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Management of obesity-related diseases through the gut microbiome

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Abstract

Obesity is a multifactorial disease that results in the excessive accumulation of adipose tissue in humans. It poses a major global public health crisis, as it increases the risk of several pathologies. The gut microbiome is considered a potential modulator in the development of obesity, alongside environmental factors, lifestyle, and genetic makeup. The qualitative and quantitative composition of the gut microbiome is greatly influenced by the type, quality, and quantity of diet. We have found that a vegetarian diet facilitates the growth and development of beneficial bacteria in the gut. This review discusses the relationship between the human gut microbiome, energy balance, and various obesity-related diseases. The metabolic products of the gut microbiome (such as short-chain fatty acids and secondary bile acids) and their effects on the gut microbiome, intestinal barrier function, and immune homeostasis are explored in the context of obesity. However, the specific roles of individual gut microbiota species and their interactions with the gut environment, host genetics, and medications (including antibiotics) require further investigation. We also discuss the potential of the gut microbiome in managing obesity-related diseases through dietary modifications, with reference to dietary fiber, resistant starch, gluten, high-fat diets, and proteins and carbohydrates from both vegetarian and animal sources.

Keywords: Obesity; Gut microbiome; Metabolism; Homeostasis; Diet and microbiota; Fecal microbiota; Probiotics

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1. Introduction

Obesity has emerged as a major global public health challenge, with prevalence rates rising rapidly across both developed and developing nations.[1] At present, over 600 million adults and 107 million children worldwide are affected by obesity, and if trends continue, it is estimated that 18% of men and 21% of women will be obese by 2025, with 20% of the global adult population projected to be obese by 2030.[2,3] Obesity is strongly associated with numerous comorbidities, including type 2 diabetes, cardiovascular disease, and various cancers, contributing significantly to both economic and social burdens.[4] Conventionally, obesity has been recognized as an interconnected condition influenced by genetic, behavioral, socioeconomic, and environmental factors. In recent

years, however, the significance of the gut microbiota in obesity has garnered increasing attention, revealing its profound impact on host energy storage and metabolic processes.[5,6] Pioneering research has demonstrated that altered gut bacterial composition, specifically, a decrease in the abundance of *Bacteroidetes* and an increase in *Firmicutes*, correlates with obesity.[7] Moreover, studies involving the transplantation of microbiota from obese and lean individuals into germ-free mice have shown that microbiota from obese individuals promote greater fat accumulation, highlighting the potential role of gut microbiota in the development of obesity.[3,7] This observation, combined with emerging theories, such as the hypothesis of metaflammation, suggests that genetic adaptations that evolved to combat infectious diseases may inadvertently contribute to the modern obesity epidemic.[8] Understanding the evolutionary origins and the complex interplay between genetics, the microbiome, and environmental factors is essential for addressing this global health crisis.[9]

Obesity is also strongly linked to an elevated risk of a range of diseases, including cardiovascular complications, diabetes, respiratory issues, and certain cancers. While the causes of obesity are multifactorial and not yet fully understood, contributing factors include unhealthy eating habits, sedentary lifestyles, environmental influences, and genetic predisposition. One of the most intriguing environmental factors linked to obesity is the gut microbiota, which has been shown to play a pivotal purpose in the development and progression of obesity and other metabolic disorders, such as diabetes and non-alcoholic fatty liver disease (NAFLD). The gut microbiota, a complex ecosystem of microorganisms inhabiting the human gastrointestinal tract, includes bacteria, fungi, viruses, archaea, and protists.[3] With a total weight of about 1 – 2 kg and containing more than 100 times the number of genes in the human genome, the gut microbiota contributes to various essential physiological functions. These include digesting and absorbing nutrients, defending against harmful microbes, and maintaining immune system balance. However, when the microbiota becomes dysbiotic, meaning it falls out of balance, it can contribute to a range of diseases, including obesity. Gut dysbiosis is thought to influence obesity through multiple mechanisms, including disruption of energy homeostasis, altered lipid synthesis and storage, modulation of central appetite and feeding behaviors, and promotion of chronic low-grade inflammation.[10] While several effective interventions for obesity exist, such as healthy lifestyle changes, weight-reducing drugs, and bariatric surgery, maintaining long-term weight loss remains a challenge. In addition, side effects associated with drugs and surgeries can further complicate treatment. Given the prominent role of the gut microbiota in obesity progression, it presents a promising target for novel therapeutic strategies. Future research should focus on better understanding the relationship between obesity and gut microbiota, uncovering the mechanisms by which the microbiota influences obesity, and evaluating the safety and efficacy of microbiota-targeted therapies as potential treatments for obesity.[11]

2. Human gut microbiome and its relation to obesity

The gut microbiota plays a central role in obesity progression, affecting microbial diversity, metabolic pathways, inflammation, immunity, and hormone regulation. Dysbiosis in obesity results in imbalanced bacterial populations, increased inflammatory markers, reduced gut barrier integrity, and alterations in metabolic functions. The gut microbiome influences energy homeostasis, shaping fat accumulation, insulin resistance, and immune responses. While beneficial microbes offer anti-inflammatory and metabolically protective effects, harmful bacteria and microbial-derived metabolites contribute to chronic inflammation and metabolic disorders. Understanding these intricate mechanisms may pave the way for microbiota-targeted interventions, offering potential therapeutic strategies to improve metabolic health and combat obesity.[12] In obese individuals, the gut microbiome is often characterized by intestinal dysbiosis, involving reduced microbial diversity, imbalanced bacterial composition, and altered metabolic functions. This dysbiosis leads to a loss of beneficial commensal bacteria, an overgrowth of pathogenic or conditionally pathogenic microbes, and an overall decline in microbial gene richness. Several studies have reported reduced gut microbiome diversity in obese populations, suggesting that a less diverse microbiota may contribute to metabolic disturbances and obesity development.

A widely observed trend in obesity is an increased *Firmicutes*/*Bacteroidetes* ratio, with *Firmicutes* being more abundant and *Bacteroidetes* being significantly reduced. Some studies have confirmed this pattern across various populations, indicating a correlation between gut microbiota composition and obesity.[13] However, newer research suggests that relying solely on phylum-level classification may be oversimplified, as differences within bacterial genera and species reveal more nuanced microbiome changes in obesity. For instance, while certain *Firmicutes* species, such as *Clostridium, Lactobacillus,* and *Ruminococcus* are found in greater abundance in obese individuals, the levels of *Faecalibacterium prausnitzii* (also within the *Firmicutes* phylum) decrease. This species is

associated with anti-inflammatory effects and metabolic health. Similarly, studies across different populations have noted variability in microbiota composition, suggesting that bacterial groups beyond the *Firmicutes/Bacteroidetes* dichotomy influence obesity risk. Beyond compositional changes, gut microbiota-derived metabolites play a major role in obesity. Short-chain fatty acids (SCFAs), including propionate, acetate, and butyrate, are produced through microbial fermentation of dietary fiber. These compounds have dual effects on metabolism – they can increase satiety, enhance energy expenditure, and reduce fat accumulation; however, excessive SCFA production may also promote lipid synthesis, potentially contributing to obesity. In addition, secondary bile acids, another group of microbial metabolites, help regulate lipid metabolism and gut hormone secretion, reinforcing their influence on energy balance. A key feature of obesity is chronic low-grade inflammation, which is largely influenced by the gut microbiota. Lipopolysaccharides (LPS), derived from Gram-negative bacteria, such as *Bacteroidetes*, are major triggers for inflammation. These endotoxins compromise intestinal barrier integrity, allowing microbial byproducts to enter systemic circulation, which activates immune responses and disrupts metabolic disruption. Elevated plasma LPS levels have been correlated with increased fat deposition, insulin resistance, and heightened inflammation**,** emphasizing the gut microbiota's role in obesity-related inflammatory responses.[14] Conversely, certain Gram-positive bacteria, such as *Lactobacillus* and *Bifidobacterium*, help strengthen gut barrier function and reduce inflammation, highlighting the potential protective role of beneficial microbiota.

