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GUT MICROBIOTA IN OBESITY AND METABOLIC SYNDROME: PATHOPHYSIOLOGY, CURRENT INSIGHTS AND THERAPEUTIC PERSPECTIVES

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ABSTRACT

The gut microbiota is increasingly recognized as a significant factor influencing the development of obesity and metabolic syndrome, not only through its role in digestion and nutrient metabolism, but also through its regulation of inflammation, intestinal barrier integrity, glucose and lipid metabolism, and hormonal signaling. The aim of this study was to present the current knowledge regarding the role of the gut microbiota in the pathophysiology of metabolic disorders, with particular emphasis on clinical data and the potential for therapeutic intervention on the microbiome. This study is a narrative review based on a systematic analysis of the literature. The full texts of 77 scientific publications from 2016–2026 were analyzed, of which 48 were included in the final synthesis. Studies on obesity, metabolic syndrome, dietary interventions, probiotics, prebiotics, synbiotics, fecal microbiota transplantation, and next-generation therapies were included. Available data indicate that dietary interventions, weight loss, increased fiber intake, and dietary strategies supporting microbiota diversity currently have the greatest practical significance. Probiotics, synbiotics, Akkermansia muciniphila, and fecal microbiota transplantation remain promising therapeutic approaches, but they still require further validation. The gut microbiota may in the future become a component of personalized treatment for metabolic disorders; however, its clinical application requires further research, standardization of methods, and identification of patient populations that may benefit the most.

KEYWORDS

Gut Microbiota, Obesity, Metabolic Syndrome, Probiotics, Fecal Microbiota Transplantation, Precision Nutrition

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1. Introduction

Obesity and metabolic syndrome are clinically heterogeneous conditions that combine excess adiposity, insulin resistance, lipid abnormalities, elevated blood pressure and chronic low-grade inflammation. Metabolic syndrome is especially relevant to internal medicine because it integrates abdominal obesity, glycemic disorders, dyslipidemia and hypertension into a pattern of increased cardiometabolic risk (Geng et al., 2022). Standard lifestyle treatment focuses on dietary change, physical activity and weight reduction (Koutoukidis et al., 2022). Bariatric procedures remain an established option for selected patients with severe obesity and metabolic disease (Chen et al., 2025). Clinical responses to these interventions are variable, which has increased interest in biological factors that may influence individual treatment response (Antwi, 2023).

The gut microbiota is one of the most intensively studied biological mediators in obesity-related metabolic disease (Liu et al., 2021). The literature describes the intestinal microbiota as a metabolically active ecosystem involved in nutrient processing, metabolite production, mucosal immune regulation and host energy balance (Gomes et al., 2018). The microbiota is clinically attractive because it can be influenced by diet, dietary fiber, prebiotics, probiotics, medications and major metabolic interventions (Perler et al., 2023). It is also clinically challenging because taxonomic profiles differ across populations, sequencing methods, diets, medications and host phenotypes (Pinart et al., 2022). Early microbiome literature often emphasized simple taxonomic ratios, particularly the Firmicutes-to-Bacteroidetes relationship, but systematic reviews and phenotype studies have shown that obesity-related microbial signatures are not consistent across cohorts (Pinart et al., 2022). More recent meta-analytic work supports the view that obesity-associated microbiota alterations are better interpreted as heterogeneous patterns involving both taxonomic and functional shifts rather than as one universal microbial profile (Chanda & De, 2024). This shift is important because future use of microbiome data in clinical practice depends less on identifying a single diagnostic bacterium and more on understanding how microbial functions influence treatment response (Jardon et al., 2022). The therapeutic relevance of gut microbiota research is strongest when it is linked to modifiable clinical exposures (Perler et

al., 2023). According to Koutoukidis et al., weight loss is associated with changes in gut microbiota diversity, composition and intestinal permeability (Koutoukidis et al., 2022). The Food4Gut trial supports inulin-type prebiotic modulation in adults with obesity (Hiel et al., 2020). Dietary fiber interventions in type 2 diabetes have been associated with gut microbiota and metabolic effects (Ojo et al., 2021). Baseline microbiota and genetic scores may help model dietary treatment selection in adults with overweight or obesity (Cuevas-Sierra et al., 2022). Predicted glycemic-response models have also been tested as a personalized dietary strategy in newly diagnosed type 2 diabetes (Rein et al., 2022). Gut microbiota may additionally predict response to short-term low-carbohydrate dietary intervention in patients with obesity (Zhang et al., 2021).

This review relates to gut microbiota in obesity and metabolic syndrome with a deliberate emphasis on therapeutic perspectives. It aims to summarize pathophysiological mechanisms, synthesize current human evidence and discuss microbiota-targeted interventions that may be relevant to personalized metabolic care. The review frames microbiota modulation as a potential tool for patient stratification, therapeutic optimization and adjunctive care rather than as a substitute for established obesity treatment.

2. Methodology

This study is a narrative review based on a structured literature search and critical analysis of scientific publications on gut microbiota in obesity and metabolic syndrome. Particular emphasis was placed on current insights and therapeutic perspectives. The literature search used PubMed/MEDLINE, Embase, Google Scholar and the Cochrane Library. Advanced queries combined Medical Subject Headings and title/abstract terms related to gut microbiota, obesity, metabolic syndrome and microbiota-targeted interventions. Core search terms included gut microbiota, gut microbiome, gastrointestinal microbiome, dysbiosis, obesity, overweight, metabolic syndrome, insulin resistance, type 2 diabetes, dyslipidemia, short-chain fatty acids, bile acids, intestinal permeability, metabolic endotoxemia, probiotic, prebiotic, synbiotic, *Lactobacillus*, *Bifidobacterium animalis*, *Hafnia alvei*, multistrain probiotic formulations, dietary fiber, inulin, Mediterranean diet, low-carbohydrate diet, ketogenic diet, intermittent fasting, metformin, GLP-1 receptor agonist, bariatric surgery, fecal microbiota transplantation, *Akkermansia muciniphila*, precision nutrition and personalized nutrition. Additional relevant publications were identified by manually screening reference lists from key reviews and meta-analyses.

