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Review

Gut microbiome and obesity care: Bridging dietary, surgical, and pharmacological interventions

Davide Masi,[1,2,4] Mikiko Watanabe,[2,4] and Karine Clément[1,3,*]
[1]Sorbonne Université, Inserm, Nutrition and Obesities: Systemic Approaches, NutriOmics Research Unit, 75013 Paris, France
[2]Sapienza University of Rome, Department of Experimental Medicine, Section of Medical Physiopathology, Food Science and Endocrinology, 00161 Rome, Italy
[3]Assistance Publique Hôpitaux de Paris, Nutrition Department Pitié-Salpêtrière Hospital, 75013 Paris, France
[4]These authors contributed equally
*Correspondence: karine.clement@inserm.fr
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SUMMARY

In the mid-2000s, mouse studies suggested that the gut microbiome might influence energy harvest, fat storage, appetite, insulin sensitivity, and inflammation. Since then, our understanding of the gut microbiome's role in obesity has advanced significantly. Mechanistic studies identified microbial metabolites, such as short-chain fatty acids, bile acids, branched-chain amino acids, tryptophan catabolites, and imidazole propionate, as key modulators of metabolism, inflammation, and gut-brain communication. Metagenomic and multi-omics technologies now provide deeper insights into the intricate interactions between microbes, metabolites, and host factors, reshaping obesity research and reinforcing the need for phenotype stratification by recognizing microbiome-driven metabolic profiles. Integrating gut microbiome data into clinical strategies may enable targeted interventions for specific obesity subtypes, advancing prevention and personalized care. However, as new anti-obesity medications emerge, it is imperative to determine how microbiome-based therapies can complement them, considering efficacy, cost, and patient-specific variability.

INTRODUCTION

Obesity is the public health challenge of the 21st century, reaching epidemic proportions globally and surpassing predictions,[1] with approximately 890 million adults and 160 million children and adolescents affected worldwide.[2,3] It is associated with an elevated risk of complications, including type 2 diabetes mellitus, hypertension, dyslipidemia, obstructive sleep apnea, atherosclerosis, osteoarthritis, metabolic-associated steatotic liver disease, cardiovascular diseases, and certain cancers.[4] In the United States alone, approximately 400,000 individuals die each year from obesity-related causes, making it the second leading cause of preventable death after smoking.[5] Recent frameworks from the European Association for the Study of Obesity[6] and the Lancet Commission on Clinical Obesity[7] move beyond BMI-centric definitions, proposing multidimensional clinical staging models that incorporate functional, metabolic, and psychosocial factors to support personalized care.

While the widespread availability of energy-dense and processed foods and increasingly sedentary lifestyles are major contributors, a complex interplay of genetic, epigenetic, environmental, and behavioral factors underlies obesity pathogenesis. Among these, the gut microbiome has emerged as a critical and dynamic interface between the environment and the host, contributing to digestion, nutrient metabolism,[8,9] vitamin biosynthesis,[10] immune regulation,[11] and defense against pathogens,[12] thus both an integrator and mediator of environmental triggers, including diet, pollutants, and lifestyle factors. Through its interactions with host metabolism, immune signaling, and endocrine pathways, the microbiome modulates the body's response to external influences, possibly shaping individual susceptibility and persistence of obesity and its complications.[13] Indeed, disruptions in its composition and function have been linked to obesity and related metabolic disorders.[14,15] Pioneering studies in germ-free mice provided the first strong evidence that gut microbes influence adipose tissue accumulation and host metabolism directly,[16] highlighting their role in energy balance and inflammation, beyond caloric intake. Advances in metabolomics also offer insights into host-microbiome-environment interactions in obesity.[17–19]

This review synthesizes the latest advances in microbiome-obesity research, emphasizing mechanistic pathways and translational relevance. Herein, we examine how research has evolved from identifying associations to some causative mechanisms, paving the way for novel therapeutic strategies. We notably explore how shifts in gut microbiota composition and microbial metabolite production contribute to the pathophysiology of obesity and its related metabolic disorders and how emerging microbiome signatures may guide precision interventions. We further evaluate the interaction between the gut microbiome

and current therapeutic strategies—pharmacologic, dietary, and surgical—highlighting challenges and opportunities in moving toward microbiome-informed care.

DECODING THE FIRST GUT MICROBIOME'S CHANGES AND LINKS TO METABOLIC HEALTH

Microbial diversity as a consistent marker of metabolic health

Recent research has elucidated the complex interactions between gut microbiota and host metabolism, providing important insights into the mechanisms underlying the development of obesity and/or the deterioration of metabolic health.[20] The human gut microbiome is a diverse ecosystem comprising trillions of microorganisms, primarily bacteria.[21] Two predominant bacterial phyla in the human gut are Firmicutes (recently reclassified as Bacillota) and Bacteroidetes (renamed Bacteroidota).[22] Relative abundances are frequently utilized as key indicators of microbiome composition. Other important phyla include Proteobacteria, Actinobacteria, and Verrucomicrobia.[23]

Together with bacterial relative abundance, indicators of gut microbial ecology including taxonomic diversity and metagenomic richness have been explored. Taxonomic diversity refers to the richness and distribution of microbial taxa. It is commonly assessed using ecological diversity metrics, such as alpha (α) diversity to describe within-sample diversity (e.g., richness [number of taxa] and evenness [relative abundance]) and beta (β) diversity to capture differences between samples. Higher α-diversity is generally associated with better metabolic phenotypes.[24] However, microbial diversity per se should not be equated directly with microbiome resilience or functional capacity, as these are distinct but potentially correlated properties shaped by ecological dynamics, microbial interactions, and host-related factors. Metagenomic richness describes the number of different microbial genes present in a sample. Measured with shotgun sequencing, it can also provide information regarding the community's functional potential, based on gene information, and adds to taxonomic data by indicating the range of metabolic pathways that may be modified by the disease condition.

Numerous studies have shown that individuals with obesity or metabolic syndrome frequently exhibit reduced gene richness and α-diversity, suggesting a less resilient and functionally limited microbiome.[14,25] Across the obesity phenotypes, a study involving 747 adults with overweight or obesity found that the metabolically unhealthy subjects had lower phylogenetic and non-phylogenetic α-diversity compared to the metabolically healthy subjects.[26] The reduction in richness and diversity has been linked to worse glucometabolic health and inflammation. Metagenomic modeling approaches suggest that such reductions also associate with impaired microbial functions involved in energy harvest, gut barrier integrity, and inflammation regulation.[14] In agreement with these first observations,[14] a meta-analysis of 1,351 fecal shotgun metagenomes from subjects with or without obesity confirms that obesity is characterized by reduced bacterial species, together with decreased virome richness and diversity. Specific species like *Ruminococcus gnavus* and *Akkermansia muciniphila* were highlighted as potential functional drivers. Moreover, viral operational taxonomic units (vOTUs) could distinguish obesity from healthy controls but with moderate accuracy (area under the curve [AUC] ≈ 0.77).[27]

Studies have also investigated the differences in microbial composition between human obesity and leanness, revealing distinct microbial signatures and functional profiles.[28] Patients with obesity often show depleted relative abundance of Bacteroidetes strains, such as *Bacteroides* spp.,[29] or enrichment of others. Consistently, there is frequently a depletion of *A. muciniphila*, a mucin-degrading bacterium associated with improved metabolic health,[30,31] and of *Faecalibacterium prausnitzii*, a butyrate-producing bacterium with anti-inflammatory properties.[32] These latter gut microbiome-derived species and others were further tested as therapeutic agents (see dietary modulations).

Overall, heterogeneity of gut microbiota composition in patients with obesity has been well documented, also revealing significant variations based on factors such as race/ethnicity, dietary patterns, socioeconomic status, and the presence of metabolic complications.[33] For instance, one study reported that the inverse relationship between α-diversity and BMI was most consistent among non-Hispanic white populations, different from Black and Hispanic populations.[33] These associations should not be solely interpreted as stemming from inherent biological differences, rather likely reflecting early-life exposures, social environments, structural inequities, and dietary habits[34,35] (see obesogenic environment and the microbiome).

