

Gut Microbiome and Its Potential Role in Obesity

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ABSTRACT

Obesity has become a major health problem due to its increasing prevalence and its association with chronic disorders that include type 2 diabetes, atherosclerosis, cardiovascular disease, and cancer. Although obesity is a result of a long-term imbalance between dietary intake and energy expenditure, dietary-induced alterations in the gut microbiome play an important role in the onset and development of this condition. Human and animal intestines contain trillions of microbes, defined as the gut microbiome or microbiota. The microbiome is largely responsible for the health of the host and varies with diet, host genotype, sex, and age. The normal gut microbiome imparts specific functions in host metabolism, including immunity, maintenance of the intestinal barrier, and protection against pathogens. The composition and activities of the microbiome are altered in obese individuals compared with their lean counterparts. Metabolic changes due to the altered microbiome in obesity include enhanced energy extraction from food, lipogenesis, and insulin resistance. Dietary manipulation of the microbiome to control obesity includes prebiotics, probiotics, and synbiotics that have been reported to reduce energy storage and lower inflammation and insulin resistance. The development of therapeutic approaches to prevent and treat obesity by microbiome manipulation are being pursued in laboratories and are of growing interest to commercial companies and governments.

Keywords: Microbiome; Obesity; Diet; Probiotics

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INTRODUCTION

Humans and other vertebrates are colonized by a wide array of microbes, collectively called the *microbiota* or *microbiome*, terms that define the microbiota genome.¹ It is estimated that the distal gut contains 10–100 trillion microbes encoding 100 times more genes than the human genome and playing a role in health and disease.² A disturbed microbiome due to altered health or environmental factors may increase the risk of infections and metabolic disorders, including obesity, insulin resistance, diabetes, dyslipidemia, high blood pressure, and cardiovascular disease.^{2–8}

The role of the microbiome in obesity was noted by observing that germ-free mice lacking a microbiome are leaner than conventionally bred mice.^{4–7} The introduction of the gut microbiome from conventionally bred mice into germ-free mice (a process called *conventionalization*) produced a rapid 60% increase in body fat within 14 days despite a lower intake of chow, normalizing adiposity to the levels of conventionally raised mice.⁷ The leaner state of mice that lacked a microbiome was attributed to their inability to ferment polysaccharide-rich food to the short-chain fatty acids that are a source of energy and lipogenesis. Transferring the microbiome from the conventional mice to the germ-free mice reversed the situation, increasing adiposity and insulin resistance.⁷

The ability to transfer the obese or lean phenotype to germ-free mice by means of the microbiome was further observed in a study using the microbiome of human female twins divergent in obesity. Gut microbiome harvested from the obese twin and transferred via gavage to germ-free mice on a low-fat diet resulted in the mice becoming obese; mice colonized with the microbiome from the lean twin remained lean.⁹

EFFECTS OF DIET

Diet modification of the gut microbiome influences obesity.^{6,8,10–17} The effect is rapid, with a high-fat diet changing the microbiome within a single day.⁸ Diet-induced changes are selective. A Western diet

that is high in both fat and sugar correlates with an increased proportion of Firmicutes microbes, which are efficient in harvesting energy from food, over the less efficient Bacteroidetes, potentially leading to obesity.¹¹ The harvested energy is generated from otherwise indigestible polysaccharides fermented by microbiome enzymes that are not encoded in the human genome. Fermentation products include monosaccharides and short-chain fatty acids that are absorbed into the circulation, stimulating synthesis of triglycerides in the liver and their incorporation into adipocytes or acting as regulatory molecules.⁷

The main short-chain fatty acids produced by the microbiome are acetate, butyrate, and propionate.^{1–3} Among the three, butyrate and propionate are predominantly antiobesogenic, whereas acetate shows more obesogenic potential.³ Acetate is oxidized by skeletal and cardiac muscle and by brain cells to carbon dioxide and other metabolites and by adipocytes for lipogenesis, wherein lies its obesogenic potential. Butyrate is metabolized to ketone bodies that provide energy to the colon epithelium. Butyrate improves insulin sensitivity, has antiinflammatory potential, reduces mucosal inflammation, and strengthens the epithelial barrier against invasion and colonization of pathogens, an important function because the disruption of the ecological equilibrium in the gut (i.e. dysbiosis) due to a weakened barrier has been associated with obesity and its related comorbidities.

