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Chapter

Gut Microbiome in Obesity Management

Hassan M. Heshmati

Abstract

Obesity is a worldwide pandemic causing increased morbidity/mortality and high cost for the society. Management of obesity requires multidisciplinary approaches including diet, food supplement, exercise, behavior change, drug, medical device, gut microbiome manipulation, and surgery. Over the past two decades, there has been a growing awareness of the importance of gut microbiome in human health and disease. Profound changes affecting the diversity and the abundance of gut microbiome are associated with several disorders including obesity. A decrease in microbiome diversity and an increase in the ratio of Firmicutes-to-Bacteroidetes phyla have been reported in obese subjects. The gut microbiome can be manipulated to change the host metabolism and manage obesity. Potential interventions include diet (e.g., low calories, low fat, and high fiber), prebiotics (e.g., inulin, lactulose, and resistant starch), probiotics (e.g., yogurt, cheese, and milk), synbiotics (combination of prebiotics and probiotics), bariatric surgery (e.g., Roux-en-Y gastric bypass), and fecal microbiota transplantation (through colonoscopy, esophagogastroduodenoscopy, orogastric tube, or oral capsule). A better understanding of the interactions between different diets and gut microbiome should help the development of new guidelines for the prevention and management of obesity.

Keywords: gut microbiome, obesity, weight management

1. Introduction

Obesity is excess body weight for a given height, defined by a body mass index (BMI) $\geq$ 30 kg/m^2. In some Asian countries (e.g., Japan), the threshold to define obesity is 25 kg/m^2. The main cause of obesity is an imbalance between energy intake and energy expenditure. Obesity is a worldwide pandemic associated with increased morbidity/mortality and high cost for the society. The prevalence of obesity is increasing exponentially. The number of adult subjects with obesity is around 700 million worldwide. Near 4 million subjects die each year from the consequences of obesity. The annual cost of obesity is more than $2 trillion [1–3].

Management of obesity requires multidisciplinary approaches including diet, food supplement, exercise, behavior change, drug, medical device, gut microbiome manipulation, and surgery [1, 4–9]. The annual obesity treatment market is around $6 billion.

The human intestine harbors a complex and diverse microbial ecosystem referred to as gut microbiome [10–14]. This rich community of microorganisms

has co-evolved in a symbiotic relationship with humans. Its diversity is influenced by several factors including host genetics, mode of birth, age, gender, pregnancy, BMI, diet, medications, and surgery [12, 15–31]. The understanding of the gut microbiome evolves at a rapid pace, but the practical application of this knowledge is still in its infancy. The gut microbiome is essential for the maintenance of human health. It is involved in protection against pathogens and regulation of immune system and metabolism [32]. Profound changes affecting the diversity and the abundance of gut microbiome (dysbiosis) are associated with several disorders including obesity [33]. The prevention and management of obesity may benefit from manipulation of gut microbiome.

2. Gut microbiome description and composition

Gut microbiome is a complex community of microorganisms living in the digestive tract, mainly in the colon (**Figure 1**). Variable pH and oxygen concentration affect the abundance of gut microbiome across the gastrointestinal tract. Gut microbiome represents up to 60% of the dry mass of feces (biomass around 1.5 kg), has more cells than host somatic cells and at least 100 times more genes than human genome [10–14].

Gut microbiome is established within the few first years of life and contains up to 100 trillion microbes, mainly bacteria (more than 1,000 species) but also fungi, protozoa, archaea, and viruses. The taxonomic ranking of gut microbiome includes species, genera, families, orders, classes, and phyla. Most of the species belong to Actinobacteria, Bacteroidetes, Firmicutes, Proteobacteria, and Verrucomicrobia phyla. The predominant phyla (90%) are Firmicutes (e.g., *Ruminococcus* and *Lactobacillus* genera) and Bacteroidetes (e.g., *Bacteroides* and *Prevotella* genera). Three enterotypes with functional differences have been defined based on variation in the level of genera: Enterotype 1 (*Bacteroides*), Enterotype 2 (*Prevotella*), and Enterotype 3 (*Ruminococcus*).