The gut microbiota also interacts with intestinal immunity, influencing both innate and adaptive immune responses. Immune cells, including goblet cells, Paneth cells, and intestinal epithelial cells, maintain gut homeostasis, with antimicrobial peptides (AMPs) playing a crucial role in pathogen defense. *Akkermansia muciniphila*, a beneficial gut bacterium, has been found to restore AMPs diminished by obesogenic diets, thereby reinforcing gut protection. In addition, Toll-like receptors (TLRs) and nucleotide-binding oligomerization domain-like receptors recognize bacterial components, such as LPS, flagellin, and peptidoglycan**,** triggering immune activation. In adaptive immunity, the intestinal microbiota influences T helper 17 cells, which release interleukin (IL) 17 and IL-22, cytokines that enhance AMP production and gut barrier integrity. Reduced immunoglobulin A (IgA) production observed in obesity has been linked to impaired immune defenses, increasing susceptibility to metabolic disturbances. The gut microbiota also modulates host immunity through microbial metabolites, including imidazole propionate and tryptophan derivatives, which influence insulin resistance and metabolic syndrome. Disrupted aryl hydrocarbon receptor (AhR) signaling, caused by altered tryptophan metabolism, contributes to obesity-related inflammation. Reduced AhR ligand production diminishes IL-22 synthesis, exacerbating gut permeability and metabolic dysfunction. Meanwhile, microbial-derived components, such as flagellin and muramyl dipeptide show potential benefits in alleviating diet-induced inflammation and insulin resistance.

3. Metabolite production by gut microbiota

The gut microbiota secretes a variety of metabolites that influence host metabolism, immune responses, and overall health. In obesity and metabolic disorders, dysbiosis disrupts the balance of microbial metabolites, leading to increased adiposity, inflammation, oxidative stress, and metabolic dysfunction. These metabolites originate from both dietary sources and endogenous compounds and include indole derivatives, SCFAs, polyamines (putrescine, spermidine, and spermine), secondary bile acids, and adenosine triphosphate (ATP). SCFAs**,** produced by bacterial fermentation of dietary fiber, play crucial roles in immune signaling by activating receptors on neutrophils, macrophages, and dendritic cells (DCs). This activation promotes the production of IL-18, IL-22, IgA, and the satiety hormone glucagon-like peptide-1 (GLP-1). SCFAs also influence intestinal gluconeogenesis through gut–brain signaling pathways and inhibit histone deacetylase activity through G protein-coupled receptor (GPCR) activation, thereby impacting metabolic regulation. Tryptophan metabolism occurs through multiple pathways, including the kynurenine and serotonin pathways.[15] Its metabolism products affect intestinal motility and insulin regulation, with indole derivatives modulating gut hormone release (e.g., GLP-1), appetite suppression, and gastric emptying. Indole compounds also regulate immune responses by activating the AhR, thereby promoting IL-22 production to maintain mucosal immunity and gut barrier integrity.

4. Bacterial metabolite production from dietary components

4.1. SCFAs

The gut microbiota plays a crucial role in energy production and metabolism by fermenting non-digestible carbohydrates in the cecum, generating SCFAs, amino acids, and vitamins. Among SCFAs, propionate, acetate, and butyrate are the most abundant, with *Bacteroides thetaiotaomicron* primarily producing acetate and *F. prausnitzii* generating butyrate. SCFAs influence metabolic pathways by activating transcription factors,

such as carbohydrate-responsive element-binding protein (CHREBP) and sterol regulatory binding protein 1 (SREBP1), promoting lipogenesis and triglyceride storage. They also inhibit fasting-induced adipocyte factor, leading to triglyceride accumulation in adipocytes. In addition, SCFAs bind to GPCRs, playing roles in lipid, glucose, and cholesterol metabolism, regulation of gut inflammation, and neurogenesis. Early studies show that SCFAs modulate adiposity and glucose tolerance by stimulating GLP-1 secretion through G protein-coupled receptor (GPR) 41 and GPR43 receptors, with GPR43 capable of dual signaling through different pathways.

Butyric acid contributes to immune homeostasis by stimulating IL-18 secretion and suppressing inflammation through GPR109A activation and histone deacetylase inhibition. Moreover, gut microbiota-derived propionate and butyrate activate intestinal gluconeogenesis through free fatty acid receptor 3 or a gut–brain neural circuit, influencing glucose metabolism. While microbiota-derived acetate serves as a pre-cursor for fatty acids and *de novo* lipogenesis in the liver, excessive acetate generation has been linked to obesity and NAFLD. Microbiota–immune system interactions further regulate metabolic homeostasis. Studies indicate that fiber-derived SCFA binding to free fatty acid receptors suppresses high-fat diet (HFD)-induced metabolic syndrome by restoring IL-22-mediated enterocyte function. In addition, *Lactobacillus johnsonii Q1–7* deficiency contributes to reduced food intake and body mass through mammalian target of rapamycin complex 1 signaling, affecting IgA production. In clinical cases, *Bacteroidetes* abundance increases while SCFA-producing *Firmicutes* decline in NAFLD patients, further emphasizing the microbiota's role in metabolic disorders. Understanding these microbial interactions highlights their significance in metabolism, immune regulation, and obesity, paving the way for microbiota-targeted therapies to enhance metabolic health.[14]

4.2. Indole derivatives

Indole and its derivatives produced by commensal bacteria, such as *Lactobacillus*, *Escherichia coli*, and *Bacteroides*, play a significant role in bacterial communication and host interactions. These metabolites are generated from dietary tryptophan through the action of tryptophanase and can reach high concentrations in the digestive tract and systemic circulation.[15,16] Indole is metabolized in the liver by cytochrome P450 2E1 into 3-indoxyl sulfate (3-IS), with low urinary levels of 3-IS indicating gut dysbiosis. Indole derivatives – including indole-3-lactic acid, indole-3-aldehyde, indole-3-acetic acid, and indole-3-propionic acid – act as ligands for AhRs, which regulate immune responses and inflammation by modulating IL-22 production and lymphoid function in the intestine. Studies suggest that reduced tryptophan metabolism into AhR agonists is a hallmark of metabolic syndrome, contributing to insulin resistance, liver steatosis, and increased intestinal permeability due to elevated LPS translocation.[17] Therapeutic approaches include administration of AhR agonists or probiotic supplementation with *Lactobacillus reuteri* to improve intestinal barrier function and increase GLP-1 secretion, thereby reversing metabolic disorders, such as low-grade inflammation and intestinal barrier dysfunction. Indole administration has been found to prevent LPS-induced abnormalities in cholesterol metabolism and liver inflammation. Research also shows that inhibiting indoleamine 2,3-dioxygenase (IDO) – a key enzyme in the kynurenine pathway – can help mitigate HFD-induced obesity and associated metabolic alterations. IDO overactivation leads to increased concentrations of inflammatory metabolites, such as xanthurenic acid, kynurenic acid, and quinolinic acid, while reducing plasma tryptophan levels, thereby contributing to metabolic dysfunction. Serotonin, another tryptophan-derived metabolite, plays a role in obesity regulation by modulating appetite and satiety. However, excessive serotonin levels suppress brown adipose tissue thermogenesis, resulting in fat accumulation. Elevated levels of 5-hydroxyindole-3-acetic acid, the end-product of serotonin metabolism, have been observed in individuals with metabolic disorders compared to healthy controls.[18] This highlights the importance of gut microbiota-derived indole metabolites in regulating inflammation, metabolic health, and obesity, suggesting potential therapeutic applications through microbiota-based interventions.

