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# Gut Microbiome in Obesity, Metabolic Syndrome, and Diabetes

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**Abstract**

**Purpose of Review** Obesity and diabetes are worldwide epidemics. There is also a growing body of evidence relating the gut microbiome composition to insulin resistance. The purpose of this review is to delineate the studies linking gut microbiota to obesity, metabolic syndrome, and diabetes.

**Recent findings** Animal studies as well as proof of concept studies using fecal transplantation demonstrate the pivotal role of the gut microbiota in regulating insulin resistance states and inflammation.

**Summary** While we still need to standardize methodologies to study the microbiome, there is an abundance of evidence pointing to the link between gut microbiome, inflammation, and insulin resistance, and future studies should be aimed at identifying unifying mechanisms.

**Keywords** Microbiome · Obesity · Metabolic syndrome · Diabetes · Inflammation · Endotoxin

## Introduction

Obesity and type 2 diabetes (T2DM) have become worldwide epidemics. In 2015, 30.3 million, representing 9.4% of Americans, had diabetes [1, 2]. Every year, 1.5 million Americans are diagnosed with diabetes. As per the latest statistics, diabetes remains the seventh leading cause of death in the USA. Obesity is intertwined with the increasing incidence of metabolic syndrome and T2DM. T2DM is associated with increased incidence of micro- and macrovascular complications and thus places a huge burden on the health care system as a whole. According to the American Diabetes Association, the total cost of diagnosed diabetes in the USA in 2017 is $327 billion.

Several studies have shown that the common underpinning of obesity, metabolic syndrome, and T2DM is dysglycemia, insulin resistance, and inflammation. In recent studies, much attention has also been focused on the role of the gut microbiota in obesity, metabolic syndrome, and T2DM, and this hypothesis forms the basis of this review [3–5].

The gut microbiota refers collectively to the microbial composition in the gut and contains several diverse sets of microorganisms such as bacteria, viruses, Archaea, fungi as well as phages [6–9]. While it was thought that microbiota are 10-fold more abundant in the human body, recent data point out that there is at least equal abundance of microbiota as the total number of somatic and germ cells in a human [10]. Among all of the different bacterial species, the five most abundant phyla include *Firmicutes*, *Bacteriodetes*, *Verrucomicrobia*, *Actinobacteria*, and *Proteobacteria* [8]. Based on the pH gradient, different microbial communities inhabit different parts of the GI tract; the proximal part has an abundance of Firmicutes (Lactobacilli) as well as *Proteobacteria*, while the distal part is concentrated with anaerobes such as *Bacteriodetes*, *Verrucomicrobia*, and *Akkermansia* [11–14].

### Gut Microbiome, Obesity, and Insulin Resistance

In the last decade, several experimental studies especially in obese mouse models have demonstrated the role of the gut

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microbiome in obesity [6, 7, 15••, 16]. One of the first studies conducted in animal models with controlled diet, environment, and genotype showed that in C57BL/6 mice, which are genetically protected from developing obesity even after consuming a high-fat/high-carbohydrate diet, colonizing them with microbiota from obese mice resulted in a profound increase (60%) in body fat, and subsequently these mice became insulin resistant despite reduced food intake [3–5]. In addition, when compared to lean mice, 16S rRNA profiling demonstrated that ob/ob mice had only half the abundance of *Bacteroidetes* and a proportional increase in *Firmicutes* [3–5]. The hypothesis was that microbiota from obese mice were more efficient at extracting energy from diet than lean counterparts. Using shotgun sequencing, the authors showed that the genome of ob/ob mice predominantly had environmental gene tags encoding glycoside hydrolase (which degrades dietary polysaccharides and starch), as well as ATP-binding cassette transporters. Furthermore, the end products, acetate and butyrate, were significantly enriched in ob/ob mice compared to lean mice, demonstrating that the gut microbiome of these mice had an increased potential to harvest energy.

Proof of concept came from studies of fecal transplantation into germ-free mice. Ridaura et al. [17••] showed that fecal microbiota transplantation from female adult twin pairs that were discordant for obesity into germ-free mice that were fed low-fat mouse feed resulted in the set of mice that received a transplant from the obese donor having increased total body mass and fat mass, in addition to metabolic phenotypes that were associated with obesity, while the other set that received the lean twin's microbiome prevented the development of increased body mass and obesity-associated metabolic phenotypes. They then fed them a saturated fat diet that also included increased consumption of fruits and vegetables. Significant differences in body composition were documented between ob/ob and ln/ln mice consuming this diet. Thus, while the donor phenotype can influence the microbiome of a recipient, they demonstrated that diet continues to regulate whether these mice developed a lean or obese phenotype.