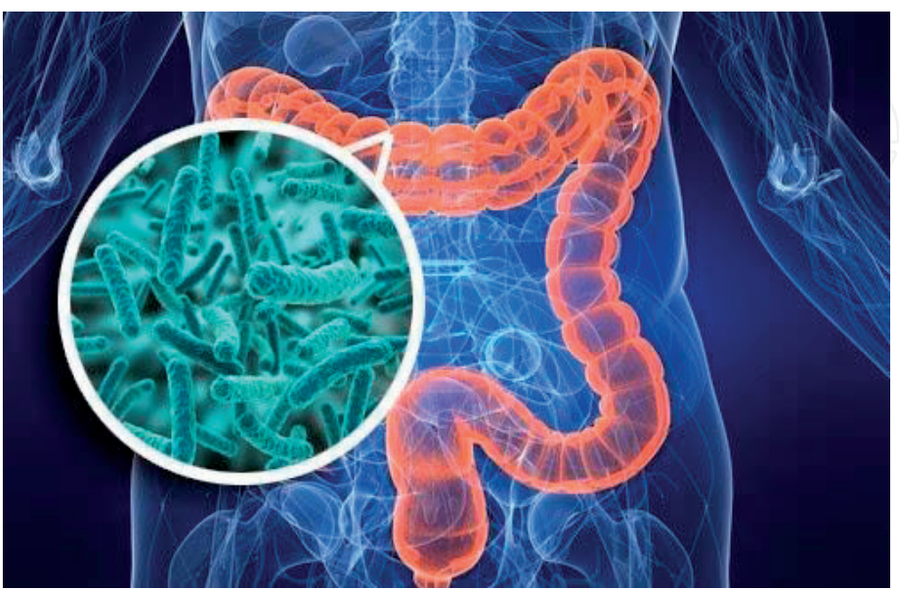

Figure 1.
Gut microbiome is mainly located in the colon (Picture downloaded from the internet).

3. Gut microbiome projects

There are two major gut microbiome projects: European Megagenomics of the Human Intestinal Tract and US Human Microbiome Project [11]. For gut microbiome studies, multiple fecal collections of the same subject are recommended. The assessments are DNA-based methods (16S rDNA sequencing, whole genome shotgun sequencing) (**Figure 2**) [32, 34, 35]. The challenges in the assessments of gut microbiome are due to the diversity and the inter/intra-individual variability caused by different factors such as age and diet.