From composition to functions in population with obesity

Early microbiome studies comparing subjects with or without obesity first focused on the Firmicutes/Bacteroidetes (F/B) ratio, and initial reports suggested an elevation in obesity.[36] Although this hypothesis generated substantial interest, subsequent studies produced inconsistent results, limiting its value as a biomarker.[37–39]

The field has since shifted from such broad compositional measures toward functionally informed and predictive frameworks. Metagenome-wide association studies (MWASs) now enable high-resolution mapping of microbial genes and pathways linked to metabolic phenotypes, offering a more precise understanding of host-microbiome interactions beyond phylum-level trends.[40,41] Tools such as HUMAnN3, directly profiling pathway abundances from shotgun metagenomes,[42] and PICRUSt2, inferring functional content from 16S rRNA data,[43] propose connection between microbiome composition and metabolic functions. While PICRUSt2 is constrained by reference database coverage and indirect inference, both approaches have highlighted recurrent alterations in short-chain fatty acid (SCFA) metabolism, amino acid biosynthesis, and xenobiotic degradation, in agreement with initial modeling studies.

For example, Wang et al.[44] applied PICRUSt2 to 16S rRNA data from adults with normal weight obesity (e.g., BMI <25 kg/m^2 but excess adiposity named "normal weight obesity"), overt obesity (BMI > 30 kg/m^2), and lean controls. Their analysis showed that normal-weight obesity subjects had enrichment of pathways related to lipid biosynthesis, glycolysis/gluconeogenesis, and xenobiotic biodegradation, together with depletion of amino acid and cofactor/vitamin biosynthesis. These functional

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shifts were partly shared with, but also distinct from, those observed in overt obesity, indicating that normal weight obesity harbors a unique and early microbial signature. Importantly, predicted pathways distinguished normal weight obesity from lean phenotypes more effectively than taxonomic composition alone, emphasizing on the importance of obesity clinical stratification. Similarly, Aranaz et al.[45] developed a predictive model of inflammatory status in obesity using data from the Obekit trial. Participants were stratified into low- and high-inflammatory groups based on waist/hip ratio, leptin/adiponectin ratio, C-reactive protein, and TNF-α levels. Distinct microbiota signatures were observed: *Methanobacteriaceae*, *Christensenellaceae*, and *Bifidobacteriaceae* were enriched in the low-inflammation group, while *Carnobacteriaceae*, *Veillonellaceae*, and *Enterobacteriaceae* predominated in the high-inflammation group. Notably, *Christensenellaceae*, a highly heritable taxon previously associated with lower BMI and reduced inflammation, emerged as a candidate "protective" family.

Metagenomics-driven metabolic signatures in large populations

To better classify overall variations in gut microbiome composition and facilitate larger population stratification, researchers have introduced the concept of "enterotypes," which group microbial communities based on dominant bacterial genera, offering insights into microbiome-driven metabolic and health profiles.

The initial three classical enterotypes were Prevotella, Bacteroides, and Ruminococcus, each associated with distinct dietary patterns and metabolic profiles. This gut microbiome stratification has been extended in the context of obesity and inflammation-related diseases in large populations.[46] Investigators have identified a fourth enterotype, Bacteroides 2 (Bact2), characterized by a low-diversity microbial community enriched in pro-inflammatory bacteria including *Alistipes*, *Escherichia coli*, and other Proteobacteria, with a relative depletion in *Faecalibacterium* spp., *Akkermansia* spp., and *Methanobrevibacter smithii* and a lower potential to produce butyrate.[47] The Bact2 enterotype is more prevalent in subjects with severe obesity and metabolic and inflammatory alterations recruited in the European MetaCardis population. After dietary or bariatric surgery-induced weight loss, an increase in gut microbiome diversity and a decrease in Bact2 prevalence were observed, suggesting a link between this enterotype and metabolic health.[47,48] In individuals with severe obesity taking statins, a lower prevalence of the Bact2 enterotype was observed, suggesting a role of medication in shaping gut microbiome composition.[49] It was proposed that the overrepresentation of pro-inflammatory species, such as members of the Proteobacteria phylum, may contribute to metabolic disturbances such as insulin resistance, altered lipid metabolism, and increased gut permeability. Bact2 could be influenced by environmental factors, including stress, antibiotic exposure, or host immune status, all of which can disrupt microbial balance and promote systemic inflammation.[50]

Beyond compositional differences that may aid in individual stratification, functional disparities in the microbiome have also been observed in population metagenomic studies, corroborating initial observations. Results indicate that the microbiome of individuals with obesity is enriched in genes associated with carbohydrate and lipid metabolism, suggesting an enhanced capacity for energy harvest from dietary sources.[29] Microbial pathways involved in amino acid biosynthesis are enriched in subjects with severe obesity, while pathways related to amino acid degradation are depleted.[51] Moreover, specific classes of microbiota-derived metabolites influencing host energy balance, fat storage, and insulin sensitivity, such as SCFAs, bile acids (BAs), and branched-chain amino acids (BCAAs), are altered in obesity.[52] Metagenomic analyses in individuals with severe obesity and microbiome dysbiosis have also demonstrated an impaired capacity for B vitamin (notably biotin) transport and synthesis. This deficiency in biotin-producing and transporting bacteria correlates with metabolic disturbances and systemic inflammation observed in severe obesity.[53]

OBESOGENIC ENVIRONMENT AND THE MICROBIOME

The development and progression of obesity are influenced by lifestyle, genetics, and many other environmental elements.[54] These factors impact the gut microbiome, which in turn contributes to shaping the development and progression of metabolic disease itself, in a bidirectional link.

In some studies, diet accounts for as much as 20% of the inter-individual variability in gut microbiota composition.[55] First relationships were made between enterotypes and dietary patterns. For instance, Prevotella enterotypes are associated with carbohydrate-rich diets, while Bacteroides enterotypes are linked to Western diets high in animal protein and saturated fat.[56] High-fat diets are associated with decreased microbiome richness and diversity, increased Proteobacteria with pro-inflammatory properties, and decreased "protective" bacteria, with reduced SCFA concentrations.[57] Conversely, fiber-rich diets are associated with increased microbial diversity and a higher abundance of beneficial bacteria, such as Prevotella and Xylanibacter.[58] However, recent studies illustrate the complexity of fiber-microbiome-host interactions. For instance, carboxymethylcellulose (CMC), a cellulose derivative that can act as a functional fiber, can disrupt the gut microbiota composition, leading to reduced diversity and alterations promoting intestinal inflammation and metabolic impairments.[59,60] On the other hand, a novel "anti-obesity" device made out of a hydrogel composed primarily by CMC crosslinked with citric acid was recently shown to improve the gut microbiome in rodents,[61] also stimulating the growth of *A. muciniphila*. Whether the observed effect is due to the mechanical properties of this device rather than its composition needs further investigation.

Regular exercise modulates the gut microbiota in both humans and animals. Professional athletes show greater diversity and enhanced metabolic capacity compared to their sedentary counterparts,[62] and the variability in response to exercise among individuals with prediabetes is associated with differential capacity for producing SCFAs and degrading BCAAs.[63]

Host genetics also play a role in shaping gut microbiome composition. Twin studies demonstrated that monozygotic twins share more gut microbiota similarities than dizygotic,[64] and specific host genetic variants associated with obesity risk interact with the gut microbiome, modulating its composition and function. For example, the LCT (lactase) variant (rs4988235) is

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associated with *Bifidobacterium* abundance and BMI in a diet-dependent manner. Variants near ZNRF3 (rs2294239) linked to body fat distribution, and NOD2, involved in innate immunity and inflammation, have also been associated with microbiome variation. Interestingly, many of these loci lie in non-coding regions previously associated with metabolic traits in genome-wide association studies.[65]

Additional environmental factors include geographical location, antibiotic use, and early-life exposures. For instance, individuals from different geographical regions harbor distinct microbial communities, likely due to differences in diet, lifestyle, and environmental exposures.[66] Antibiotic use, particularly in early life, can profoundly alter the gut microbiome and has been associated with an increased risk of obesity in C57BL/6J mice.[67]

The specific ways in which the microbiome mediates lifestyle and environmental effects on obesity are not yet clear, and further research is required to quantify how much of these influences occur through microbiome-dependent mechanisms. Saad and Santos proposed the "metaflammation hypothesis," suggesting that past pathogen exposure selected immune genotypes which, in today's obesogenic environments, favor excess adiposity through immune-microbiome interactions.[68] This perspective positions the gut microbiome as both a mediator of metabolic disease and an evolutionary driver of obesity susceptibility.