5. Metabolite production by the host and biochemical alteration by gut bacteria

5.1. Secondary bile acids

Secondary bile acids, metabolized by gut microbiota, play a pivotal role in fat digestion, lipid metabolism, glucose regulation, and inflammation. They shape the bile acid pool and influence bile acid-activated receptors, including farnesoid X receptors (FXRs), pregnane X receptors, and GPCRs, which regulate various metabolic processes.[19] Dysregulation of these pathways can contribute to metabolic disorders. Among the major secondary bile acids, deoxycholic acid and lithocholic acid support energy homeostasis by activating Takeda G protein-coupled receptor 5, thereby influencing metabolic functions. Clinical studies suggest that bile acid composition is modulated by diet and medication. For instance, the anti-diabetic drug acarbose alters bile acid profiles, while HFDs elevate overall bile acid levels and shift the balance

between primary and secondary bile acids.[20,21] Research indicates that gut microbiome deficiency can modulate cytochrome P450 family 7 subfamily A member 1 expression, alleviating HFD-induced metabolic syndrome, and thus represents a potential therapeutic target for obesity.[16] Experimental treatments further demonstrate the significance of bile acid modulation in metabolic health. In obese mice, colesevelam (a bile acid sequestrant) enhanced GLP-1 secretion and improved glucose levels through FXR-dependent mechanisms, suggesting potential for type 2 diabetes treatment. In addition, antibiotic interventions have been shown to suppress FXR signaling, improving glucose tolerance and reducing hepatic steatosis. Dietary interventions also influence bile acid metabolism. A high-protein diet increased the abundance of *Eubacterium* species, which metabolize bile acids through 7α-dehydroxylation, resulting in elevated deoxycholic acid and lithocholic acid levels. Specific dietary modifications appear beneficial for metabolic regulation and obesity prevention. Methionine restriction stabilizes lipid profiles in HFD-induced metabolic disorders, while extruded legumes and cereals enhance bile acid excretion, promoting lipid homeostasis. Notably, common buckwheat supplementation has shown promise in preventing NAFLD and dyslipidemia by regulating primary bile acid biosynthesis and modulating gut microbiome composition. Overall, secondary bile acids play an integral role in metabolic regulation, with potential therapeutic applications through dietary and pharmacological interventions.[22]

5.2. Taurine, ATP, and polysaccharide A (PSA)

Several key metabolites, including taurine, ATP, and PSA, play pivotal roles in immune regulation within the gut. ATP, secreted by certain intestinal bacteria, interacts with P2X and P2Y receptors, amplifying T cell receptor signaling, promoting inflammatory responses in macrophages and DCs, and influencing immune activation. It binds to seven P2X receptors (P2X1R–P2X7R) and eight GPCRs (P2Y1R–P2Y14R), leading to ion exchange and cellular immune modulation. Taurine, an essential amino acid found abundantly in immune cells, supports intestinal microbial metabolism, enhances T cell proliferation, stimulates SCFA production, and reduces LPS levels, thereby contributing to gut homeostasis. PSA, produced by gut bacteria, plays a protective role by activating TLR2 on DCs, stimulating IL-10 secretion by T cells, and directly binding to TLR2 on forkhead box P3-positive regulatory T cells, further increasing IL-10 production to regulate inflammation.[23] PSA has also been shown to counteract gut inflammation by suppressing mucosal effector T cell (T helper 17 cell) activity, thereby mitigating conditions, such as colitis. Together, these metabolites help maintain immune balance, gut health, and metabolic stability, making them essential for overall wellbeing.[24]

6. Mechanisms of impact of gut microbiota on obesity

The human gut microbiome, composed of trillions of bacteria, plays a crucial role in digestion, immune function, and brain activity. Recent studies challenge the traditional belief that obesity results solely from excessive calorie intake, highlighting the significant role of the gut microbiota in metabolic disorders that lead to weight gain. Certain bacterial species, such as *Firmicutes*, enhance energy extraction from food by fermenting complex carbohydrates into SCFAs, which regulate metabolism, satiety, and energy expenditure through interactions with gut hormones. Microbial metabolites, including bile acids and SCFAs, influence lipid absorption, glucose balance, and thermogenesis. Disruptions in the gut microbiota can impair intestinal barrier integrity, allowing harmful LPS to enter circulation and triggering inflammation and metabolic dysfunction.[9] Furthermore, the gut–brain axis plays a vital role in appetite regulation, with gut bacteria producing neurotransmitters, such as gamma-aminobutyric acid (GABA) and serotonin, which influence feeding behavior and mood. Dietary choices significantly impact the gut microbiota; diets rich in saturated fats and low in fiber promote pro-inflammatory bacteria, contributing to insulin resistance, fat storage, and adipose tissue inflammation – key features of obesity. Understanding these mechanisms has opened new possibilities for microbiota-based interventions to improve metabolic health and address obesity.[25]

7. Energy homeostasis disruption

The fate of energy extracted by the gut microbiota from dietary components that escape digestion and absorption in the small intestine represents a fundamental bioenergetic principle linking diet, microbial activity, and the energy ultimately available to the human host. This energy, derived from microbial fermentation, is predominantly generated from carbohydrates in the host's diet and, to a lesser extent, from proteins. Approximately 90% of the caloric intake from a meal is absorbed in the small intestine, with absorption rates ranging between 83% and 97%.[26,27] Upon reaching the colon, undigested dietary components undergo microbial fermentation, producing energy that is either absorbed by the host, utilized for microbial biomass growth, or excreted in feces. The energy absorbed by the host is typically estimated as a percentage of consumed energy, after deducting energy lost in a feces that is not fully utilized by either the host or the microbiota; this is referred to as metabolizable energy.[28]

In the context of precision nutrition, fecal energy loss varies among individuals (ranging from 2% to 16%) due to methodological and biological differences.[26,27]

7.1. Digestible energy uptake

Research suggests that the gut microbiota in obese individuals enhances energy extraction from food compared to non-obese controls. This occurs through increased secretion of nutrient transporters and fermentation of enzymes. Specifically, an elevation in *Clostridium ramosum* (from the *Firmicutes* phylum) has been associated with upregulated expression of GLUT2 (a glucose transporter) and CD36 (a fatty acid translocase), thereby improving energy absorption. In addition, a higher *Firmicutes*/*Bacteroidetes* ratio in obese individuals correlates with increased digestion of polysaccharides, leading to greater production of monosaccharides and SCFAs, such as acetate and butyrate. SCFAs contribute significantly to the body's energy supply – providing around 5 – 15% of total caloric intake and fulfilling 60 – 70% of the energy requirements of colonic epithelial cells. Furthermore, interspecies hydrogen (H_2) transfer between bacteria and archaea enhances energy uptake in obesity.[29] The coexistence of H_2-utilizing methanogenic archaea alongside H_2-producing bacteria facilitates the breakdown of polysaccharides into SCFAs by relieving thermodynamic constraints during fermentation processes.

7.2. Energy expenditure

The absorption of food energy in the small intestine determines the fraction that can reach the colon. The energy that arrives in the colon then becomes available to the gut microbiota for fermentation. The ultimate fate of the energy extracted by gut microorganisms remains unclear, yet it is a crucial component of overall energy balance.[26,27] A compelling set of hypotheses has emerged regarding the quantitative exchange of energy between humans and gut microbes. It has been established that the negative energy balance achieved through the alteration of the gut microbiota through a high-fiber, whole-food diet is partially due to the diversion of energy from microbial activity in the colon toward microbial biomass proliferation rather than host energy reserves.[26] This is likely a significant quantitative factor in energy balance, as mathematical modeling and previous studies[30,31] indicate that 25 – 50% of fecal energy originates from microbial biomass. The correlation observed between microbial biomass and changes in energy absorption on a high-fiber, whole-food diet suggests that microbial growth serves as a mechanism to modify energy balance through precision nutrition.[26] Further research is needed to quantify the bidirectional energy transfer between microorganisms and the host and to identify the biological, physiological, and sociodemographic factors that contribute to interindividual variability.[32]

7.2.1. Energy regulation

Multiple bacterial taxa have been associated with energy absorption or obesity.[33] However, the mechanisms underlying these associations in humans remain unclear, due to the reliance on relative abundance metrics of microbial composition and the lack of investigation into community-wide functional interactions. *A. muciniphila* is a widely studied species inversely correlated with obesity in various model systems.[34] A distinctive feature of *A. muciniphilla*'s action is that a surface protein (a postbiotic) mediates several of its metabolic effects. Its protective mechanisms against obesity involve enhanced energy expenditure and increased fecal energy loss.[35] *B. thetaiotaomicron* has shown decreased relative abundance in individuals with obesity. Treatment of mice with live *B. thetaiotaomicron*, but not heat-killed variants, has been shown to reduce fat accumulation and increase lean mass.[36] *Methanobrevibacter smithii*, the predominant methanogen in the gastrointestinal tract, is thought to contribute to energy extraction by interacting with SCFA-producing bacteria.[37] Activation of the Takeda G protein-coupled receptor 5 in brown adipose tissue enhances mitochondrial biogenesis and thermogenesis by increasing thyroid hormone activation. Similarly, activation of *FXR* in the intestine stimulates fibroblast growth factor 15/19 secretion, which alters bile acid composition and promotes fat burning. However, gut dysbiosis associated with obesity reduces beneficial bile acid levels, impairing these energy-expending processes.[7]

