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The role of gut microbiome in obesity and metabolic dysfunctions: Insights and therapeutic potential

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Abstract

Obesity is a chronic inflammatory disease defined by an excessive accumulation of body fat. The human gut microbiota (GM) is an intricate ecosystem of microorganisms living symbiotically within the gastrointestinal tract and has emerged as a key player in health and metabolic diseases. Recently, several studies have increasingly revolved around understanding the specific compositions and strains of GM and their potential impact on obesity. This review provides a summary of the most recent findings regarding obesity and newly developed therapies that show exceptional efficacy in treating this condition. In addition, it explores different GM strains that may contribute to the progression and development of obesity. This article summarizes the molecular insights involved in the relationship between obesity and GM, the characteristics of this ecosystem, and its involvement in human metabolism, energy balance, and inflammation leading to obesity. Furthermore, it examines the bacteria most engaged in managing obesity. These findings contribute to a better understanding of this significant and intricate relationship, ultimately aiding in obesity prevention.

Keywords: Microbiota; Weight loss; Weight gain; Obesity; Diversity; Gut microbiome

1. Introduction

Obesity is a condition linked to an abnormal accumulation of body fat. It involves various intricate mechanisms. The buildup of fat, a process called adipogenesis, can

manifest as hypertrophy, where adipocytes increase in size, or as formation of new fat cells, a mechanism known as hyperplasia.[1,2] This pathogenesis can trigger inflammation, dyslipidemia, insulin resistance, hypertension, and vascular endothelium dysfunction and is associated with serious health conditions such as cardiovascular diseases, non-alcoholic fatty liver disease, type 2 diabetes mellitus (T2DM), and cancers.[3]

The gut microbiota (GM) is made up of over 1500 species from fifty distinct phyla. Among them, *Firmicutes*, *Bacteroidetes*, *Proteobacteria*, *Actinobacteria*, and *Verrucomicrobia* are the dominant types. *Firmicutes* and *Bacteroidetes* are the most abundant, making up at least 90% of the human gut microbial population.[4] This complex ecosystem plays an essential role in monitoring the progression of various human diseases. Moreover, the role of GM in numerous health conditions has been increasingly elucidated through the extensive application of deep sequencing technologies.[5]

In recent years, increased investigations have suggested that an imbalance in the GM could be a contributing factor to obesity.[6-11] Low-grade inflammation present in obesity is a consequence of GM alterations, which are, in turn, linked to disorders in numerous metabolic pathways and molecules.[12,13] Together, obesity and gut dysbiosis can lead to the alteration of metabolic pathways.[14]

2. Obesity

Obesity has been presented as an abnormal fat accumulation according to the World Health Organization (WHO). The pathogenesis of obesity involves various intricate mechanisms. The buildup of fat, a process called adipogenesis, can manifest as hypertrophy, where adipocytes increase in size, or through the formation of new fat cells, a mechanism known as hyperplasia.[1,2] Body mass index (BMI) is a commonly used metric to estimate total body fat, calculated as weight in kilograms divided by the square of height in meters. It serves as an effective indicator of the risk of diseases associated with overweight and obesity. Recently, waist circumference (WC) has emerged as a potentially more accurate measure of obesity.[15] The Global Burden of Disease study affirmed that, since the 1980s, the occurrence of obesity has expanded rapidly in over seventy countries, with a continuous upward trend observed in the majority of other nations.[16(p25)] In 2013, the American Medical Association officially recognized obesity as a disease requiring medical treatment and follow-up.[17] Health risks linked to this disease have escalated to alarming levels, making obesity a major global concern.[18] In 2022, data showed that more than 1 billion individuals worldwide were living with obesity and 43% of them were adults.[19] By 2035, it is projected that 51% of the global population will be classified as either overweight or obese,[20] prompting WHO member states to agree on a global plan to accelerate the response to obesity by 2030.[21] Further data from the WHO European Region reclaim that obesity is prevalent in nearly 60% of adults, affecting one in three children, with prevalence rates of 27% among girls and 29% among boys.[22] Furthermore, the current evidence indicates that obesity now exceeds underweight in prevalence across all regions except sub-Saharan Africa and Asia. Previously correlated with high-income countries, obesity has become increasingly prevalent in middle- and low-income countries, where its incidence has been dramatically increasing.[23]

Obesity is linked to a multitude of serious health conditions and non-communicable diseases, including type 2 diabetes (T2D), cardiovascular diseases, chronic kidney disease, as well as certain types of cancer.[3,24] In addition, it is linked to other health risks such as inflammation, dyslipidemia, insulin resistance, and hypertension.[3] A systematic review and meta-analysis of almost 1 million participants identified a significant association between obesity and T2D, as well as coronary artery disease (CAD).[25] CAD is a type of heart disease characterized by the narrowing or blockage of the coronary arteries, primarily due to the accumulation of cholesterol and fatty deposits within the arterial walls, leading to plaque formation.[26] Other study has demonstrated high levels of liver fat fractions in patient affected by T2DM and morbid obesity. The findings showed that hepatic steatosis was associated with different measures of insulin sensitivity in patients suffering from T2DM and severe obesity.[27]

2.1. Common risk factors of obesity

Obesity and overweight can be attributed to a multitude of factors, including unhealthy lifestyle habits such as poor dietary patterns, physical inactivity, or insufficient sleep, in addition to certain medications, genetic predispositions, or family history. The pathophysiological mechanisms of obesity are complex, encompassing numerous overlapping genetic and environmental factors.[28] The main cause of overweight and obesity is an energy imbalance between caloric intake and energy expenditure, affected by some genetic predisposition, feeding behavior, and lifestyle factors.[29]

A familial history of obesity is a significant risk factor for both obesity and its early onset in childhood. In addition, it is associated with the severity of obesity.[30,31] Previous research has shown a significant relationship between maternal pre-pregnancy obesity and childhood obesity, including overweight and obesity combined, as

well as overweight alone.[32] Accordingly, sleeping <7 h has been positively associated with an increase in BMI and the development of obesity, compared to individuals who attain an adequate and healthy amount of sleep.[33]

Eating habits play a significant role in the management of metabolic disorders and obesity. In this context, mindful eating has been demonstrated to be effective in reducing uncontrolled and emotional eating behaviors. However, when combined with caloric restriction, weight loss was not significantly greater than with either approach alone.[34] On the other hand, intermittent fasting, such as the 16:8 or 14:10 approach, has demonstrated a significant reduction in body weight (BW) while also improving glycemic and lipid profiles in obese patients with T2D. Experimental findings have shown an advantage for the 16:8 approach.[35]

Regarding time-restricted feeding, Xie *et al.*[36] discovered that eating meals early in the day increased insulin sensitivity, reduced body mass, and lowered inflammation more significantly than diets restricted to the middle of the day. However, in the context of constant caloric intake, a time-restricted diet failed to significantly decrease weight or enhance glycemic markers when compared to a standard diet, indicating that the beneficial effects observed in other studies may be related to overall caloric reduction.[37] Furthermore, the order of food consumption has been explored: eating vegetables first, regardless of meal speed, significantly decreased postprandial glucose and insulin peaks, indicating that this simple method may provide metabolic benefits.[38] Pharmacologically, the use of glucagon-like peptide-1 receptor agonist (GLP-1RA), such as exenatide, has shown that adolescents with lower postprandial leptin responses are better at maintaining weight loss.[39] In the same context, Libyan health professionals have highlighted that some changes in lifestyle of young people, including sleeping late, waking up late, and skipping breakfast, are closely related to the development of overweight and obesity.[40]