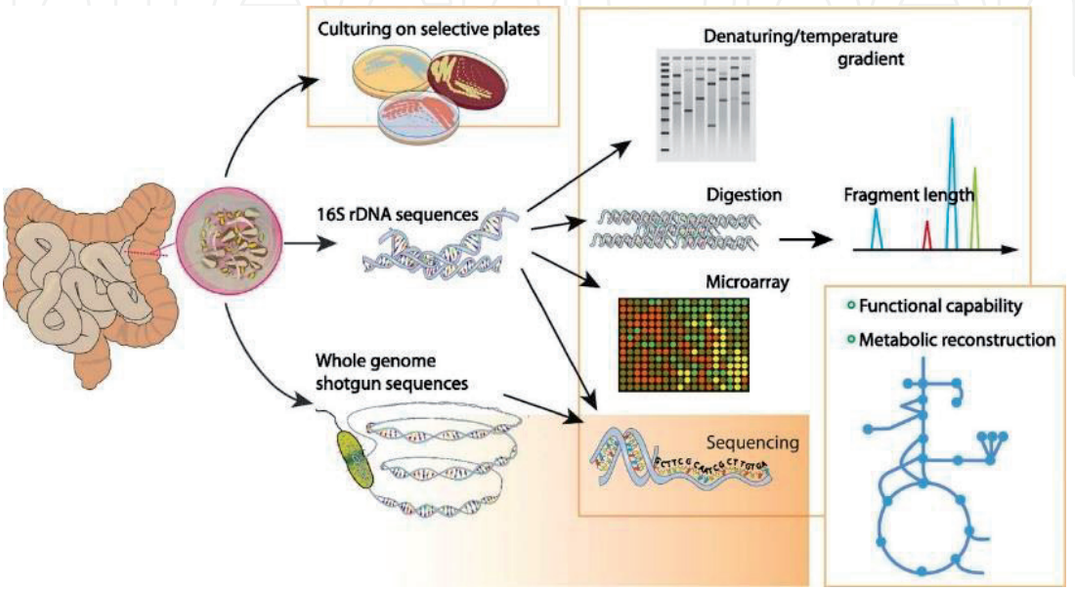

Figure 2.
Assessment of gut microbiome (Picture downloaded from the internet).

4. Gut microbiome metabolism

4.1 Nutrition sources

The sources for nutrition of gut microbiome are ingested dietary components (carbohydrate, protein, lipid) and host-derived components (shed epithelial cells, mucus).

4.2 Metabolites

Several metabolites are produced by gut microbiome. They include short-chain fatty acids (following carbohydrate fermentation), phenolic substances (following protein fermentation), and vitamins (vitamin B, vitamin K).

5. Gut microbiome changes

Gut microbiome is diverse, varies between individuals, and can fluctuate over time. Western gut microbiome has less species than non-Western gut microbiome.

In addition to several pathological conditions that can alter gut microbiome composition, multiple factors are responsible for the changes in gut microbiome (**Figure 3**) [12, 15–31].

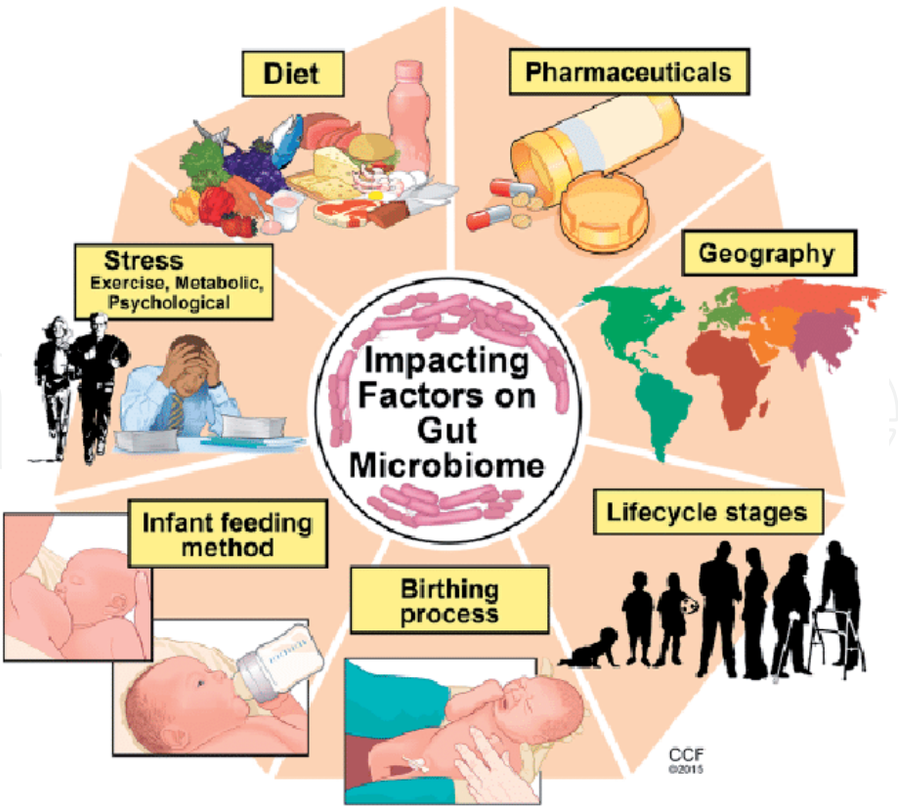

Figure 3.
Multiple factors can impact gut microbiome (Picture downloaded from the Internet).