7.3. SCFAs and metabolic impact

Fecal and circulatory metabolites can indicate host–diet–microbiome interactions that influence energy balance.[38] It is improbable that metabolites derived from microbes significantly influence energy absorption directly, as the energy content lost in feces is anticipated to be minimal.[39] Nonetheless, there may be indirect involvement in energy balance associated with signaling processes or due to these metabolites serving as indicators of fermentation. The signaling roles of SCFAs are well-documented in pre-clinical models and are thought to influence adipose tissue through enhanced expression and signaling from G-protein-coupled receptors 41 and 43.[40] SCFAs may also induce a transition from lipogenesis to fat oxidation through peroxisome proliferator-activated receptor gamma-mediated signaling.[40] Nonetheless, there is debate as to whether individuals with obesity generate a greater or lesser quantity of SCFAs, rendering

the mechanisms in humans ambiguous.[41] The most compelling evidence regarding the significance of SCFAs in human energy balance comes from a study conducted by Canfora *et al.*[42] They administered colonic infusions of SCFA combinations in men with obesity (n = 12) at concentrations and ratios similar to those achieved with a high-fiber diet. The study revealed enhancements in fat oxidation, energy expenditure, and peptide YY, accompanied by elevated lipolysis due to SCFA colonic infusion.[42] While fermentation products, such as SCFAs serve as readily absorbable energy sources for both bacteria and the host, the quantitative effect on energy balance remains uncertain and likely varies among individuals.[42] SCFAs (propionate, acetate, butyrate) are produced through bacterial fermentation of dietary fiber. Increased SCFA levels in obese individuals are linked to a higher abundance of *Firmicutes* and H_2-utilizing methanogenic archaea. SCFAs can influence energy expenditure in conflicting ways – some studies suggest they suppress fasting-induced adipose factor, reducing fat oxidation. Conversely, butyrate can enhance mitochondrial activity, stimulate thermogenesis, and increase fatty acid oxidation in brown adipose tissue.[43]

7.4. Overall contribution to obesity

The gut microbiota contributes to obesity progression through both elevated digestible energy intake (via enhanced nutrient absorption and fermentation) and reduced energy expenditure (due to bile acid depletion and uncertain SCFA effects). While SCFAs show potential for promoting fat burning, their role remains controversial and requires further research.[44]

7.5. Lipid synthesis and storage

Altered gut microbiota in obese individuals influences lipid synthesis and storage through several mechanisms.

7.6. Bile acid reduction and lipogenesis

A decrease in *Bacteroides* and *Lactobacillus* leads to lower bile acid levels, weakening FXR activation in the liver. This results in increased SREBP1c expression, promoting hepatic *de novo* lipogenesis. Similarly, reduced fibroblast growth factor 19 signaling further enhances lipogenesis.[45]

7.7. Digestible energy absorption and lipid synthesis

A key physiological element that may influence variations in energy absorption is intestinal transit time. Colonic transit time exhibits significant variability across individuals and influences gut microbial metabolism, as it determines the duration during which colonic bacteria can ferment food substrates.[46] The interplay between gut bacteria and colonic transit may be significant for human energy absorption. A mathematical model indicated that, although intestinal transit time was not directly correlated with metabolizable energy, it was essential for explaining interindividual variability in metabolizable energy.[26,39] Research indicates that colonic transit time correlates with fecal energy losses, with individuals exhibiting faster transit times experiencing reduced fecal energy losses.[47] A study comparing diets rich versus poor in microbiota-accessible carbohydrates found no difference in colonic transit time by diet; however, transit time accounted for 5% of the diversity in the gut microbiome.[48] Additional gastrointestinal physiological traits may influence energy absorption. Gastric emptying regulates the rate at which nutrients are delivered to the small and large intestines, thereby influencing satiety and body weight.[49] Consequently, it may affect the absorption of microbially derived energetic substrates. Nonetheless, the role of gastric emptying in energy absorption has not been established in either rats or humans.[26,49] An augmented intestinal mucus layer may result in diminished energy absorption by the host.[50] This corresponds with findings that Western diets are linked to increased energy absorption and a microbial community more inclined to utilize the mucus layer as an energy source. A diminished mucus layer correlates with increased intestinal permeability, which may be the mechanism enhancing the absorption of energetic substrates.[26,32] Higher GLUT2 expression elevates serum glucose levels, stimulating key transcription factors (SREBP1, ChREBP) that drive lipid accumulation. Increased SCFAs, especially acetate, provide pre-cursors for fatty acid and cholesterol synthesis, contributing to lipid buildup.

7.8. Inflammation and lipid storage

Elevated levels of LPS in obese individuals induce metabolic endotoxemia, leading to chronic inflammation. This inflammatory state increases the expression of pro-inflammatory cytokines, such as IL-6 and tumor necrosis factor-alpha (TNF-α), thereby disrupting insulin signaling and contributing to insulin resistance and excess fat storage. In addition, LPS promotes adipocyte pre-cursor proliferation, further amplifying fat accumulation.[51]

7.9. Gut microbiota and fat regulation

The gut flora may also influence bodily energy reserves through alterations in energy expenditure. To date, human studies have not demonstrated a correlation between the gut microbiome and energy expenditure.[26,32] The extent of anaerobic microbial thermogenic activity in humans remains unknown. Microbial thermogenesis cannot be quantified using the indirect calorimetry techniques currently employed to assess human energy

expenditure. Innovative approaches must be developed to determine whether gut bacteria influence thermogenesis in humans.[52] Dysbiosis suppresses neuropeptide-related genes involved in energy homeostasis, including *GCG* (encoding preproglucagon) and *BDNF* (encoding brain-derived neurotrophic factor), and induces leptin resistance through suppressor of cytokine signaling-3, thereby exacerbating obesity. The reduction of *L. paracasei* removes its inhibition of lipoprotein lipase, allowing more triglycerides to be absorbed by adipocytes, thereby facilitating lipid storage (Figure 1).

8. Feeding behavior and central appetite

8.1. The gut–brain axis

The gut–brain axis is a complex, bidirectional communication system that transmits nutritional and metabolic information between the gut and the central neurological system through various pathways, including the vagus nerve, the neural system, and the gut endocrine system. Recent research has highlighted the significant role of the gut microbiota in this interaction, leading to the concept of the microbiota–gut–brain axis. Studies suggest that this correlation plays an important in both gastrointestinal and neurological conditions, such as Parkinson's disease and irritable bowel syndrome. Given that the gut–brain axis plays a major role in regulating appetite and feeding behavior, disruptions in the gut microbiota (gut dysbiosis) in obese individuals may impact food intake and contribute to obesity progression. This underscores the importance of gut microbiota in both metabolic and neurological health.[53]

8.2. The functions of gut microbiota: Feeding behavior and regulation of central appetite

The gut microbiota plays a critical part in regulating central appetite and feeding behavior through multiple mechanisms, as outlined in the following subsections.

8.3. Bacterial metabolites and satiety

Certain bacteria (*Bifidobacterium*, *Lactobacillus*) produce lactate, which supports neuronal activity and prolongs satiety. SCFAs, such as acetate and butyrate, derived from bacterial fermentation, influence appetite regulation by affecting neuropeptides in the hypothalamus and activating the vagus nerve.

8.4. Gut hormones and appetite control

Intestinal hormones, such as GLP-1 and peptide YY are produced by enteroendocrine cells and are modulated by bile acids, SCFAs, and indoles. These hormones act as anorexigenic signals, binding to receptors in neurons, the hypothalamus, and the brainstem to suppress appetite.[54]

8.5. Neurotransmitters and feeding behavior

Gut bacteria contribute to the production of neurotransmitters, including serotonin and GABA, which regulate appetite. GABA stimulates feeding behavior, while serotonin suppresses appetite by modulating melanocortin neurons, which help maintain energy balance.