Propionate has been found to inhibit cholesterol synthesis and to inhibit the expression of resistin,³ an adipocyte-derived signaling polypeptide implicated in obesity-mediated insulin resistance. Furthermore, butyrate and propionate help regulate weight by stimulating anorexogenic gut hormones, which promote a decrease in food intake.

Most studies on the effects of short-chain fatty acids on metabolism, including obesity, have been done with rodents and have often produced contradictory results. Depending on the gut microbiome and the digested food, short-chain fatty acids may have different metabolic effects, resulting in reduced as well as increased obesity.¹¹

Studies with humans show that gut differences and diet affect the microbiome and energy balance.^{12–16} For example, individuals prone to obesity may harbor a gut microbiome that transports monosaccharides more efficiently and executes more effective extraction and storage of energy from the diet than the microbiome of lean individuals. In a study addressing the relationship between diet modification of the microbiome and adiposity, 12 obese people were assigned for 1 year to a low-calorie diet that was either fat-restricted or carbohydrate-restricted. A genetic analysis of stool samples showed that 70% of the microbial species were unique to each person and remained constant over time, with members of the Bacteroidetes and Firmicutes divisions dominating the microbiome.¹² Obese people had fewer Bacteroidetes and more Firmicutes than did lean control subjects. Weight loss increased the proportion of Bacteroidetes over Firmicutes, regardless of diet type.^{10,13} In another study with 12 lean and 9 obese people consuming diets that varied in caloric intake (2400 vs. 3400 kcal), researchers found that a higher caloric intake that increased body weight was directly related to a 20% increase in Firmicutes and a 20% decrease in Bacteroidetes.¹⁶

INFLUENCE OF DIET CONTENT ON THE MICROBIOME

Changes in diet and lifestyle that began with the introduction of agriculture and animal husbandry are thought to have given rise to alterations in the gut microbiome. Fillippo *et al.* studied the gut microbiome of children 1–6 years of age from the Mossi ethnic group living in a small village in Boulpon, Burkina Faso (BF), West Africa. The investigators considered the diet of these children as representative of a traditional African diet. They compared the microbiome of the BF children with that of children of the same age living in the urban area of Florence, Italy. The BF children's diet consisted mostly of millet grain, sorghum (both ground into flour and made into a porridge), and black-eyed peas and other vegetables. The diet was low in calories and high in carbohydrates, fiber, and nonanimal protein. The children from Florence consumed a diet that the investigators considered typical of the

Western world, a diet high in fat, animal protein, sugar, and starch but low in fiber. The investigators put forth that the isolation of the BF village where the children lived, compared with urbanized areas, suggested that their diet probably resembled that of the Neolithic populations following the agricultural revolution.¹⁷ Using genetic sequencing and biochemical analyses, the researchers in that study found that the BF children had higher levels of Bacteroidetes and lower levels of Firmicutes than the Florentine children, implying that the microbiome of the BF children had coevolved with a high consumption of low-calorie, fiber-rich diets and that the microbiome of the Florentine children was modified by the high-fat and high-sugar diet that could potentially predispose them to future obesity.¹⁷

CHILDHOOD MICROBIOME IN RELATION TO LATER OBESITY

The prevalence of certain microbiome species in early childhood may be linked to overweight and obesity in later life.¹⁸ Normal-weight infants aged 6 and 12 months showed higher levels of bifidobacteria than children of the same ages who developed obesity at the age of 7 years. Breastfeeding played a determining role in the microbiome composition and in lowering the propensity to obesity in later life.¹⁸ Bifidobacteria, especially *Bifidobacterium breve*, *B. infantis*, and *B. longum*, typically colonized the gut microbiome of healthy breastfed infants, reducing the risk of these children being overweight or obese in childhood by 13%–22%. The longer an infant was breast-fed, the lower the likelihood of later-life obesity.¹⁸

