38] Administration of *Bifidobacterium breve* and LA to mice increases levels of *cis*-9, *trans*-11 CLA in the large intestine and liver by a factor of two compared to feeding of LA alone.[39] Likewise, strains of *Lactobacillus rhamnosus* fed to mice increase levels of both *cis*-9, *trans*-11 and *trans*-10, *cis*-12 CLA in the serum.[37] One small human study found administration of one trillion colony forming units (CFU) per day of *L. rhamnosus* to four healthy individuals increased serum levels of *cis*-9, *trans*-11 and *trans*-10, *cis*-12 CLA in 3 of the 4 and 4 of the 4 subjects, respectively.[40] Elevation of probiotic-derived CLA has been associated with marked antiobesity effects in animals. Mice fed high-fat diets along with CLA-producing probiotics gain significantly less weight compared to mice fed high-fat diets alone.[25,37] The CLA produced by probiotics has also been shown to significantly blunt increases in blood glucose resulting from high-caloric intake and weight gain.[25,37] These preliminary data suggest CLA production may be an important means whereby probiotics can promote weight loss and mitigate the adverse metabolic effects of obesity.

One of the likeliest mechanisms by which bifidobacteria and lactobacilli exert a regulatory effect on weight gain is by modulating inflammatory processes. Obesity and common comorbidities such as diabetes, dyslipidemia, hypertension, and cardiovascular disease are associated with chronic, low-grade inflammation.[41-44] High-fat feeding in mice sufficiently elevates plasma levels of the proinflammatory lipopolysaccharide (LPS) to induce significant body weight gain.[45] Endogenous LPS derives primarily from the cell walls of Gram-negative bacteria. Translocation of LPS from the gut lumen into the body triggers production of inflammatory cytokines, chemokines, enzymes, eicosanoids, adhesion agents, and free radicals.[46] Bifidobacteria and lactobacilli improve gut barrier function, directly bind LPS in the gut lumen, and reduce levels of Gram-negative organisms in the intestinal tract through competitive exclusion, secretion of bacteriocins, and inhibition of bacterial adhesion.[47] Prebiotics show potential benefit in weight loss and mitigation of metabolic syndrome primarily by increasing gut *Bifidobacterium* populations. Animal studies indicate supplemental bifidobacteria and lactobacilli significantly diminish both intestinal and plasma levels of LPS.[48,49] In one study, rats subjected to hemorrhagic shock were pretreated with either oral bifidobacteria or a saline solution. Postmortem analysis revealed plasma LPS levels were significantly lower in the bifidobacteria-treated group.[49] LPS-lowering effects in experimental models have also been noted for *Lactobacillus* organisms such as *L. rhamnosus*.[50] Additional human research has confirmed a link between LPS-induced endotoxemia and impaired glycemic control. In healthy human volunteers, the rise in plasma LPS following injection of LPS produces significant elevations in plasma and adipose markers for inflammatory cytokines and adipokines as well as a significant increase in insulin resistance.[51] While definitive conclusions cannot yet be reached, these data suggest manipulations of the intestinal microbiota favoring growth of *Bifidobacterium* and *Lactobacillus* downregulates LPS-mediated inflammation that contributes to the development of obesity and metabolic syndrome.