Zheng *et al.*[41] confirmed through a systematic review the existence of a relationship between rapid weight gain (RWG) and obesity. Fifteen studies indicated that RWG in infancy is linked to overweight and obesity in both childhood and adulthood, reaffirming that RWG at an early age is a significant predictor of obesity later in life.[41] A list of medications associated with significant weight gain among Canadian individuals has been defined, including antipsychotics, antidepressants, antihyperglycemics, and other medications that contribute to this issue.[42] Accordingly, there is an urgent need in implementing new pharmacotherapies that have fewer negative impacts on weight. Psoriasis, a chronic autoimmune skin condition, is linked to obesity, which aggravates its progression and complicates treatment. Conversely, psoriasis can also impact the development of obesity. The treatment of this disease highlights the considerable influence of weight loss on symptom severity.[43]

Dysfunction in the thyroid is linked to changes in BW, fluctuations in body temperature, and alterations in both total and resting energy expenditure, regardless of physical activity levels. In addition, weight gain frequently occurs following the treatment of thyroid dysfunction.[44] Thyroid hormones and body composition are closely interlinked. Hypothyroidism, a condition in which the thyroid gland fails to produce an adequate amount of thyroid hormones, is linked to reduced thermogenesis, a lower metabolic rate. It has been demonstrated to be positively related to both an elevated BMI and a higher prevalence of obesity.[45] Clinical evidence suggests that even mild thyroid dysfunction, such as subclinical hypothyroidism, can cause significant alterations in BW, representing a risk factor for overweight and obesity.[45] Furthermore, research has demonstrated a negative association between BMI and serum-free T4 (FT4) levels.[46] Fat accumulation has been linked to lower FT4 levels[46,47] and increased thyroid-stimulating hormones levels in individuals who are slightly overweight but euthyroid.[47,48]

2.2. Protective factors against obesity

A literature review conducted on individuals with obesity has highlighted different physiological advantages associated with increased physical activity. As an illustrative example, the findings underscore its potential for promoting weight loss.[49] Moreover, as a part of a clinical trial, obese individuals aiming to lose weight participated in an 8-week stress management program while following diet restrictions to maintain a healthy lifestyle. The intervention group, in particular, experienced a notable decline in BMI in comparison to the control group and improvements in anxiety and depression scores.[50]

As is widely recognized, diet plays a crucial role in managing obesity. A meta-analysis of randomized controlled trials has identified a protective effect of high dietary fiber intake. Dietary fiber plays a crucial role in maintaining a healthy BW.[51] It is associated with the production of beneficial metabolites, the amelioration of obesity, and improved immune responses.[52,53] In this context, another type of dietary fiber, resistant starch (RS), has been used as a dietary supplement to affect obesity-related outcomes. An 8-week RS supplementation was found to contribute to body mass reduction (mean: 2.8 kg) and improve insulin resistance in individuals with overweight or obesity.[54]

Tea is a common beverage consumed daily, and it contains natural compounds with many health benefits,

including polyphenols. One of their main roles is to prevent the digestion fats and carbohydrates from food. This is due to their ability to block some digestive enzymes responsible for breaking down nutrients, such as pancreatic lipase, which helps digest fats, and amylases, which break down carbohydrates into sugars that the body can absorb.[55]

During Ramadan, dietary habits and fasting programs change. Ramadan intermittent fasting (RIF) affects gut hormones, including leptin, and ghrelin, GLP-1. RIF has proven to be an effective strategy to modulate appetite-regulating hormones, resulting in improved body composition indices and a reduction in obesity.[56]

Certain bioactive compounds, including curcumin and zinc, have shown promising effects in obesity management. Curcumin has demonstrated strong anti-inflammatory effects related to obesity. An umbrella review indicated that curcumin intake could reduce WC, BMI, and BW.[57] Moreover, the intake of curcumin, curcuminoids, or turmeric has demonstrated notable anti-inflammatory properties. Individuals consuming different amounts of these three compounds exhibited reductions in C-reactive protein (CRP), tumor necrosis factor-alpha (TNF-α), and interleukin (IL)-6.[58] Furthermore, zinc and resveratrol have shown promising potential in modulating leptin levels and glucose signaling, which may have beneficial effects on energy regulation in obese individuals and cardiovascular health. However, a longer exposure time is suggested to be necessary to fully assess their impact on energy homeostasis.[59]

Obesity is one of the major metabolic syndromes (MetSyn).[7] Significant weight loss is considered the primary and only curative treatment to address MetSyn, as it can influence many of its components. In addition to high-dose GPL-1RAs, new medical treatment options are being developed to manage MetSyn. These include dual or triple hormonal agonists targeting the GLP-1, glucose-dependent insulinotropic polypeptide (GIP), and glucagon receptors. GLP-1 plays a role in controlling blood sugar and appetite, while GIP works alongside GLP-1 to enhance insulin sensitivity, and glucagon helps regulate blood sugar levels.[60,61] In addition, leptin, a key hormone in appetite regulation, plays an essential role in regulating appetite and energy balance, which can influence BW and obesity.[62]

In this regard, researchers have investigated the effects of various medications on weight loss. Levothyroxine, a medication used as a substitute for thyroid hormones,[63] is administered to restore hormonal balance.[64] Results have shown that after 6 months of levothyroxine treatment in individuals with hypothyroidism, resting energy expenditure increased, which suggests that bodies are burning more calories. This resulted in weight loss due to a decrease in fat-free mass (0.8 kg). However, fat mass remained unchanged.[65] The mechanisms underlying this association remain unclear and require further clarification.

New medications have recently emerged to treat obesity and promote weight loss. Semaglutide and tirzepatide are two well-known drugs currently used to treat obesity. Semaglutide, a GLP-1 analog, imitates the effects of native GLP-1, improving glycemic control and promoting weight loss by decreasing caloric intake, reducing hunger, and increasing satiety and satiation.[66] In patients suffering from obesity-related heart failure with preserved ejection fraction and T2D, semaglutide resulted in greater declines in heart failure symptoms and significant weight loss than the placebo after 1 year.[67] Another study found that participants receiving 2.4 mg of semaglutide per week experienced an average BW reduction of 15.3 kg.[68]

Similarly, the effects of tirzepatide have been investigated. A recent systematic review and meta-analysis of randomized controlled trials discovered the positive effect of tirzepatide. The weekly treatment with tirzepatide resulted in significant increase in BW and lower hemoglobin A1C levels, without a significant increase in serious or life-threatening adverse events.[69]

Colchicine is another pharmaceutical drug known to reduce inflammation in multiple diseases. It has the ability to reduce inflammatory markers, including CRP, glycoprotein acetylation, and certain inflammatory cytokine serum concentrations.[70-72] In the context of obesity, colchicine has shown a considerable effect on leukocyte populations implicated in both innate and adaptive immune responses.[73]

