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The Gut Microbiome in Obesity and Diabetes: Emerging Links and Modulation Strategies

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ABSTRACT

The intestinal microbiome is a dense, metabolically active ecosystem that shapes host energy balance, immunity, and endocrine signaling. In obesity and type 2 diabetes (T2D), characteristic alterations reduced microbial diversity, depletion of fiber-fermenting taxa, expansion of mucus-degraders and pathobionts, and shifts in the virome/mycobiome associated with insulin resistance (IR) and glycemic dysregulation. Mechanistically, dysbiosis modifies production of short-chain fatty acids (SCFAs), bile-acid (BA) pools, and tryptophan-derived indoles; increases branched-chain amino acids and imidazole propionate; perturbs intestinal barrier integrity; and primes innate immunity via endotoxin (LPS) and other microbe-associated molecular patterns. These changes alter gut–brain and gut–liver axes, decrease GLP-1/peptide YY signaling, promote hepatic steatosis, and impair skeletal-muscle insulin signaling. Interventions that restore eubiosis, dietary fiber and polyphenols, Mediterranean/plant-forward patterns, time-restricted feeding, physical activity, and sleep regularity consistently improve metabolic endpoints. Clinical trials of pre-, pro-, and synbiotics show modest but reproducible benefits on IR and inflammatory markers; fecal microbiota transplantation (FMT) yields transient improvements in insulin sensitivity in selected recipients but lacks durable efficacy without diet/lifestyle co-intervention. Emerging strategies include defined microbial consortia, engineered commensals, bacteriophages, and targeted postbiotics (e.g., SCFA donors, secondary BA modulators). Precision microbiome medicine combining metagenomics, metatranscriptomics, metabolomics, and host genomics/immune profiling may identify responder endotypes and guide individualized therapy. This review synthesizes current evidence linking the gut ecosystem to obesity/T2D pathophysiology, maps metabolite and immune pathways to clinical phenotypes, and evaluates modulation strategies across lifestyle, nutritional, and microbial therapeutics, emphasizing pragmatic translation and safety.

Keywords: gut microbiome; insulin resistance; short-chain fatty acids; bile acids; fecal microbiota transplantation

INTRODUCTION

Obesity and T2D arise when chronic caloric excess meet insufficient metabolic flexibility across liver, skeletal muscle, adipose tissue (AT), and pancreas. The gut microbiome is now recognized as a key modifier of this host network[1–3]. By transforming otherwise indigestible dietary substrates and reshaping host signaling, gut microbes can either buffer nutrient stress or amplify it. Associations between dysbiosis and metabolic disease are robust across populations, yet causality is nuanced and context-dependent. This introduction outlines the organizing principles that connect microbial ecology to metabolic outcomes and frames the therapeutic opportunities[4–7].

First, diet builds the substrate landscape. Complex carbohydrates and resistant starches feed saccharolytic microbes that generate SCFAs, acetate, propionate, butyrate, a key regulator of epithelial integrity, immune tone, and energy homeostasis. Low-fiber, high-fat, ultra-processed patterns impoverish these communities, reduce butyrate supply, and increase fermentation of protein and bile-tolerant taxa[8, 9-14]. Second, microbial metabolism modifies host signaling molecules. Secondary BAs engage FXR/TGR5 to tune glucose/lipid metabolism and GLP-1 secretion; indole derivatives from tryptophan activate AhR to maintain barrier integrity and temper inflammation; microbial production of imidazole propionate and branched-chain amino acids has been linked to impaired insulin signaling[15–19]. Third, microbe–host structural interfaces matter. The mucus layer, tight junctions, and antimicrobial peptides form a barrier that, when weakened, permits increased translocation of LPS and other MAMPs, driving low-grade inflammation ("metaflammation") through TLR/NLR pathways that propagate IR in AT, liver, and muscle[20-26].

Fourth, endocrine communication connects the gut to systemic physiology. SCFAs act via FFAR2/3 and inhibit histone deacetylases to influence incretin release (GLP-1, PYY), adipose lipolysis, and sympathetic activity. BA pools, sculpted by microbial bile-salt hydrolases and dehydroxylases, signal through FXR/TGR5 to regulate hepatic gluconeogenesis, thermogenesis in brown/beige fat, and islet function. Microbial metabolites reach the brain via vagal and humoral routes, affecting appetite, circadian timing, and stress responses, all relevant to obesity risk[27-34].