PREBIOTIC & PROBIOTIC SUPPORT FOR OBESITY

The emerging link between LPS-induced inflammation and both obesity and diabetes suggests manipulation of the intestinal microbiota to minimize LPS endotoxin exposure may be a rational approach to managing weight and metabolic disease. Healthy modification of the intestinal microflora can be achieved by improving diet and/or administering probiotic and prebiotic supplements. Probiotics are living microorganisms that confer health benefits when consumed.[52] Prebiotics are nutritive materials that selectively support the growth and activity of beneficial microorganisms in the intestinal tract. Prebiotic properties have been best documented for digestion-resistant oligosaccharides such as inulin-type fructans and galactooligosaccharides.[53,54] Feeding inulin-type fructans to genetically obese mice significantly elevates cecal levels of bifidobacteria and lactobacilli while reducing intestinal permeability, plasma levels of LPS, inflammatory mediators, and fat deposition in visceral, epididymal, and subcutaneous adipose tissues.[55] Rats administered a standard diet enriched with 10% oligofructose for four weeks lose significantly more weight than rats fed the same diet without oligofructose.[56] There are few human intervention trials involving weight maintenance and prebiotics. In one study of adolescent males, intake of 8 g/day of inulin-type fructans was associated with less weight gain and reduced total fat mass, especially in subjects who maintained adequate calcium intake.[57] In another study, obese, dyslipidemic, premenopausal women were given daily doses of a syrup containing 0.14 g/kg of inulin-type fructans which led to a reduction in weight, body mass index (BMI), fasting insulin levels, and LDL-cholesterol.[58] In perhaps the only blinded, randomized, controlled clinical trial examining the effects of prebiotics on weight loss,

21 g/day of oligofructose or an equicaloric control was administered to obese and overweight individuals with a BMI > 25 kg/m2. After 12 weeks, persons in the oligofructose group lost approximately 1 kg of body weight, most of it fat mass from the trunk region, while slight increases in body weight and fat mass were recorded for the placebo group. Additionally, beneficial changes were observed in levels of the satiety hormones peptide-YY (+13% increase) and ghrelin (-23% decrease).[59] Preclinical and clinical data also support the use of probiotics for weight management. Rats fed high-cholesterol diets along with the probiotic *Lactobacillus plantarum* experience significantly reduced gains in total body, liver, and fat pad weight.[60] Similar reductions in body weight gain are observed in rats administered high-fat diets along with *Bifidobacterium* organisms compared to rats fed high-fat diets alone.[61] In humans, researchers have found persons administered approximately 2 billion CFU/day of *Lactobacillus acidophilus* lose significantly more weight following Roux-en-Y gastric bypass surgery than do control subjects.[28] Women who receive dietary counseling plus *L. rhamnosus* and *Bifidobacterium lactis* during their first trimester of pregnancy are significantly less likely to develop central adiposity at six months postpartum than are women who receive dietary counseling alone.[62] *L. rhamnosus* and *B. lactis* supplementation in pregnant women has also been shown to significantly reduce the risk of developing gestational diabetes.[63] In a blinded, randomized trial examining the effects of pre- and postnatal intervention with a probiotic supplement on the risk of overweight in children, 10 billion CFU/day of *L. rhamnosus* or placebo was given to pregnant women four weeks prior to delivery and, after delivery, for an additional six months to either breastfeeding mothers or to infants who were bottle-feeding. The results, although falling shy of statistical significance, revealed a clear trend towards reduced weight gain in the probiotic group at four years of age.[64] And a randomized, double-blind, placebo-controlled study involving overweight adults evaluated the anti-obesity effects of the probiotic *Lactobacillus gasseri*. A fermented milk beverage with or without 100 billion CFU/day of *L. gasseri* was administered to 87 obese men and women. After 12 weeks, participants in the *L. gasseri* group experienced significant reductions in BMI, waist-to-hip ratio, total body fat mass, and abdominal visceral fat area compared to control subjects who experienced mild to moderate increases in each of these variables.[65]