To enhance nutrition and public health, more than 45 countries have imposed taxes on sugar-sweetened beverages.[74] In several nations, these taxes have been related to higher pricing and reduced sales and consumption of taxed beverages.[75] A significant decrease in the purchase of these beverages and obesity rates has been observed in middle- and upper-middle-income countries. These findings confirm that imposing high taxes on SBBs could be an effective solution to combat obesity and related health risks.[76]

3. GM

The GM consists of a community of microorganisms, including viruses, bacteria, archaea, and fungi, residing within the gastrointestinal tract (GIT), with bacteria reign over this niche.[77,78] Most of these microorganisms predominantly inhabit the large intestine.[79,80] The most dominant and prevalent bacterial phyla within the gut

are Bacillota and Bacteroidota.[81] Until recent years, the majority of gut microorganisms remained unidentified, mainly due to their anerobic nature, which made them difficult to cultivate.[82] The advent of the polymerase chain reaction targeting the 16S rRNA gene, coupled with next-generation sequencing and advanced bioinformatics tools, has facilitated the precise identification of various bacterial strains and the functional attributes of GM.[83,84]

Many factors, including nutritional, chemical, and immunological gradients along the gut, can affect the composition and density of GM. Indeed, it varies according to different intestinal regions, where pH levels, oxygen tension, host secretions, and substrate availability fluctuate.[85]

In the small intestine, transit time is short, with generally elevated levels of acids, oxygen, and antimicrobials.[86] These properties hinder bacterial proliferation, allowing only facultative anerobes characterized by rapid growth and adherence to epithelia or mucus to survive.[86]

Meanwhile, the colon provides different conditions that support a diverse bacterial community, mainly anerobes capable of metabolizing complex carbohydrates that go through incomplete digestion in the small intestine.[87] It has been shown that *Firmicutes* (60 – 80%), *Bacteroidetes* (20 – 40%), the *Verrucomicrobia*, the *Actinobacteria,* and a reduced presence of *Proteobacteria* are five predominantly phyla of bacteria in the normal human GM.[88]

3.1. GM: Coevolution with human life

The human fetus has long been considered microbiologically sterile. The predominant assumption suggests that the first human encounter and interaction with bacteria occur at birth when the newborn comes into contact with the surrounding environment.[89,90] However, some studies suggest that the human GM is generally established before birth.[91]

This exposure to microbiota is highly beneficial and plays a critical role in programming the maturation of an infant's immunity during fetal life. Bacterial DNA is a key factor in this process.[92] Other research indicates that contact with maternal microbiota through the placenta has been associated with adverse outcomes, including preterm birth, spontaneous abortion, and intrauterine infections, as observed in cases of listeriosis throughout pregnancy.[93]

The mode of delivery is a key factor shaping the composition of an infant's microbiota.[94,95] Infants delivered by cesarean section (C-section) have a different GM composition and colonization timeline compared to those delivered vaginally.[95,96] The colonization of bacteria in an infant's gut occurs gradually, beginning with the first contact with the maternal microbiota during birth and culminating in a highly dense and diverse microbial community.[97] It has been shown that facultative anerobic bacteria are usually the first colonizers, followed by strictly anerobic genera, including *Bacteroides, Bifidobacterium*, *Eubacterium*, and *Clostridium*.[98,99]

Breast milk also has a potential role in GM development. A study of 94 premature mother-child dyads found that 30 – 40% of the bacteria present in an infant's gut were also found in breast milk, suggesting bacterial transfer. These interactions were influenced by dietary practices and antibiotic use.[100]

The GM of a newborn takes around 2 – 3 years to develop and stabilize into a profile similar to that of an adult.[101] In normal and healthy individuals, the GM is principally dominated by *Firmicutes*, *Bacteroidetes*, *Proteobacteria*, and *Actinobacteria*.[102] An analysis of GM in Moroccan residents showed a large percentage of *Bacteroides* (62.6%). In addition, the genera *Prevotella*, *Prevotella copri*, and *Prevotella stercorea*, as well as *Fecalibacterium prosnitzi*, were significantly dominant in these samples.[103]

Throughout life, human GM undergoes multiple changes related to lifestyle. A high-fiber diet increases the abundance of beneficial bacteria such as *Lactobacillus*, *Akkermansia*, and *Bifidobacterium* while reducing opportunistic pathogenic bacteria such as *Desulfovibrio* and *Klebsiella.*[104] In 2010, researchers compared the GM of European children to that of children living in a rural village of Burkina Faso, where a fiber-rich diet is common. The results have showed significant differences in microbial composition. Burkinabe children had a high abundance of *Bacteroides* and a clear reduction in *Firmicutes*, with increased *Prevotella* and *Xylanibacter*, both adapted to fiber degradation, and higher short-chain fatty acid (SCFA) levels ($P < 0.001$). Moreover, pathogenic bacteria such us *Shigella* and *Escherichia* were significantly less common in these children than in European children.[105]

Poor sleep also affects GM, as shown by the critical role of the brain-gut-microbiota axis in sleep intensification. Recent research has explored the impact of sleep disorders such as fragmentation, sleep deprivation, obstructive sleep apnea, insomnia, and circadian rhythm sleep disorders on GM composition.[106] Similarly, physical activity could affect GM by increasing beneficial bacteria, while a healthy GM may, in turn, improve exercise performance.[107]

The GM presents diurnal oscillations on a global scale, with its levels and rhythms fluctuating in accordance with a 24-h cycle. Using cosinor-based rhythmometry, diurnal signals were detected across different taxonomic levels of the GM, with 57% of phyla following a 24-h rhythmic

cycle.[108] On the other hand, microbiome seasonal variations are widespread. It has been shown that some bacteria follow two distinct profiles or patterns, which have been detected in many regions around the world.[108]

Among Ukrainian individuals, gut bacterial composition fluctuates with the seasons. *Actinobacteria* abundance and the *Firmicutes*-to-*Bacteroidetes* ratio were higher in samples collected during summer compared to other seasons. In the contrary, *Bacteroidetes* were less abundant during the summer.[109]

In healthy conditions, *Firmicutes*, *Bacteroidetes,* and *Actinobacteria* are the three major microbial phyla in the GM.[110,111] However, in cases of intestinal inflammation, there is a notable increase in *Proteobacteria*, particularly within the *Enterobacteriaceae* family, accompanied by a decline in strict anerobes.[112] A study evaluating the impact of seasonal fluctuations in vitamin D levels on the composition of GM among Caucasians patients with chronic inflammatory bowel disease (IBD) found that low vitamin D levels were associated with an increased abundance of bacteria associated with inflammation, such as *Proteobacteria* (including *Helicobacter* spp.), *Actinobacteria*, and Fusobacteria. However, it was noted that low Vitamin D levels did not always correlate with severe dysbiosis. In some ulcerative colitis samples, an increased abundance of beneficial bacteria, such as *Faecalibacterium prausnitzii*, was detected, along with a lower abundance of *Escherichia/Shigella*, which is commonly associated with inflammation. On the other hand, it was demonstrated that high level of Vitamin D in autumn and summer was associated with a decrease in bacteria linked to inflammation and an increased presence of potentially beneficial or anti-inflammatory bacteria, such as *Pediococcus* spp., *Clostridium* spp., and *Escherichia*/*Shigella* spp.[113] Another study found significant changes in GM composition at the genus level, including an increase in *Lachnospira*, a genus associated with anti-inflammatory effects among Vitamin D-supplemented individuals. However, no changes were noted in alpha diversity between the study groups, nor were there notable variations in community composition between samples.[114]

