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Cindy D. Davis, PhD, is director of grants and extramural activities at the Office of Dietary Supplements, National Institutes of Health, Bethesda, Maryland.

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Correspondence: Cindy D. Davis, PhD, Office of Dietary Supplements, National Institutes of Health, 6100 Executive Blvd, Ste 3801, Bethesda, MD 20892-75173 (davisci@mail.nih.gov).

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The Gut Microbiome and Its Role in Obesity

Cindy D. Davis, PhD

The human body is host to a vast number of microbes, including bacterial, fungal, and protozoal microorganisms, which together constitute our microbiota. Evidence is emerging that the intestinal microbiome is intrinsically linked with overall health, including obesity risk. Obesity and obesity-related metabolic disorders are characterized by specific alterations in the composition and function of the human gut microbiome. Mechanistic studies have indicated that the gastrointestinal microbiota can influence both sides of the energy balance equation, namely, as a factor influencing energy utilization from the diet and as a factor that influences host genes that regulate energy expenditure and storage. Moreover, its composition is not fixed and can be influenced by several dietary components. This fact raises the attractive possibility that manipulating the gut microbiota could facilitate weight loss or prevent obesity in humans. Emerging as possible strategies for obesity prevention and/or treatment are targeting the microbiota to restore or modulate its composition through the consumption of live bacteria (probiotics), nondigestible or limited digestible food constituents such as oligosaccharides (prebiotics), or both (synbiotics) or even fecal transplants. Nutrition Today. 2016;51(4):167–174

For the analyses of gut microbiota composition, several different techniques have been used. Traditional techniques included the isolation and culturing of microorganisms in different growth media. However, most of the bacteria in the colon are anaerobic and cannot be cultured under aerobic conditions, so only approximately 30% of the gut bacteria can be analyzed this way. More recently, culture-independent DNA-based methods have allowed for a more extensive characterization of the gastrointestinal microbiota. Deoxyribonucleic acid–based microbiome studies usually fall into 1 of 2 categories. Targeted studies, which focus on 1 or a few marker genes, use these markers to identify the composition and diversity of the microbiota. Targeted studies are frequently based on the analysis of 16S ribosomal RNA, which is a part of the small subunit of the bacterial ribosome. Other studies use a metagenomic approach. Metagenomics refer to the collective study of all genomes within a sample and can be performed by “shotgun sequencing” (Table) in which representative gene fragments are sequenced. Although metagenomics can provide information about the genetic potential of the microbial community, it only provides information on the encoded functional capacity of the microbiome and not on whether specific genes are expressed. In addition, metagenomics provides less detailed information on the specific microorganisms present than targeted studies. Thus, a combination of both
approaches provides the best information on which microbes are there and what they potentially can do.

**THE DYNAMIC RELATIONSHIP BETWEEN OBESITY AND THE GUT MICROBIOTA**

The bacteria in our gut not only play an important role in digestion, but research indicates that our microbiome could also play a major role in whether we become obese.

**Animal Studies**

Gut microbes play a major role in energy extraction from food through a variety of mechanisms. Many plant polysaccharides and complex carbohydrates cannot be digested by the host; however, the gut microbes can metabolize these to short-chain fatty acids, such as butyrate, propionate, and acetate. Butyrate is used as the primary energy source for colonic epithelial cells, whereas propionate and acetate are necessary for lipogenesis and gluconeogenesis in the liver. Differences in short-chain fatty acid levels have been observed in obese and lean mice. For example, in a genetic model of obesity, ob/ob mice have increased butyrate and acetate concentrations in their ceca and less energy, determined by bomb calorimetry, in their feces compared with their lean counterparts.