MICROBIAL MECHANISMS IN ENERGY HOMEOSTASIS AND METABOLISM

In addition to the exploration of gut microbiome in population, mechanistic understanding of host-microbiota interactions has relied on complementary experimental approaches. Typically, gnotobiotic animal models, which allow for colonization with defined microbial communities, have been essential for demonstrating causal relationships between specific microbes and metabolic phenotypes whereas their translational relevance is frequently discussed. Additionally, *in vitro* systems and transcriptomic analyses have helped characterize microbial functions. Metabolomics, studying the complete set of small-molecule metabolites within a biological sample, allows to depict the functional state of cells, tissues, and organisms,[69] emerging as a powerful tool for understanding complex interactions between the gut microbiota and host metabolism in obesity.[70] Techniques like nuclear magnetic resonance (NMR) spectroscopy and mass spectrometry (MS) have revolutionized metabolomics, enabling the detection and quantification of a wide range of metabolites in various biological samples.[71]

The gut microbiota thus regulates host metabolism and energy balance through several mechanisms, including direct effects on nutrient absorption and energy extraction, as well as through indirect signaling pathways. Among these, the gut-brain axis is a critical bidirectional communication system linking the enteric microbiota with the central nervous system circuits involved in appetite regulation, energy expenditure, and glucose homeostasis.[72] This axis integrates microbial signals, including metabolites, hormones, and neuroactive compounds, via neural (particularly vagal), endocrine, and immune pathways.

Corroborating metagenomics studies, altered blood and fecal metabolomic profiles have been observed in individuals with obesity and type 2 diabetes. While modulation of the usual metabolic regulators, such as SCFAs and related pathways, has been extensively studied, the recurrent systemic elevation of BCAAs, including leucine, isoleucine, and valine, as well as aromatic amino acids such as phenylalanine, tyrosine, tryptophan, and methionine, is currently being investigated.[18]

Energy homeostasis

Gut microbes influence energy homeostasis through multiple interconnected mechanisms, including modulation of SCFA production, BA metabolism, neuroactive metabolite signaling, and maintenance of gut barrier integrity.

The gut microbiota contributes to host metabolism by extracting energy from otherwise indigestible carbohydrates. Unlike humans, many gut bacteria produce carbohydrate-active enzymes (CAZymes) such as glycoside hydrolases and polysaccharide lyases that degrade complex fibers and resistant starches.[73] For example, *Bacteroides thetaiotaomicron* genome encodes over 260 of such enzymes. Fermentation of these substrates yields SCFAs e.g., acetate, propionate, and butyrate, which supply up to 10% of human daily energy needs and support intestinal barrier integrity.[74]

Beyond their caloric contribution, SCFAs modulate appetite and energy expenditure through gut-brain signaling. They stimulate secretion of anorexigenic hormones such as GLP-1 and PYY via FFAR2 and FFAR3 receptors on enteroendocrine cells.[75] In both human and mouse intestinal organoid models, SCFAs double the number of GLP-1-producing L cells.[76] Propionate specifically enhances PYY release, promoting satiety and reducing food intake.[77] SCFAs also act on the nervous system; butyrate increases vagal afferent firing, and FFAR3 signaling on these neurons mediates appetite suppression, as shown in vagal-FFAR3 knockout mice with hyperphagia.[78] Evidence from animal studies suggests that SCFAs may boost mitochondrial function and brown-adipose thermogenesis, although these mechanisms remain incompletely defined and inconsistently replicated in humans.[79]

Metagenomic studies have consistently described the depletion of butyrate producers such as *F. prausnitzii* and *Roseburia* spp. in individuals with obesity.[80] Although lower SCFAs might suggest less energy extraction, these metabolites have key regulatory roles in promoting satiety, maintaining gut barrier integrity, and reducing inflammation, which likely outweigh their modest caloric contribution. Human data on SCFA levels remain inconsistent; some studies report higher fecal butyrate or acetate in obesity, while others lower propionate or no difference at all.[81,82] These discrepancies highlight the complexity of SCFA-host interactions, suggesting that the type, amount, and proportion of SCFAs may exert different actions. These inconsistencies likely arise from variations in methodology, diet, microbiota composition, and the distinction between SCFA production and absorption, in addition to complex inter-individual phenotype variability. SCFA fecal levels reflect not only microbial synthesis but also intestinal transit and uptake. Elevated fecal SCFAs in obesity may therefore indicate reduced absorption or impaired host-microbial communication rather than increased fermentation. The exact mechanisms by which SCFAs and related metabolites regulate human energy balance remain incompletely understood.

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BAs, synthesized in the liver, are extensively modified by gut microbes into secondary BAs (SBAs) that act as signaling molecules. SBAs activate the nuclear receptor farnesoid X receptor (FXR) and the G protein-coupled receptor TGR5, promoting a negative energy balance. TGR5 activation stimulates type 2 iodothyronine deiodinase in brown adipose tissue and skeletal muscle, increasing local thyroid hormone activity and energy expenditure in mice.[83] Both FXR and TGR5 signaling induce GLP-1 secretion from enteroendocrine cells, coupling BA signaling to appetite and glycemic control.[84]

The gut microbiota also regulates energy homeostasis through the production of neuroactive metabolites, particularly along the tryptophan-serotonin-kynurenine pathway. Intestinal bacteria and metabolites, including SCFAs, stimulate serotonin synthesis in enterochromaffin cells by upregulating tryptophan hydroxylase-1 (TPH1); peripheral serotonin influences gut motility, nutrient absorption, and vagal signaling via 5-HT3 receptors, potentially modulating feeding behavior.[85] In rodents, hyperphagia is associated with reduced luminal kynurenic acid (KYNA) and depletion of *F. prausnitzii*, whereas KYNA restoration suppresses binge-like eating.[86] In humans, lower KYNA levels are reported in bulimia nervosa, but causality and mechanisms need to be identified.[86] The precise sites of KYNA production—whether intestinal, systemic, or central—remain unclear, and its metabolic effects likely depend on the balance among kynurenine-pathway metabolites, host genetics, diet, and microbiota composition.

Indoles, also produced by bacterial metabolism of tryptophan, constitute another class of microbiota-derived metabolites relevant to energy homeostasis. Indole acutely stimulates GLP-1 secretion from enteroendocrine cells through Ca^{2+}-dependent pathways, enhancing satiety and glycemic control.[87] Through activation of the aryl hydrocarbon receptor (AhR), indoles strengthen intestinal barrier integrity and reduce metabolic endotoxemia and systemic inflammation.[88] Preclinical studies indicate that certain indole derivatives reduce hepatic lipogenesis and promote β-oxidation, suggesting a broad role in peripheral energy metabolism.[89]

Emerging human evidence indicates that meal structure influences postprandial metabolite patterns in the upper gastrointestinal tract (GI), affecting satiety and glucose regulation. In a pilot crossover study, liquid and solid meals produced distinct early metabolite signatures that correlated with appetite perception and glycemic response, suggesting a functional connection between digestive kinetics, metabolite signaling, and central appetite control.[90]

Lipid metabolism and storage

After absorption, SCFAs are transported to various organs, including the liver, adipose tissue, brain, and muscle, where they may influence fat storage and utilization; in the brain, their effects are mediated predominantly through vagal signaling.[82] SCFAs seem to influence lipid metabolism by modulating liver and fat gene expression like peroxisome proliferator-activated receptor-γ (PPARγ) in mouse models; in selective adipose- or liver-PPARγ knockout mice, acetate, propionate, and/or butyrate supplementation protects against high-fat diet-induced obesity through a PPARγ-dependent metabolic shift from lipogenesis to fat oxidation.[91]