5.1 Host genetics

There are possible relations between host genetic profile and gut microbiome composition, but additional studies are needed for a better understanding of these relations [15].

5.2 Mode of birth

Mode of birth has an important influence on gut microbiome composition [12, 16]. With vaginal delivery, infants are colonized by maternal vaginal bacteria (dominated by *Lactobacillus* and *Prevotella* genera) while following C-section delivery, infants are colonized by maternal skin bacteria (dominated by *Staphylococcus*, *Corynebacterium*, and *Propionibacterium* genera).

5.3 Age

Age is associated with important changes in gut microbiome [12, 17]. The changes occur mainly before 20 and after 70 years. The diet plays a significant role. In preterm infants, there is a predominance of Proteobacteria phylum. There are marked changes in infants. The choice of diet after birth (breast milk or formula milk) affects the colonization process in the newborn. With age, the introduction of solid food from 2 years and the production of sex hormones from puberty (to menopause in females) bring additional richness and complexity to gut microbiome. There is a relative stability of gut microbiome between 20 and 70 years (predominance of Firmicutes phylum). In elderly subjects, Bacteroidetes phylum is predominant.

5.4 Gender

Gender specificity of gut microbiome appears at puberty with the production of sex hormones [12, 18]. There is a lower abundance of Bacteroidetes phylum in women (role of estrogen).

5.5 Pregnancy

Elevated levels of estrogen and progesterone observed during pregnancy have important impact on gut microbiome [12, 16, 19]. The changes are characterized by a decrease in richness of gut microbiome, a higher abundance of Proteobacteria and Actinobacteria phyla, a decrease in *Faecalibacterium* genus, and an increase in Firmicutes-to-Bacteroidetes phyla ratio.

5.6 BMI

BMI is associated with gut microbiome composition particularly in women [18]. Bacteroidetes phylum is less abundant in subjects with high BMI. The role of estrogen has been proposed.

5.7 Diet

Diet has an important influence on gut microbiome composition [20–25]. However, there is a high interindividual variability. A diet high in fat (≥ 55% of total macronutrients) is associated with increased Firmicutes and Proteobacteria phyla and decreased Bacteroidetes phylum while a diet rich in fiber (≥ 30 g/day) has the opposite effect. The changes in gut microbiome (composition and functionality) induced by diet can be observed as early as 2 days. However, major changes in gut microbiome require long-term change in dietary habits.

Important differences in gut microbiome have been reported in children between Europe and rural African village of Burkina Faso (polysaccharide-rich diet) with Firmicutes-to-Bacteroidetes phyla ratios of 2.8 and 0.5, respectively [26].

Diet may also contribute to the seasonal variations of gut microbiome likely due to different availability of fresh produce containing complex carbohydrates [27].

5.8 Medication

Several medications (e.g., antibiotics, nonsteroidal anti-inflammatory drugs, proton pump inhibitors, and metformin) affect gut microbiome [28–30]. The use of antibiotics is associated with increased Firmicutes phylum, with higher sensitivity in infants.

The impact of prebiotics and probiotics on gut microbiome is presented in Section 8.

5.9 Surgery

Since colon is the main reservoir of gut microbiome, surgical removal of colon may affect gut microbiome [31]. Indeed, right hemicolectomy for colorectal cancer has been reported to be associated with a decrease in diversity and richness of gut microbiome.

The impact of bariatric surgery on gut microbiome is presented in Section 8.

6. Gut microbiome functions

The gut microbiome is involved in multiple physiological functions (**Table 1**) [32, 36–41].

Function of gut microbiome	Mechanism and target
Protection	Killing or inhibiting unwanted organisms competing for nutrients
Immune system	Influencing production of cytokines and antibodies
Metabolism	Regulating energy homeostasis, producing short-chain fatty acids and vitamins, impacting glycemic control, interacting with incretins, regulating metabolism of lipids and bone

Table 1.
Physiological functions of gut microbiome.

6.1 Protection against pathogens

Gut microbiome can protect against pathogens by killing or inhibiting unwanted organisms (e.g., *Clostridium difficile* genera) that are competing for nutrients.