A link between obesity and the gut microbiota was initially suggested based on studies in germ-free mice. These mice are raised in a sterile environment and have no microorganisms living in or on the animal. Conventionally reared mice have a 40% higher body fat content and 47% higher gonadal fat content than germ-free mice although they consume less food than their germ-free counterparts. Furthermore, when the distal gut microbiota from the normal mice was transplanted into the gnotobiotic mice, there was a 60% increase in body fat within 2 weeks without any increase in food consumption or obvious differences in energy expenditure suggesting that the gut microbiota affects phenotypic characteristics related to obesity of the host. Mechanistic studies revealed that the transplanted microbiota not only increased caloric release from dietary plant polysaccharides but also modulated host genes that affect energy deposition in adipocytes including fasting-induced adipocyte factor. Fasting-induced adipocyte factor is a circulating...
lipoprotein lipase inhibitor, and its suppression is essential for the microbiota-induced deposition of triglycerides in adipocytes. These findings suggest that the presence of a gut microbial community may affect the amount of energy that is extracted from the diet and thus the adiposity of the host.\(^9\)

In contrast to mice with a gut microbiota, germ-free animals are protected against the obesity that develops after consumption of a Western-style, high-fat, sugar-rich diet.\(^7\) Their continuously lean phenotype is associated with increased skeletal muscle levels of adenosine monophosphate-activated protein kinase, and its downstream targets are involved in fatty acid oxidation such as acetyl-coenzyme A carboxylase and carnitine-palmitoyl transferase.\(^8\) Moreover, germ-free knockout animals lacking fasting-induced adipocyte factor are not protected from diet-induced obesity because of reduced expression of genes involved in fatty acid oxidation.\(^9\) These findings suggest that the gut microbiota can influence both sides of the energy balance equation, namely, as a factor that influences energy utilization from the diet and as a factor that affects host genes that regulate how energy is expended and stored.\(^1\) It is not currently known whether the microbiota has a similar effect on energy utilization and gene expression patterns in humans. Associations between obesity and changes in microbiota composition such as reduced bacterial diversity and/or altered representation of bacterial genes and metabolic pathways have been observed. Mice that are genetically obese (ob/ob) have a higher proportion of intestinal Firmicutes and 50% fewer Bacteroidetes and a parallel enrichment of microbial genes involved in polysaccharide degradation than their lean siblings.\(^9\) When germ-free mice were colonized with either the microbiota from obese (ob/ob) or lean (+/+ ) littermates, the mice given the microbiota from obese mice extracted more calories from their food and had a significantly greater increase in total body fat than in mice colonized with the microbiota from lean mice (mean percentage of fat gain, 47% vs 27%, representing a difference of 4 kcal or 2% of total calories consumed).\(^6\) These data suggest that differences in the efficiency of caloric extraction from food may be determined by the microbiota, further suggesting a microbial component in the pathogenesis of obesity.

Transplantation studies using the gut microbiota from human twins discordant for obesity have shown that germ-free mice inoculated with microbiota from obese or lean human twins take on the microbiota characteristics of the donor.\(^10\) Those receiving the obese microbiota had an increase in adiposity, whereas those receiving the lean microbiota remained lean. Interestingly, co-housing of mice harboring cultured bacteria from an obese twin with mice harboring cultured bacteria from a lean twin prevented the development of increased adiposity in the obese mice.\(^10\) This occurred in tandem with successful colonization of obese mice intestine with bacteria, particularly Bacteroidetes from the lean mice. In contrast, obese microbes did not transmit to lean mice, and these mice remained lean,\(^10\) which indicated that transmissibility of intestinal microbes and adiposity phenotype were tightly linked and the lean phenotype is dominant.

Although rodent models have provided an understanding about the contributions of the gut microbiota to obesity, they are limited by physiological and metabolic differences from humans. Gnotobiotic pig models have been developed, and gnotobiotic pigs colonized with human microbiota are a powerful research tool.\(^11\)

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**The use of antibiotics may contribute to the development of obesity.**

The use of antibiotics may also be contributing to the obesity epidemic.\(^12\) The cecal microbiota from 18-week-old controls and penicillin-treated mice were transferred to 3-week-old germ-free mice to investigate the effects on body composition and metabolism. Mice whose mothers were treated with penicillin before the birth of the pups and throughout the weaning process had a markedly altered body composition in adulthood, with increased total and fat mass, increased hepatic expression of genes involved in adipogenesis, decreased bone mineral content, and increased bone surface area. However, the body composition of adult male mice who had received penicillin after weaning was similar to that of controls.\(^12\) These results suggest that the use of antibiotics during early life can induce lasting effects on the body composition by altering the intestinal microbiota.