The principal publication window was 2016–2026. Eligible sources included narrative reviews, systematic reviews, meta-analyses, observational studies, randomized controlled trials and other human clinical studies. Priority was given to studies in adults with obesity, overweight, metabolic syndrome, insulin resistance or type 2 diabetes. Animal-only studies, case reports, conference abstracts, editorials, letters and papers not directly related to gut microbiota, obesity, metabolic syndrome or metabolic interventions were excluded from the main analysis. The first database search was conducted on April 9, 2026. Overall, 77 articles were selected for full-text substantive review. Ultimately, 48 publications were included in the final synthesis and used to formulate the narrative conclusions. Because this was a narrative review, no formal PRISMA flow diagram was prepared; however, the selection process followed its general screening principles. The selected literature was organized into major pathophysiological processes and therapeutic categories, including dietary modulation, probiotics, prebiotics, synbiotics, pharmacological microbiome effects, bariatric surgery, fecal microbiota transplantation, next-generation microbial therapeutics and precision nutrition. Findings were interpreted with attention to clinical applicability, reproducibility, limitations and implementation barriers.

3. Results

3.1. Gut microbiota as a modifiable factor in metabolic health

The gut microbiota contributes to metabolic regulation by fermenting dietary substrates, producing short-chain fatty acids, transforming bile acids and interacting with the mucosal immune system. Under physiological conditions, the gut microbiota supports intestinal epithelial barrier integrity and immunological tolerance through host–microbe signaling (Gomes et al., 2018). In obesity and metabolic syndrome, these interactions may shift toward dysbiosis, altered metabolite production and increased inflammatory signaling (Liu et al., 2021).

Human studies do not support one universally reproducible microbiota signature of obesity. A systematic review and meta-analysis comparing obese and non-obese individuals found variable microbial differences across studies, which supports caution when interpreting individual taxa as diagnostic markers (Pinart et al., 2022). A phenotype-based study also demonstrated that obesity-related microbiota patterns vary between subgroups rather than representing a single microbial state (Stanislawski et al., 2019). A later meta-

analysis reported reproducible obesity-associated microbial alteration patterns, but it also emphasized functional shifts and methodological heterogeneity (Chanda & De, 2024).

The clinical value of microbiota research may therefore lie more in functional interpretation than in simple taxonomic classification (Chanda & De, 2024). Functional interpretation includes microbial effects on short-chain fatty acids, bile acid signaling, gut permeability, inflammatory tone, insulin sensitivity and postprandial metabolism (Puljiz et al., 2023). This approach is particularly relevant to therapy because many interventions influence microbial functions without necessarily producing stable or universal taxonomic changes (Roager et al., 2019).

The gut microbiota is modifiable through everyday exposures, especially diet quality, fiber intake, energy balance and medication use (Perler et al., 2023). Large-scale human phenotyping linked habitual diet, microbiome features and host metabolic profiles, supporting the concept that dietary patterns shape microbiome-metabolism interactions (Asnicar et al., 2021). Precision nutrition reviews argue that microbiota, genetics, clinical markers and behavioral data may help individualize dietary recommendations in obesity and type 2 diabetes (Antwi, 2023).

3.2. Pathophysiological pathways linking microbiota with metabolic dysfunction

Short-chain fatty acids are central microbial metabolites generated during bacterial fermentation of non-digestible carbohydrates, especially dietary fiber (Gomes et al., 2018). Acetate, propionate and butyrate are relevant to obesity and metabolic syndrome because they may influence intestinal barrier integrity, hepatic and peripheral energy metabolism, appetite-related signaling and inflammatory tone (Puljiz et al., 2023). Their interpretation should remain context dependent because short-chain fatty acids may contribute to host energy extraction while also acting as signaling molecules that support metabolic homeostasis (Perler et al., 2023).

Dysbiosis may disturb epithelial barrier function and increase the interaction between microbial products and host immune pathways (Liu et al., 2021). In obesity-related metabolic dysfunction, impaired barrier integrity may increase exposure to bacterial lipopolysaccharide and thereby promote inflammatory signaling associated with insulin resistance (Geng et al., 2022). Obesity-focused reviews emphasize that gut permeability, immune activation and microbial metabolism should be interpreted together rather than as isolated mechanisms (Gomes et al., 2018).

Low-grade inflammation integrates microbial signals with adipose tissue dysfunction and systemic insulin resistance in obesity (Geng et al., 2022). Lipopolysaccharide-related activation of innate immune pathways may amplify metabolic inflammation and interfere with insulin signaling (Saad et al., 2016). Human microbiome studies remain heterogeneous, and associations between dysbiosis and inflammatory-metabolic phenotypes are influenced by diet, medications, adiposity, geography and study methodology (Pinart et al., 2022).

Bile acid metabolism provides another route through which the intestinal microbiome may influence host metabolic regulation. Gut bacteria transform primary bile acids into secondary bile acids, which can participate in signaling pathways involved in glucose and lipid metabolism (Puljiz et al., 2023). Dietary macronutrient composition may indirectly modify this pathway by shaping microbial composition and metabolic outputs, which supports the relevance of nutritional context in microbiome-targeted therapy (Jardon et al., 2022). A synbiotic randomized trial in type 2 diabetes linked improved metabolic outcomes with changes in gut microbiota, bile acid profiles and GLP-1-related signaling (C. Zhang et al., 2025).