However, gut microbiome's influence on lipid metabolism extends beyond SCFAs, with the contribution of bacteria in the expression modulation of host genes involved in fat storage and energy expenditure[92] that may affect intestinal efficiency of lipid digestion and absorption. For instance, administering *Bacteroides thetaiotaomicron* to high-fat diet-fed mice promotes weight gain, glucose intolerance, and liver steatosis through enhanced intestinal lipase activity via upregulation of fatty acid transporter genes and suppression of angiopoietin-like protein 4 (Angptl4), a lipoprotein lipase inhibitor.[93]

Gut bacteria can also modify BAs, crucial in fat emulsification and absorption. Moreover, BA-mediated FXR activation regulates ceramide expression, involved in the signaling pathways that modulate lipid metabolism,[45] and reduces lipogenesis through blunted expression of sterol regulatory element-binding protein 1c (SREBP-1c) and other lipogenic genes.[94] BAs modulate in turn the gut microbiome, creating a complex interplay between BAs, gut microbiota, and metabolic health.[95]

Glucose metabolism

SCFAs act on receptors expressed in various tissues, including fat and enteroendocrine L-type cells, such as GPR41/FFAR3 and GPR43/FFAR2, and influence glucose metabolism by promoting glucose-stimulated insulin secretion from β cells.[77,96]

The interaction between BAs and the TGR5 receptor also contributes to glucose homeostasis. In the intestine, BA-induced activation of TGR5 stimulates GLP-1 secretion, enhancing insulin secretion and improving glucose tolerance.[95] A recent study demonstrated that BA-mediated FXR activation in the liver and intestine regulates GLP-1 and fibroblast growth factor 15/19 (FGF15/19) expression involved in glucose metabolism signaling pathways.[45]

BCAAs can also be produced and degraded by the gut microbiome, contributing to their circulating levels in the host.[83] Elevated BCAAs are associated with obesity and predict insulin resistance and type 2 diabetes, up to 20 years before clinical onset, preceding changes in other established metabolic biomarkers by roughly a decade.[97] In obesity and insulin resistance, tissue BCAA metabolism is dysregulated,[98] with BCAA oxidation often impaired in fat and liver, as shown in *db/db* mice, a model of severe insulin resistance.[99] Moreover, acute infusion of BCAAs elevates blood glucose and plasma insulin in old mice. BCAA infusion during hyperinsulinemic-euglycemic clamps also impairs insulin sensitivity.[100] Conversely, pharmacological stimulation of BCAA oxidation by 3,6-dichlorobenzo(b)thiophene-2-carboxylic acid (BT2) improves glucose tolerance in high-fat-fed mice, suggesting that abnormal glycemic control in obesity may be causally linked to high circulating BCAAs.[100] Corroborating this, dietary manipulation associated with a reduction in certain BCAA may drive toward improved food preference and could be linked with a healthier metabolic phenotype.[101]

New metabolites such as imidazole propionate (IMP), produced by gut microbiota, emerged as contributors of glycemic disturbances associated with obesity. IMP is produced by microbial fermentation of the amino acid histidine by members of the Firmicutes phylum, including *Eggerthella lenta*, and is found higher in obesity, prediabetes, and diabetes. Indeed, elevated IMP in individuals with diabetes interferes with insulin signaling via activation

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of the liver p38γ-mTORC1 pathway, blunting insulin-induced Akt phosphorylation and contributing to hepatic insulin resistance.[102] Furthermore, increased IMP is associated with the Bact2 enterotype. IMP levels correlate with fasting glucose, insulin resistance, inflammatory markers, as well as unhealthy dietary patterns. Studies on IMP were extended to heart failure, a complication of obesity, showing that it could represent a risk biomarker.[103] These findings support the hypothesis that IMP may represent a critical link between diet, microbiome, and glycemic control[104] and cardiac health, potentially serving as both a biomarker and a mechanistic effector of metabolic dysfunction.

Finally, tryptophan-derived indole metabolites, particularly indole and indole-3-propionic acid (IPA), have emerged as other important microbial regulators of glucose homeostasis. Indoles stimulate incretins secretion, including GLP-1 and PYY, through AhR and pregnane X receptor (PXR) activation on L cells. This gut-brain-endocrine axis contributes to enhanced insulin secretion, improved glycemic control, and reduced appetite. These effects position indole metabolites as key links between microbial metabolism, nutrient sensing, and host endocrine function.

Inflammation and intestinal barrier integrity

Gut microbiota and metabolites are critical in maintaining intestinal barrier integrity and modulating immune responses due to their proximity to the gut epithelium.[105]

Commensal bacteria can enhance the expression of tight junction proteins like claudin-3 and occludin, strengthening the barrier function. Conversely, pathogenic bacteria can disrupt tight junctions, potentially leading to increased intestinal permeability.[106] Preclinical evidence demonstrated that the commensal microbiota can weaken barrier integrity by suppressing epithelial neuropilin-1 (NRP1) and Hedgehog (Hh) signaling.[107] Typically, increased permeability allows microbial products, such as lipopolysaccharides (LPS) from Gram-negative bacteria, to enter the bloodstream, triggering chronic systemic and tissue low-grade systemic inflammation, a hallmark of obesity and cardiometabolic disorders. The inflammatory response triggered by LPS involves the activation of Toll-like receptor 4 (TLR4), leading to the production of pro-inflammatory cytokines and the activation of inflammatory pathways impairing insulin signaling.[108] In obesity, intestinal permeability disruption is debated, also due to difficulty in measuring it,[109] although it has been clinically shown that dietary lipid intake in severe obesity increases jejunal permeability.[110]

SCFAs play an important role in regulating immune and epithelial homeostasis, thus influencing intestine barrier. SCFAs influence DNA methylation patterns, modulate histone acetylation, and regulate microRNA (miRNA) and long noncoding RNA (lncRNA) expression.[111] By affecting these epigenetic processes, SCFAs may help restore balance in gene expression disrupted by altered gut microbiota composition, potentially offering therapeutic approaches for metabolic and inflammatory disorders.

Research by Chassaing and colleagues has significantly advanced our understanding of how gut bacteria influence intestinal barrier and permeability[112] and how it can be altered also illustrating the complexity. They demonstrated that the intake of common food additives, such as emulsifiers, leads to alteration of mucus barrier and gut microbiota composition, involving increased abundance of mucin-degrading bacteria like *A. muciniphila* and *Ruminococcus gnavus*. This microbial shift reduces the protective mucus layer and shortens the distance between bacteria and epithelial cells, increasing epithelial exposure to microbial products. Whereas *A. muciniphila* is proposed as a beneficial microbe, these observations illustrate the complexity of the environment-intestine barrier interaction in impacting host metabolism. Moreover, the response to emulsifiers can be subjective, varying with host genetics and baseline microbiome configuration.[113]

GUT MICROBIOME ALONG THE BOWEL: THE EMERGING ROLE OF THE UPPER SMALL INTESTINE MICROBIOME

The gut microbiome exhibits significant variations along the GI tract, reflecting the changing chemical properties and physiological conditions.[114] The stomach and proximal duodenum present a highly acidic environment with the presence of bile and pancreatic enzymes, limiting bacterial growth to the most resilient species.[115] Moving along the small intestine, the pH gradually increases, and nutrient availability changes, allowing for a more diverse microbial community. Most studies have focused on the most accessible fecal microbiome,[116] but this approach may provide an incomplete picture of metabolic diseases.