One of the most durably effective treatments for severe obesity is gastric bypass surgery. Despite its powerful effect on weight loss, the cost and associated risk of this procedure prevent its application to a larger population of severely obese patients, prompting a search for less invasive treatments. In a study using a mouse model of gastric bypass surgery to characterize changes in the gut microbiota, gastric bypass induced substantial, rapid, and sustained changes in the gut microbial communities that were independent of both diet and the weight loss associated with this procedure because mice given a sham procedure and put on a calorie-restricted diet had the decreased weight loss but not the change in microbiota.\(^13\) Moreover, transfer of the surgically altered microbial community to nonoperated germ-free mice resulted in weight loss despite higher food intake in the animals that got the microbiota from the gastric bypass animals than in those that received the microbiota from the sham animals. This was associated with alterations in the microbiota composition. These observations demonstrate
that specific alterations in the gut microbiota contribute to the beneficial effects of bariatric surgery on energy balance and obesity.

**Human Studies**

The association between the gut microbiota and obesity has also been observed in humans. In overweight/obese humans, low fecal bacterial diversity is associated with more marked overall adiposity and dyslipidemia, impaired glucose homeostasis, and higher low-grade inflammation. Investigators have used genetic sequencing of fecal samples to identify the different strains of bacteria in the gut of 12 obese individuals and compared them with 5 lean volunteers. Obese individuals had more Firmicutes and nearly 90% less Bacteroidetes than the lean individuals. Furthermore, when obese volunteers consumed a low-fat or low-carbohydrate diet for 1 year and lost as much as 25% of their body weight, the proportion of Firmicutes in their colon dropped, and that of the Bacteroidetes rose. However, the levels of the 2 types of bacteria never reached those of the group that was lean in the beginning. In another study, variations in the fecal microbiota of 12 lean and 9 obese individuals during diets that varied in caloric content (2400 vs 3400 kcal/d) showed that an altered nutrient load induced rapid changes in the gut bacterial community. Moreover, the higher caloric intake was associated with a 20% growth of Firmicutes and a 20% reduction in Bacteroidetes, which was directly related to the gain in body weight. Differences in fecal microbiota of infants (6 and 12 months) have been associated with the risk of being overweight or obese at 7 years old. Children of normal weight had higher Bifidobacterial and lower Staphylococcus aureus concentrations at ages 6 and 12 months than did children who became overweight/obese. These results suggest that differences in the microbiota precede overweight/obesity. Although other studies have found changes in gut microbial composition in obese individuals, an increase in the Firmicutes-Bacteroidetes ratio in obesity and an increased abundance of Bacteroidetes during weight loss have not been observed consistently. Confounding factors such as the composition of the diet, energy content of the diet, fasting, and use of antibiotics affect gut microbial composition and may explain the discrepancies between findings in these studies. Future work is needed to determine whether manipulation of the gut microbial community could be an approach for the treatment and/or prevention of obesity.

**Can Diet Influence the Composition of the Gut Microbiota?**

The composition of the intestinal microbiota is strongly affected by dietary patterns. A high-fat and high-sugar “Western-style” diet increases the relative abundance of Firmicutes at the expense of Bacteroidetes in animal models. Moreover, switching from a low-fat, plant polysaccharide–rich diet to a high-fat/high-sugar “Western” diet may shift the composition of the microbiota within a single day in gnotobiotic mice colonized with bacteria from human feces. Similar results have been obtained in humans. In a controlled feeding study, gut microbial changes occurred within 24 hours of initiating a high-fat/low-fiber or low-fat/high-fiber diet. Moreover, De Filippo et al. examined to what extent consumption of a Western diet differentially affects human gut microbial composition as compared with the diets of our ancestors, which was characterized by large amounts of dietary fiber and other plant polysaccharides and lower amounts of fat and animal protein. In this study, the fecal microbiotas of 14 healthy children living in Burkina Faso, Africa, were compared with the fecal microbiotas of 15 healthy children from Florence, Italy. Compared with the feces of children from Italy, the feces of the African children contained higher amounts of Bacteroidetes and lower amounts of Firmicutes. Although mammals have large interindividual variation in the composition of the gut microbiota, it is unknown whether host genetics or dietary intake is the stronger influence on microbial composition. A very recent study has suggested that diet dominates host genotype in shaping the microbiota of mice. When 5 inbred and greater than 200 outbred mouse strains were fed a low-fat, high-plant polysaccharide diet or a high-fat, high-sugar diet, their microbiota shifted with diet. Consumption of the high-fat, high-sugar diet consistently led to decreased Bacteroidetes and increased Firmicutes regardless of mouse genotype. These results emphasized the importance of diet on microbiota composition.