Gut-brain and enteroendocrine pathways are therapeutically relevant because microbiota-derived metabolites may influence appetite regulation, satiety signaling and incretin biology (Liu et al., 2021). Recent work on GLP-1 receptor agonists frames the microbiome as a potential mediator or modifier of obesity treatment response, although direct human evidence remains limited (Johnson et al., 2026). These mechanisms are useful for interpreting therapeutic interventions, but they should not be presented as fully established causal pathways in routine clinical practice (Koutoukidis et al., 2022).

The main pathophysiological processes considered in this review are summarized in Table 1.

Table 1. Main pathophysiological processes linking gut microbiota with metabolic dysfunction.

Pathophysiological process	Clinical relevance	Key supporting source
Short-chain fatty acids	Microbial fermentation products may influence energy metabolism, gut barrier function, appetite signaling and inflammation.	Puljiz et al. (2023)
Metabolic endotoxemia	Barrier disruption may increase host exposure to microbial products, including lipopolysaccharide, and contribute to inflammatory signaling linked with insulin resistance.	Geng et al. (2022)
Low-grade inflammation	Microbial signals, adipose tissue inflammation and metabolic stress may interact across tissues in obesity-related insulin resistance.	Geng et al. (2022)
Bile acid signaling	Microbial bile acid transformation may influence glucose and lipid metabolism.	Puljiz et al. (2023)
Gut-brain and enteroendocrine signaling	Microbiota-related metabolites may interact with appetite regulation and GLP-1-related pathways.	Johnson et al. (2026)

3.3. Human clinical evidence

The strongest human evidence for microbiota involvement in obesity comes from systematic reviews, meta-analyses and phenotype studies rather than from a single diagnostic microbial marker. Pinart et al. reported that gut microbiome composition differs between obese and non-obese persons across studies. However, the observed variability in results prevents the formulation of reliable conclusions, further research is needed in this direction (Pinart et al., 2022). Stanislawski et al. showed that obesity-related microbiota phenotypes can differ across individuals, which reinforces the need for subgroup and functional interpretation (Stanislawski et al., 2019). Chanda and De identified recurrent obesity-associated alteration patterns while also emphasizing functional shifts and methodological variation (Chanda & De, 2024).

Human dietary and weight-loss studies provide a more direct route toward clinical practice. A systematic review and meta-analysis found that weight loss is associated with changes in gut microbiota diversity, composition and intestinal permeability (Koutoukidis et al., 2022). A whole-grain randomized crossover trial showed reductions in body weight and systemic low-grade inflammation without major changes in the gut microbiome, which indicates that metabolic benefit does not always require large taxonomic remodeling (Roager et al., 2019). A gut-microbiota-targeted dietary study demonstrated that fermented-food and high-fiber dietary strategies can modulate immune and microbiome-related outcomes in humans (Wastyk et al., 2021).

Intervention trials in adults with obesity or type 2 diabetes support the clinical relevance of prebiotics and fiber. The Food4Gut randomized placebo-controlled trial linked inulin-type prebiotic intervention with gut microbiota and health outcomes in adults with obesity (Hiel et al., 2020). A systematic review and meta-analysis in type 2 diabetes found that dietary fiber interventions modulated gut microbiota dysbiosis in randomized controlled trials (Ojo et al., 2020). A related meta-analysis reported effects of dietary fiber on gut microbiota, lipid profile and inflammatory markers in patients with type 2 diabetes (Ojo et al., 2021).

Microbiome-informed dietary personalization is supported by studies that combine baseline microbiota with clinical or genetic information. Cuevas-Sierra et al. developed a weight-loss model using baseline microbiota and genetic scores to select dietary treatments in adults with overweight or obesity (Cuevas-Sierra et al., 2022). Rein et al. tested a personalized diet based on predicted glycemic responses in newly diagnosed type 2 diabetes and reported effects on glycemic control and metabolic health (Rein et al., 2022). Zhang et al. reported that baseline gut microbiota could help predict outcomes of a short-term low-carbohydrate diet intervention in patients with obesity (Zhang et al., 2021).

3.4. Therapeutic perspectives

3.4.1. Therapeutic hierarchy and clinical plausibility

Microbiota-targeted therapy should be interpreted as a hierarchy of evidence rather than as one uniform treatment category (Jardon et al., 2022). Lifestyle and dietary strategies are currently the most clinically plausible microbiota-related interventions because they are scalable, already used in metabolic care and supported by human dietary trials (Koutoukidis et al., 2022). Probiotics, prebiotics and synbiotics are plausible adjuncts, but their effects depend on strain, substrate, dose, population and intervention duration (Zhou et al., 2025). Fecal microbiota transplantation remains investigational in obesity and metabolic syndrome because available studies are limited and protocols are heterogeneous (Zecheng et al., 2023). Next-generation microbial therapeutics such as Akkermansia muciniphila also remain investigational despite promising proof-of-concept human data (Depommier et al., 2019).