In the above study, the authors also measured increased levels of butyrate and propionate in mice that were colonized with lean human gut microbiota when compared to the gut microbiota from the obese [17••]. Additionally, they were able to demonstrate that when they performed fecal microbiota transplantation from lean human donors to obese human recipients with metabolic syndrome, this resulted in significant improvement in insulin sensitivity [18]. Furthermore, in a double-blind, randomized trial of controlled intervention, they showed that treatment with probiotics such as *Lactobacillus gasseri* resulted in significant reduction in body weight in both overweight and obese subjects [19]. These studies point to the role of the gut microbiome in regulating body weight.

## Gut Microbiome, Insulin Resistance, and Type 2 Diabetes

With regard to T2DM, one of the first studies came from the group of Larsen et al. [20] who studied 18 lean and 18 overweight males with T2DM. While the bacterial abundance was similar in both groups, the abundance of *Firmicutes* bacteria was significantly increased in controls compared to participants with T2DM. There was a corresponding upregulation in *Bacteriodetes*, but this was not statistically significant. Also, the authors did not report on the confounding effect of antidiabetic treatment on gut microbiome composition in this study.

Qin et al. [21] performed an association case-control study of metagenomes in a population of subjects with T2DM in China. Among the intestinal bacteria, compared to the controls, subjects with T2DM showed a decrease in *Clostridum* species, *Fecalibacteria* and *Roseburia*, all butyrate-producing bacteria of the *Firmicutes* phylum. There was a concomitant increase in *Bacteriodetes* species and *Escherichia coli*. Pathway analysis showed that in T2DM, there is increased membrane sugar as well as branched-chain amino acid transport and sulfate reduction. These results appear to suggest that butyrate-producing pathogens afford protection against T2DM [22, 23].

Similar to the study by Larsen et al. in males, Karlsson et al. [24] studied the fecal microbiome of 145 older women, of whom 53 had T2DM, 49 had impaired glucose tolerance, and 43 were normal. They reported that in women with T2DM, there was enrichment of four *Lactobacillus* species and decreases in the abundance of five *Clostridium* species. Furthermore, the abundance in *Lactobacillus* species correlated positively with glycated hemoglobin and glucose levels while *Clostridium* species correlated negatively. They also showed that *Roseburia* and *Fecalibacterium prausnitzii*, which are known butyrate producers, were associated with T2DM.

## Factors that Contribute to Altered Microbial Composition in Obesity and Diabetes

Insulin resistance states such as metabolic syndrome and T2DM are associated with low-grade subclinical inflammation [25, 26]. While alterations in gut microbiome in the metabolic syndrome are reported, the relationship between inflammation, gut microbiome, and metabolic derangements is not well studied. Mice that were fed a diet rich in fiber have been shown to have increased levels of short-chain fatty acids and developed less allergic lung inflammation than mice fed a low fiber diet. Also, treatment with one of the short-chain fatty acids, propionate, resulted in an abundance of macrophage and dendritic cells.

Inflammation plays a key role in metabolic disease involving insulin resistance such as obesity, metabolic syndrome and T2DM [27–29]. In one of the pioneering studies, Cani et al. [30••, 31, 32] demonstrated a link between the gut microbiome and the pro-inflammatory state of the metabolic syndrome. In mice fed high fat diet, there was increased endotoxinemia, and this was associated with decreased abundance of gram-negative *Bacteriodes* and gram-positive *Clostridia* and bifidobacteria. In support of these preclinical findings, the DESIR study examined the development and pattern of metabolic syndrome and associated complications and also reported dysbiosis of the gut microbiome, evidenced by decreased bacterial DNA content and increased abundance of *Proteobacteria* in those patients that progressed to have cardiovascular events [33].

Two studies in humans provided further proof of concept. In both of these studies [34, 35], the authors assessed the fecal gut microbiome of 12 obese participants that enrolled in a weight loss program for 1 year, and followed a low-calorie diet that was either fat restricted or carbohydrate restricted. They reported increased abundance of *Firmicutes* and decreased *Bacteriodetes* in obese compared to lean individuals whose microbiome signature showed remarkable stability over the year. Both diets caused weight loss and this correlated to decreased content of *Firmicutes* as well as to increased amounts of *Bacteroidetes* (3–15%). Thus, all of the studies point to the gut microbiome as a contributing factor to obesity. Kalliomäki et al., in a prospective study of children that were followed from birth up to the age of 7 years [36], collected fecal specimens at 6 and 12 months of age. They showed increased *Bifidobacterium* taxa and decreased *Staphylococcus aureus* in normal weight compared to overweight or obese children.

