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TODAY'S DIETITIAN

Gut Bacteria

By Megan D. Baumler, PhD, RD, CD

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Imagine that foods are not calorically equal for every individual: A bran muffin may provide 200 kcal for one person but only 150 kcal for another. Also imagine that these caloric differences all boil down to the type of bacteria living in someone's colon, and that an individual may favorably influence these bacteria for optimal personal health. Recent research shows this may indeed be the case.

There are 10 times more bacterial cells in our bodies than there are actual human cells, and we house more bacterial genes than human genes. Not all bacteria are bad. In fact, most are good, including those that take up residence in our gastrointestinal (GI) tract. Our gut bacteria, also known as the gut flora or microbiome, rely on our bodies as a place to live. For their own survival, they promote our health in what is known as symbiosis, a mutually beneficial relationship. They rely on us and we rely on them.

Because gut bacteria are anaerobic, making them exceptionally difficult to study, little has been known about their complex symbiotic relationship with our health. However, new research techniques—high throughput sequencing technology and the use of germ-free animal models—have allowed researchers to study gut flora in both animals and humans to gain a better understanding of their influence on our health. Researchers are examining the connection between specific gut flora profiles and health outcomes by looking for associations with certain health characteristics and those specific gut flora profiles. Most remarkable, given the obesity epidemic, is the finding that gut bacteria may contribute to a metabolic predisposition to obesity.[1]

It's unclear whether the presence of specific gut flora is a contributor or consequence of obesity, but compelling evidence suggests a strong association. Researchers are looking for the determinants of individuals' gut flora profiles to establish whether there are any potential therapeutic implications. Gut flora profiles differ among individuals, and diet is considered a primary determinant of a gut flora profile.[2] This begs the question, could certain diets or foods be recommended on the basis of promoting a specific gut flora profile to positively influence health outcomes?

This continuing education course explores the relationship among diet, gut flora, and health outcomes, and discusses the concept that gut flora may be a therapeutic target for obesity and related chronic diseases.

Good Bugs

The development of a thriving gut flora begins at birth. In utero, the fetus lives in a sterile environment, but upon birth, babies are quickly inoculated with bacteria from their mothers, and by about age 1, they have a well-developed gut flora.[3]

Approximately 100 trillion bacterial cells live in the GI tract, mostly in the large intestine.[4] While colonic bacteria predominantly are from two bacterial phyla, *Bacteroidetes* and *Firmicutes*, there are about 400 species represented and the gut flora profile (type of bacteria and amounts of each type) is highly variable from one individual to another and even within individuals over time.[5] Family members, however, share more similar gut flora than unrelated individuals.[6]

Gut bacteria have many critical functions, including supporting the normal development of the GI tract and immune system. Research has shown that germ-free animals (raised and maintained in sterile environments) have underdeveloped GI tracts and are susceptible to infection.[7] In promoting the host's immunity, the gut bacteria ensure that they won't be taken over by pathogenic (disease-causing) bacteria. Friendly gut bacteria act as a physical barrier and also secrete antimicrobial proteins that prevent the colonization of pathogenic bacteria.[8] In addition to supporting development of the GI tract and the immune system, gut bacteria synthesize essential nutrients, including biotin and vitamins B_{12} and K, although not in sufficient enough quantities to meet our requirements.

Gut bacteria also are capable of harvesting energy from food that's indigestible in the upper small intestine. In doing so, they produce short-chain fatty acids, an energy substrate absorbed by colonic epithelial cells that's either subsequently used for energy by the colonic cells themselves or absorbed into the bloodstream. While this energy the gut bacteria produces is beneficial to maintain colonic epithelial cells, in this age of obesity, the extra energy absorbed into the bloodstream isn't exactly welcome. The role that gut bacteria play in energy harvest is being examined closely to determine whether it's adding to the obesity problem and whether it may be a therapeutic target.

Obesity

The beneficial bacteria that live in the GI tract indisputably are linked to our health. Researchers are examining the nature of this relationship by exploring the types of bacteria that affect our metabolism and the manner in which they do so, with provocative results so far.