The most practical clinical model is therefore not to replace established therapy with microbiome products but to integrate microbiota knowledge into existing metabolic care (Antwi, 2023). In this model, diet quality, fiber intake and weight management remain first-line strategies with microbiota-related benefits (Koutoukidis et al., 2022). Metformin may influence gut microbiome composition and circulating short-chain fatty acids, but its clinical use remains based on metabolic indications (Mueller et al., 2021). Bariatric surgery can also alter gut microbiota structure, but it remains a procedure indicated for severe obesity and metabolic disease rather than for microbiome modulation alone (Chen et al., 2025). Precision nutrition and microbiome-informed prediction may eventually help select the most appropriate dietary or adjunctive intervention for individual patients (Cuevas-Sierra et al., 2022).

For routine clinical use, microbiota-related interventions should be prioritized according to feasibility, safety and strength of human evidence (Antwi, 2023). Structured weight-loss programs currently have greater practical value than experimental microbial transfer approaches because they are easier to deliver and have broader metabolic evidence (Koutoukidis et al., 2022). Whole-grain dietary patterns are also clinically relevant because they can improve body weight and low-grade inflammation even without major microbiome remodeling (Roager et al., 2019). Prebiotic strategies may be especially useful when they are integrated into dietary counseling rather than prescribed as isolated supplements (Hiel et al., 2020). Probiotic or synbiotic supplementation should be considered only as a strain-specific adjunct, because evidence from type 2 diabetes trials cannot be generalized to all commercial products (Zhou et al., 2025). FMT should remain in research settings until larger and longer randomized studies confirm efficacy and safety (Zecheng et al., 2023). Next-generation bacteria require similar confirmatory evidence before routine clinical use (Depommier et al., 2019).

Patient selection is likely to become an important part of microbiota-informed dietary therapy (Cuevas-Sierra et al., 2022). Baseline microbiota composition predicted response to lean donor fecal microbiota transplantation in metabolic syndrome, which indicates that microbial context can influence therapeutic response (Kootte et al., 2017). Baseline microbiota and genetic scores were also used to model dietary treatment selection in adults with overweight or obesity, which supports patient stratification in dietary therapy (Cuevas-Sierra et al., 2022). Predicted glycemic response models in type 2 diabetes show that personalized dietary advice can be linked to metabolic outcomes rather than only to general dietary categories (Rein et al., 2022). Baseline gut microbiota predicting short-term low-carbohydrate diet response further supports the concept that microbiota may help identify responders and non-responders before treatment begins (Zhang et al., 2021).

3.4.2. Weight loss, energy balance and dietary patterns

Weight reduction is one of the most clinically relevant interventions linking obesity treatment with gut microbiota changes. The systematic review and meta-analysis by Koutoukidis et al. found associations between weight loss and changes in microbiota diversity, microbial composition and intestinal permeability. These findings suggest that weight reduction may influence both microbial ecology and gut barrier-related outcomes, although causality and durability remain uncertain (Koutoukidis et al., 2022).

Dietary fiber is a central therapeutic substrate because it can be fermented into short-chain fatty acids and can support beneficial microbial functions (Gomes et al., 2018). In randomized trials summarized by Ojo et al., dietary fiber interventions were associated with changes in gut microbiota dysbiosis in patients with type 2 diabetes (Ojo et al., 2020). A separate meta-analysis by Ojo et al. found that dietary fiber affected gut microbiota, lipid profile and inflammatory markers in type 2 diabetes (Ojo et al., 2021). These data are relevant to metabolic syndrome because type 2 diabetes, dyslipidemia and inflammation overlap with core metabolic syndrome mechanisms (Puljiz et al., 2023).

Inulin-type prebiotic therapy is supported by the Food4Gut multicenter randomized placebo-controlled trial in adults with obesity. That study linked inulin intervention with gut microbiota and health outcomes, which supports the idea that selected prebiotics may be clinically meaningful in obesity management (Hiel et al., 2020). General reviews of prebiotics also describe their role in selectively supporting microbial substrates and modifying gut microbial composition (Yoo et al., 2024).

Whole-grain and plant-rich dietary patterns deserve attention because they can improve metabolic outcomes even when microbiome changes are modest. Roager et al. found that a whole grain-rich diet reduced body weight and systemic low-grade inflammation without inducing major gut microbiome changes. This finding is clinically important because it prevents overinterpretation of microbiome change as the only relevant outcome of a diet intervention (Roager et al., 2019). Polyphenol-rich plant foods may also influence gut microbiota, including *Bifidobacterium*-related modulation, although this evidence is more supportive than central for obesity treatment (Toderescu et al., 2026).

Anti-inflammatory dietary patterns are relevant because inflammation is one of the proposed links between dysbiosis and insulin resistance (Saad et al., 2016). Bagheri et al. reviewed evidence suggesting that anti-inflammatory dietary patterns can modulate gut microbiota and contribute to obesity control. These patterns should be considered supportive lifestyle strategies rather than microbiome-specific therapies because their effects involve multiple dietary and metabolic pathways (Bagheri et al., 2022).

Intermittent fasting combined with protein pacing has been studied as a dietary strategy with microbiome and metabolomic effects. Mohr et al. reported that protein pacing with intermittent fasting improved gut microbiome remodeling and metabolomic profiles compared with continuous caloric restriction. This study is relevant to therapeutic perspectives because it integrates energy restriction, meal timing, macronutrient distribution and microbiome response (Mohr et al., 2024).

Low-carbohydrate dietary strategies may influence the gut microbiota and may be partly predictable from baseline microbial features. Zhang et al. reported that gut microbiota could predict outcomes of a short-term low-carbohydrate diet in patients with obesity (Zhang et al., 2021). Very-low-calorie ketogenic diets have also been studied in relation to gut microbiota in individuals with obesity, but interpretation requires caution because study designs and outcomes remain heterogeneous (Wang et al., 2025).