These findings suggest that diurnal and seasonal variations could significantly influence gut microbial profiles, potentially influencing the interpretation of microbiome analyses and making the definition of normal GM very challenging.[108]

The seasonal oscillations of some gastrointestinal pathogens are now become registrable through syndromic diagnostic platforms such as Biofire Syndromic Trends by Biomerieux, which is designed to rapidly detect and identify infectious diseases, including gastrointestinal infections caused by multiple viruses (e.g., rotavirus and norovirus) and bacteria (e.g., *Salmonella* and *Escherichia coli*). For example, rotavirus infections are more prevalent in the winter.[115] However, in 2023 and 2024, the Biofire platform has registered high levels of diarrheagenic infection caused by *E. coli* or *Shigella* throughout the summer.[116] This platform has become essential for the rapid identification of epidemics and for adapting prevention and treatment strategies accordingly.[117]

Dysbiosis of GM is an alteration in the microbial composition resulting from various factors, including infections, diet, drugs, antibiotics, and small bacterial overgrowth.[118] Furthermore, numerous studies have validated the implication of gut dysbiosis and various pathological conditions, such as cardiovascular disease,[119] hypertension,[120] cancer,[121] and chronic kidney disease.[122] A growing body of scientific evidence supports a causal link between GM and dermatological disorders, namely atopic dermatitis, acne, psoriasis, and alopecia areata. Nevertheless, further efforts are required to prioritize the functional features of this relationship.[123] Besides dysbiosis, bariatric surgery has also been shown to influence GM, leading to microbial changes that may contribute to the metabolic benefits observed after surgery.[124]

Meanwhile, recent research suggests that dysbiosis originates from changes in the host environment. It occurs when the host loses the ability to control oxygen levels and certain electron acceptors, leading to increased oxygen diffusion into the colonic lumen. This promotes the growth of facultative anerobic bacteria. Some researchers argue that modifications in GM are a consequence rather than the primary cause of dysbiosis.[125]

The symbiosis between the intestinal microbiota and its host is critical for maintaining physiological balance and shaping host-microbe interactions. In a gnotobiotic bee model, researcher employed the mutagenesis atmospheric and room-temperature plasma approach to induce bacterial mutations and identify those that enhance survive in a host. Their investigation into the genetic mechanisms promoting *Snodgrassella* bacterial adaptation to non-native hosts revealed that mutations in the *mglB* gene, which regulates bacterial motility through type IV pili, provided a competitive advantage for colonizing honeybee guts (*Apis mellifera*). These findings underline the importance of bacterial mobility in symbiosis and provide new avenues for investigating host-microbe interactions using novel experimental paradigms.[126]

Based on the findings presented, it is evident that numerous variables affect microbiota composition, complicating the interpretation of results. The overall composition of the microbiota is influenced by various

factors, including the analytical techniques used, sampling location (biopsies or stools), inflammatory state (inflamed or non-inflamed sites), disease activity, and individual characteristics such as age and lifestyle.[127]

3.2. Fecal transplantation: Transferring features and characteristics

Fecal microbial transplantation (FMT) is a promising intervention to reshape GM, offering potential treatment for metabolic dysfunction and autoimmune diseases.[128] It has been investigated in various contexts, including *MetSyn*, non-alcoholic fatty liver disease, and obesity in both animal and human studies.[129] Patients with reduced GM diversity have shown a significant increase in microbial diversity after receiving fecal transplants from lean and healthy donors.[130] In addition, FMT has shown promising results in slowing the progression of chronic kidney disease[122] and in the treatment of Parkinson's disease.[131]

Germ-free (GF) mice are animals derived from other animals that are delivered through aseptic C-section. These rodents remained completely devoid of microorganisms from birth throughout their entire lifespan. They are characterized by lower BW and notable variations in immune system, metabolism, and neurodevelopment.[132-134]

Animal studies have demonstrated that fat accumulation and insulin resistance levels can be influenced through FMT. It was demonstrated that FMT can modify the GM.[135] Bäckhed *et al.*[136] showed that adipose tissue accumulation occurs in GF mice when they are colonized with the GM of conventional mice, leading to an increase in adipose tissue mass, fat content, and insulin resistance levels.[136] In addition, Turnbaugh *et al.*[137] conducted an experiment in which GM from obese mice was transplanted into GF mice, resulting in significant weight gain and increased fat accumulation in the recipients. These findings confirm that GM dysbiosis can lead to obesity. These results have been further confirmed by recent research.[138]

FMT from lean donors to individuals with severe obesity did not demonstrate any significant changes in insulin resistance or other primary metabolic variables between the groups. Meanwhile, the allogenic FMT group experienced beneficial changes in metabolic pathways, appetite regulation, and GM, with potential implications for low-density lipoprotein levels.[139]

The effects of FMT combined with fiber supplementation in obese patients with *MetSyn* were also assessed. Among the four study groups, only the group treated with FMT and low-fermentable (LF) fiber showed a significant improvement in insulin sensitivity after 6 weeks. The GM composition also showed favorable and long-lasting alterations in this group, with an increase in beneficial bacteria, including *Bacteroides* and *Akkermansia muciniphila*.[140] These findings suggest that the combination of FMT and LF fiber represents a safe and effective strategy to address metabolic dysfunction and modify GM over time.

A critical question that arises is why certain individuals exhibit a more favorable response to FMT than others. Addressing this question requires an exploration of recipient-related factors. In this regard, a study showed that recipients with greater baseline microbiome diversity and a specific microbial composition, characterized by low *Prevotella* levels, responded more effectively to FMT. These individuals exhibited greater improvements in insulin sensitivity and a higher degree of donor bacterial engraftment, including *Roseburia* spp. and *Christensenellaceae* spp. Meanwhile, other studies have reported no notable effects of FMT on human metabolism or weight in adults with obesity.[141,142]

Bäckhed *et al.*[136] highlighted some differences between GF mice and conventional raised counterparts. The study reported that GF mice display 42% less total body fat than their conventional counterparts, despite ingesting 29% more calories.[136] Furthermore, when subjected to a high-fat diet (HFD), GF mice experienced reduced weight gain, offering a protection against diet-induced glucose intolerance and the onset of insulin resistance.[143-145] In addition, the ability of microbiota to control the BW was stated. Through colonizing GF mice with the GM of conventionally raised mice, a subsequent increase in body fat content and insulin resistance was observed.[146] This confirms the essential role of GM in BW regulation.

