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# Role of the Microbiome in Energy Regulation and Metabolism




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**Intestinal microbes regulate metabolic function and energy balance; an altered microbial ecology is believed to contribute to the development of several metabolic diseases. Relative species abundance and metabolic characteristics of the intestinal microbiota change substantially in those who are obese or have other metabolic disorders and in response to ingested nutrients or therapeutic agents. The mechanisms through which the intestinal microbiota and its metabolites affect host homeostasis are just beginning to be understood. We review the relationships between the intestinal microbiota and host metabolism, including energy intake, use, and expenditure, in relation to glucose and lipid metabolism. These associations, along with interactions among the intestinal microbiota, mucus layer, bile acids, and mucosal immune responses, reveal potential mechanisms by which the microbiota affect metabolism. We discuss how controlled studies involving direct perturbations of microbial communities in human and animal models are required to identify effective therapeutic targets in the microbiota.**

*Keywords:* Obesity; Energy Expenditure; Bile Acids; Gut Microbiota.

The obesity pandemic presents a considerable challenge for health care systems worldwide. More than 500 million people are obese, and the prevalence of obesity is increasing rapidly.[1] Obese people are at risk for developing dyslipidemia, nonalcoholic fatty liver disease, and insulin resistance.[2] Notably, approximately one-half of all obese people develop metabolic syndrome, which is strongly associated with greater amounts of abdominal adipose tissue, although little is understood about the mechanisms of this association.[2] However, obese insulin-resistant patients who undergo either subcutaneous adipose tissue removal[3] or surgical removal of intra-abdominal adipose tissue do not have increased insulin sensitivity.[4]

What other factors could contribute to insulin resistance in obese people? Based on findings from animal studies, the intestinal microbiota is involved in the development of insulin resistance.[5] Metabolic syndrome is a chronic inflammatory disease, and translocation of intestinal bacteria has been proposed to promote metabolic endotoxemia.[6] Several studies have associated obesity with insulin resistance and increased levels of plasma lipopolysaccharide (LPS)-binding protein.[7,8] Transplantation of fecal preparations from lean donors can temporarily improve insulin sensitivity.[9] These findings indicate a relationship among the intestinal microbial, bacterial translocation, and host metabolism.

It is a challenge to study the effects of the microbiota on human metabolism. The human intestinal microbiome includes 3000 to 5000 species that share a collective (meta) genome comprising nearly 5 million genes.[10] High-throughput sequencing has allowed for comprehensive analyses of the intestinal metagenome based on the genetic material from fecal samples. When metagenomic analysis data are compared with clinical symptoms or disease, the analysis is called a metagenome-wide association study.[11] Such studies have shown significant differences in the composition of the intestinal microbiota metagenome between metabolically healthy and unhealthy subjects.[12,13] Studies of germ-free mice have implicated the intestinal microbiota in drug metabolism and macronutrient digestion,[14] and antibiotic treatments aimed at reducing the bacterial load in the intestine have profound effects on the production of metabolites by the gut microbiota.[15]

***Abbreviations used in this paper:*** **FMT, fecal microbial transplantation; LPS, lipopolysaccharide; RYGB, Roux-en-Y gastric bypass; SCFA, short-chain fatty acid; TMA, trimethylamine; TMAO, trimethylamine-*N*-oxide.**


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Obesity and insulin resistance are closely related to the presence of (visceral) adipose tissue inflammation. For example, adipose tissue produces numerous inflammatory cytokines,[16] and there is evidence that visceral adipose tissue—and, to a lesser extent, subcutaneous adipose tissue—can promote insulin resistance.[17] The presence of subcutaneous adipose tissue macrophages and crown-like structures (or accumulated CD68-positive macrophages) correlates with expression of genes that control inflammation,[18] indicating a role for the innate immune system in insulin resistance.[19] Changes in intestinal microbiota cause long-term changes in inflammation in obese subjects[12]; bacterial endotoxins such as LPS activate pattern recognition receptors such as Toll-like receptors, leading to an innate immune response and insulin resistance.[20] The intestinal microbiota also produces many molecules that promote inflammation, such as peptidoglycans[21] and flagellins,[22] which activate inflammatory pathways, resulting in obesity and insulin resistance.