6.2 Regulation of immune system

Gut microbiome regulates immune system by influencing the production of cytokines and antibodies.

6.3 Regulation of metabolism

Gut microbiome is involved in several metabolic processes. These processes include regulation of energy homeostasis and body weight, production of short-chain fatty acids (following fermentation of nondigestible fibers) and vitamins (vitamins B, vitamin K) [32, 36], glycemic control [37, 38], interaction with incretins [39], and metabolism of lipids [40] and bone [41].

7. Gut microbiome in diseases

Dysbiosis is observed in several medical conditions including obesity, malnutrition, type 2 diabetes, inflammatory bowel diseases, neurological disorders, and cancer [33, 42–48]. The dysbiosis can be the cause and/or the consequence of these diseases.

Gut microbiome influences drug pharmacokinetics and bioavailability, and thus, affects the efficacy and safety of several drugs used to treat diseases [49].

8. Gut microbiome and obesity

8.1 Gut microbiome composition in obesity

Although there are some conflicting data, most studies have reported that in obesity, there is a lower gut microbiome diversity, a higher abundance of Firmicutes

phylum, a lower abundance of Bacteroidetes phylum, and a higher Firmicutes-to-Bacteroidetes phyla ratio [33, 42–45]. There is also a higher abundance of *Lactobacillus* (genus belonging to Firmicutes phylum).

According to most studies, the low-grade inflammation stimulated by lipopolysaccharide production is the prime mechanism by which gut microbiome induces obesity [50].

8.2 Gut microbiome in obesity management

Gut microbiome can be manipulated for the purpose of obesity management using different tools (**Table 2**) [20, 21, 50–60].

Tool for gut microbiome manipulation	Description
Diet	Low calories, low fat, high fiber
Prebiotics	Inulin, lactulose, resistant starch
Probiotics	Yogurt, cheese, milk
Synbiotics	Combination of prebiotics and probiotics
Bariatric surgery	Roux-en-Y gastric bypass
Fecal microbiota transplantation	Addition of healthy stool

Table 2.
Different tools used for gut microbiome manipulation in obesity management.

8.2.1 Diet

Diet is an important factor for the manipulation of gut microbiome and management of obesity. The amount of daily caloric intake and the content of food significantly affect gut microbiome but with high interindividual variability [20, 21, 51]. A diet that is low in calories, low in fat (< 20% of total macronutrients), and high in fiber (≥ 30 g/day) has a favorable effect on gut microbiome (increase in richness, decrease in Firmicutes-to-Bacteroidetes phyla ratio) and weight control (weight loss).

8.2.2 Prebiotics

Prebiotics are chemicals (nondigestible food ingredients) inducing growth and/or activity of bacteria [50, 52]. Prebiotics must be able to resist gastric acidity, resist enzymatic hydrolysis, resist absorption in the upper gastrointestinal tract, and be fermentable by the gut microbiome. Examples are inulin, lactulose, and resistant starch. Prebiotics can be found in many foods (e.g., leek, asparagus, onion, and soybean).

By modulating gut microbiome and lowering the production of lipopolysaccharide, prebiotics have the potential to manage obesity. In a double-blind, placebo-controlled clinical study, administration of oligofructose-enriched inulin (8 g/day) to overweight/obese children for 16 weeks caused a significant increase in *Bifidobacterium* (genus belonging to Actinobacteria phylum) and significantly slowed the body weight gain compared with placebo [53].

8.2.3 Probiotics

Probiotics are nonpathogenic living microorganisms with direct or indirect effect on gut microbiome [50, 54, 55]. Products containing probiotics should be

tested for safety risks before marketing. Probiotics can be found in several foods (e.g., yogurt, cheese, and milk).

Probiotics can manage obesity by reducing the production of lipopolysaccharide through an impact on gut microbiome. In a double-blind, placebo-controlled clinical study, administration of fermented milk containing *Lactobacillus gasseri* species (LG2055) to overweight/obese adults for 12 weeks caused a significant decrease in body weight [56].