3.4.3. Probiotics, prebiotics and synbiotics

Probiotics are widely discussed as microbiota-targeted interventions, but their clinical effects cannot be generalized across all strains or formulations (Zhou et al., 2025). A systematic review and meta-analysis of probiotics combined with metformin reported improved glycemic outcomes in type 2 diabetes compared with metformin alone, but this evidence applies specifically to the studied populations and formulations (Memon et al., 2023). A broader meta-analysis of gut microbiome-targeted therapies in type 2 diabetes reported changes in glucose parameters, inflammatory markers and gut microbiota outcomes across randomized trials. These findings support probiotics as potential adjuncts in metabolic dysfunction rather than as stand-alone obesity therapies (Zhou et al., 2025).

A randomized controlled trial in adults with overweight and obesity found that *Bifidobacterium animalis subsp. lactis 420*, administered with or without polydextrose fiber, was associated with favorable changes in body fat mass and waist circumference in per-protocol analyses (Stenman et al., 2016). A six-month double-blind randomized controlled trial of a lactobacilli and bifidobacteria consortium reported reductions in body weight, BMI, waist circumference and waist-to-height ratio in adults with overweight or obesity (Michael et al., 2020). A multicenter randomized double-blind placebo-controlled study of *Hafnia alvei HA4597* during a moderate hypocaloric diet reported a higher proportion of participants achieving at least 3% weight loss and greater fullness than placebo, supporting further evaluation of targeted appetite-related probiotic strategies (Déchelotte et al., 2021).

Synbiotics may offer advantages because they combine live microorganisms with substrates that support their survival or metabolic activity. In a randomized, double-blind, placebo-controlled trial, C. Zhang et al. reported greater improvement in fasting glucose with synbiotic supplementation than with probiotic supplementation alone in patients with type 2 diabetes. The same trial linked metabolic effects with changes in gut microbiota, bile acid profiles and GLP-1-related signaling, making it relevant to therapeutic interpretation of microbiome-related pathways (C. Zhang et al., 2025).

A 12-week double-blind randomized controlled trial in adults with obesity showed that MN-Gup-GOS-XOS synbiotic supplementation reduced body fat percentage, waist circumference and LDL cholesterol, with accompanying changes in gut microbiota, bile acids and gut hormone-related pathways (Niu et al., 2024). At

the broader metabolic-syndrome level, a systematic review and meta-analysis of 11 randomized controlled trials found that probiotic or synbiotic supplementation reduced BMI, LDL cholesterol and fasting blood glucose, although no significant benefit was demonstrated for systolic blood pressure (Chen et al., 2024).

Prebiotics have a stronger conceptual link to diet-based therapy because they serve as substrates for microbial fermentation (Yoo et al., 2024). Inulin-treated adults with obesity in the Food4Gut trial provide a clinically relevant example of prebiotic modulation in an obese population (Hiel et al., 2020). Dietary fiber meta-analyses in type 2 diabetes support the broader metabolic relevance of fermentable substrates and gut microbiota modulation (Ojo et al., 2020, 2021).

The main limitation of probiotic and synbiotic clinical application is heterogeneity of products, strains, doses and study designs. A benefit observed with one strain or synbiotic combination should not be generalized to unrelated products. Future trials should identify exact strains, justify dose selection, report adherence and evaluate durability after discontinuation (Zhou et al., 2025).

3.4.4. Pharmacological and surgical-based microbiota modulation

Metformin is one of the clearest examples of a metabolic medication with measurable gut microbiome effects. In a randomized trial, Mueller et al. reported that metformin affected gut microbiome composition, gut microbiome function and circulating short-chain fatty acids. The clinical use of metformin remains based on glycemic and metabolic indications, but its microbiome effects may help explain some metabolic and gastrointestinal responses (Mueller et al., 2021).

GLP-1 receptor agonists and related incretin therapies are increasingly important in obesity management, but their microbiome effects are still emerging (Johnson et al., 2026). A systematic review of GLP-1 analogues and agonists summarized evidence that these therapies may affect gut microbiota, but available studies remain heterogeneous (Gofron et al., 2025). Johnson et al. described a potential complex interplay between GLP-1 receptor agonists, the gut microbiome and obesity management, which supports cautious discussion rather than strong clinical conclusions (Johnson et al., 2026).

Bariatric surgery is a major metabolic intervention that can substantially change weight, glucose metabolism and gut microbiota structure (Chen et al., 2025). A meta-analysis of bariatric surgery studies reported changes in gut microbiota structure following surgery. These microbiome changes are clinically relevant, but the therapeutic efficacy of bariatric surgery should not be reduced to microbiome effects alone because anatomy, bile acid signaling, appetite regulation and energy intake also change after surgery (Chen et al., 2025).

Pharmacological and surgical-based interventions should therefore be described as microbiota-interacting treatments rather than purely microbiota-targeted treatments. Metformin provides a pharmacological example of microbiome interaction in metabolic therapy (Mueller et al., 2021). Bariatric surgery provides a procedural example of microbiome interaction in metabolic therapy (Chen et al., 2025). This distinction is important because patients may misinterpret microbiome effects as the primary mechanism or indication for these therapies (Johnson et al., 2026). Clinical decision-making should continue to follow established indications while microbiome research clarifies mechanisms and response predictors (Antwi, 2023).

3.4.5. Fecal microbiota transplantation

Fecal microbiota transplantation is the most direct method of transferring a complex microbial community, which makes it a valuable research model for testing whether altering microbial community structure can affect human metabolic phenotypes. In metabolic syndrome, lean-donor FMT improved insulin sensitivity in selected recipients, and the response was partly driven by baseline intestinal microbiota composition (Kootte et al., 2017).