8.6. Mood and reward pathways

The gut microbiota influences mood through immune responses, microbial metabolites, and vagus nerve

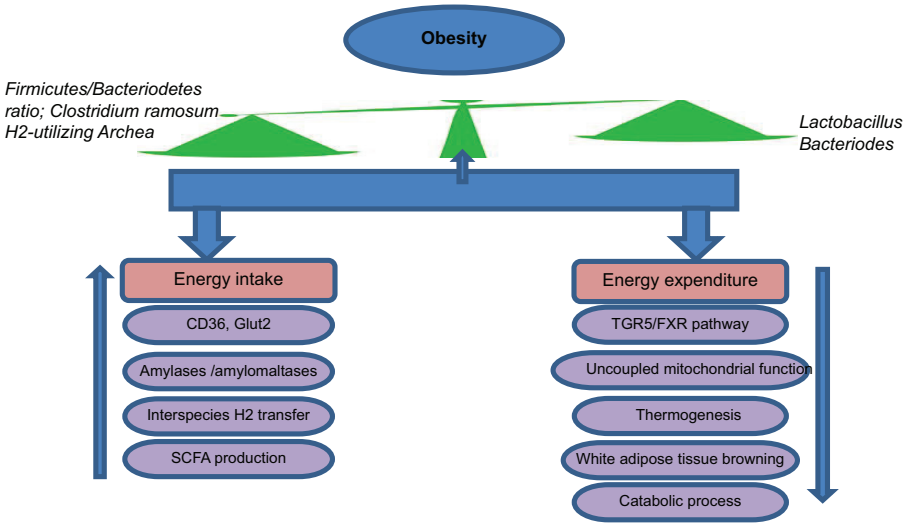

Figure 1. Energy homeostasis disruption
Abbreviations: CD36: Cluster of differentiation 36; FXR: Farnesoid X receptor; Glut2: Glucose transporter 2; H2: Hydrogen; TGR5: Takeda G-protein-coupled receptor 5.

activation. Psychological stress can trigger hedonic signaling pathways, leading to increased consumption of high-calorie foods. In addition, bacterial fermentation products, such as propionate have been linked to reduced reward responses to unhealthy food, thereby influencing feeding behavior.[55]

8.7. Chronic inflammation

Chronic low-grade inflammation is a key trait of obesity, primarily driven by increased levels of LPS – endotoxins released by Gram-negative bacteria, such as *Veillonella*. In obese individuals, excessive LPS disrupts the gut barrier by activating the TLR4/myeloid differentiation primary response 88 (MyD88)/IL-1 receptor-associated kinase 4 (IRAK4) signaling pathway, allowing bacterial byproducts to enter the bloodstream. Reduced levels of *A. muciniphila*, which helps maintain gut barrier integrity, further contribute to this process. In addition, high-fat diets (HFD) facilitate LPS absorption and transport into circulation through chylomicrons. Once in the bloodstream, LPS triggers immune responses in adipose tissue and the liver. It forms complexes with LPS-binding protein and cluster of differentiation 14**,** leading to the stimulation of nuclear factor kappa B (NF-κB) and activator protein 1, which drive the release of pro-inflammatory cytokines, such as TNF-*α*, IL-6, and monocyte chemoattractant protein (MCP) 1. These cytokines, in turn, stimulate adipocytes to secrete additional inflammatory signals, exacerbating metabolic dysfunction. Despite the inflammatory effects of LPS, SCFAs – especially butyrate – exert anti-inflammatory properties. Butyrate promotes IL-18 secretion, supports regulatory T cell differentiation, and suppresses NF-κB activation, thereby reducing inflammation.[56] However, it remains unclear whether these beneficial effects are sufficient to counteract LPS-induced chronic inflammation, indicating the need for further research.

9. Factors affecting homeostasis

9.1. Composition of infants' microbiota

The composition and development of the infant gut microbiota differ significantly from that of adults, undergoing a dynamic process of establishment. Colonization begins at birth, with some evidence suggesting maternal bacterial transmission may occur during gestation. In neonates, the gut microbiota consists primarily of *Enterococcus, Escherichia/Shigella, Streptococcus,* and *Rothia* species, while infants aged 1 – 6 months show increased colonization of *Bifidobacterium* and *Collinsella*. By 4 months of age, additional bacteria, such as *Lactobacillus, Granulicatella,* and *Veillonella* become prevalent, although full microbiome maturation continues until at least two years of age, reaching adult-like complexity by age three. Several factors influence early microbiota development, including mode of delivery, maternal microbiota, feeding practices, antibiotic exposure, and dietary changes. The maternal gut microbiota directly affects infant colonization, with *Bifidobacteria* being a dominant species transmitted through breast milk and fecal matter.[57] Mode of delivery also plays a significant role in microbiota composition, with vaginally born infants showing higher levels of *Bacteroides*, while Cesarean-section-delivered infants exhibit increased levels of *Hungatella*. Feeding practices shape microbial diversity – formula feeding leads to greater microbiome development compared to breastfeeding. In addition, antibiotic use rapidly alters the gut microbiota, reducing beneficial bacterial populations, while dietary changes, such as the introduction of complementary foods, further influence microbiome diversity.[58]

9.2. Composition of the adult microbiota

In healthy adults, the gut microbiota is comparatively stable, unlike in infants, whose microbiome is still developing, and the elderly, who tend to have a less diverse and more unstable gut microbiome (Figure 2). The dominant bacterial phyla in the adult gut microbiota are *Firmicutes* and *Bacteroidetes*, alongside other phyla, such as *Actinobacteria*, *Verrucomicrobia,* and *Proteobacteria*. While microbial diversity varies among individuals, gut bacteria consistently perform essential physiological functions, including metabolism, fermentation, methanogenesis, and immune regulation.[59]

However, several factors can disrupt microbiota homeostasis, including host genetics, diet, medications, infections, and circadian rhythm disturbances**.** Diet-induced obesity is associated with shifts in microbiota composition that differ from those of normal-weight individuals. Antibiotics and other xenobiotics can rapidly alter microbiome diversity and function, and prolonged exposure may lead to antibiotic resistance and microbiome imbalance. Maintaining a stable microbiota is critical for immune system homeostasis, as it helps resist pathogenic infections; however, infections can significantly disrupt microbiota composition. In addition, circadian rhythm plays a role in microbiota balance – disruptions in feeding patterns can lead to gut flora imbalances and metabolic disorders, including obesity. Overall, maintaining gut microbiota stability is essential for supporting metabolic health and immune function, with various internal and external factors influencing its composition and resilience.[60]

10. Alteration of gut microbiota by antibiotics leading obesity

Diet and antibiotics play a fundamental role in shaping gut microbiota composition, with diet exerting a more

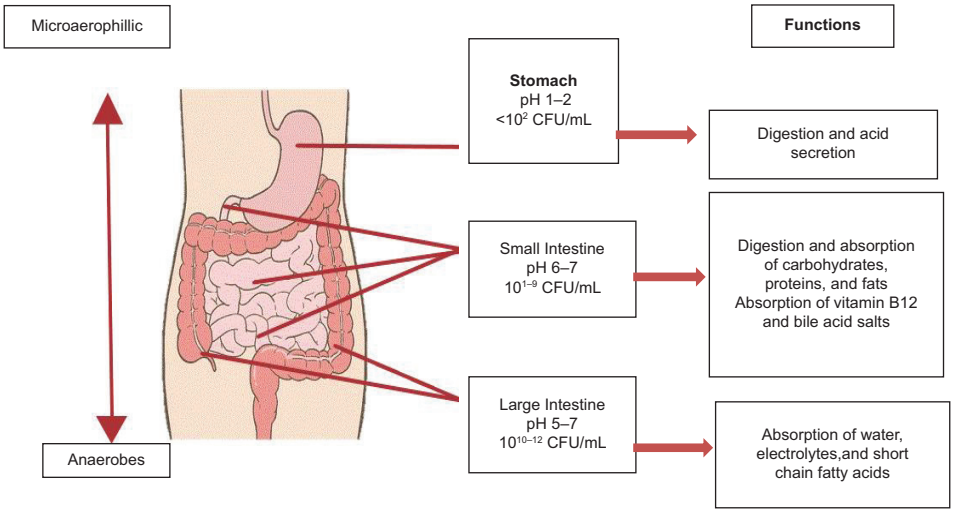

Figure 2. Key physiologic and microbiological features of the gut

substantial influence than obesity itself. Studies comparing resistin-like molecule b-deficient mice – which are resistant to high-fat diet-stimulated obesity – with wild-type mice showed that both groups experienced similar gut microbiota shifts, reinforcing the idea that dietary intake is the primary determinant of microbiota changes, rather than obesity alone. Beyond dietary impact, long-term antibiotic use can cause lasting alterations in gut microbiota. Research has demonstrated that a 7-day clindamycin regimen in humans irreversibly modified *Bacteroides* populations for up to two years, without signs of recovery. Similarly, exposure to ciprofloxacin significantly reduced gut microbial diversity, and while most species restored their populations within a month, certain bacterial taxa failed to recover even 6 months after treatment.[61]