Backhed and colleagues conducted a landmark study in 2004 providing the first real clues that gut bacteria may have a notable role in energy balance and thus in the development of obesity.[1] In this study, germ-free mice were colonized with bacteria from the intestines of normal mice. Within 14 days, the formerly germ-free mice had an astonishing 60% increase in body fat content despite reduced food intake. The formerly germ-free mice also had greater carbohydrate absorption and increased triglyceride storage in their adipocytes. The authors concluded that the gut microbiota are an environmental factor—akin to diet and exercise—that regulate fat storage. Before modern times in which food is readily available, increased fat storage caused by gut bacteria would have been beneficial. But now, it intensifies the risk of obesity and the associated chronic diseases that are rampant in the population.

Even more intriguing is a follow-up study in which germ-free mice were colonized with gut bacteria from obese or lean mice.[9] The germ-free mice that were colonized with bacteria from obese mice had a 47% increase in body fat compared with a 27% increase in body fat in the mice colonized with bacteria from lean mice, suggesting that gut bacteria may have a causal relationship with body fat. Characterization of the gut flora profile of the obese and lean mice revealed that the former had more *Firmicutes* compared with the *Bacteroidetes* type, suggesting that it was the difference in gut flora profile that led to the increased fat accumulation since it was the only variable in the study that changed between the groups. Furthermore, the gut flora in the obese mice's colons was found to have greater capacity to ferment indigestible carbohydrate. The obese mice lost fewer calories in their feces, indicating that the gut flora in the obese mice led to increased energy harvest.

In a related study by Turnbaugh and colleagues, when mice were "humanized" with fecal flora from humans and switched from a low-fat, high-plant-polysaccharide diet to a Western-style high-fat, high-sugar diet, dramatic changes occurred in the gut flora within one day and resulted in increased fat stores.[10] This study showed that specific diet patterns result in changes in gut flora and subsequent health outcomes, lending support to the notion that we may favorably influence our gut flora profile through diet.

To see whether gut bacteria profiles predicted weight status, researchers analyzed the fecal microbiota of infants and compared gut flora profiles with weight status later in life.[11] Children who became overweight or obese had less *Bifidobacteria* in their gut flora during infancy and through childhood compared with children who maintained a normal weight. This is the only prospective study to date that followed subjects over time to explore a connection between gut flora and weight status, and it found that specific gut flora profiles precede development of overweight, suggesting potential causation. This study didn't control for other variables that may have contributed to weight status, such as diet, so conclusions are limited.

Regardless of whether the relationship is causal, it's clear that obesity is associated with a certain gut flora. Ley and colleagues found that a mouse model of obesity by leptin resistance had a 50% reduction in *Bacteroidetes* and an increase in *Firmicutes* bacteria in their gut flora.[12] The association between obesity and gut flora is less clear in human studies because of inconsistent findings, possibly related to differences in research techniques.[13,14] Another interesting study by Ley and colleagues found key differences in the gut flora between people who were obese and lean.[15] People who were obese had more *Firmicutes* compared with *Bacteroidetes* bacteria in their gut flora, and more importantly, following one year of significant weight loss through dietary changes, formerly obese individuals had gut flora that was more similar to that of lean individuals.

To date, studies indicate that obesity is associated with changes in the gut flora. While some evidence suggests that gut bacteria may be causally linked to obesity, it's still too early to determine the exact nature of the relationship. Differences in research methodologies and the complexity of human subjects, their diets, and gut flora prevent definitive conclusions.

More recently, studies have focused on defining enterotypes (certain gut flora profiles) and characterizing gut flora by the metabolic profiles, such as the capacity to harvest energy, rather than by traditional lineage of phylum, genus, and species.[16] There are multiple ways to characterize gut flora profiles; the most valuable method is the one that holds true most consistently and may lead to the development of novel therapeutic approaches for obesity and other metabolic disorders. A subject of controversy is whether it's more useful to categorize gut bacteria by lineage or metabolic potential for purposes of developing a therapeutic approach to obesity. It's unclear whether the effect of diet on gut flora and the association between gut flora and health outcomes become more apparent with one or the other classification scheme. Until a consensus on this is reached, it's difficult to conduct reviews and meta-analyses for more convincing results because of differences in methods of classifying gut profiles.