Fifth, heterogeneity is the rule. Taxonomic shifts (e.g., Firmicutes/Bacteroidetes ratios) vary across cohorts and can mislead when treated as universal biomarkers. Functional readouts, metabolic pathways, and metabolite profiles better explain host phenotypes than taxonomy alone. Enterotypes and diet-linked guilds (e.g., Prevotella vs Bacteroides) predict postprandial glycemic responses and intervention outcomes[35-42]. The mycobiome, virome, and archaeome add layers that may modulate bacterial functions; bacteriophages shape community dynamics and can be harnessed therapeutically.

Finally, translation demands rigorous evidence. Germ-free and gnotobiotic mouse models, human FMT studies, and diet-intervention RCTs support causal links between microbiome features and metabolic traits, but effects are often small-to-moderate and context-sensitive[43-49]. Durable benefit likely requires aligning diet/lifestyle with microbial therapeutics and tailoring to individual microbial and host immunogenetic states. Safety, manufacturing quality, and equitable access are practical constraints as the field moves from associations to interventions[50-55].

In the sections that follow, we: summarize core mechanisms by which gut microbes influence energy balance and insulin action; review barrier function and immune activation in metabolic disease; detail metabolite-mediated endocrine crosstalk; evaluate diet, lifestyle, and environmental modulators; appraise current and emerging microbiome-targeted therapies; and outline a precision-medicine roadmap for integrating microbiome data into obesity/T2D care.

2 Microbiome Signatures in Obesity and T2D: From Taxa to Functions

Microbiome studies in obesity/T2D consistently report decreased α-diversity and functional redundancy, with depletion of fiber-fermenting obligate anaerobes (e.g., certain Ruminococcaceae, Lachnospiraceae) and expansion of BA-tolerant, mucus-degrading, or pro-inflammatory taxa (e.g., some Proteobacteria)[56-60]. However, effect sizes vary, and taxonomic markers fail to generalize across geographies and diets. Consequently, function-centric metrics better capture metabolic risk: reduced butyrate-producing pathways; increased proteolytic fermentation and urease activity; altered BA-transforming enzymes; and elevated microbial genes for endotoxin synthesis[61-66].

Energy harvest concepts evolved from early observations of increased caloric extraction in obese microbiomes. Current models emphasize *partitioning* over total harvest. In low-fiber diets, microbes prioritize simple sugars and host mucin, reducing SCFA output and thinning the mucus layer[67-70]. Butyrate scarcity weakens colonocyte β-oxidation and tight-junction expression, while excess acetate can promote lipogenesis under certain hormonal contexts. Elevated microbial biosynthesis of branched-chain amino acids correlates with circulating BCAA levels and IR; mechanistically, BCAAs and their ketoacids activate mTORC1 and impair insulin signaling in muscle[71-77].

Key taxa with putative protective roles include *Akkermansia muciniphila*, associated with improved barrier function and metabolic profiles; enrichment or pasteurized preparations of *Akkermansia* have shown early promise[78-84]. *Prevotella*-rich configurations may enhance glycemic responses in high-fiber diets by boosting propionate production and GLP-1 release, but benefits depend on substrate availability and host genetics. The virome (bacteriophages) can modulate bacterial abundance and metabolism; phageome shifts have been linked to obesity, suggesting both biomarker and therapeutic potential[85-88].

Ultimately, metabolic phenotypes align most with *pathway* shifts and metabolite outputs rather than single taxa. Integrative metagenome-metabolome analyses that quantify SCFAs, secondary BAs, indoles, phenolic metabolites, imidazole propionate, and TMAO provide actionable signatures linked to IR, hepatic steatosis, and cardiovascular risk[89-94]. These signatures offer targets for diet design and microbial therapeutics, while reminding clinicians that microbiome features are plastic and responsive to environmental change.

3. Barrier Dysfunction, Endotoxemia, and Metaflammation

The intestinal barrier separates the antigen-rich lumen from systemic circulation. Its components, mucus layers (MUC2), epithelial tight/adherens junctions (occludin, claudins, E-cadherin), antimicrobial peptides, secretory IgA, and lamina propria immune cells, maintain tolerance while containing microbes[95]. In obesity/T2D, dietary patterns low in fermentable fiber and high in emulsifiers, sweeteners, and saturated fats erode this defense. Reduced butyrate deprives colonocytes of their preferred fuel, downregulates tight-junction proteins, and increases oxygen diffusion, favoring facultative anaerobes and a pro-inflammatory niche[24].