Alterations caused by antibiotics extend beyond gut microbiota and can significantly influence metabolic health and obesity progression. For instance, administering norfloxacin and ampicillin improved glycemic control in diet-induced obese mice, suggesting a potential role for antibiotics in obesity management. However, early-life exposure to antibiotics has been linked to increased adiposity, particularly in newborn mice, highlighting a critical time window during which antibiotic intervention can lead to lasting metabolic consequences. Studies found that newborn mice were more vulnerable to low-dose penicillin than mice treated later, with early exposure leading to increased fat storage and metabolic shifts. Moreover, transplanting microbiota from penicillin-exposed mice into germ-free mice induced obesity-like phenotypes, further establishing a causal connection between gut microbiota alterations and obesity development. Human studies reinforce this connection, showing that antibiotic therapy has been associated with increased obesity risk**,** particularly when administered in early childhood. Research in Finnish pre-school children using metagenomics identified significant correlations between infant antibiotic exposure and obesity prevalence, suggesting long-term effects on microbial diversity and metabolic health. Given the widespread use of antibiotics, their unintended influence on gut microbiota could contribute to metabolic dysfunctions, insulin resistance, and weight gain over time (Figure 3). Overall, dietary patterns and antibiotic interventions strongly shape gut microbiota balance, impacting metabolic regulation, immune function, and obesity risk.[62] While targeted antibiotic use may offer therapeutic potential, caution is necessary regarding early-life exposure, as disruptions in microbiota composition can have lasting metabolic consequences.

11. Microbiota and diseases associated with obesity

Obesity induces persistent low-grade inflammation in multiple organs, which is linked to metabolic disorders, including glucose intolerance, insulin resistance, and cardiovascular illnesses (Table 1).[63] Inflammation is a significant risk factor for metabolic disorders associated with diabetes, metabolic syndrome, and cardiovascular disease.[64] Hotamisligil *et al.*[65] were the first to elucidate inflammation in metabolic disease, demonstrating that adipocytes can express the cytokine TNF-α, with its expression being heightened in the adipocytes of obese mice. The gut microbiota intensifies inflammation by the action of LPS, a crucial element of the cell walls of Gram-

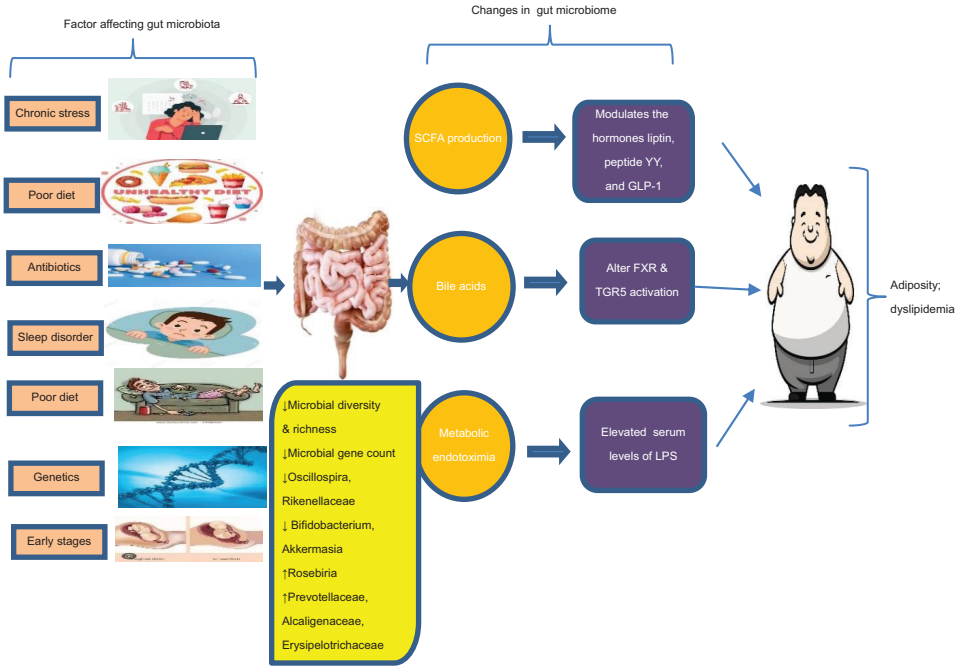

Figure 3. Factors altering gut microbiome leading to obesity
Abbreviations: FXR: Farnesoid X receptors; LPS: Lipopolysaccharide; SCFA: Short-chain fatty acid; TGR5: Takeda G-protein-coupled receptor 5c.

Table 1. Microbial taxa in obese individuals with metabolic disorders

Metabolic disorders	Risk-enhancing Bacteria	Protective or risk-lowering bacteria
Metabolic syndrome	*Coriobacteriaceae*	*Faecalibacterium prausnitzii, Parabacteroides, Bacteroides caccae, Parabacteroides distasonis,* and *Oscillospira*
Impaired glucose tolerance or insulin resistance	*Bacteroides ovatus* and *Enterobacteriaceae Prevotellaceae* and *Veillonella*	*Coprococcus, Haemophilus parainfluenzae, Parabacteroides, Bacteroides caccae* *Oscillibacter sp., Agathobaculum butyriciproducens, Haemophilus parainfluenzae, Veillonella parvula, Dialister invisus*
High diastolic blood pressure	*Clostridium* and *Clostridiaceae*	-
Low HDL cholesterol	*Lachnospiraceae*, *Gemellaceae*, and *Turicibacter*	-
Cardiovascular disorders	*Prevotellaceae* and *Veillonella*	*Coriobacteriaceae*

negative bacteria.[66-68] The proliferation of Gram-negative bacteria in obese individuals, such as *Veillonella*, can result in an increased concentration of LPS in the colon.[69] The increase of LPS can compromise the gut barrier by stimulating the TLR4/MyD88/IRAK4 signaling pathway in intestinal epithelial cells, subsequently leading to the transfer of LPS from the intestine into the systemic circulation.[70] Furthermore, the reduction of *A. muciniphila* facilitates the transfer of microbial by-products due to its role in preserving gut barrier integrity.[71] Moreover, a high-fat diet facilitates the integration of LPS into chylomicrons, thereby enhancing the absorption of LPS in the intestine and its subsequent transfer to the systemic circulation through lymphatic fluid.[72] These pathways lead to increased LPS levels in circulation. LPS can trigger immunological reactions in adipose tissue and the liver during systemic circulation. LPS initially associates with the LPS-binding protein and then forms a complex with cluster of differentiation 14.[73] This complex subsequently stimulates the NF-κB and activator protein 1 by activating TLR4 present on macrophages and adipose tissue, thereby facilitating the production of pro-inflammatory chemokines and cytokines, including MCP-1, TNF-α, and IL-6.[43,73] These cytokines can influence adipocytes, prompting them to release more cytokines and chemokines through paracrine and autocrine mechanisms.[74] Furthermore, overexpression

of MCP-1 in adipose tissue has been established as associated with heightened macrophage infiltration in rodents.[75] Significantly, SCFAs serve as a crucial link between inflammatory reactions and the gut microbiota, demonstrating strong anti-inflammatory characteristics, particularly butyrate.[76] Butyrate safeguards the gut against inflammation by inducing IL-18 production and facilitating the development of regulatory IL-10-producing T cells and T cells through GPR109a.[32,77] Moreover, butyrate can upregulate peroxisome proliferator-activated receptor gamma, enhance the production of anti-inflammatory cytokines, and inhibit NF-κB activation triggered by LPS, thereby demonstrating its anti-inflammatory effects.[78,79] The genera *Fusobacterium*, *Pseudomonas*, *Escherichia-Shigella*, and *Campylobacter* are commonly associated with obesity.[80,81] LPS from members of the *Desulfovibrionaceae* and *Enterobacteriaceae* families exhibit endotoxin activity that is 1,000-fold greater than that of LPS from *Bacteroideaceae*.[82]