Diseases Related to Obesity

The relationship between gut bacteria and chronic disease risk may go beyond obesity. This isn't surprising, since obesity increases the risk of other diseases and because metabolic changes, as purported to occur with changes in gut flora, may alter risk of diseases other than obesity.

Insulin Resistance

The groundbreaking study from Backhed and colleagues in 2004 not only found that mice raised germ free and subsequently colonized with gut flora from normal mice quickly developed increased fat stores, but also that they developed insulin resistance.[1] In comparison with germ-free mice, the formerly germ-free mice that were colonized with gut flora had increased fasting serum glucose concentration as well as increased leptin and insulin concentrations. The possible influence of gut bacteria on the development of insulin resistance may be exerted through inflammatory signals.[17] The short-chain fatty acids and other molecules that gut bacteria produce as a metabolic by-product can act as inflammatory triggers by binding to toll-like receptors, which begin a cascade of inflammatory signaling. Human studies support a connection between gut bacteria and diabetes: People with type 2 diabetes have been found to have reduced levels of *Firmicutes* in their gut bacteria profiles compared with those without diabetes.[13] Currently, it's unclear whether a gut flora profile is directly related to insulin resistance or indirectly related and dependent on the development of obesity.

Atherosclerotic Heart Disease

Atherosclerosis is considered a disease that begins with inflammation. Because gut bacteria can trigger inflammation (see next section), researchers examined whether gut flora were associated with the development of atherosclerosis. When germ-free mice were colonized with gut bacteria, serum trimethylamine N-oxide and foam-cell formation were increased, which both are related to the progression of atherosclerotic cardiovascular disease. Subsequent inhibition of the gut bacteria blocked the progression of the atherosclerosis, strongly suggesting a role for gut bacteria in heart disease.[18]

Another study found no difference in gut flora profiles between those with and without atherosclerotic heart disease, but researchers did find an association between specific gut bacteria and serum cholesterol levels.[19] Gut bacteria are needed for deconjugation and

excretion of bile acids, thus decreasing the cholesterol pool, so it's plausible that different gut bacteria may affect bile acids and, subsequently, serum cholesterol levels differently.

While many intriguing discoveries have been made in the last several years on the contribution of gut bacteria to chronic disease risk, much research remains to be done. Once there's more evidence-based research on the influence of certain types of bacteria on metabolism and energy balance, we'll be closer to making dietary recommendations to promote an optimal gut flora profile to reduce disease risk.

Mechanism of Effect

The proposed mechanisms by which gut bacteria may contribute to obesity and its comorbidities include increased energy harvest from the diet, a change in gene expression, and the promotion of inflammation. Understanding these mechanisms may lead to novel therapeutic approaches to obesity and related metabolic disorders.

Colonic bacteria metabolize nondigestible dietary carbohydrates and subsequently produce the short-chain fatty acids butyrate, acetate, and propionate. Butyrate is the preferred energy source for colonic epithelial cells, while peripheral organs and the liver use acetate and propionate for lipogenesis.[20] Primary evidence of gut bacteria's capacity to harvest dietary energy includes the fact that germ-free animals lose more calories in their feces than normal animals. People who are obese also show signs of greater gut bacterial metabolic activity and decreased loss of calories in their stool, indicating increased energy absorption.[21,22] The consensus is that gut bacteria increase the energy harvest from the diet; however, whether the increased energy harvest is substantial enough to affect weight is unclear and appears to depend on the gut bacteria profile.

Another way gut bacteria may contribute to obesity is through gene expression regulation. The increased size of fat stores in colonized mice compared with germ-free mice is dependent on bacterial suppression of a gene called fasting-induced adipose factor (FIAF), which regulates the enzyme lipoprotein lipase, causing increased cellular uptake of fatty acids and thus, increased fat stores.[1] While normal germ-free mice were resistant to weight gain from high-fat feed, germ-free mice that were bred void of the FIAF gene had the same increase in body weight in response to high-fat feeding as did colonized mice, indicating that gut bacteria may regulate body fat stores by regulating FIAF gene expression.