Furthermore, under typical conditions, mice are coprophagic (i.e., consumption of feces). It has been illustrated that obese mice were protected from further weight gain by consuming microbiota from lean cage mates. However, in the reverse scenario, where lean mice consumed feces from obese mice, no significant weight gain was observed.[147] Studies in human patients further suggest that, when combined with lifestyle interventions, FMT can induce beneficial changes in lipid metabolism.[148]

Other research has investigated the role of the gut virome in diabetes, revealing its unexpectedly and remarkable effects. It was found that gut virome not only stabilizes blood glucose levels and reduces host weight but also capable of modifying the gut microbial profile and influencing the expression of genes related to glucose metabolism, leptin signaling, and fat breakdown.[149]

Based on these findings, GM contributes significantly to a range of physiological functions, and microbiota

transplantation appears to be a viable approach for transferring these characteristics.

4. Microbiota-mediated obesity: Molecular insights

During the past decades, increasing evidence has demonstrated that GM plays a significant role in the onset and development of obesity.[150] Several studies have analyzed the link between obesity and GM, highlighting that an imbalance in GM can be a contributing factor to obesity.[151-153]

4.1. SCFAs: Key players in the obesity development

GM has diverse functions, including the fermentation of indigestible carbohydrates into metabolites, such as SCFAs, which are the primary byproducts of bacterial fermentation of dietary fiber in the GIT.[154] SCFAs encompass a range of metabolites, with acetate, propionate, and butyrate being the most prevalent in the human colon.[155,156]

Recently studies have confirmed that SCFAs play an essential role in host health by acting at multiple levels, such as cells, tissues, and organs, through mechanisms related to glucose homeostasis, gut barrier function, and obesity.[157] Furthermore, SCFAs are recognized for their role in controlling obesity-associated health conditions across the lifespan by managing energy balance, controlling appetite, and increasing energy expenditure.[158]

Studies suggest that obese individuals show increased levels of SCFA than lean individuals, suggesting a possible role of SCFAs in the energy dynamics associated with obesity, as they serve as energy-rich metabolites.[159,160] Some investigations propose that elevated SCFA levels in obese individuals contribute to increased adiposity by providing extra energy from dietary fiber fermentation.[161,162] Contradictory findings indicate that SCFA levels are notably decreased in obese individuals,[163-165] highlighting that the link between SCFAs and obesity remains incompletely understood.

Butyrate and acetate serve as energy sources that the liver relies on to generate energy through the tricarboxylic acid cycle, a crucial pathway for metabolism that takes place in mitochondria.[166] However, they also alter liver function and influence adipose tissue metabolism by modifying mitochondrial uncoupling protein 2 (UCP2) expression through peroxisome proliferator-activated receptor gamma. This mechanism increases the adenosine monophosphate (AMP)/adenosine triphosphate (ATP) ratio, which promotes aerobic metabolism through AMP-activated protein kinase (AMPK) signaling. These results suggest that SCFAs may alleviate *MetSyn* by increasing energy utilization and metabolic efficiency.[167] Moreover, SCFAs stimulate the release of GLP-1, which improves insulin sensitivity and inhibits glucagon production.[168,169] These studies emphasize the multifaceted role of SCFAs in obesity, energy metabolism, and overall health, as well as their regulatory effects on the liver, adipose tissue, and intestinal health.

Breast milk contains small amounts of SCFAs,[170] with concentrations varying greatly between individuals.[171] It contains microbiota that interacts symbiotically with the infant gut. Certain microbes are beneficial for neonatal health by producing breast milk butyrate acid (C4), which plays an important role in enforcing immune and metabolic development by influencing the abundance of the infant GM.[172]

SCFA production can be influenced by both dietary and genetic factors such as leptin resistance. In a recent study, they have found that diet-induced obesity in mice significantly decreased SCFA production in the early stage (day 14), with production dynamics differing distinctly from those of control mice on a standard diet.[173] In contrast, genetic obesity caused by leptin resistance initially showed SCFA production like controls, but a significant reduction occurred at the mid-stage (day 60). These results suggest that diet has a greater effect on the production of SCFAs, while genetic factors like leptin resistance can also impact SCFA production, though with a delayed and moderate effect.[173]

4.2. Conjugated linoleic acid (CLA)

Firmicutes and *Actinobacteria*, of particular interest, have the ability to generate polyunsaturated omega-6 fatty acids in addition to CLA. Modification in the synthesis of this fatty acid is particularly related to obesity. CLA has different features, including anti-obesity effects, such as enhanced energy metabolism, increased lipolysis, as well as reduced adipogenesis and lipogenesis.[158] According to a meta-analysis and systematic review, CLA significantly increases triglyceride levels and decreases total cholesterol (TC) compared to placebo and olive oil. They found that in obese individuals (BMI ≥ 25) aged over 25 years, consuming more than 3 mg/day of CLA for at least 8 weeks resulted in a significant reduction in TC levels.[174]

In addition, numerous studies have demonstrated that CLA reduces *de novo* lipid synthesis and triggers adipocyte apoptosis.[175] This apoptotic effect on adipose tissue is associated with the activation of TNF-α and UCP2. UCP2 disrupts electron transfer across the inner membrane of mitochondria, redirecting energy toward thermal dissipation rather than its storage in the form of ATP.[176] Furthermore, it has been revealed that certain strains of Bifidobacterium spp. and Lactobacillus spp. produce beneficial CLA, which enhances energy metabolism and lipolysis, ultimately affecting BW.[177]

To highlight CLA's potential role in regulating interactions between the GM, host metabolism, and immunity in attenuating insulin resistance, a study evaluated its effects in a mouse model of insulin resistance induced by a HFD. CLA supplementation improved hyperglycemia, hyperlipidemia, glucose intolerance, and insulin resistance. It enhanced antioxidant capacity and reduced fat deposits and inflammation in adipose tissue. It also promotes fatty acid oxidation and insulin signaling pathways.[178] In addition, transcriptomic analysis revealed that CLA inhibited inflammatory signaling pathways while activating several beneficial metabolic pathways, including phosphoinositide 3-kinase-Akt, AMPK, and insulin-related pathways. It also regulated specific metabolic processes, such as those related to arachidonic acid, linoleic acid, arginine, and proline metabolism. In the same mice model, CLA supplementation effectively reduced weight gain, adipose tissue weight, and adipocyte size compared to HFD-fed mice without supplementation.[178]

4.3. Bile acids metabolites

Bile acids are metabolites derived from cholesterol in the liver and subsequently metabolized by gut bacteria in the intestines. The decrease of both primary and secondary bile acid subtypes after the consumption of low-calorie weight-loss diets has shown a prominent correlation with improving adiposity, fat accumulation, and energy metabolism. This suggests that specific subtypes of bile acids could serve as potential biomarkers for predicting long-term weight-loss success and an individual's response to dietary interventions.[179] The GM assists in bile acid metabolism by facilitating deconjugation and dehydroxylation processes inside the intestinal lumen. These mechanisms convert primary bile acids into secondary bile acids, such as cholate into deoxycholate and chenodeoxycholate into lithocholate.[180,181] This process is promoted by bile salt hydrolase enzymes, which mainly found in *Firmicutes* and *Bacteroidetes*, notably in *Clostridium* genera clusters.[182]

After analyzing the postprandial responses of bile acids, the bile acid synthesis marker C4, fibroblast growth factor 19 (FGF19), and farnesoid X receptor (FXR)-regulated FGF19 in obese patients before and after surgery, researchers observed a significant increase in total plasma bile acid levels, while fecal excretion of these molecules decreased. Furthermore, FGF19 levels increased, whereas C4 levels decreased, indicating enhanced FXR activity in the gut. The increase in bile acid levels and the activation of FXR may contribute to the observed metabolic benefits.[183]

Understanding the role of these bacterial metabolites in weight loss remains an active area of research.