PREBIOTIC AND PROBIOTIC SUPPORT FOR METABOLIC SYNDROME

Significant preclinical and clinical research shows prebiotics and probiotics can favorably influence blood glucose regulation and insulin function. Prebiotic modulation of satiety hormones may curb excess caloric intake. One hormone in particular, glucagon-like peptide 1 (GLP-1) influences not only satiety, but insulin function, and is believed to play an important role in prebiotic-mediated glucose regulation.[66] GLP-1 is secreted by intestinal L cells in response to food ingestion and stimulates insulin release and pancreatic β-cell proliferation. In a mouse model of diabetes, inulin-type fructans significantly improved glycemic control. This effect depended on proper functioning of GLP-1. In GLP-1 receptor knockout mice or mice treated with a GLP-1 receptor antagonist, the antihyperglycemic effect of inulin-type fructans was abolished. Inulin-type fructans increase intestinal and blood levels of GLP-1.[67] In humans, prebiotics have been shown to exert a regulatory effect on glucose and insulin levels. Inulin-type fructans significantly reduce postprandial glycemic response. In humans, the antihyperglycemic effect of inulin-type fructans occurs in the absence of changes in plasma GLP-1 levels, perhaps reflecting differences in study methodologies or differing mechanisms of glycemic control in mice vs. humans. In a trial involving healthy, middle-aged people, 10 grams/d of inulin significantly decreased plasma insulin concentrations.[68] In another study, 8 g/day of inulin-type fructans administered to type 2 diabetic subjects significantly lower blood glucose levels after four weeks.[69] However, another study failed to find any effects on plasma glucose or insulin levels in type 2 diabetics after four weeks of supplementation with 20 g/day of fructooligosaccharides.[70] This last result notwithstanding, most of the available evidence suggests a beneficial effect of prebiotics on insulin function and glucose homeostasis.

Clinical data thus support the use of probiotic and prebiotic supplements for maintaining healthy body weight and optimizing glycemic control.

Supplemental *Lactobacillus casei* in a mouse model of type 2 diabetes reduces plasma levels of glucose, insulin, and inflammatory cytokines.[71] *L. rhamnosus* GG supplementation in streptozotocin-induced diabetic rats significantly improved glucose tolerance and lowered HbA1C levels.[72] In humans with type 2 diabetes, administration of a yogurt containing *L. acidophilus* and *B. lactis* for six weeks beneficially modified blood lipids such that total cholesterol:HDL-C and LDL-C:HDL-C ratios were significantly reduced.[73] In a randomized, prospective study involving pregnant women at higher risk for developing blood glucose dysregulation, women receiving dietary advice plus 10 billion CFU/day of the probiotics *L. rhamnosus* and *B. lactis* experienced significantly lower blood glucose levels during pregnancy and over a 12-month postpartum period. At the third trimester, when insulin resistance is typically highest, there was greater insulin sensitivity in the probiotic/diet group compared to the control group.[74]

CONCLUSION

Mounting evidence indicates the intestinal microbiota contributes to the regulation of energy homeostasis, body weight, and glycemic control. Microbiotal organisms play an important role in extracting energy from the diet, producing bioactive substances that influence carbohydrate and lipid metabolism, and modulating both intestinal and systemic inflammatory processes. Efforts to link obese and lean phenotypes with particular microbial profiles have yielded conflicting data, but recent studies suggest weight gain and obesity are associated with reduced microfloral diversity and diminished populations of lactobacilli and bifidobacteria. These two probiotic genera antagonize enteric Gram-negative bacteria and thus help reduce intestinal and systemic levels of proinflammatory LPS. LPS-induced inflammation has been posited as a contributory factor to obesity, blood glucose dysregulation, and possibly other metabolic disorders. Attenuation of LPS levels appears to be one of the principal mechanisms by which probiotics favorably impact body weight and glycemic control. Clinical studies confirm *Lactobacillus* and *Bifidobacterium* probiotics are effective weight management tools. Prebiotics are nutritional supplements that support the growth of lactobacilli and bifidobacteria within the intestinal tract and thus augment the benefits of probiotics. Prebiotics also exert an inhibitory effect on appetite by modulating satiety hormones and have been shown to facilitate weight loss and improve glucose regulation in overweight and diabetic subjects. Clinical data thus support the use of probiotic and prebiotic supplements for maintaining healthy body weight and optimizing glycemic control. Future research should help clarify the links between the microbiota and metabolic dysregulation and provide further insights into how manipulation of the microflora may help stem the twin epidemics of obesity and diabetes.

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