Other evidence suggests that gut bacteria may influence inflammation levels, which may affect metabolism and energy balance. In a study by Cani and colleagues, mice that were fed a high-fat diet had an increase in gram-negative bacteria in their gut flora, leading to an increase in bacterial lipopolysaccharides (LPS) in the plasma.[23] Bacterial LPS originate in the cell walls of gram-negative bacteria and have been found to trigger inflammation by promoting synthesis of proinflammatory cytokines. Mice that were infused directly with LPS developed insulin resistance and weight gain. Interestingly, mice resistant to LPS did not develop insulin resistance or weight gain. The authors speculated that LPS originating from gram-negative gut bacteria trigger inflammation and subsequent metabolic disease. If this is the case, diets that reduce gram-negative bacteria in the gut flora may prevent LPS-stimulated inflammation. Pinpointing the mechanism of effect by which gut bacteria influence metabolism will be helpful

in trying to find a way to manipulate bacteria or develop pharmaceutical agents to block signals in order to reduce disease risk.

Gut Bacteria Adapt to Diet

The concept that gut flora can affect health becomes particularly interesting because of the notion that we can potentially influence our gut flora profile. Whether we can do this purposefully through specific dietary changes rests on clarification of the effects of diet on our gut flora profile.

Several studies have examined the influence of diet on the gut flora. In one study, the gut flora of children aged 1 to 6 from Europe and Africa were compared.[24] The children from Europe, who were breast-fed until age 1, had a traditional Western diet high in animal protein, sugar, starch, and fat and low in fiber. The average fiber intake of the European diet was 8.4 g/day, and the average calorie intake was 1,512 kcal/day. The children from Africa, who were breast-fed until age 2, had a traditional rural African diet low in fat and animal protein but high in starch, fiber, and plant polysaccharides (consisting of cereals, legumes, and vegetables). Average fiber intake in the African diet was 14.2 g/day, and the average calorie intake was 996 kcal/day.

When gut flora profiles of the two populations were compared, African children were found to have significantly more *Bacteroidetes* and much fewer *Firmicute*s compared with European children. African children had an abundance of bacteria that contain genes for metabolizing cellulose and xylan (plant starches) compared with the European children. African children also had significantly greater diversity in their gut flora compared with the European children. Diversity in gut flora is considered to be potentially beneficial in that it increases the likelihood of good bacteria. The study results are of great significance because they indicate that gut flora adapt to dietary differences. Whether different health outcomes in these children will arise because of the different gut flora profiles remains to be seen.

In a different study, the diets of 98 healthy individuals were assessed by food-frequency questionnaires to determine whether long-term dietary patterns and specific nutrients were associated with specific gut flora profiles.[25] The authors found that long-term dietary patterns were associated with enterotypes, indicating that diets affect gut flora. In a follow-up study by the same authors, 10 individuals participated in a 10-day controlled feeding study to determine whether gut flora changed in response to a high-fat/low-fiber diet and a low-fat/high-fiber diet. Interestingly, results indicated that changes in the gut flora occurred within 24 hours of beginning the diets. Regardless of which diet the subjects followed, they experienced rapid, significant changes in their gut flora.

A recent study suggested that it's not just the type of food in the diet or dietary patterns that may influence an individual's gut flora profile, it's also the amount of calories someone consumes relative to needs. Jempertz and colleagues studied the influence of various caloric loads on gut flora profiles in both lean and obese people.[26] Two important findings emerged. First, changes in caloric load (either a 2,400- or 3,400-kcal diet) resulted in prompt changes in the gut flora. The higher the calorie provisions were above weight maintenance needs, the greater the increase in *Firmicutes* and the decrease in *Bacteroidetes* in the gut flora. Even

more interesting, a 20% increase in Firmicutes was associated with an increased nutrient absorption of 150 kcal. Thus, the more calories consumed relative to needs, the more calories were absorbed rather than lost in the stool. The fewer the calories consumed, the more *Bacteroidetes* in the gut flora and the more calories lost in the stool. These findings correlate with previous research showing that following weight loss, individuals tend to have reduced *Firmicutes* and increased *Bacteroidetes*.[15] Together, these studies suggest that the gut flora adapt to changes in caloric consumption and that these adaptations affect the amount of nutrient absorption from dietary intake.