A phase 2 randomized trial in severe obesity and metabolic syndrome evaluated FMT with fiber supplementation and emphasized the importance of donor selection, recipient microbiota and co-interventions when interpreting therapeutic effects (Mocanu et al., 2021).

Meta-analyses of randomized FMT studies in metabolic syndrome and obesity metabolism suggest possible effects on insulin resistance or selected metabolic parameters, but heterogeneity in protocols, donor characteristics and outcomes limits routine clinical application (Qiu et al., 2023).

A double-blind randomized clinical trial in patients with severe obesity undergoing bariatric surgery found that lean-donor FMT did not improve preoperative or postoperative weight loss compared with autologous FMT, reinforcing the need for cautious interpretation (Lahtinen et al., 2022).

FMT should therefore remain an investigational strategy in obesity and metabolic syndrome until larger, longer and better standardized trials clarify efficacy, durability, safety and responder profiles (Zecheng et al., 2023).

3.4.6. Next-generation microbial therapeutics and Akkermansia muciniphila

Akkermansia muciniphila is one of the most discussed next-generation microbial candidates in metabolic disease because it is associated with mucin metabolism, intestinal barrier regulation and metabolic homeostasis (Jian et al., 2023). Depommier et al. conducted a randomized, double-blind, placebo-controlled proof-of-concept study of live and pasteurized Akkermansia muciniphila supplementation in overweight or obese insulin-resistant volunteers. The study reported that supplementation was safe and well tolerated over three months. In the same trial, pasteurized Akkermansia muciniphila was associated with improvements in insulin sensitivity, insulinemia and total cholesterol compared with placebo (Depommier et al., 2019). More recent clinical evidence suggests that response may depend on the recipient's baseline microbiota profile rather than on universal supplementation. A 12-week randomized, double-blind, placebo-controlled phase 2 trial in patients with overweight or obese type 2 diabetes showed that AKK-WST01 colonization and metabolic benefits were most evident in participants with low baseline fecal Akkermansia muciniphila levels (Y. Zhang et al., 2025).

This finding supports a microbiota-guided model in which next-generation microbial therapeutics may be selected according to baseline microbial features rather than prescribed uniformly to all patients (Y. Zhang et al., 2025). A systematic review on Akkermansia muciniphila in obesity concluded that the available evidence remains preliminary and depends heavily on preclinical studies, which means that human findings should still be interpreted cautiously (Abuqwider et al., 2021). Broader review literature also emphasizes that Akkermansia muciniphila may influence metabolic homeostasis through gut–liver–brain signaling, gut barrier regulation and immune-metabolic pathways, although these mechanisms require further clinical validation (Jian et al., 2023). Until larger and longer trials are available, Akkermansia muciniphila should be presented as an investigational but biologically plausible therapeutic candidate rather than as an established obesity treatment.

3.4.7. Precision nutrition and microbiome-guided treatment

Precision nutrition is especially relevant to microbiota research because metabolic responses to diet vary between individuals (Antwi, 2023). Jardon et al. described dietary macronutrients and the gut microbiome as part of a precision-nutrition approach to cardiometabolic health (Jardon et al., 2022). Antwi reviewed precision-nutrition strategies for improving risk factors of obesity and type 2 diabetes (Antwi, 2023).

Large human phenotyping data support links between habitual diet, microbiome features and host metabolism. Asnicar et al. reported microbiome connections with host metabolism and habitual diet in deeply phenotyped individuals. These data support the concept that microbiome information can be integrated with dietary, metabolic and clinical variables (Asnicar et al., 2021).

Prediction studies provide more direct evidence for microbiome-informed personalization. Cuevas-Sierra et al. used baseline microbiota and genetic scores to model dietary treatment selection in adults with overweight or obesity (Cuevas-Sierra et al., 2022). Rein et al. tested personalized diets based on predicted glycemic responses in newly diagnosed type 2 diabetes (Rein et al., 2022). Zhang et al. reported that gut microbiota could predict outcome after a short-term low-carbohydrate diet intervention in patients with obesity (Zhang et al., 2021).

The practical promise of precision nutrition is not limited to microbiome testing alone. Clinically useful models may combine microbiota data with anthropometry, diet records, continuous glucose monitoring, medication profiles, genetics, metabolomics and patient preferences (Antwi, 2023). Such integration could help clinicians select between fiber-focused strategies, low-carbohydrate diets, structured calorie restriction, prebiotics or adjunctive microbiota-targeted therapies (Cuevas-Sierra et al., 2022).

Implementation remains challenging because algorithms trained in selected cohorts may not generalize across ethnic, socioeconomic or clinical populations (Antwi, 2023). A Cochrane review of precision nutrition interventions in children and adolescents found limited evidence for pediatric obesity management, which illustrates the need for careful age- and population-specific validation (Huey et al., 2025). Adult metabolic care also requires validation against high-quality standard dietetic support, not only against minimal advice or placebo (Antwi, 2023).

Selected human clinical studies and meta-analyses relevant to therapeutic modulation of gut microbiota are summarized in Table 2.

Table 2. Selected human evidence for therapeutic modulation of gut microbiota in obesity and metabolic dysfunction.