4.4. Trimethylamine N-oxide (TMAO)

TMAO is a compound belonging to the amine oxides class, chemically represented as $(CH_3)_3NO$. TMAO is produced through the metabolism of dietary choline, L-carnitine, and betaine by the intestinal microbiota.[184,185] Specifically, it is derived from the oxidation of trimethylamine (TMA).[186-188] Moreover, the differentially expressed microbial genes summarized in the Kyoto Encyclopedia of Genes and Genomes Orthology (KO) suggest that these genes are responsible for encoding the trimethyl N-oxide reductase enzyme, which plays a crucial role in the conversion of TMAO to TMA.[189]

TMAO levels increased in tandem with BMI, displaying a positive association with both fatty liver index and visceral adiposity index.[190] A recent study revealed persuasive results regarding the relationship between TMAO levels and obesity, identifying that individuals in the highest TMAO category exhibited an increase of 0.56 kg/m^2 in BMI. Furthermore, a dose-dependent association was observed between circulating TMAO levels and obesity in individuals categorized as apparently healthy. Notably, this study represents the first meta-analysis to unveil these positive dose-dependent associations between the concentration of circulating TMAO and obesity.[191] In addition, patients with obesity and colorectal cancer display distinct GM characteristics, including a reduced abundance of butyrate-producing bacteria, accompanied by increased TMAO levels, increased pro-inflammatory cytokine IL-1β, and enhanced intestinal permeability.[192]

On the other hand, there are viable solutions to modulate TMAO levels. The Mediterranean diet, a high-fiber diet, and probiotics have demonstrated their ability to reduce the effects of TMAO.[193] A high-fiber diet led to an increase in the abundance of beneficial bacteria such as *Lactobacillus*, *Akkermansia*, and *Bifidobacterium* while reducing the opportunistic pathogenic bacteria such as *Desulfovibrio* and *Klebsiella*.[104]

5. Bacteria taxa implicated in the control of BW

Evidence from various studies consistently demonstrates that certain gut bacteria significantly influence obesity-related metrics, metabolic parameters, and fat accumulation by impacting intestinal health. The following table summarizes intestinal bacteria associated with obesity based on studies conducted on mice and humans of different ages and weights. Table 1 compiles results derived from several studies, highlighting the role of various GMs in BW regulation. Each bacterium's specific influence is examined individually.

Table 1. Correlation of bacterial taxa to BMI and obesity

Reference study	Type (Animal/Human)	Publication year	Results
Tavella *et al.*[194]	Human (Italian elderly)	2021	The relative abundance of *Christensenellaceae Porphyromonadaceae* and *Rikenellaceae* was inversely related to host BMI.
Alemán *et al.*[195]	Human (Postmenopausal women)	2018	The relative abundance of *Christensenellaceae* was inversely related to host BMI.
Depommier *et al.*[11]	Human (Overweight/obese insulin-resistant volunteers)	2019	Supplementation with *Akkermansia muciniphila* reduced body weight, fat mass, and hip circumference.
Deng *et al.*[196]	60 male age matched C57BL/6 mice	2020	*Akkermansia muciniphila* improved metabolic aspects related to obesity and metabolic syndromes.
Everard *et al.*[197]	10-week-old, C57BL/6 male mice	2013	Abundance of *Akkermansia muciniphila* decreased in obese mice.
Park *et al.*[198]	4-week-old, C57BL/6J male mice	2017	*Lactobacillus plantarum* HAC01 led to a reduction in mesenteric adipose tissue.
Mohd Hasali *et al.*[199]	7-week-old, 30 male C57BL/6 mice	2024	*Lactobacillus brevis* NJ42 reduced weight gain among the HFD-fed group.
Yang *et al.*[200]	6-week-old, 36 male C57BL/6 mice	2022	A mixture of *Lactobacillus acidophilus* and *Clostridium cochlearium* showed lower body weight gain among the HFD-fed group.
Mu *et al.*[201]	6-week-old, 60 specific pathogen-free C57/BL6J mice (30 females, 30 males)	2020	*Lactobacillus plantarum* KFY02 showed a reduction in body weight in mice.
Shirouchi *et al.*[202]	4-week-old, 12 Sprague–Dawley rats	2016	*Lactobacillus gasseri* SBT2055 was linked to higher carbohydrate oxidation, resulting in increased energy expenditure leading to body weight reduction.
Schellekens *et al.*[203]	5-week-old, 40 male C57BL/6 mice	2021	*Bifidobacterium longum* APC1472 decreased body weight gain after fifteen weeks of administration.
Solito *et al.*[204]	Human (Children and adolescents)	2021	*Bifidobacterium breve* BR03 and *B. breve* B632 showed improvements in metabolic parameters and reduction in weight and *Escherichia coli* levels.
Zhang *et al.*[205]	Obese mice	2024	*Bifidobacterium adolescentis CCFM8630* showed anti-obesity effects through modulation of tryptophan metabolism related to GM.
Yang *et al.*[206]	7-week-old, 72 male C57BL/6 mice	2023	*Faecalibacterium prausnitzii* strains reduced body weight gain.
Navab-Moghadam *et al.*[207]	Human (Type 2 diabetes individuals/ healthy controls)	2017	*Faecalibacterium prausnitzii* was negatively correlated with BMI.
Yoshida *et al.*[208]	Human (Obese individuals) and mice	2021	*Bacteroides* probiotics could be used for treating obesity.
Seong *et al.*[209]	Human (Patients with metabolic syndrome)	2021	*Bacteroides* spp. showed a negative correlation with BMI.
Luo *et al.*[210]	10-week-old diabetic mice db/db.	2022	*Bacteroides* spp. exhibited an inverse correlation with BMI.
Yang *et al.*[211]	C57BL/6 (B6), CD11c-Cre, Villine-Cre, and LysM-Cre mice; Atg7f/f mice	2017	*Bacteroides acidifaciens* JCM10556 aids in the prevention of metabolic disorders such as diabetes and obesity.
Cano *et al.*[212]	6 – 8-week-old, 32 male wild-type C57BL-6 mice	2012	*Bacteroides uniformis CECT 7771 significantly decreased body weight gain in HFD-fed mice.*
You *et al.*[213]	Human (Healthy Korean)	2023	*Bacteroides vulgatus SNUG 40,005 was associated with a significant reduction in body weight.*
Dong *et al.*[214]	Human (Obese and non-obese)	2022	Obesity was linked to an increased *P/B* ratio.
Hjorth *et al.*[215]	Human (Overweight participants)	2019	A high *P/B* ratio aids weight loss.
Hjorth *et al.*[216]	Human (Participants with increased waist circumference)	2020	Pre-treatment *P/B* ratio led to highly individualized weight loss.
Hjorth *et al.*[217]	Human (Participants with increased waist circumference)	2018	A higher *P/B* ratio was more likely to reduce body fat on diets rich in whole grains and fiber.