Indeed, microbiome diversity reaches its peak in the lower GI tract, with *Streptococcus* and *Lactobacillus* being enriched in the duodenum, with significant differences in microbial diversity between mucosal and luminal samples along the lower GI tract. Specifically, mucosal α-diversity was higher in the jejunum and ileum compared to luminal samples, while the opposite was true for the large intestine.[117]

Recent research highlights the importance of examining the microbiome along the entire GI tract, particularly in the upper small intestine,[118] as it plays a crucial role in nutrient sensing, absorption, and metabolic regulation.[119] Gut barrier integrity alteration in this region is associated with increased surface and accumulation of innate and adaptive immune cells, linking to metabolic deteriorations in human subjects with obesity.[120]

Moreover, the human duodenojejunal microbiome shares similarities with the oral microbiome, suggesting a potential continuum of microbial communities from the mouth to the upper small intestine due to the constant influx of oral bacteria through swallowing. Our pilot comparative analysis of duodenojejunal, oral, and fecal microbiomes in limited number of patients with obesity and normal-weight subjects shows that the duodenojejunal microbiome exhibits stronger associations with obesity and nutrition compared to fecal microbiome.[121] Moreover, if reduced fecal microbiota diversity was confirmed,[25,53] we found increased proximal small intestine microbiota richness associated with obesity.[121] This finding underscores the importance of studying the upper small intestine microbiome in metabolic disorders, as it may provide relevant insights into the host-microbe interactions influencing obesity and related conditions.

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Table 1. Gut microbiome modulation strategies: Interventions and their effects

Intervention	Mechanisms of action	Documented outcomes
Dietary modifications	- high-fiber diets ↑ SCFA production (butyrate, acetate, propionate) - polyphenols ↑ *Bifidobacterium*, *Lactobacillus*, *Faecalibacterium* - ketogenic diet ↑ *A. muciniphila* and Bacteroidetes - ↓ proteobacteria and LPS-producing taxa	- ↑ insulin sensitivity and GLP-1 secretion - ↑ gut barrier integrity - ↓low-grade inflammation and endotoxemia - modulation of bile acid metabolism
Prebiotics	- GOSs, FOSs, and XOSs ↑ *Bifidobacterium* spp., *Lactobacillus* spp. - induction of butyrate producers (e.g., *Blautia hydrogenotrophica*) - ↓ Enterorhabdus and other opportunists - modulation of bile acids and mucosal immunity	- ↑ bowel function and colon health - ↓ constipation and intestinal permeability - ↑ SCFA biosynthesis and metabolic health markers
Probiotics	- specific strains (e.g., *L. reuteri*, *L. casei*, *B. breve*) ↑ GLP-1, ↓ LPS - SCFA-mediated appetite regulation via FFAR3/FFAR2 - reinforcement of tight junctions and ↓ gut permeability	- ↓ fasting glucose, total cholesterol, triglycerides - ↑ HDL-cholesterol - ↓ visceral adiposity and systemic inflammation - modest effect size notably on weight in humans
Synbiotics	- ↑ survival of probiotics through fiber support - ↑ SCFA production and epithelial signaling - immune modulation via Treg/Th17 balance	- ↓ inflammatory cytokines (IL-6, TNF-α) - ↑ microbial resilience and metabolic flexibility - ↓ gut dysbiosis and improved glycemic control
Postbiotics	- SCFAs: ↑ PYY/GLP-1, ↑ thermogenesis - bacterial peptides: ↓ adipogenesis, modulate lipid transporters - exopolysaccharides: ↑ epithelial defense - heat-killed strains: ↓ body fat, ↑ energy expenditure	- ↓ adipose inflammation and hepatic steatosis - improved body composition - ↓inflammation and oxidative stress - clinical benefit shown with strains like *B. animalis*
Fecal microbiota transplant (FMT)	- transfer of microbial community from lean donors - functional restoration of SCFA production, bile acid conversion - ↑ microbial gene richness (transient)	- modest improvement in insulin sensitivity - limited impact on weight loss in human trials - ↑ inter-individual variability and donor effect
Bariatric surgery	- ↑ *A. muciniphila*, *Veillonella*, *Clostridiales* - ↑ SCFAs and altered bile acids (↑ TGR5, FXR) - ↑ GLP-1, ↓ ghrelin, improved bile acid profiles	- sustained weight loss and metabolic improvement - ↓ inflammation and insulin resistance - microbiota associated with glucose metabolism changes

LPS, lipopolysaccharide; SCFA, short-chain fatty acid; GLP-1, glucagon-like peptide-1; GOSs, galactooligosaccharides; FOSs, fructooligosaccharides; XOSs, xylooligosaccharides; FFAR2, free fatty acid receptor 2; FFAR3, free fatty acid receptor 3; Treg, regulatory T cell; Th17, T helper 17 cell; IL-6, interleukin-6; TNF-α, tumor necrosis factor alpha; PYY, peptide YY; TGR5, Takeda G protein-coupled receptor 5; FXR, farnesoid X receptor. This table is a summary of main interventions and effects and not an exhaustive description.

THERAPEUTIC INTERVENTIONS TARGETING THE MICROBIOME-METABOLOME AXIS

Obesity care traditionally relies on comprehensive, multiprofessional strategies, combining dietary interventions, physical activity, behavioral support, and sometimes psychological support, adapted to the complexity and heterogeneity of each patient, with bariatric surgery offered in severe cases.[122] Alongside these approaches, intensive research has explored microbiome-directed therapies such as pre- and pro-synbiotics and even fecal microbiota transplant (FMT). With the advent of GLP-1 analogs, obesity management is rapidly evolving, raising new questions about how best to integrate microbiome-metabolome targeting into comprehensive care. These approaches can be broadly distinguished into (1) therapeutic procedures that modulate the gut microbiome and (2) therapeutic products derived from the microbiome itself, each with distinct benefits and limitations (Table 1). Looking forward, combining these strategies with precision nutrition and next-generation microbiome therapeutics may open new avenues for individualized obesity care (Figure 1).

Dietary modulations

Calorie restriction and intermittent fasting

Dietary interventions significantly impact the gut microbiome and metabolome, thereby influencing host metabolism and health outcomes (reviewed in Masi et al.[123]). Calorie restriction (CR) is a common strategy for weight loss and metabolic health improvement, and early clinical evidence indicates that CR induces marked shifts in the gut microbiota, albeit with important inter-individual variability. In the CR intervention study in people with overweight or obesity by Cotillard et al.,[25] baseline microbial richness significantly associates with the response to the intervention. Participants with low microbial richness showed an increase in diversity following CR, whereas greater metabolic and inflammation improvements were observed in those with higher baseline richness.[25,31] Subsequent studies confirmed that CR increases microbial diversity and modulates the abundance of specific taxa such as *A. muciniphila* and *Bacteroides* spp.[124] Furthermore, animal studies have demonstrated that transferring the microbiota from CR-treated mice to germ-free recipients can reproduce metabolic benefits,