Practical Implications

At this point, the practical implications for dietitians are limited until research advances. However, it's reassuring that high-fiber diets are associated with lower energy harvests, which supports current dietary recommendations to include good sources of dietary fiber daily. Furthermore, having an energy balance may help maintain a gut flora profile that's associated with reduced disease risk.

The use of probiotics has the potential to positively influence health outcomes, likely through their effect on the gut flora. In one study, overweight adults who consumed *Lactobacillus gasseri* (200 g/day of fermented milk containing the probiotic for 12 weeks) had a 5% decrease in abdominal visceral fat compared with the control group.[27] In another study, pregnant mothers who were given *Lactobacillus rhamnosus* GG and *Bifidobacterium lacti*s Bb12 had a significantly reduced risk of gestational diabetes compared with the control group.[28] Other research found that patients who consumed probiotics after Roux-en-Y gastric bypass surgery experienced significantly more weight loss compared with those who didn't take the probiotics after surgery.[29]

While these studies didn't involve gut flora sequencing to determine whether the groups that consumed the probiotics had changes in their gut flora profile, it seems reasonable to surmise that if the probiotics caused the change in health outcomes, it may have been via a change in gut flora caused by the probiotics.

A study is under way to determine whether fecal microbiota transplantations are effective for resolving *Clostridium difficile* infections. It will be interesting to determine whether fecal transplants may be used in the future to influence other health outcomes by way of establishing a new gut flora. A more desirable practical implication would be to recommend specific dietary patterns to promote particular gut flora profiles for optimal health outcomes.

Bottom Line

The current consensus is that gut bacteria have metabolic consequences for the host, including an influence on the number of calories absorbed from the diet. The short-chain fatty acids of gut flora may add approximately 140 to 180 kcal/day to our energy absorption, which may lead to significant weight changes over time.[30] Diets with less fat and protein plus more plant-based starch and dietary fibers result in greater fecal calorie loss, which is desirable in a culture battling an obesity epidemic. Less clear is whether gut bacteria actually contribute to obesity and other metabolic disturbances.

While research has come a long way, the field still is in its infancy. The National Institutes of Health recently launched its Human Microbiome Project with more than $100 million supporting research on the health effects of gut bacteria, so look forward to rapidly advancing knowledge on shaping gut bacteria through diet as a therapeutic target for obesity.

—Megan D. Baumler, PhD, RD, CD, is a professor and the director of the graduate program in dietetics at Mount Mary College in Milwaukee.

Inflammatory Bowel Diseases

Obesity and its comorbidities aren't the only areas of research concerning gut bacteria. Researchers are exploring gut bacteria's role in other conditions, such as inflammatory bowel disease (IBD).

Because gut bacteria are involved in the development and regulation of host immunity, they may play a role in IBD since the immune system is responsible for inflammation. Research is under way to determine whether gut bacteria may be therapeutic targets for the management of IBD. Evidence that supports a strong role for gut bacteria in the progression of IBD includes the increased risk of irritable bowel syndrome (IBS) because of gut bacteria disruption following enteric infection.[1] Current consensus accepts that for people who are genetically predisposed to IBD, a disruption in their gut bacteria, possibly because of antibiotics or enteric infection, may precipitate the inflammation and disease onset. It's less clear whether probiotics or diets that promote certain gut flora may help manage IBD symptoms.

Research has shown that people with IBS have reduced levels of *Lactobacilli* and *Bifidobacteria* and increased levels of *Streptococci* and *E coli* in their gut.[2] Furthermore, abnormal microbiota composition and decreased gut bacteria diversity are common in patients with Crohn's disease or ulcerative colitis.[3] The fact that people with IBD have different gut bacteria profiles suggests that there may be a therapeutic implication—that modulation of gut bacteria with diet and probiotics may improve IBD outcomes. Probiotics have been shown to reduce intestinal permeability and improve immune function, both of which are involved in IBD. Studies have shown that probiotics may be helpful in reducing IBS symptoms, although many of these studies are limited by their research designs.[4] There has been one controlled trial examining the effects of prebiotics (galacto-oligosaccharides) on IBS, and results indicated reduced symptoms and increased growth of *Bifidobacteria*.[5] Some evidence suggests that the use of antibiotics may improve symptoms of IBD, possibly by selectively reducing the pathogenic bacteria.[6] Finally, the FODMAP (fermentable oligo-, di-, and monosaccharides and polyols) diet, in which poorly absorbed but highly fermentable (by gut bacteria) foods are avoided, has been shown to be effective in managing symptoms of IBD and IBS.[7,8] The likely mechanism of this diet is through regulation of the gut bacteria.