The administration of antibiotics has an opposite effect on gut microbiome [37]. Toll-like receptors (TLRs) are a family of key pattern recognition receptors that aid cells in recognizing ligands such as endotoxin and mediating inflammation and immunity. We and others have shown increased expression and activity of TLRs that are present on cell surfaces in patients with obesity, diabetes, and metabolic syndrome [38–40]. Recently, studies have focused on the role of the gut microbiome in regulating TLR-mediated insulin resistance. TLR5-deficient mice are hyperphagic and develop obesity, insulin resistance, and features of the metabolic syndrome, a process that is associated with dysregulation of interleukin-1$\beta$ signaling [41]. When gut microbiota of these mice are transplanted into wild-type TLR5 mice, the recipient mice also influence the gut microbiome in a way that predisposes to the metabolic syndrome. Similarly, TLR2-deficient mice are reported to have increased *Firmicutes* and decreased *Actinobacteriai*, and they subsequently develop insulin resistance, obesity, and metabolic syndrome. Treatment with antibiotics decreased the abundance of *Firmicutes* and eventually improved insulin action and sensitivity. Furthermore, since *Bifidobacterium* can result in increased gut permeability, it is possible that a dysregulated microbiome could lead to a leaky gut, thereby yielding increased metabolic endotoxemia and increased TLR activity, begetting more inflammation. We have previously shown that both TLR2 and TLR levels and activity are increased in monocytes of patients with metabolic syndrome and diabetes. Furthermore, when either TLR2 or TLR is deficient, there is decreased preponderance of diabetic complications such as diabetic nephropathy [42–48]. Thus, the gut microbiome may also contribute to insulin resistance and associated diabetic vasculopathies, and this area will be a key area of future investigation.

Inflammasomes also regulate inflammation by sensing endogenous or exogenous damage-associated molecular patterns referred to as DAMPs [49, 50]. These proteins exist as multiprotein complexes and convert pro-inflammatory cytokines such as interleukin (IL)-1β and IL-18 to their active forms in response to "alarm" signals. In NLRP6 deficiency [49, 51], there are decreased IL-18 levels and altered fecal microbiota, characterized by increased abundance of *Bacteroidetes* (*Prevotellaceae*). We have recently shown that NLRP3 inflammasome activation in the diabetic milieu increases monocyte activation and alters gut microbiota resulting in gut dysbiosis, all of which are eliminated via knockout of the inflammasome pathway [51].

## Anti-Diabetic Therapy and Gut Microbiome

There are several therapies that are used to treat insulin resistance and diabetes, one of the most popular of these and used as first-line therapy is metformin. Some of the beneficial effects of metformin could be attributed to alteration in gut microbiota [52, 53, 54•, 55]. Metformin therapy, in addition to improving the glycemic profile of mice fed a high-fat diet, also increases abundance of *Akkermansia*, a mucin-degrading bacterium, when compared to controls fed a high-fat diet without metformin. Human studies from Danish, Swedish, and Chinese participants with T2DM on metformin therapy have corroborated these findings [52, 53, 54•, 55]. Multivariate analysis has shown that there are significant differences in gut composition between metformin-untreated participants with T2DM vs controls and significant increases in *Escherichia* species and decrease in *Intestinibacter* after metformin therapy.

Morbid obesity can be improved by gastric bypass or bariatric surgery. Diet-induced obese (DIO) C57BL/6 J mice that were fed a high-fat diet underwent Roux-en-Y gastric bypass (RYGB) surgery, sham surgery, or sham surgery along with caloric restriction [56–58]. RYGB altered gut microbial composition as early as 1 week post-surgery and stabilized after 5 weeks. Mainly, RYGB produced enrichment of *Bacteroidetes*, *Verrucomicrobia*, and *Proteobacteria*. In a set

of provocative experiments, when the authors inoculated lean, germ-free mice from RYGB donors, there was a significant reduction in body weight, improved insulin sensitivity, and decreased triglycerides [56–58]. Whether other widely used antidiabetic drugs such as glucagon-like peptide 1 (GLP-1) receptor agonists and GLP-1 degradation inhibitors [59–62] act via altering microbiota awaits results of large trials.

## Conclusions

The last few decades have shed light on the role of the gut microbiome in linking inflammation and insulin resistance. We are just at the tip of the iceberg of understanding host-microbiome interactions and specific mechanisms of modulation. Methodologies to identify gut microbial composition and function need to be standardized to allow the performance of meta-analyses, and facilitate the understanding of the role of mechanistic pathways involving short-chain fatty acids, propionate, butyrate, bile acids, lipopolysaccharide, TLRs, and NLRP inflammasomes in the pathogenesis of complications of obesity, metabolic syndrome, and diabetes.

### Compliance with Ethical Standards

**Conflict of Interest** Xinpu Chen and Sridevi Devaraj declare that they have no conflict of interest.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

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