Intervention/evidence area	Key finding	Main sources
Weight loss	Weight loss is associated with changes in microbiota diversity, composition and intestinal permeability.	Koutoukidis et al. (2022)
Inulin-type prebiotic	Inulin intervention in adults with obesity linked gut microbiota with health outcomes.	Hiel et al. (2020)
Dietary fiber	Fiber interventions modulated gut microbiota dysbiosis and metabolic markers in type 2 diabetes trials.	Ojo et al. (2020, 2021)
Whole grains	A whole grain-rich diet reduced body weight and inflammation without major microbiome remodeling.	Roager et al. (2019)
Protein pacing with intermittent fasting	This dietary strategy improved microbiome remodeling and metabolomic profiles versus continuous caloric restriction.	Mohr et al. (2024)
Synbiotics	A synbiotic intervention improved type 2 diabetes outcomes more than probiotic alone in a randomized trial.	Zhang et al. (2025)
Metformin	Metformin affected gut microbiome composition, function and circulating short-chain fatty acids in a randomized trial.	Mueller et al. (2021)
FMT	Lean donor FMT increased insulin sensitivity in metabolic syndrome, but later evidence remains heterogeneous.	Kootte et al. (2017); Qiu et al. (2023)
Akkermansia muciniphila	Pasteurized A. muciniphila was safe and associated with selected metabolic improvements in a proof-of-concept trial.	Depommier et al. (2019)
Precision nutrition	Baseline microbiota and predicted glycemic responses may help personalize dietary treatment.	Cuevas-Sierra et al. (2022); Rein et al. (2022); Zhang et al. (2021)

4. Discussion

The reviewed evidence supports the gut microbiota as a relevant therapeutic aspect rather than a single independent treatment target in obesity and metabolic syndrome (Jardon et al., 2022). Pathophysiological literature provides plausible pathways through short-chain fatty acids, endotoxemia, inflammation, bile acids and enteroendocrine signaling (Puljiz et al., 2023). Human evidence shows that microbiota features are associated with obesity and metabolic dysfunction, but reproducible taxonomic markers remain limited (Pinart et al., 2022).

The therapeutic evidence is strongest for interventions that are already embedded in metabolic care. Weight-loss interventions are clinically feasible and supported by systematic review and meta-analysis data on microbiota-related outcomes (Koutoukidis et al., 2022). Dietary fiber and prebiotic substrates have evidence from randomized trials and meta-analyses in type 2 diabetes and metabolic dysfunction (Ojo et al., 2020). Whole-grain dietary patterns have human trial evidence for reducing body weight and low-grade inflammation without requiring major microbiome remodeling (Roager et al., 2019). These interventions should be presented as microbiota-friendly metabolic strategies rather than as narrow microbiome treatments (Perler et al., 2023).

Probiotics and synbiotics occupy an intermediate position in the therapeutic hierarchy. Meta-analytic evidence suggests that microbiome-targeted therapies may improve glucose parameters, inflammatory markers and microbiota outcomes in type 2 diabetes. A synbiotic randomized trial supports the possibility that combined organism-substrate interventions may outperform probiotics alone in selected metabolic contexts. Clinical generalization remains limited because strain identity, dose, intervention duration and baseline patient phenotype influence outcomes (Zhou et al., 2025).

Metformin illustrates how a conventional metabolic drug can interact with the gut microbiome. A randomized trial showed that metformin affected gut microbiome composition, microbial function and circulating short-chain fatty acids (Mueller et al., 2021). GLP-1 receptor agonist literature suggests potential microbiome interactions, but the evidence remains less mature than for clinical weight-loss efficacy (Johnson et al., 2026). Bariatric surgery changes gut microbiota structure, but its clinical effects involve multiple anatomical, hormonal and behavioral pathways (Chen et al., 2025).

FMT remains experimental but scientifically important because randomized and meta-analytic evidence suggests that transferred microbiota can influence selected metabolic outcomes in humans (Zecheng et al., 2023). Response to lean-donor FMT appears to depend partly on baseline recipient microbiota composition in metabolic syndrome (Kootte et al., 2017). Meta-analyses suggest possible metabolic effects of FMT, but heterogeneity and protocol differences limit routine clinical application (Qiu et al., 2023). Akkermansia muciniphila is a next-generation microbial therapeutic candidate supported by proof-of-concept human data, and newer trial evidence suggests that baseline Akkermansia muciniphila abundance may influence response to supplementation (Y. Zhang et al., 2025).

Precision nutrition may be the most innovative long-term application for microbiota science in obesity and metabolic syndrome (Antwi, 2023). Baseline microbiota and genetic variables may help predict response to weight-loss diets in adults with overweight or obesity (Cuevas-Sierra et al., 2022). Baseline gut microbiota may also predict response to low-carbohydrate dietary intervention in patients with obesity (Zhang et al., 2021). Predicted glycemic response models may help personalize dietary therapy in type 2 diabetes and related metabolic disorders (Rein et al., 2022). These approaches fit an interdisciplinary framework because they combine clinical medicine, nutrition, microbiome science, data modeling and patient behavior.

Implementation barriers remain substantial (Antwi, 2023). Microbiome tests differ in sequencing method, analytical pipeline, taxonomic resolution and interpretation, which makes clinical comparability difficult (Pinart et al., 2022). Many intervention trials are small, short-term or conducted in selected volunteers, which limits external validity for routine internal medicine practice (Zhou et al., 2025). Social determinants such as access to fiber-rich foods, cost of testing, health literacy and medication adherence may influence whether microbiota-informed therapy can be implemented equitably (Antwi, 2023).

Safety must also be interpreted according to intervention type (Qiu et al., 2023). Fiber and prebiotic interventions are generally practical but may cause gastrointestinal intolerance in some patients, especially when introduced rapidly or at high doses (Yoo et al., 2024). Probiotic and synbiotic products require strain-specific interpretation and should not be considered interchangeable (Zhou et al., 2025). FMT carries distinct donor-screening, infectious and regulatory considerations that are not comparable to routine dietary interventions (Qiu et al., 2023).