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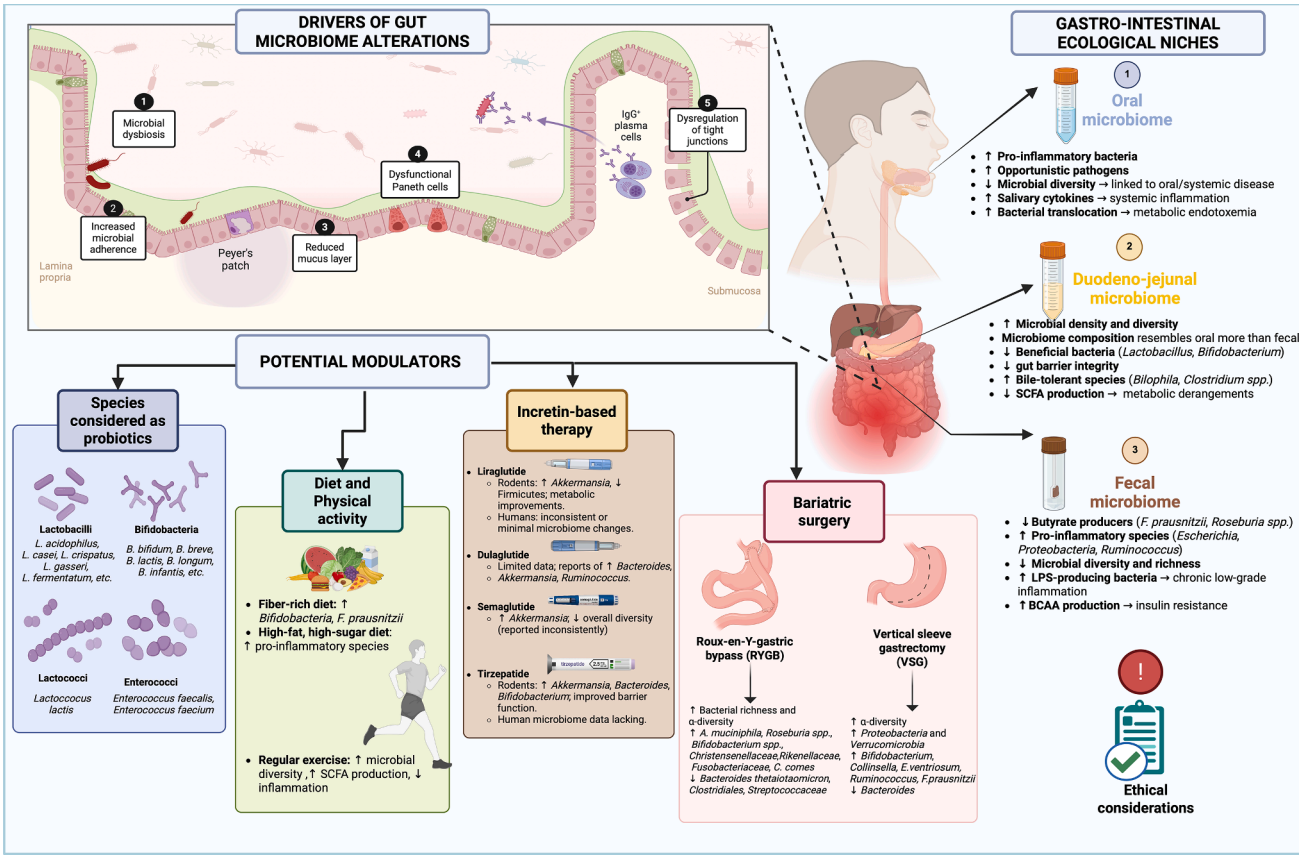

Figure 1. Described drivers of gut microbiome alterations in obesity: Ecological niches, contributing factors, and potential modulators

The top image illustrates key intestinal alterations: microbial dysbiosis, increased mucosal adherence, reduced mucus layer, Paneth cell dysfunction, and impaired tight junctions, contributing to gut barrier disruption and systemic inflammation. The right image outlines microbiome shifts in distinct gastrointestinal niches—oral, duodeno-jejunal, and fecal—highlighting changes in microbial diversity, metabolite production (e.g., SCFAs, LPS, and BCAAs), and associated metabolic consequences. The bottom image summarizes main modulators of the gut microbiome: probiotic species, metabolic surgery (RYGB and VSG), and diet/exercise. Ethical considerations related to microbiome research are noted.

SCFA, short-chain fatty acid; LPS, lipopolysaccharide; BCAA, branched-chain amino acid; RYGB, Roux-en-Y gastric bypass; VSG, vertical sleeve gastrectomy.

suggesting a causal role of the gut microbiota in mediating the effects of CR.[125]

Intermittent fasting and time-restricted eating, also showing metabolic improvements, have been associated with increases in microbial richness and diversity, with concomitant enrichment of specific taxa such as *Akkermansia* and *Lactobacillus*; however, mechanistic support is currently stronger in animal models than in humans, and metabolic benefits appear highly context dependent.[126]

The ketogenic diet (KD), though not routinely recommended for obesity treatment, markedly influences gut microbiota composition.[127] Unlike CR, both humans and mice studies show that KD reduces overall microbial diversity but increases specific taxa such as *A. muciniphila*, *Parabacteroides*, or *Bacteroides*. In our pilot study, a very low-energy ketogenic diet (VLEKD) produced significant weight loss in both post-bariatric and bariatric-naive individuals and led to enriched *A. muciniphila*, with more pronounced microbiota shifts in the latter group. This paradoxical rise in diversity may result from the combined effects of severe CR and a ketogenic macronutrient profile, which together create a unique metabolic and microbial environment distinct from conventional KD regimens.[128]

Fibers and prebiotics

High-fiber diets and polyphenol-rich foods have consistently demonstrated favorable effects on gut microbiota composition and host metabolism. Polyphenols, particularly when combined with fermentable fibers, enhance microbial diversity and promote the growth of beneficial taxa such as *Bifidobacterium* and *Lactobacillus*.[129] Prebiotics, e.g., non-digestible fibers with health benefit that selectively stimulate beneficial microbes, have shown similar efficacy in modulating the gut microbiota and improving metabolic outcomes. For instance, resistant starch is linked to enhanced lipid metabolism and bacterial community restructuring, while fructooligosaccharide (FOS) supplementation consistently raises *Bifidobacterium* and *Lactobacillus* levels and enhances genera like *Faecalibacterium* and *Ruminococcus*.[130,131] Galactooligosaccharides (GOSs) similarly support the growth of *Bifidobacterium*, *Lactobacillus*, and *Lactococcus*, with clinical improvements reported in constipation, intestinal permeability, and colon health.[132] Xylooligosaccharides

(XOSs), emerging as a promising class of prebiotics, resist upper GI digestion and instead nurture *Bifidobacterium* and *Blautia hydrogenotrophica*, while reducing potentially harmful taxa like *Enterorhabdus* and *Slackia*.[133,134] Prebiotic efficacy in mouse models is often robust, yet human studies typically show smaller effect sizes with modest clinical benefits.[135] Delzenne and colleagues have also elegantly highlighted that baseline microbiome characteristics strongly influence individual responses to inulin-type fructans, underscoring the need for precision approaches in translating these findings and positioning them in overweight and obesity care.[136]

Probiotics: From historical strains to next-generation probiotics

While dietary fibers and prebiotics modulate the gut microbiota by stimulating the growth of beneficial taxa, an alternative strategy has been the direct administration of probiotics. These interventions have evolved from the historical use of milk-fermenting bacteria such as *Lactobacillus* and *Bifidobacterium*, often targeted by prebiotics themselves, to the exploration of next-generation commensals with specific metabolic potential in obesity.

Milk-fermenting bacteria. Probiotic supplementation with classical strains has demonstrated modest improvements in metabolic variables in individuals with obesity or type 2 diabetes. Meta-analyses report that *Lactobacillus* and *Bifidobacterium* strains (notably if combined) can reduce fasting blood glucose, total cholesterol, triacylglycerols, and insulinemia and liver markers, while increasing HDL-cholesterol in people with overweight and obesity, albeit with moderate effect sizes. These benefits are thought to be mediated by enhanced gut barrier integrity, reduced systemic inflammation, modulation of BA and SCFA metabolism, and improvement in microbial diversity.[137] Among the most studied strains, *Lactobacillus acidophilus*, *L. casei*, and *L. rhamnosus* have shown glucose-lowering and anti-inflammatory effects, while interestingly *L. reuteri* has been linked to increased GLP-1 secretion and moderate appetite reduction. Similarly, *Bifidobacterium lactis* and *B. longum* improve lipid metabolism and insulin sensitivity, whereas *B. breve* strains have been associated with reductions in visceral fat and inflammatory markers.[137] Historically, these taxa have been at the forefront of probiotic research, with *Bifidobacterium* supplementation in obese mice shown to significantly improve metabolic parameters and reduce systemic and tissue inflammation.[138] However, while animal data are compelling, human trials generally reveal modest and variable effects, highlighting translational limitations.