Abbreviations: BMI; Body mass index; *P/B* ratio: *Prevotella*-to-*Bacteroides* ratio.

The abundance of *Porphyromonadaceae*, *Christensenellaceae*, and *Rikenellaceae* has been inversely correlated with host BMI.[194,195] *A. muciniphila* is linked to the reduction of BW,[11] and its abundance has been shown to decrease in obese mice.[196,197] Other experiments conducted on mice and rats have demonstrated that *Lactobacillus* species[198-202] and *Bifidobacterium* species[203-205] show a revers correlation with BW gain, affirming their ability to improve metabolic parameters. *Faecalibacterium prausnitzii* acts similarly, contributing to reduced BW gain.[206,207] Furthermore, Bacteroides species are also inversely correlated with BMI[208-210,212,213] and have been shown to help prevent metabolic disorders including diabetes and obesity.[211] Notably, Bacteroides can be used as probiotics in treating metabolic disorders.[208] In addition to the beneficial effects of Bacteroides, the complex interactions between different bacterial species in the GM play a crucial role in regulating weight and metabolism. Among these interactions, *Prevotella*-to-*Bacteroides* (*P/B*) ratio has been particularly studied. Individuals with a high *P/B* ratio before any treatment have been shown to achieve greater weight loss on high-fiber diets compared to those with a lower *P/B* ratio.[214-217]

A detailed examination of each bacterium will now follow.

5.1. *Lactobacillus* species

Lactobacillales are a phylogenetically diverse order of lactic acid-producing organisms.[218] *Lactobacillus* spp. is Gram-positive, non-spore-forming rods that are catalase-negative and facultatively anerobic, typically thriving in environments with lower oxygen levels. Numerous studies have highlighted the positive influence of *Lactobacillus* spp. in mitigating metabolic disorders, including obesity.[219]

Crovesy et al.[220] provided a summary of the influence of Lactobacillus on BW among overweight individuals. They reported a negative correlation between Lactobacillus paracasei and obesity. In addition, they also noted significant correlations between *Limosilactobacillus reuteri* and *Lactobacillus gasseri* with obesity. Another study found that the abundance of *Lactobacillus* spp. was higher in the stool of obese patients and individuals with metabolic diseases,[221] identifying this species as an obesity-associated taxon.[221]

Lactobacillus plantarum is a widespread member of the genus *Lactiplantibacillus*. There are divergent perspectives on the impact of L. plantarum on obesity and weight regulation.[198] In this context, it has been observed that the administration of L. plantarum, either alone or in combination with inulin, may decrease food intake and prevent weight loss in diabetic rats.[202,222] Similarly, Shirouchi *et al.*[202] demonstrated that L. gasseri SBT2055 contributes to BW reduction in rats by promoting higher carbohydrate oxidation, resulting in increased energy expenditure.[202] Despite that, no noticeable difference in food intake was observed between both groups in this study.[202] A similar pattern was observed with *Lactobacillus brevis* NJ42.[199]

Other results showed that administering *Lactobacillus fermentum* and *Lactobacillus ingluviei* was related to noticeable increase in weight, while administering *L. plantarum*, *Lactobacillus acidophilus*, and *L. gasseri* was coupled with weight loss in both obese humans and animals.[201-223]

5.2. *Faecalibacterium prausnitzii*

F. prausnitzii is a Gram-positive bacterium that belongs to *Ruminococcaceae* family[224] and *Firmicutes* phylum.[225] It is one of the highly widespread anerobic bacteria in the gut,[202,226] constituting approximately 1 – 6% of the total fecal microbiota.[224,227] A reduction of *F. prausnitzii* has been related to chronic inflammation, a key manifestation of obesity.[228-230]

There have been conflicting outcomes regarding the relationship between *F. prausnitzii* abundance and obesity. For instance, a Chinese study reported a decrease in the abundance of *F. prausnitzii*, *Bacteroides*, and *Akkermansia* among pre-diabetic obese patients.[231] In contrast, another study on obese adults in China found a positive correlation between fasting glucose levels and *F. prausnitzii* in men.[232] Similarly, an earlier study carried out in Southern India discovered reduced abundance of *F. prausnitzii* in non-obese children compared to obese children.[233] Meanwhile, numerous studies have reported opposing findings. A 2017 Iranian study has shown a negative correlation between *F. prausnitzii* and BMI.[207]

Hippe *et al.*[234] have demonstrated that after weight loss, patients suffering from T2D exhibited increased levels of *F. prausnitzii*. They also revealed that samples from lean individuals had a lower expression of *F. prausnitzii* genes compared to obese individuals and those with T2D. In addition, *F. prausnitzii* is being explored for its potential in treating obesity and its related comorbidities. Mice on HFD treated with *F. prausnitzii* twice a week showed a notable decrease in adipocyte size and cell infiltration of adipose tissue compared to the control group.[235] Another study has identified *F. prausnitzii* as a species with lower prevalence in obesity and associated disorders,[236] which lead to its proposal as a next-generation probiotics for treating obesity and its related disorders.[237]

Butyrate, is a SCFA produced by bacterial fermentation of indigestible fibers in the colon.[238] *F. prausnitzii* is one of the bacteria that produce butyrate and bioactive

anti-inflammatory molecules similar to shikimic and salicylic acids.[239] It is considered one of the most important butyrate producers in the human gut, capable of degrading inulin and producing butyrate.[240-242] Butyrate plays an essential role in gut health, serving as the principal energy source for colonocytes and exerting beneficial effects on the GM, ultimately contributing to overall human health.[238,241] In addition, *F. prausnitzii* has demonstrated beneficial effects on the gastrointestinal health of obese patients. The metabolites it produces, including butyrate, have demonstrated good results in the treatment of obesity.[243,244]

F. prausnitzii's supernatant has been observed to regulate T helper 17/regulatory T cells differentiation by suppressing proinflammatory pathways, including signal transducer and activator of transcription 3/IL-17 and IL-6. This is accomplished through the targeting of histone deacetylase 1.[245,246] This proinflammatory pathway is implicated in obesity.[234] Further observations found that treatment of HDF-fed mice with *F. prausnitzii* reduced inflammation in adipose tissue, validating previously reported results.[235]

5.3. *A. muciniphila*

A. muciniphila is among the bacterial species that influence BW. These anaerobic bacteria which contribute to mucus layer degradation, reside within the intestinal mucosa of both humans and rodents.[247] Analysis of stool microbiota revealed a reduced concentration of *A. muciniphila* in obese and overweight children compared to lean children.[248] These results were confirmed by other studies reporting an inverse correlation between this bacterium and BW in humans and rodents.[11,197] They have shown that *A. muciniphila* abundance decreases in both obese and type 2 diabetic mice.[197] In addition, in a group of patients on a HFD for 8 weeks, *Akkermansia* bacteria increased significantly.[104] *A. muciniphila* has been shown to reduce fat mass, BW, and hip circumference in obese or overweight insulin-resistant volunteers[11] while also improving metabolic aspects related to obesity and other *MetSyn*.[196]