**Can We Prevent Obesity by Modulation of the Gut Microbiota?**

Targeting microbiota may present new avenues for therapeutic interventions aimed at preventing or treating obesity and associated metabolic disorders. These strategies include dietary manipulation such as the use of prebiotics, probiotics, or synbiotics, as well as transplantation of fecal microbial communities.

**Prebiotics**

A prebiotic is a food ingredient that cannot be digested by the host and whose beneficial effects on the host result from the selective stimulation of growth and/or activity of the gut microbiota, particularly lactobacilli and bifidobacteria.
Most of the attention in this area has been aimed at nondigestible oligosaccharides. Common prebiotics include inulin, other oligosaccharides, lactulose, and resistant starch. In principle, all dietary fibers that are fermented are assumed to have prebiotic properties. Inulin occurs naturally in several foods such as leek, asparagus, chicory, Jerusalem artichoke, garlic, artichoke, onion, wheat, banana, oats, and soybeans. However, these may not be biologically significant sources because Manning and Gibson estimate that an individual would need to consume 4 to 8 g/d of fructooligosaccharide to significantly (approximately 1 log10 value) elevate bifidobacteria in the human gut. A functional food approach has been used to add inulin to more frequently consumed products, such as cereals, biscuits, infant foods, yogurts, breads, and drinks, at concentrations at which a prebiotic effect may occur. There are also a number of dietary supplements that contain fructooligosacharides, primarily inulin, that are commercially available.

Gut hormones such as glucagonlike peptide-1 (GLP-1) play a critical role in relaying signals of nutritional and energy status from the gut to the central nervous system to control food intake. Studies have shown that GLP-1 is up-regulated by prebiotics in obese mice suggesting that alterations in intestinal microflora may stimulate or suppress the secretion of gastrointestinal hormones. In a double-blind, placebo-controlled study of 16 adults, administration of an inulinlike prebiotic fiber was associated with a significant decrease in hunger and significantly greater satiation after a meal and increased plasma GLP-1 compared with a similar-tasting placebo (dextrin/maltose). These results suggest that prebiotics may be useful for controlling food intake.

In a double-blind, placebo-controlled, crossover trial, consuming 30-g/d isomalt (a sugar substitute made from beet sugar) for 4 weeks led to a 65% increase in the proportion of bifidobacteria and a 47% increase in total bifidobacteria cell counts compared with feeding sucrose. In another study in which 12 volunteers ingested 10-g/d inulin for 16 days in comparison with a control period without any supplement intake, showed the strongest response, increasing from 0.89% to 3.9% of the total microbiota. Therefore, supplementing the diet with prebiotics can alter the gut microbial composition.

Prebiotics can alter the gut microflora.

Probiotics
Probiotics have been defined by the World Health Organization as “live microorganisms which when adminis-
There is also evidence from human studies that probiotics may be beneficial against obesity, but the data are less consistent. VSL#3, a commercial multispecies probiotic, was protective against body mass gain and fat accumulation in healthy men (body mass index < 25) consuming a high-fat (55% fat), hypercaloric diet (+1000 kcal/d) for 4 weeks compared with placebo.38 A randomized-controlled trial in humans demonstrated that consumption of fermented milk containing the probiotic Lactobacillus gasseri SB2055 (LG2055) for 12 weeks led to a significant reduction in abdominal visceral fat area (8.5% decrease, P < 0.01) compared with control subjects.39 In a study examining the impact of perinatal probiotic intervention on the development of overweight and obesity in children older than 10 years, 159 women were randomized to either Lactobacillus rhamnosus or maltodextrin for 4 weeks before expected delivery and 6 months postpartum. The authors observed that probiotic treatment may prevent excessive weight gain during the first years of life.40 In contrast, other studies have shown no benefit of probiotics for the prevention/treatment of obesity. One meta-analysis has suggested that probiotics may promote weight loss in adults but weight gain in children.41 Another meta-analysis demonstrated that the same Lactobacillus strain may promote weight gain in undernourished individuals, whereas it may reduce weight gain in obese individuals.42 Thus, the effects of probiotics might not only depend on the strain but also on the characteristics of the host including age and baseline body weight. More rigorously designed, randomized controlled trials are necessary to examine the effect of probiotics on body weight in greater detail.