Next-generation probiotics. Research has shifted toward next-generation probiotics identified through metagenomics and mechanistic studies as potential actors in obesity and metabolic health. The prototypical strain is *A. muciniphila*, currently developed both as a live biotherapeutic product (LBP) and explored by the agro-food industry. In mice, seminal paper showed that it improves gut barrier function, reduces inflammation, and enhances insulin sensitivity.[139] Moreover, in a proof-of-concept randomized trial (initially developed for safety) in subjects with overweight and obesity, pasteurized (but not live) *A. muciniphila* improved insulin sensitivity (−34.1%) and lowered total cholesterol (∼−8.7%), albeit without significant weight change.[140] *F. prausnitzii*, a butyrate-producing and anti-inflammatory commensal, is considered a pharma-oriented LBP candidate; it improves weight gain, hepatic steatosis, and glycemic control in mice, though robust human trials are lacking in obesity.[141,142] *Dysosmobacter welbionis*, another LBP candidate, shows inverse associations with body mass index and glycemia in human and protects against diet-induced obesity, improves insulin resistance, and stimulates brown adipose thermogenesis in mice.[143] In contrast, *Hafnia alvei* (strain HA4597) has already been developed as a food supplement. It produces a peptide, ClpB, an α-melanocyte-stimulating hormone mimetic (αMSH), which reduces food intake and adiposity in mice. A human trial reported modest weight loss and improved body composition.[144] *Christensenella minuta*, associated with leanness in metagenomic studies,[145] remains a pharma-oriented early-stage candidate with preclinical evidences but no human randomized controlled trials (RCTs) to date.[64] *Anaerobutyricum soehngenii* (formerly *Eubacterium hallii*), a potent SCFA producer, has reached pilot human trials. Interestingly, an oral or duodenal administration improved insulin sensitivity, glycemic control, and blood pressure, supporting its development as an LBP.[146,147] Several, other candidates, including *Parabacteroides distasonis*, *Bacteroides uniformis*, and SCFA-producing taxa such as *Roseburia* and *Clostridium butyricum* (the latter already used as a probiotic in Asia), remain at various preclinical or early translational stages.[148] Collectively, these next-generation probiotics highlight a shift from broad barrier/immune effects toward targeted modulation of host energy metabolism, endocrine signaling, and BA/SCFA pathways. However, large, well-controlled clinical trials are urgently needed to establish efficacy, dose-response relationships, mechanisms, long-term safety across diverse populations, and positioning in obesity care. Indeed, while most next-generation probiotics (*Akkermansia*, *Faecalibacterium*, *Dysosmobacter*, and *Anaerobutyricum*) primarily demonstrate metabolic improvements without clear weight-loss effects, *Hafnia alvei* remains a candidate with limited early clinical evidence of weight reduction, underscoring the gap between relevant metabolic modulation and anti-obesity efficacy.

Fecal microbiota transplantation

Given that obesity is often characterized by reduced microbial richness and diversity and that supplementation with a single bacterial strain may not suffice to restore metabolic balance, FMT can be considered a broader strategy to transfer entire microbial communities. By enabling the transfer of complex microbial consortia and their metabolites from donors to recipients, FMT provides an opportunity to directly test the influence of specific microbiome profiles on host metabolism. In mice, FMT from lean donors to obese recipients has reduced weight gain and partly improved metabolic outcomes.[149] In humans, the seminal study by Vrieze et al.[150] demonstrated that transfer of microbiota from lean donors to individuals with metabolic syndrome transiently improved peripheral insulin sensitivity, establishing a clinical precedent for microbiota-based interventions in metabolic diseases. Subsequent work by Kootte et al.[151] refined the findings by showing that the metabolic response to lean-donor FMT was driven by baseline microbiome composition, with individuals of low microbial diversity deriving the greatest benefit. This illustrates that translating these findings to broader metabolic disease care is challenging.[152] As of 2025, at least six major

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RCTs have examined FMT's role in obesity management but have shown a limited or no effect on body weight.[153] For example, in a recent trial among bariatric surgery patients, FMT failed to improve weight loss compared with placebo.[154] These controversial results not only challenge the simplistic view of microbiome-driven weight regulation but also highlight the complexity of microbial interactions in human metabolism, the critical importance of donor selection and FMT preparation methods, as well as the need for refined, potentially personalized strategies. While preclinical and small-scale human studies suggest metabolic benefits, the magnitude and consistency of these effects in clinical settings is modest if any. Therefore, microbial manipulation alone, via FMT, may be insufficient to induce clinically meaningful weight loss and even significant metabolic improvement. A further limitation is that many interventions affect both the microbiome and host pathways simultaneously, complicating causal interpretation. Thus, although the microbiome remains an appealing therapeutic target, more rigorous, mechanistically driven studies are required to determine whether specific microbial signatures can be leveraged or engineered to achieve durable and predictable benefits in obesity care. In this context, synthetic microbial consortia[155] and defined microbiota therapeutics are being developed as the next step beyond FMT, aiming to combine safety with targeted efficacy by using standardized mixtures of selected strains with known and complementary metabolic functions. Early-phase trials in inflammatory diseases, such as recurrent *Clostridioides difficile* infection and inflammatory bowel disease, have demonstrated the feasibility of this approach.[156,157] Whether extending such strategies tailored to restore diversity, improve energy metabolism, and modulate inflammation in a predictable way into a complex disease like obesity is a challenging approach.

Bariatric surgery and the gut microbiome: Impacts and interactions

While the previous sections focused on dietary strategies and microbiome-directed interventions, bariatric surgery is undoubtedly the most effective and durable therapy for severe obesity, at least until the recent arrival of GLP-1 analogs. In addition to producing sustained weight loss and marked metabolic and inflammatory improvements,[158–160] procedures like Roux-en-Y gastric bypass (RYGB) and vertical sleeve gastrectomy (VSG) reshape the gut microbiome via anatomical changes, dietary shifts, BA metabolism, gut hormone secretion, and probably host metabolic and inflammatory improvements.[161] Consistent surgical patterns include increased microbial diversity and gene richness after RYGB and VSG, as demonstrated in prospective human cohorts and systematic reviews (e.g., increased Shannon index and species richness).[48] Longitudinal shotgun metagenomic studies also show persistent microbial remodeling post-RYGB.[162] RYGB is typically associated with enrichment of taxa such as *A. muciniphila*, *Veillonella*, and Proteobacteria.[163] The type of surgery influences the microbiome response. In mice, RYGB induces more dramatic compositional shifts, including greater increases in Verrucomicrobia and Proteobacteria that may influence BA and gut-brain messaging, whereas VSG is consistently associated with elevated SCFAs and favorable BA profiles, potentially enhancing glucose metabolism. VSG favors anaerobic groups such as Clostridiales.[164,165] In human, *Akkermansia* expansion is one of the most reproducible microbiome changes after surgery, although its direct contribution to metabolic outcomes is uncertain.[31] Similarly, the consistent rise in Proteobacteria taxa like *Escherichia*, *Klebsiella*, and *Enterobacter* may reflect adaptive metabolic roles rather than pathogenic threats, though inter-cohort variability persists.[31] Microbial composition after surgery appears to correlate with clinical outcomes in some studies.[160,166] For instance, persistent type 2 diabetes after RYGB is associated with enrichment in Bacteroidia; transplanting this microbiota into germ-free mice recapitulates impaired glucose metabolism.[167] Overall, bariatric surgery-induced microbiome shifts, such as increases in *A. muciniphila*, SCFA producers, and BA-modulating taxa, are plausibly linked to metabolic and inflammatory improvements. Yet, delineating the weight of microbial versus host-driven mechanisms remains elusive.