ARTIFICIAL SWEETENERS AND OBESITY

Artificial sweeteners consumed to combat weight gain may contribute to obesity by altering the microbiome and inducing metabolic changes associated with the metabolic syndrome.¹⁹ Mice fed saccharine, sucralose, or aspartame for 11 weeks showed glucose intolerance, compared

with control mice fed glucose or sucrose, which remained glucose tolerant. Saccharine exerted the most profound effect and was used in further studies as the prototype sweetener. A high-fat diet induced glucose intolerance in mice fed saccharine but not in control mice fed glucose. Antibiotic treatment that killed the microbiome prevented glucose intolerance. Feces transplanted from glucose-intolerant, saccharine-fed mice to germ-free mice induced glucose intolerance in the germ-free mice, suggesting that metabolic derangements that occurred following the intake of the artificial sweetener were mediated by the gut microbiome.¹⁹

In a human study, long-term intake of saccharine by 381 individuals without diabetes (44% males, 56% females) correlated with weight gain and a higher fasting glucose level.¹⁹ In a prospective study, healthy volunteers (five males and two females, ages 28–36 years) who had not used artificial sweeteners consumed the U.S. Food and Drug Administration maximal daily accepted dose of commercial saccharine (5 mg/kg body weight) for 5 days. Most (four of seven) of the volunteers showed glucose intolerance within days after saccharine consumption. Three were nonresponders and remained glucose-tolerant after saccharine consumption, indicating differences in human metabolic responses to the artificial sweetener. The responders showed pronounced changes in their microbiome, whereas nonresponders had few alterations. Taking stool from responders before and after saccharine consumption and transferring it into germ-free mice resulted in a changed microbiome and glucose intolerance only in the mice given stool from the saccharine consumers, taken after saccharine consumption. By contrast, mice that received stool from nonresponders displayed normal glucose tolerance and an unchanged microbiome.¹⁹

These studies suggest that using certain sugar substitutes to prevent obesity may potentially increase the risk of obesity in some people by altering the gut microbiome and inducing metabolic changes associated with obesity. Responses and the final outcome, however, are individualized, driven by personal differences in the microbiome and the possibility of its modification by a particular sweetener.

DIETARY MANIPULATION OF THE GUT MICROBIOME

PREBIOTICS

Prebiotics are nondigestible foods that stimulate the growth and/or activity of colonic microbes.^{20–27} They offer a safe means of modulating the gut microbiome with a potential to improve host–bacterial interactions in obesity.^{21,22} Prebiotics alter the microbiome, predominantly by increasing the concentration of bifidobacteria.^{25,26} The reported metabolic changes that take place include a reduction in hepatic cholesterol and triglyceride, a lowering of inflammation markers,²³ enhanced satiety,²⁴ and reduced body fat in children with obesity.²⁶ Volunteers ingesting the fructooligosaccharide inulin at 10 g/day for 16 days showed an increase in *Bifidobacterium adolescentis* from 0.89% at baseline to 3.9%.²⁵

PROBIOTICS

Probiotics are live bacteria and are found in yogurt, kefir, fermented cheese, and standardized supplements. Probiotics modulate the microbiome, but in contrast to prebiotics, they persist for short periods after intake and do not become permanent members of the microbiome.²⁸

Animal and human studies provide evidence that selective probiotics may help prevent adiposity.^{29–31} Investigators tested the effects of a proprietary probiotic formula on weight control, using the probiotic supplement VSL#3 that contains eight strains of live bacteria: *Streptococcus thermophilus*, *B. brevis*, *B. longum*, *B. infantis*, *Lactobacillus acidophilus*, *L. plantarum* and *L. paracasei*. In the study, 20 nonobese healthy young males consumed a high-fat diet for 2 weeks, with 10 given VSL#3 and the other 10 a placebo. The probiotic-treated males gained less weight than those on placebo.²⁹

SELECTIVE PROBIOTICS MAY PROMOTE WEIGHT GAIN

Probiotics have been used in agriculture to promote the growth of farm animals. Under certain circumstances, selected microbes may similarly affect humans by modifying the microbiome.³² High

levels of certain intestinal lactobacilli can increase weight and hyperglycemia in healthy adults, though the effects are strain- and dose-specific. Both the bacterial strain and the host are important in determining whether a probiotic preparation will play a role in inhibiting or promoting weight gain, and it is possible that certain marketed probiotics may contain strains that favor obesity. *Lactobacillus acidophilus* intake, as well as *L. fermentum* and *L. ingluviei*, were associated with weight gain in humans and animals, whereas intake of *L. gasseri* or *L. plantarum* by obese humans and animals resulted in weight loss.^{32,33} Because most commercial probiotic preparations include *Lactobacillus* strains, it may be advisable to monitor the strains of *Lactobacillus* in the preparation.