Moreover, several studies suggest the potential role of *A. muciniphila* as a therapeutic option. Research has found that *A. muciniphila* treatment has the ability to alleviate BW gain and reverse HFD-induced metabolic disorders, including metabolic endotoxemia, fat-mass gain, and adipose tissue inflammation.[197,249] These findings suggest that *Akkermansia* is often associated with better weight management and a reduced risk of obesity.[250,251]

5.4. *Bifidobacterium*

Bifidobacterial flora is among the first microbes to colonize the human GIT.[252] Usually, colonization starts during the first few days after delivery and can constitute up to almost 80% of the GM composition during infancy.[253]

Numerous *Bifidobacterial* strains have been reported to exert useful effects in different clinical conditions. The effects of different *Bifidobacterium* species have been studied in diet-induced obesity (DIO) mouse models. In the study, four *Bifidobacterial* groups (*B*. FS31-12, *B*. M13-4, *B*. L75-4, and *B*. L66-5) were administered to mice on HFD, with only *Bifidobacteria* L66-5 demonstrating weight-loss properties.[254] Another study found that supplementation with *Bifidobacterium adolescentis* promoted weight loss and improved steatosis and steatohepatitis, which are fatty liver diseases related to excess fat buildup in the liver. These positive effects were observed in mouse and rat models.[205,255,256] Similar findings were reported in other studies. After 15 weeks of supplementation, *Bifidobacterium longum* APC1472 was shown to reduce BW gain in mice.[203] In addition, *Bifidobacterium breve* BR03 and *B. breve* B632 were associated with improvements in metabolic parameters, decreased weight, and reduced *E. coli* counts.[204] Moreover, a reduction in visceral fat and insulin resistance has been observed after treatment with other *Bifidobacterium* strains in rodent models.[257]

5.5. Bacteroides and Prevotella

Bacteroides is a genus of Gram-negative, non-spore-forming, and obligate anerobic bacteria[258] that predominantly inhabit the lower intestinal tract of human.[259] Bacteroides species have been inversely correlated with BMI[208-210,212,213] and play a role in preventing metabolic disorders, including diabetes and obesity.[211] Notably, they have also been it can be used as probiotics treating metabolic disorders.[208]

Prevotella is a Gram-negative bacterium belonging to the *Bacteroidetes* phylum. This genus is commonly associated with carbohydrate-rich diets, such as plant-based foods. Its fiber fermentation activity could potentially play a role in carbohydrate metabolism.[105,260]

Prevotella and Bacteroides constitute two of the largest bacterial groups and are among the major microbial populations found within sheep and cattle rumens across multiple diet regimens.[260] In addition, they represent two of the most prevalent groups of anerobic bacteria within the human colon.[260,261] They play an essential role in breaking down and converting food components, with *Bacteroides* spp. being particularly involved in metabolizing both plant-derived and host-derived polysaccharides.[261]

Individuals with a high *P/B* ratio, compared to those with a low (*P/B*) ratio, have been observed to experience greater reductions in both body fat and BW. This suggests that individuals with a high *P/B* ratio are more

susceptible to weight loss following a fiber-rich diet.[215] Other efforts were made to describe the role of *P/B* ratio in weight gain, indicating that individuals with a high *P/B* ratio are more prone to weight regain than those with a low *P/B* ratio.[262] This effect becomes more crucial and important when combined with low dietary fiber consumption and altered glucose metabolism.[262] A high *P/B* ratio has been associated with increased fermentation of dietary fibers, resulting in the production of SCFA, which enhances energy metabolism and satiety. This was demonstrated in a study showing that *Prevotella* is highly efficient at metabolizing complex polysaccharides found in dietary fibers,[263,264] which is beneficial in the context of caloric restriction. These findings align with the previous research,[215] where participants with a high *P/B* ratio experienced greater weight loss on an HFD. This demonstrates the significance role of dietary fiber in enhancing the beneficial effects of GM, particularly *Prevotella*, by promoting the synthesis of beneficial SCFAs. As a result, fiber intake could potentially lead to an imbalance in microbial metabolic functions, which might explain the observed differences in individual responses based on the *P/B* ratio.[265]

Furthermore, Kootte *et al.*[266] showed that insulin resistance may reduce the effectiveness of SCFAs in enhancing insulin sensitivity, which might worsen fat storage rather than promote fat oxidation. The metabolic response appears to also depend on the baseline microbial diversity of patients.[266] Low microbial diversity that reflects an imbalance or functionally compromised microbiota can justify this metabolic response. Patients with lower microbial diversity are more likely to benefit from the good bacteria transplanted or introduced through FMT. Conversely, patients with greater microbial diversity tend to have a more stable GM which may limit the integration and beneficial effects of transplanted microbiota.

Further investigations[214,267] support this notion, where they found that higher Prevotella levels ($P = 0.004$) and lower Bacteroides levels ($P = 0.03$) are linked to obesity.[214] Interestingly, although their functional similarities and ability to predominate the GM independently, they rarely coexist in high relative abundance, suggesting a co-exclusionary relationship.[268]

Another study has highlighted that the *P/B* ratio before treatment is a notable indicator associated with changes in body fat resulting from unrestricted high-fiber diets. It has been shown that obesity is linked to an increase in the *P/B* ratio.[214] However, it was demonstrated that individuals with a higher *P/B* ratio responded more effectively to fiber- and whole grain-rich diets, exhibiting greater reductions in body fat compared to those consuming an average Danish diet. In contrast, individuals with a lower *P/B* ratio did not show significant differences in body fat reduction.[217]

6. Conclusion

In summary, this review highlights the complex relationship between GM strains and obesity. The evidence shows an existing relationship between the composition of GM and its role in regulating metabolism and overall obesity. Interactions between GM and the host's metabolic processes reveal potential pathways for therapeutic interventions aimed at treating and preventing the development of obesity. The relationship between GM and BW is influenced by various factors, including physical activity, diet, sleep, and medication, making it a complex area of study that requires further studies. Standardizing experimental conditions is essential to reduce bias and ensure comparable results in GM studies. Given that numerous factors affect GM composition, it is crucial to consider variables such as patient age, diet, origin, and temporal fluctuations, including seasonal and circadian variations. For instance, to prevent circadian variations in the microbiota, fecal samples should ideally be collected from each patient at a consistent time of day (morning or evening). Similarly, because seasonal differences affect the microbial composition, investigations conducted in the winter should be compared only to those conducted under similar seasonal conditions.

Further research is needed to evaluate GM alterations after newly developed drug treatments or bariatric surgery, especially involving patients who experience weight regain. These studies should take into account the host's environment, initial microbiota composition, and its role in metabolic regulation. In addition, personalized medicine should be considered as a solution for modulating GM, with the goal of designing tailored probiotics for each patient to prevent and treat obesity and its associated health effects.

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Conflict of interest

The authors declare that they have no competing interests.

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