Synbiotics

The combination of a probiotic with a prebiotic has been termed a “synbiotic.”43 Synbiotics have the potential to induce more substantial effects on the gut microbiota and host health than isolated intake of prebiotics or probiotics because they provide the probiotic bacteria in combination with a prebiotic component that stimulates probiotic bacteria survival and growth in the gastrointestinal tract. Evidence suggests that synbiotics may be efficacious in altering the composition of the microbiota. For example, the synbiotic combination of a specific oligofructose-enriched inulin (SYN1) and Lactobacillus rhamnosus GG and Bifidobacterium lactis Bb12 for 12 weeks caused 16% and 18% increases in the numbers of Lactobacillus and Bifidobacterium, respectively, and a 31% decrease in the numbers of Clostridium perfringens.44 In vitro studies have demonstrated that synbiotics were more effective than prebiotics or probiotics in modulating the gut microbiota.45 These findings need to be documented in well-controlled human intervention studies. To date, there have only been a limited number of human studies investigating the potential benefits of synbiotics on obesity.46

Fecal Microbial Transplant

Fecal microbial transplants have been found to be an efficacious treatment for patients with Clostridium difficile infections, but their benefits for other conditions are less well studied.17 A randomized controlled trial in obese subjects was conducted to investigate the effects of fecal transplantation on insulin resistance.48 Subjects underwent small intestinal biopsies and subsequent bowel lavage through a duodenal tube, followed by random assignment to receive either homogenates of their own feces (autologous) or from healthy, lean donors (allogenic). Results showed a significant improvement in insulin sensitivity (median rate of glucose disappearance after a challenge) in subjects receiving fecal microbiota from lean donors lasting up to 6 weeks but no change in those getting their own fecal microbiota.48 A trend toward improvement in hepatic insulin sensitivity was also observed. Gut microbial diversity, particularly an increase in butyrate-producing bacteria, occurred after allogenic transplants but not after autologous transplants. These experiments suggest that increased bacterial diversity is associated with reduced insulin resistance. However, this was a small study, and there was variability in the response—only samples from specific donors had beneficial effects so further studies are needed.

It should be noted that there are dangers associated with fecal microbial transplants because it is not possible to eliminate viral pathogens by filtering and should only be used as a final treatment for human conditions such as recurrent Clostridium difficile infection. Moreover, fecal microbial transplants may also have adverse effects on obesity. A recent case report described a patient who underwent a successful fecal microbial transplant for Clostridium difficile infection but then developed new-onset obesity after receiving stool from an overweight donor.49 These data suggest that the microbial composition can be transmissible and that manipulation of the intestinal microbiota may be a potential therapeutic target for the prevention of obesity.

Future Directions

Overall, current evidence supports the potential role of the human gut microbiota in obesity. There are data that suggest that the bacterial composition of gut microbiota differs between obese and lean individuals and that a Western-style diet that is high in fat and refined carbohydrates may promote increased intestinal bacteria linked to obesity. This raises the question whether altering the microbiota can modulate obesity risk or whether knowledge about an individual’s microbiota can be used to develop personalized diets for obesity prevention. Perhaps the most exciting data to suggest the importance of the interrelationship between diet and an individual’s microbiome come from a recent study that demonstrated
that information about a subject’s gut microbiome can be used to design personalized diets for glucose homeostasis. In the study, the authors found that there was large variation in the glycemic response to the same food items between subjects, as well as to the consumption of standardized meals. In an attempt to explain this variation in the glycemic response, the gut microbiome was analyzed with both 16S rDNA and whole metagenomic sequencing and combined with traditional measures, such as blood sugar, diet, physical activity, and body measurements, to create a machine-learning algorithm that accurately predicts personalized responses to real-life meals. Moreover, the algorithm accurately predicted glycemic response in a separate validation cohort and in a follow-up dietary intervention study. This study provides an exciting framework to better understand an individual’s response to dietary interventions based on his/her microbiota. Perhaps the next step would be to use a similar approach to investigate whether information about an individual’s microbiota can predict dietary energy availability and better personalized diets for obesity prevention and/or treatment.

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