12. Effects of diet on obesity

The composition of the gut microbiota is significantly influenced by dietary habits. A diet rich in fats and sugars, characteristic of Western cuisine, increases the relative prevalence of *Firmicutes* while diminishing *Bacteroidetes* in animal models.[83] Furthermore, transitioning from a low-fat, plant polysaccharide-rich diet to a high-fat/high-sugar "Western" diet can alter microbiota formation within a single day in gnotobiotic mice colonized with human fecal bacteria.[84] The nature of diet, combined with elevated caloric intake along with reduced physical activity, is among the principal factors contributing to the rising incidence of obesity.[85] The origins and progression of obesity can be explained by the carbohydrate-insulin model and/or the energy balance model (EBM).[86] The EBM model posits that the brain, particularly the hypothalamus, regulates body weight by controlling food intake through complex internal endocrine, metabolic, and neural signals from peripheral organs, as well as external cues from the food environment.[87] The increased availability of ultra-processed foods (UPFs), characterized by high energy density and elevated levels of fat and sugar, but low in protein, fiber, vitamins, and minerals, may result in a positive energy balance and fat accumulation (adiposity), regardless of the diet's macronutrient composition. Typical examples of UPFs include refined cereals, sweet and savory snacks, margarine, reconstituted and ready-to-eat frozen meals, and carbonated and alcoholic beverages.[88] The carbohydrate-insulin model emphasizes diet quality, namely, chemical composition, over quantity.[89] UPFs and other refined products are high in sugars, which elevate both glycemic index and glycemic load. Elevated glycemia triggers excessive insulin production, leading to increased adiposity and the inhibition of energy release from adipose tissue. Post-prandial energy substrate deficiency in the bloodstream is detected by the hypothalamus, stimulating appetite and reducing energy expenditure, potentially resulting in a positive energy balance due to hyperphagia.[90] Excessive consumption of UPFs can affect gut flora and has been associated with a higher incidence of obesity, metabolic syndrome, hypercholesterolemia, and hypertension.[91] Diets high in protein and fat are typically linked to *Bacteroides*-dominant (enterotype I) microbiota, while high-carbohydrate diets are associated with *Prevotella*-driven (enterotype II) microbiota profiles. This aligns with the findings of Wu *et al.*,[92] who reported that *Bacteroidetes* and *Actinobacteria* positively correlate with dietary fat and negatively with dietary fiber, while *Firmicutes* and *Proteobacteria* show the opposite trend. Conversely, Brinkworth *et al.*[93] found that high-fat/low-fiber diets reduced the abundance of *Bifidobacteria* compared to low-fat/high-fiber diets. Lower carbohydrate and fiber intake resulted in a decline in bacteria, such as *Eubacterium rectale*, *Roseburia* spp., and *Bifidobacterium* spp. in obese adults.[94] Dietary fiber increased the abundance of *Prevotella*, whereas bile-resistant taxa, such as *Bilophila* and *Bacteroides* were associated with high-fat, animal-based diets.[95]

Vegetarians generally exhibit greater bacterial diversity, higher *Prevotella* to *Bacteroides* ratios, and reduced levels of *Enterobacteriaceae*, including *E. coli*, compared to omnivores.[96] Moreover, vegetarians and vegans show a greater abundance of *Lachnospiraceae* (e.g., *Roseburia*, *Anaerostipes*, *Blautia* genera) and *Ruminococcaceae* (e.g., *Ruminococcus* and *F. prauznitzii* genera), along with a reduced presence of *Bacteroides*, *Parabacteroides*, and *Alistipes*.[97]

The Western-style diet, marked by a high intake of protein and fats (particularly saturated fats), is associated with an increased prevalence of metabolic disorders, such as type 2 diabetes, cardiovascular diseases, and obesity.[98] It also correlates with increased abundances of *Bacteroides*, *Alistipes*, and *Bilophila*, and decreased levels of *Lactobacillus*, *Roseburia*, *Eubacterium*, and *Enterococcus* genera.[99] In contrast, the Mediterranean diet – rich in dietary fiber from cereals, vegetables, legumes, nuts, and fruits; unsaturated fatty acids from fish and vegetable oils; and antioxidants, such as flavonoids and polyphenols – enhances overall microbial diversity.[100] This includes increases in families, such as *Clostridiaceae* and *Lactobacillaceae*, and genera, such as *Bacteroides*, *Prevotella*, *Bifidobacterium*, *Roseburia*, *Lactobacillus*, *Clostridium*, and *Faecalibacterium* (Table 2), while reducing the abundance of *Proteobacteria*.[101]

Table 2. Comparison of gut microbiota in obese and non-obese individuals

Group	↑ Gut microbes	↓ Gut microbes	*Firmicutes: Bacteroidetes*	References
Non-obese individuals	*Actinobacteria* (phylum), *Bacteroidetes* (phylum), *Bifidobacterium*, *Bacteroides*, *Prevotella*	*Firmicutes* (phylum), *Lactobacillales* (order), *Clostridium*	0.9	127
Obese individuals	*Firmicutes* (phylum), *Lactobacillales* (order), *Clostridium*	*Actinobacteria* (phylum), *Bacteroidetes* (phylum), *Bifidobacterium*, *Bacteroides*, *Prevotella*	1.7	127

13. Obesity and cardiovascular disorders

The gut microbiota, when subjected to unhealthy dietary patterns, metabolizes dietary nutrients into metabolically harmful substances. Examples include imidazole propionate, branched-chain amino acids (BCAAs), and trimethylamine N-oxide (TMAO).[102] The microorganisms *Bacteroides vulgatus* and *Prevotella copri* promote the synthesis of BCAAs, whereas *Eggerthella lenta* and *Streptococcus mutans* are known to produce imidazole propionate. Elevated circulating levels of BCAAs are significant risk factors for insulin resistance, and BCAA-related microbial metabolites, such as imidazole propionate, adversely affect insulin signaling cascades. TMAO has garnered significant interest because of its potential role in cardiovascular disease.[103] Trimethylamine is produced by the gut microbiota from compounds, such as choline, phosphatidylcholine, betaine, and L-carnitine, which are abundant in seafood, egg yolks, dairy products, and red meat. Trimethylamine is absorbed into the portal circulation and oxidized to TMAO in the liver by flavin-containing monooxygenase 3.[104] TMAO and its dietary pre-cursors promote arteriosclerosis through pathways involving inflammation, platelet aggregation, oxidative stress, and thrombosis.[96] Consequently, gut dysbiosis results in elevated plasma TMAO levels, which are associated with cardiovascular disease and increased overall mortality.[103]

LPSs are glycolipid molecules that constitute crucial components of the outer membrane components of Gram-negative bacteria and act as bacterial endotoxins, contributing to cardiometabolic abnormalities. Elevated LPS levels can induce the expression of pro-inflammatory cytokines, leading to endothelial damage, enhanced oxidation of low-density cholesterol particles, and foam cell formation, processes that collectively accelerate atherosclerosis.[105]

14. Prevention of obesity by modulation of gut microbiota

14.1. Probiotics

The World Health Organization defines probiotics as "living microorganisms that provide the host with beneficial effects when administered in sufficient quantities."[106] Probiotics are currently widely applied in the prevention and treatment of various diseases, including periodontal conditions and gastrointestinal infections, with particular emphasis on *Lactobacillus* and *Bifidobacterium* species.[107] As commensal microorganisms in the human gut, probiotics are believed to exert beneficial effects through mechanisms, such as competing with pathogenic bacteria, enhancing gut barrier function, and regulating immune responses.[108] Recent studies involving both animals and humans have demonstrated that probiotics can effectively improve metabolic disorders, reduce inflammation, and mitigate weight gain in individuals with obesity. The probiotic VSL#3, which includes *Bifidobacteria* and *Lactobacillus* strains, has been utilized in mouse models to address obesity by enhancing insulin sensitivity, decreasing food intake, and inhibiting weight gain.[109] In a randomized controlled trial, VSL#3 usage in human subjects demonstrated improvements in insulin sensitivity and lipid profiles.[110] The probiotic powder *Lactobacillus plantarum* Dad-13 demonstrated the ability to alter gut microbiota composition in a double-blind, placebo-controlled trial, resulting in a decrease in *Firmicutes* and an increase in *Bacteroidetes*, alongside significant reductions in body weight and body mass index.[111] Another double-blind, randomized trial found that the supplementation with a probiotic mix (*Bifidobacterium*, *Lactococcus*, and *Lactobacillus*) in overweight and obese individuals increased antioxidant enzyme activity and reduced abdominal adiposity. Nonetheless, a recent meta-analysis of randomized controlled human studies indicated that the association between weight loss and probiotics treatment was not statistically significant.[112] Furthermore, the specific bacterial species, optimal dosages, and treatment durations necessary to effectively enhance obesity management require additional research.