Incretins and gut microbiome

Although bariatric surgery has long been the gold standard for durable weight loss and metabolic improvement in severe obesity, the advent of GLP-1 receptor agonists (GLP-1RAs) and newer dual or triple incretin agonists such as tirzepatide (GLP-1/GIP) and retatrutide (GLP-1/GIP/glucagon) is dramatically reshaping obesity care,[168] as their clinical effects on body weight now approach those achieved with bariatric surgery. In SURMOUNT-1 trial, tirzepatide induced mean weight loss of ~20.9% at 72 weeks,[169] while in the TRIUMPH-1 trial, retatrutide achieved a reduction of ~24.2% at 48 weeks.[170] Incretin-based therapies are thus transforming obesity management,[171] shifting clinical practice toward phenotype- and complication-driven care.[172]

Beyond their effects on appetite, weight loss, and glycemic control, emerging evidence indicates that GLP-1RAs may modulate the gut microbiota.[173] However, most mechanistic insights come from animal models. Rodent studies have shown that liraglutide alters microbiota composition and diversity, often increasing *A. muciniphila* and reducing obesity-associated Firmicutes, changes associated with weight reduction, improved lipid profiles, and attenuation of steatosis or metabolic-associated steatotic liver disease.[174–178] In contrast, human data remain limited and heterogeneous.[179] Reviews aggregating preclinical and clinical work indicate that ~70% of published liraglutide studies are conducted in animals, with relatively few in humans.[180] While clinical trials consistently confirm weight loss and metabolic improvements, evidence that liraglutide reproducibly remodels the human microbiome is less robust: some studies report enrichment of beneficial taxa such as *Akkermansia*,[181] whereas others show minimal or inconsistent changes.[182,183]

Data on other GLP-1RAs and dual agonists are more sparse but intriguing. For instance, dulaglutide has been linked to increases in *Bacteroides*, *Akkermansia*, and *Ruminococcus*[184]; semaglutide has been associated with *Akkermansia* expansion but paradoxically reduced overall diversity[185]; and exenatide/exendin-4 shows mixed effects, beneficial in rodents,[186] but occasionally linked to inflammation-associated taxa in humans. Tirzepatide has been shown in preclinical models to remodel the gut microbiota and reinforce intestinal barrier integrity, enriching

Akkermansia, *Bacteroides*, and *Bifidobacterium*, while upregulating tight-junction proteins and reducing systemic inflammation.[187] Still, causality remains uncertain, as these shifts may reflect weight loss or inflammation and hormonal changes.

While pharmacological agents such as incretin mimetics likely influence the gut microbiota via systemic hormonal and neuroendocrine mechanisms, dietary interventions act more directly by modulating substrate availability for microbial fermentation. These modalities thus differ in their magnitude, duration, and specificity of action. However, they may be synergistic when combined: for instance, dietary fiber may potentiate incretin-microbiota interactions by enriching taxa that metabolize fiber into SCFAs, further enhancing GLP-1 secretion and metabolic benefits. The revised perspective introduces the potential of integrating pharmacologic and dietary strategies to optimize therapeutic efficacy. Moreover, baseline microbiota composition may eventually serve as a stratification tool, enabling personalized interventions.

Baseline microbiota composition may also influence therapeutic response. In a seminal preclinical study, Grasset et al.[188] showed that depletion of *Lactobacilli* and *Porphyromonadaceae* conferred GLP-1 resistance in mice via impaired neuronal nitric oxide synthase (nNOS) signaling, an effect transferable to germ-free animals. Translating this to humans in type 2 diabetes context, Tsai et al.[183] found that responders to liraglutide or dulaglutide displayed distinct microbial signatures: *Bacteroides dorei* and *Roseburia inulinivorans* correlated positively with improved HbA1c, while *Prevotella copri* and *Alistipes obesi* correlated negatively. These findings suggest that the gut microbiome may eventually act both as a mediator of incretin efficacy and as a predictive biomarker of clinical response, opening the way to personalized, microbiome-guided obesity therapies.

Integrative perspective: Converging microbial signatures across obesity interventions and future directions

Across the heterogeneous interventions including CR, prebiotic supplementation, metabolic bariatric surgery, FMT, and incretin-based therapies, human data consistently converge on a set of microbiome and metabolite features considered "usual suspects" possibly involved in metabolic health. Some interventions indeed tend to improve ecological diversity and modulate key metabolites (SCFA, BA, tryptophane derivate, etc.), taxa (e.g., *Akkermansia*, *Faecalibacterium*, and *Anaerobutyricum*), and functional pathways that may enhance epithelial barrier integrity while reducing inflammation, alongside depletion of low-diversity, Bact2-like configurations and Proteobacteria expansions. These recurring patterns suggest that metabolic improvement reflects the restoration of microbiome-mediated resilience, rather than the action of a single "key microbe."

Looking ahead, priorities emerge: first, clearly defining microbial signatures that may predict intervention responses. This approach may require integrated multi-omics analyses embedded within clinical trials of dietary manipulation, surgery, or pharmacotherapy. The added value of "omics" integration, compared to easy measurable clinical variables, in prediction models is nevertheless still to be demonstrated.

Second, bridging rodent and human findings will demand parallel experimental designs, enabling mechanistic hypotheses to be tested from gnotobiotic models (and other preclinical models) to human intervention and vice versa.

Third, microbiome-nutrition strategies may become actionable through stratified approaches based on a small number of reproducible microbiome-metabolome profiles in a precision nutrition approach; proper clinical trial designs are thus mandatory to strengthen the relevance of such approach. Fourth, dedicated investigation of the small-intestinal microbiome, including its roles in nutrient handling, BA dynamics, and incretin physiology, is awaited to provide key mechanistic insights that cannot be captured by stool-based profiling alone. Finally, next-generation probiotics, postbiotics, and defined microbial consortia must advance into adequately powered human trials to determine whether targeting microbial functions can not only provide prevention approach but also enhance the durability of weight loss and metabolic control achieved by existing therapies.

Taken together, there is still room to demonstrate the usefulness of integration of gut microbiome into obesity care as a prevention action and/or a modulator of treatment responsiveness and long-term metabolic resilience. Rigorous, mechanistically grounded human studies are essential to translate these converging signals into clinically actionable strategies.

CONCLUSIONS

The field of microbiome research is rapidly evolving, providing new insights into the complex interplay between lifestyle, gut microbiota, host metabolism, and obesity. While compelling evidence supports associations between microbiome composition and metabolic health, the precise causal role of gut microbes in obesity, whether through energy harvest, immune modulation, gut-brain signaling, or epithelial function, remains context dependent and incompletely delineated.

Therapeutic manipulation of the microbiome through several strategies leads to increased microbial diversity, enriched beneficial taxa, and reduced pro-inflammatory signatures. Engineered or "next-generation" probiotics represent an emerging avenue, with promising preclinical evidence though still modest and inconsistent human findings.

Novel anti-obesity medications are transforming obesity management, knowing they are expensive, not universally effective, and sometimes associated with adverse effects. Moreover, frequent discontinuation leads to weight regain, just as with bariatric surgery.[189] In this context, gut microbiome-based strategies need to be positioned and, for example, explored in long-term weight maintenance, by promoting microbial resilience, stabilizing host-microbiome interactions, and buffering against rebound metabolic dysfunction. Importantly, as the gut microbiome may mediate inter-individual variability in treatment response, integrating microbiome-targeted therapies with incretin-based treatments could enhance efficacy, reduce side effects, and extend therapeutic durability. Research on bariatric surgery should likewise explore whether microbiome-targeted adjuncts, such as GLP-1 analogs or next-generation probiotics, could synergize with surgery to enhance and sustain long-term efficacy.

Beyond these approaches, novel microbiome-directed strategies are emerging: some postbiotics may directly improve insulin sensitivity, gut barrier function, and appetite regulation,[190]

bacteriophage therapy selectively depletes detrimental taxa, while engineered live biotherapeutics are being designed to deliver hormones or metabolites such as GLP-1 mimetics. Rationally defined microbial consortia and microbiota-derived metabolites are also under development as more controllable alternatives to FMT. Although these concepts remain largely preclinical, they highlight the expanding therapeutic toolbox targeting the microbiome in metabolic diseases.

Prevention remains a cornerstone of overweight/obesity management. Nutritional strategies that promote microbial resilience represent measures with a broad population-level impact, potentially reducing obesity risk and lowering reliance on pharmacotherapy. Significant challenges remain; today existing evidence is mostly cross-sectional, reproducibility across cohorts is still limited, and substantial inter-individual variability demands tailored interventions. As the field advances, ethical considerations, including data privacy, informed consent, and equitable access, will be crucial to ensure that microbiome-based precision medicine reduces, rather than exacerbates, health disparities.

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AUTHOR CONTRIBUTIONS

D.M., M.W., and K.C. contributed to the research and writing of this review. K.C. contributed to the conceptualization and editing of this text. All authors accept the text in its current form.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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