Short-chain fatty acids (SFCAs) are produced by intestinal bacteria and may play important roles in dampening the adverse effects of intestinal pathogens on host metabolism. Diet-derived fibers are metabolized and fermented to SCFAs such as acetate, propionate, and butyrate by intestinal bacteria.[23] Germ-free mice produce almost no SCFAs and therefore have altered responses to inflammatory stimuli.[24] SCFAs may serve as an energy source for the intestinal epithelium and liver, given their transport predominantly via the portal vein after intestinal absorption. SCFAs might also modulate the immune response by reducing intestinal permeability.[25] This hypothesis is supported by the observation that translocation of LPS from the gut to the portal vein produces obesity-associated low-grade inflammation and subsequent insulin resistance in mice, which can partly be reversed by administration of the propionate-producing bacteria *Akkermansia muciniphila*.[26]

Besides obesity, the intestinal microbiota might also be involved in atherogenesis. Specific dietary nutrients characterized by trimethylamine groups (eg, choline, phosphatidylcholine, and carnitine) are metabolized into the atherogenic compound trimethylamine-*N*-oxide (TMAO) by bacteria.[27,28] Studies using germ-free mice or mice given broad-spectrum antibiotics showed that the intestinal microbiota is required for formation of trimethylamine (TMA) and TMAO.[29] Further, bacterial colonization of germ-free mice increases their plasma levels of TMAO, indicating that the intestinal microbiota is required for generation of TMA from sources of dietary choline or carnitine (such as eggs, milk, and red meat).[30] For example, carnitine is an abundant nutrient in red meat, and the intestinal microbiota mediates production of TMAO from dietary L-carnitine.

## Alteration of the Gut Microbiota in Obesity and Diabetes

The intestinal microbiota is altered in humans and animal models of obesity.[31] The intestinal (cecum-derived) microbiota of *ob/ob* mice has a 50% reduction in levels of Bacteroidetes and an increased proportion of Firmicutes compared with wild-type mice.[32] The composition of the fecal microbiota of obese human subjects is similarly affected but changes with weight loss.[33] Studies in germ-free mice provide insights into the effects of the intestinal microbiota on host metabolism. Germ-free mice fed high-fat, high-sugar diets did not have the same metabolic disturbances as the littermates that were not germ free.[34] Transfer of intestinal microbiota from obese mice resulted in significantly greater adiposity in recipients than transfer of microbiota from lean donors.[35]

One way in which intestinal microbes might affect host metabolism is by extracting calories from otherwise indigestible carbohydrates[36]; these carbohydrates are fermented by intestinal microbes to produce SCFAs.[38] SCFAs may act as an energy substrate as they are absorbed by the intestinal epithelium and metabolized in the liver.[37] Mouse models of obesity and human obese subjects have increased intestinal (cecal) levels of SCFA and decreased energy content in their feces.[23]

Studies have associated changes in proportions of Bacteroidetes and Firmicutes with obesity and metabolic syndrome. Metagenome-wide association studies by Qin et al[13] (performed in China) and Karlsson et al[12] (performed in Europe) reported metagenomic differences between a cohort of patients with type 2 diabetes mellitus and a group of healthy subjects. Clusters of genomic sequences were used as signatures for specific groups of bacteria, and each study found independently that the microbiota of subjects with type 2 diabetes mellitus had a lower proportion of butyrate-producing Clostridiales (*Roseburia* and *Faecalibacterium prausnitzii*), and greater proportions of Clostridiales that do not produce butyrate, as well as pathogens such as *Clostridium clostridioforme.* Other associations differed between the 2 studies. Karlsson et al[12] detected an increased proportion of *Lactobacillus gasseri* and *Streptococcus mutans* (commensal bacteria in the mouth and upper intestinal tract) in their cohort with type 2 diabetes mellitus. Qin et al[13] observed a greater proportion of *Escherichia coli* (which produce LPS to cause endotoxemia) in patients with type 2 diabetes mellitus. These studies raise interest in the association between type 2 diabetes mellitus and reduced production of butyrate because diets supplemented with butyrate were previously shown to prevent and reverse insulin resistance in mice that became obese on high-calorie diets and increase energy expenditure.[38] Combined results from human and animal studies of obesity suggest that reduced butyrate production by the microbiota contributes to the development of insulin resistance.

## Microbiota and Bile Acids

Bile acids are secreted as glycine, taurine, or sulfate conjugates. Compounds excreted in bile reach the intestinal tract, where they can be deconjugated by gut microbiota, aided by populations of microorganisms with their own hydrolytic enzymes such as $\beta$-glucuronidase and sulfatases.[39] Most liver-secreted bile acids (95%) are reabsorbed in the ileum to be taken up by the liver in the enterohepatic