The Gut Microbiota

The Gateway to Improved Metabolism

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KEYWORDS

• Microbiota • Metabolism • Bariatric surgery • Enteroendocrine hormones
• Lipid absorption • Probiotics • Prebiotics • Synbiotics

KEY POINTS

- Shifts in the gut microbiome are inseparably associated with the development of obesity and comorbidities.
- Transfer of dysbiotic microbial communities confers disease phenotypes in recipients, supporting a central role for microbe-mediated regulation of metabolism.
- Bariatric surgery, the most effective treatment of morbid obesity, results in rapid changes in the gut microbiota, with concurrent improvements in metabolic parameters.
- Deeper understanding of host-microbe interactions may hold promise in the treatment of obesity, which remains a global epidemic.

INTRODUCTION: OBESITY AND THE GUT MICROBIOTA

The increase of obesity and its related comorbidities in westernized countries over the past 4 decades presents an emerging global epidemic with profound challenges to world health care economies and societies. In the past 35 years, the rate of adult obesity has risen by 75% globally.[1,2] This number is greater among children.[3,4] Stratified assessment of body mass index further shows disproportionate increases among the most severely obese ($\geq$35 kg/m^2), compared with the lesser obese ($\geq$30 kg/m^2), showing the scale of the problem. However, obesity and its comorbidities,[5] including metabolic syndrome, diabetes, and heart disease, have detrimental effects on quality of life and substantial costs to individuals and societies. Thus, the need for understanding the complexity of pathophysiologic events and elucidating effective interventions remain urgent.

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The cause of obesity is multifactorial, including the complex interaction of genetics and environment, which encompasses diet, developmental factors, lifestyle (eg, hedonistic tendencies, altered sleep patterns), and antibiotic use. Intestinal microbes are affected by all of these factors in their community structure and function, and in turn initiate host-microbe interactions that may disrupt metabolic and immune homeostasis. Fecal microbiota transplant (FMT) of microbes under environmental stressors, like diet and obesity, can induce a similar phenotype in recipients.[6] The gut microbiome is by definition a microbial organ (vital to intestinal and systemic functions), and one that people cannot live without, but is also an organ that is transplantable (ie, via FMT). This technique is commonly used for *Clostridium difficile* infection and has only recently been studied for use in other conditions, including obesity. However, other therapies targeting the microbiome, such as prebiotics and probiotics, may confer modest, but positive, improvements for symptoms associated with obesity and its comorbidities.

Although an extreme measure reserved for the morbidly obese, one of the most effective strategies to decrease obesity is bariatric surgery, which profoundly changes the gut microbiota and energy balance, and alters physiologic and endocrine metabolic states.[7] It is expected that by changing metabolic set points, desired weight can be achieved. Therefore, understanding of the mechanisms behind bariatric surgery and associated changes in the gut microbiota may be leveraged to develop new therapies to fight the obesity epidemic. This article explores these concepts by providing an overview of altered microbial structure and function in obesity, host-microbe interactions driving obesity, dietary influence on the microbiome, improvements in metabolism and microbial structure with Roux-en-Y gastric bypass (RYGB), the host-microbe interactions driving obesity, and current therapies targeting the gut microbiome to facilitate positive metabolic outcomes.

PARADIGMS IN GUT MICROBIOTA DURING OBESITY

Obesity-Driven Alterations in Gut Microbiota

The human body contains huge numbers of microbes, including thousands of bacterial species, in addition to many eukaryotes, Achaea, protists, and viruses, which collectively contain an estimated 5 million genes that have profound metabolic and immunomodulatory effects on their mammalian hosts.[8] The community of microbes is termed the microbiota, whereas their collective genes are called the microbiome. Both the state of obesity and westernized diets are associated with microbial dysbiosis, which is a deviation from microbial organization that would otherwise promote optimal metabolic homeostasis. Dysbiotic microbiota in obesity is characterized by decreased diversity in the microbial community and by an increased ratio of the phylum Firmicutes to the phylum Bacteroidetes.[9] The change in the Firmicutes/Bacteroidetes ratio occurs in both mice and humans, and weight loss restores microbial composition.[9–11] Note that 3 genera of bacteria are often overrepresented in obesity in humans: *Bacteroides* and *Prevotella* (both Bacteroidetes) and *Ruminococcus* (Firmicutes).[12] In addition to composition, major functional differences are observed in metabolic capacity of the microbial community. For instance, decreases in short-chain fatty acid (SCFA) producers, such as from the phylum Actinobacteria and blooms in pathogenic bacteria from the phylum Proteobacteria, occur in obesity.[13] In addition to bacteria, recent work shows that the microbiota metabolic networks include yeast and archaea, which synergistically produce and use metabolites collectively with bacteria.[14] Although this area is still underexplored, recent work suggests that yeast species abundance is lower in obesity, and supplementation with *Saccharomyces cerevisiae* improves metabolic parameters and adiposity.[15–17]