8.2.4 Synbiotics

Synbiotics are combination of prebiotics and probiotics. They have the potential to induce more effects on gut microbiome and body weight than prebiotics or probiotics alone.

8.2.5 Bariatric surgery

Bariatric surgery can modify gut microbiome and further affect body weight [57, 58]. The mechanisms include reduced caloric intake, reduced gastric emptying, and alterations in gastric acid production and bile acids.

After Roux-en-Y gastric bypass surgery in obese subjects, there is a decrease in Firmicutes-to-Bacteroidetes phyla ratio and an increase in Proteobacteria phylum [57, 58].

8.2.6 Fecal microbiota transplantation

Fecal microbiota transplantation, which consists of transfer of feces from a healthy donor to a recipient, is an exciting therapy with important potential. It can modify gut microbiome for the purpose of obesity management [59, 60]. The addition of healthy stool can be done through colonoscopy, orogastric tube, esophagogastroduodenoscopy, or oral capsule. It is important to carefully select and screen the donor to avoid risk of infection, aggravation of obesity, or other complications [61, 62].

Available clinical data are very preliminary and limited. Several studies are ongoing. There is no regulatory guidance for the use of fecal microbiota transplantation in the management of obesity.

8.2.7 Cost of gut microbiome manipulation

Cost of gut microbiome manipulation in obesity management is reported in **Table 3**.

Tool for gut microbiome manipulation	Average cost (range)
Diet	Cost of food
Prebiotics	< $100/month
Probiotics	< $100/month
Synbiotics	< $100/month
Bariatric surgery (Roux-en-Y gastric bypass)	$23,000 ($20,000–$30,000)
Fecal microbiota transplantation	$1,800 ($1,600–$2,000) + cost of administration/dose

Table 3.
Cost of different tools used for gut microbiome manipulation in obesity management in the USA.

8.3 Gut microbiome after weight loss

After successful weight loss, there is a decrease in Firmicutes phylum, an increase in Bacteroidetes phylum, and a decrease of Firmicutes-to-Bacteroidetes phyla ratio [45, 51, 57, 58].

9. Clinical study design to assess gut microbiome in obesity

Well-designed clinical studies are urgently needed to better understand the interactions between obesity/obesity treatment and gut microbiome.

Several factors affect the quality of weight-loss studies aimed to assess gut microbiome. A well-calculated sample size allowing subgroup analysis is a key factor. Relevant stratification factors (e.g., race, age, gender, BMI, diet, and medications) at randomization will make the study more informative. Any underestimation of these stratification factors, as it has been the case in several clinical studies, especially in relation to diet and medications, may lead to misleading and conflicting results. The duration of the clinical studies has to be sufficient to allow both short-term and long-term/follow-up assessments. Adequate adjustments should be made during the statistical analysis.

10. Ideal gut microbiome

An ideal gut microbiome should have high diversity. At the level of phyla, the ideal gut microbiome should have low Firmicutes phylum and high Bacteroidetes phylum with a Firmicutes-to-Bacteroidetes phyla ratio < 1.0. At the level of genera, the ideal gut microbiome should be rich in *Prevotella* genus.

The recommended diet to reach the above objectives is a diet adequate in calories (adjusted to the activity), low in fat (< 20% of total macronutrients), and rich in fiber (≥ 30 g/day).

11. Conclusions

Gut microbiome influences normal physiology and susceptibility to diseases. Profound changes affecting the diversity and the abundance of gut microbiome are associated with obesity. A decrease in microbiome diversity and an increase in the ratio of Firmicutes-to-Bacteroidetes phyla have been reported in obese subjects.

Gut microbiome can be manipulated to change the host metabolism and manage obesity. Potential interventions include diet, prebiotics, probiotics, synbiotics, bariatric surgery, and fecal microbiota transplantation.

A better understanding of the interactions between different diets and gut microbiome should help the development of new guidelines for feeding humans to prevent or manage obesity.

Conflict of interest

The author received honorarium for consultancy from Gelesis, Inc.

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