Probiotics may be targets for phage infection. So far, there has been limited scientific interest in the identification of phages specific for probiotic bacteria. New methods are needed to prevent or limit the potential negative effects of phage infections on probiotic cultures.³⁴

ALTERING THE MICROBIOME BY SYNBIOTICS AND FECAL TRANSPLANTS

Synbiotics that combine prebiotics and probiotics support the survival of probiotic strains by providing them with prebiotic substrates for fermentation.³⁵ Though *in vitro* studies have shown that synbiotics are more effective than prebiotics or probiotics in altering the gut microbiome, human studies on the use of synbiotics in treating obesity are limited.³⁶ Fecal transplant from lean to obese persons as a means to treat obesity was reported to increase insulin sensitivity.³⁷ Using this method as an antiobesity treatment requires caution because of the danger of including viral pathogens in the fecal transplant.

CLINICAL CONSIDERATIONS

Diet can selectively modify the composition of the microbiome within 1 day. Both the content of the

diet and its caloric value are critical. High-fat diets or diets rich in calories from carbohydrates increase the proportion of Firmicutes over Bacteroidetes, stimulating lipogenesis and weight gain. A hypocaloric (either low-carbohydrate or low-fat) diet increases the proportion of Bacteroidetes over Firmicutes in parallel with weight loss. The source of fat is important. As seen in animals, saturated fats have different effects on the gut microbiome; a changed microbiome following a feeding of unsaturated fats can protect against weight gain induced by saturated fat.⁶

A small number of trials have shown that modifying the diet by prebiotics, probiotics, or synbiotics reduces metabolic markers associated with obesity.^{31,35} Large prospective studies are needed to provide conclusive answers. Prebiotics such as inulin alter the microbial composition. Probiotics must be taken regularly for an effect because the microbes do not become permanent populations in the gut. Different sources of probiotics vary in the types and counts of microbial species. Consequently, they may increase or decrease weight, depending on their content of microbial species and the receiving host.^{32,33} More studies are needed to identify and promote the growth of gut microbes that would be most effective in reducing obesity.

The ingestion of selected artificial sweeteners has been shown to increase markers of the metabolic syndrome and obesity by disrupting the microbiome.¹⁹ The effects in humans were rapid. In a small prospective study, people consuming high doses of saccharin showed insulin resistance after only 5 days. An important point was the fact that the responses varied, with some individuals unaffected by the artificial sweetener.¹⁹ These unexpected results on the role of artificial sweeteners in weight gain must be confirmed in larger human studies.

POTENTIAL FUTURE DIRECTIONS

Fighting obesity by regulating the gut microbiome is of growing interest to researchers, commercial companies, and governments. Biotechnology companies are already investing hundreds of millions of dollars in developing a drug based on the

human microbiome that will transform the medical treatment of obesity. The White House announced a National Microbiome Initiative in May 2016 to support collaborations between the public and private sectors in developing technologies to generate insight into and expand education on the microbiome.

A greater understanding of the relationships among diet, age, sex, and the microbiome, including host–microbe and microbe–microbe interactions, as well as the modifying effects of specific prebiotics and probiotics, will be crucial in developing a remedy to help control obesity.³⁸ Approaches may include

identifying foods that affect microbiome genes in relation to obesity and elucidating communication pathways between the gut microbiome and the satiety center in the brain. In summary, a combination of cutting-edge techniques and well-designed human studies are necessary to unravel some of the complexities associated with the microbiome, human genetics, and lifestyle, as well as to help remedy the growing global problem of obesity.

COMPETING INTERESTS

The author declares she has no competing interests.

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