14.2. Prebiotics

Prebiotics are indigestible components specifically used by host microbiota, offering beneficial effects primarily by alleviating gut dysbiosis.[113] Several studies have indicated that prebiotics may improve dysbiosis, metabolic disorders, and chronic inflammation associated with obesity.[114] Common prebiotics include inulin, various forms of lactulose, oligosaccharides, and resistant starch. It is

generally accepted that all fermentable dietary fibers possess prebiotic properties.[115] A functional food strategy has been implemented to incorporate inulin into widely consumed items, such as cereals, biscuits, infant foods, yogurts, breads, and beverages at levels capable of eliciting a prebiotic effect.[116] Various dietary supplements containing fructo-oligosaccharides, mainly inulin, are also commercially available. Gut hormones, such as GLP-1 are essential for transmitting signals regarding nutritional and energy status from the gut to the central nervous system, thereby regulating appetite. Research indicates that prebiotics upregulate *Glp1* expression in obese mice, indicating that changes in gut microbiota may influence gastrointestinal hormone secretion.[117] In genetically obese mice, prebiotic treatment was associated with weight loss, improved glucose tolerance, and reduced inflammation, alongside an increase in *Bacteroidetes* and a decrease in the *Firmicutes* phylum. In a double-blind, placebo-controlled trial, supplementation with oligofructose-enriched inulin in overweight or obese children led to a significant reduction in serum IL-6 levels and body weight.[118] In addition, a randomized, placebo-controlled trial examining fecal samples from obese individuals consuming inulin-type fructans revealed an increase in *Bifidobacterium* abundance and a reduction in fecal calprotectin, a marker of gut inflammation, compared to controls.[119] Consequently, incorporating prebiotics into the diet holds significant potential to beneficially modulate gut microbiota composition.

14.3. Synbiotics

A synbiotic refers to a combination of a probiotic and a prebiotic. Synbiotics may have a more significant impact on gut microbiota and host health compared to the isolated consumption of either prebiotics or probiotics. This is because they provide probiotic bacteria along with a prebiotic component that enhances the survival and growth of these beneficial microbes within the digestive tract. Evidence suggests that synbiotics can be effective in modifying the composition of the gut microbiota. For instance, the synbiotic combination of particular oligofructose-enriched inulin (SYN1) with *Lactobacillus rhamnosus* GG and *Bifidobacterium lactis* Bb12 over a 12-week period resulted in a 16% and 18% increase in *Bifidobacterium* and *Lactobacillus* populations, while also leading to a 31% reduction in *Clostridium perfringens* counts.[120] *In vitro* investigations have shown that synbiotics outperform prebiotics and probiotics in their ability to modulate gut microflora. However, it is essential to document these findings through rigorously controlled human intervention studies. At present, there is a limited number of human studies examining the potential benefits of synbiotics in relation to obesity.[121]

14.4. Fecal microbiota transplantation

Fecal microbiota transplantation (FMT) is defined as the introduction of fecal suspension from healthy donors into

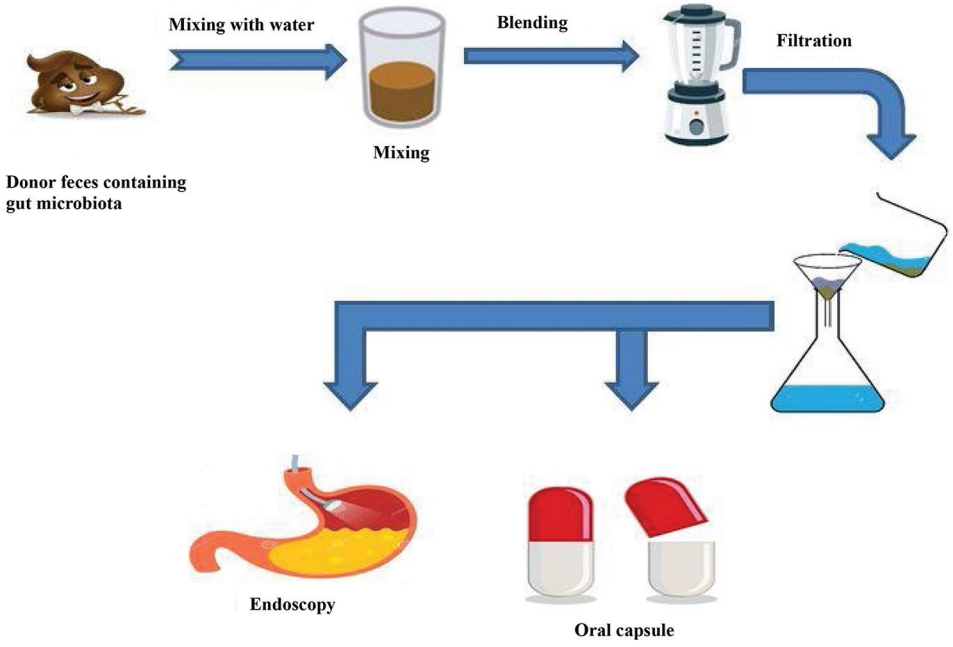

Figure 4. Schematic diagram of the fecal microbiota transplantation process

a patient's gastrointestinal tract, with the aim of restoring gut microbiota and treating related disorders.[122] Unlike probiotics, FMT provides recipients with a complete community of gut microbiota and its metabolites from healthy donors, rendering it a potentially more effective therapeutic intervention.[123] The remarkable efficacy of FMT in treating *Clostridium difficile* infections suggests that it is becoming a promising therapeutic option for other conditions linked to gut dysbiosis, including persistent irritable bowel syndrome, constipation, and ulcerative colitis.[124] A pilot human study demonstrated a substantial improvement in peripheral insulin sensitivity among nine obese individuals with metabolic syndrome following the transplantation of fecal microbiota from lean donors. Nevertheless, in several recent randomized clinical trials, FMT did not demonstrate significant effects on metabolic profiles and weight reduction.[125] There are also risks associated with FMTs, as viral pathogens cannot be eliminated through filtration. Therefore, FMT should be utilized only as a last resort for conditions, such as recurrent *C. difficile* infection (Figure 4). Furthermore, FMTs may have detrimental impacts in the context of obesity. A recent case report described a patient who underwent a successful FMT for *C. difficile* infection but subsequently developed new-onset obesity after receiving stool from an overweight donor.[126]

15. Conclusion

In conclusion, the gut microbiome plays a pivotal role in obesity development and associated metabolic disorders by influencing energy metabolism, immune responses, inflammation, and nutrient absorption. The intricate relationship between diet, antibiotic exposure, and microbiota composition demonstrates how external factors shape gut health, potentially leading to obesity when dysbiosis occurs. Understanding the mechanisms by which gut microbiota impacts obesity, including microbial metabolites and immune modulation, offers valuable insights into prevention and treatment strategies. Dietary interventions, particularly plant-based diets, contribute to greater microbial diversity, fostering a healthier gut environment. Moreover, strategies, such as probiotic, prebiotic, and synbiotic supplementation, as well as fecal microbiota transplantation, have emerged as promising therapeutic approaches for restoring microbial balance, improving metabolic function, and preventing obesity-related complications. However, the effects of microbiota treatments may vary from person to person, over time, and depending on factors, such as diet, concurrent medical treatments, and coexisting diseases. The complex interactions between the native gut microbiota, the quality and quantity of transplanted microbiota, the gut environment, host genetics, and interactions with various medications, including antibiotics, still require further investigation. The role of different species of gut microbial species also warrants greater focus in future microbiological research. Various studies have revealed that metabolic activities of gut microbiota facilitate the extraction of energy (calories) from ingested dietary food and aid in storing this energy for later usage by the host. By leveraging gut microbiota modulation, novel treatments can pave the way for sustainable obesity management, providing effective alternatives to conventional weight-loss strategies. Advancing research on microbiome-targeted therapies will be essential for optimizing clinical applications and ensuring that interventions are tailored to individual microbiota profiles for improved health outcomes.

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The authors declare that they have no competing interest.

Author contributions

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Writing – review & editing: Amar P. Garg

Ethics approval and consent to participate

Not applicable.

Consent for publication

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Availability of data

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