Future trials should evaluate microbiota-related interventions against clinically meaningful comparators. A microbiome-informed algorithm has limited practical value if it is compared only with minimal advice and not with structured dietetic support or optimized pharmacotherapy (Antwi, 2023). Microbiome outcomes should be paired with outcomes such as HbA1c, waist circumference, blood pressure, lipid profile, insulin sensitivity, quality of life and weight maintenance (Zhou et al., 2025). Safety endpoints should be reported consistently for dietary supplements, next-generation microbes and FMT because the risk profile differs substantially across these interventions (Qiu et al., 2023). Cost-effectiveness should also be assessed when interventions require sequencing, metabolomics, digital platforms or repeated monitoring (Antwi, 2023).

Commercial microbiome testing is a potential source of overinterpretation in obesity management (Antwi, 2023). The absence of a universal obesity-associated microbiome means that a single stool test should not be used as a stand-alone diagnostic tool for obesity or metabolic syndrome. Test interpretation is also limited by differences in sequencing methods, databases and bioinformatic pipelines (Pinart et al., 2022). Clinicians should explain that microbiome results may be hypothesis-generating or supportive but are not yet equivalent to validated metabolic biomarkers such as HbA1c, lipid profile or blood pressure (Antwi, 2023). This communication is important because patients with obesity are frequently exposed to supplement and testing claims that exceed the strength of available clinical evidence (Zhou et al., 2025).

Digital health tools may strengthen microbiota-informed care when they are used to support dietary monitoring, glucose tracking and adherence rather than to replace clinical judgment (Rein et al., 2022). Continuous or repeated metabolic measurements can make personalized nutrition more actionable because they link dietary exposure with individual glycemic or metabolic response (Rein et al., 2022). Microbiome-informed algorithms should be validated against high-quality dietetic care because predictive accuracy alone is not the same as clinical effectiveness. These models should also be tested in populations with different

socioeconomic backgrounds because diet quality, food access and health literacy influence both microbiota and metabolic outcomes (Antwi, 2023). Public health implementation will require simple recommendations that translate microbiome science into practical behaviors such as increasing fiber, improving diet quality and supporting long-term adherence (Perler et al., 2023).

4.1. Limitations

The major limitation of current microbiota research is heterogeneity across methods, populations and outcomes. Sequencing platforms, bioinformatic pipelines, sampling procedures, dietary assessment and medication control differ between studies, which complicates comparison and synthesis. This methodological heterogeneity helps explain why obesity-associated microbiota signatures are inconsistent across studies.

Causality remains difficult to establish in many studies. Cross-sectional data can show associations between obesity and microbiota features, but they cannot determine whether dysbiosis contributes to obesity, results from obesity or reflects diet and medication use. Interventional studies provide stronger evidence, but many trials have small samples, short follow-up and limited clinical endpoints.

Future research should integrate metagenomics with metabolomics, bile acid profiling, inflammatory markers and clinically meaningful endpoints. Microbiome outcomes should not be considered sufficient unless they translate into metabolic benefit. Long-term outcomes such as sustained weight maintenance, HbA1c reduction, waist circumference, blood pressure and cardiovascular risk markers are more clinically relevant than short-term microbial shifts alone.

Future probiotic and synbiotic trials should report strain identity, dose, viability, formulation, adherence and adverse events. Future FMT trials should standardize donor selection, administration route, safety screening, durability assessment and responder analysis. Future precision-nutrition studies should validate algorithms in diverse populations and compare microbiome-informed strategies with high-quality standard care.

Research should also evaluate whether microbiome information changes clinical decisions beyond standard variables such as BMI, waist circumference, HbA1c, diet quality, medication use and physical activity. Cost-effectiveness analyses will be necessary if clinical models involve sequencing, metabolomics, proprietary algorithms or repeated monitoring. Implementation studies should include primary care, community and workplace settings because obesity and metabolic syndrome are influenced by everyday environments as well as biology.

5. Conclusions

The gut microbiota is a clinically relevant component of obesity and metabolic syndrome research, but it should not be interpreted as a stand-alone diagnostic or therapeutic target. Current evidence supports several plausible links between microbial metabolites, metabolic endotoxemia, inflammation, bile acid signaling, gut barrier function and metabolic dysfunction. At the same time, studies show substantial heterogeneity, and no universal taxonomic signature can currently define obesity or metabolic syndrome across populations.

Therapeutic perspectives are strongest for lifestyle and dietary interventions, particularly weight-loss strategies, fiber-rich dietary patterns, prebiotic substrates and individualized dietary approaches. Probiotics and synbiotics may provide additional metabolic benefits in selected contexts, especially in type 2 diabetes and insulin resistance, but their clinical application is limited by variation in strains, doses, formulations, populations and intervention duration. Metformin, GLP-1 receptor agonists and bariatric surgery may interact with microbiome-related pathways, but their use should remain based on established metabolic and clinical indications rather than presumed microbiome effects alone. Fecal microbiota transplantation and next-generation microbial candidates such as Akkermansia muciniphila remain promising but investigational.

Future care models should integrate microbiome science with individualized nutrition, metabolic pharmacotherapy, digital health tools and public health implementation. The most realistic clinical value of gut microbiota research may lie in improving patient stratification, predicting treatment response and designing more personalized and sustainable interventions. Further studies should use standardized microbiome methods, adequately powered human trials, clinically meaningful endpoints and longer follow-up before microbiota-targeted strategies can be recommended as routine components of obesity and metabolic syndrome management.

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