Evidence generally is strong for the use of probiotics for the prevention of pouchitis and management of ulcerative colitis.[9,10] While evidence is promising, controlled studies that consistently show a therapeutic role for probiotics and specific diets in the management of Crohn's disease are lacking. However, with the exception of a compromised immune system and gut permeability, probiotics generally are safe and therefore worth trying. Future studies to

establish whether the changes in gut bacteria associated with IBD are a cause or an effect of the disease will be helpful in further clarifying a role for probiotics, although this is challenging to determine because of difficulty in identifying whether the differences were present before or after disease onset.

— *MDB*

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Examination

1. Which of the following are health benefits of gut bacteria?
A. Slowed metabolism
B. Development of immune function
C. Improved vision
D. Increased lung capacity

2. Which of the following statements about gut bacteria is true?
A. There are more human cells in our bodies than gut bacteria cells.
B. Gut bacteria aren't fully developed until adulthood.
C. Gut bacteria metabolize food that's indigestible in the small intestine.
D. The energy produced by gut bacteria is excreted in the feces.

3. How might gut bacteria contribute to obesity?
A. Gut bacteria increase dietary caloric value by salvaging energy from food that's indigestible in the small intestine.
B. Gut bacteria may decrease basal metabolic rate.
C. Gut bacteria decrease levels of general inflammation, thereby increasing the risk of obesity.
D. Gut bacteria may change appetite so that higher calorie foods are preferred.

4. Studies examining the influence of diet on gut flora by comparing the gut flora of children from Europe with that of children from Africa demonstrated which of the following?
A. African children had fewer *Bacteriodetes* and more *Firmicutes* than did European children.
B. African children had more *Bacteriodetes* and fewer *Firmicutes* than did European children.
C. African children had less diversity in gut flora than did European children.
D. African children had fewer bacteria containing genes for metabolizing cellulose and xylan than did European children.

5. The potential role of gut bacteria in the promotion of cardiovascular disease was suggested based on what evidence?
A. When gut bacteria were inhibited, atherosclerosis progression was blocked.
B. Germ-free mice do not develop cardiovascular disease.
C. Individuals with and without cardiovascular disease have major differences in their gut flora profiles.
D. A heart-healthy diet promotes heart healthy gut flora.

6. The theory that the number of calories consumed relative to needs may influence a gut flora profile is based on what evidence?
A. Obese and lean individuals have very similar gut flora profiles.
B. Consumption of a higher-calorie diet led to changes in gut flora associated with fewer calories excreted in feces and thus increased energy absorption.
C. Obese individuals show evidence of lower energy harvest from their diet.
D. A 20% decrease in *Firmicutes* following excess caloric intake was associated with an increased nutrient absorption of 150 kcal.

7. High-fiber diets are associated with lower energy harvests, which support current dietary recommendations to include good sources of dietary fiber daily.
A. True
B. False

8. What has changed about the perception of the symbiotic relationship between gut bacteria and human health since the obesity epidemic?
A. The increase in dietary energy harvest is more beneficial than it used to be.
B. Obesity may reduce the benefits of the symbiotic relationship.
C. The increase in dietary energy harvest is no longer as beneficial as it may have been before food abundance.
D. The use of antibiotics may interfere with the symbiotic relationship.

9. What evidence supports an association between gut flora and diabetes?
A. Pregnant women who took probiotics had a significant increase in gestational diabetes.
B. People with diabetes had different gut flora than people without diabetes, and germ-free mice had improved glucose tolerance and insulin sensitivity.
C. Gut bacteria activate the insulin receptor gene.
D. Gut bacteria cause a reduction in glucose absorption.

10. Based on current knowledge about the relationship between gut flora and human health, what are the practical implications for nutrition professionals?
A. Continue to promote fiber intake and the avoidance of excess calorie consumption.
B. Promote a vegan diet.
C. Promote a traditional African diet.
D. Promote a hunting and gathering lifestyle.