Microbial and dietary components breach the barrier and engage pattern-recognition receptors. LPS from Gram-negative bacteria activates TLR4 on epithelial, immune, and metabolic tissues, promoting NF-κB–driven cytokines (TNF-α, IL-6) that impair insulin signaling. Peptidoglycan, flagellin, and β-glucans engage

NOD/TLR pathways; microbial DNA stimulates cGAS–STING responses[25]. This "metabolic endotoxemia", like a modest chronic elevation in circulating LPS, correlates with IR, hepatic steatosis, and adipose inflammation. Concomitantly, bile and dietary lipids form chylomicron–LPS complexes that facilitate systemic transport of endotoxin[25].

The mucus layer buffers mechanical and chemical stress. *A. muciniphila* can stimulate mucin turnover and tight-junction expression, yet in low-fiber diets, excessive mucin foraging by other species thins the layer. Paneth cell dysfunction (reduced antimicrobial peptide secretion) and goblet cell depletion further compromise defense. Dysbiosis also perturbs IgA coating patterns, altering microbial containment[26].

Downstream, portal venous drainage exposes the liver to gut-derived LPS and metabolites, activating Kupffer cells and hepatic stellate cells. In AT, innate lymphoid cells and macrophages respond to LPS and bacterial products with pro-inflammatory polarization, sustaining IR. Interventions that restore barrier integrity, fermentable fiber, butyrate donors, certain polyphenols, vitamin D sufficiency, and sleep regularity lower endotoxemia and improve insulin action[26]. Avoiding emulsifiers (e.g., carboxymethylcellulose, polysorbate-80) and limiting ultra-processed foods may reduce mucus erosion and permeability. Together, rebuilding the barrier dampens systemic inflammation that couples the gut to metabolic disease.

4. Metabolite-Mediated Endocrine Crosstalk: SCFAs, Bile Acids, Indoles, and Beyond

Microbial metabolites bridge the intestinal lumen and host endocrine networks. SCFAs signal through FFAR2/3 on enteroendocrine L cells to increase GLP-1 and PYY, slow gastric emptying, reduce appetite, and improve insulin secretion/sensitivity[27]. Butyrate supports epithelial β-oxidation, tight-junction integrity, and anti-inflammatory Treg differentiation (via HDAC inhibition). Propionate enters gluconeogenic pathways in the liver but also stimulates GLP-1; acetate can fuel lipogenesis yet supports appetite regulation via central circuits. Net effects depend on concentrations, sites of production, and host hormonal state[27].

Bile acids are co-hormones shaped by microbes. Bacterial bile-salt hydrolases deconjugate primary BAs; 7α-dehydroxylases generate secondary BAs (e.g., DCA, LCA) that differentially activate FXR and TGR5. TGR5 signaling in L cells promotes GLP-1; in brown/beige adipocytes, it enhances thermogenesis. FXR activation in the intestine induces FGF19/15 to regulate hepatic gluconeogenesis and BA synthesis; dysbiotic shifts in BA pools alter this axis, contributing to IR and steatosis[4, 6, 7, 15]. Pharmacologic BA modulators (sequestrants, FXR/TGR5 ligands) exemplify postbiotic-adjacent therapies.

Tryptophan metabolites add another layer. Indole and indole-3-propionate engage AhR and PXR to strengthen barrier function and suppress inflammation; lower levels associate with IR. Conversely, imidazole propionate, produced by specific microbial pathways, impairs insulin signaling by activating p38 MAPK and mTORC1, inhibiting IRS–Akt. Phenolic acids from polyphenol metabolism (e.g., urolithins) exhibit mitophagy-promoting and anti-inflammatory effects, though responses depend on metabotypes (e.g., urolithin producers vs. non-producers)[28].

Other metabolites with cardiometabolic relevance include trimethylamine N-oxide (TMAO), generated from choline/carnitine by microbial TMA lyases and hepatic FMO3; elevated TMAO links to atherosclerosis risk more than glycemia per se, but intersects with hepatic lipid metabolism[29]. Hydrogen sulfide and nitric-oxide–related metabolites modulate vascular tone and inflammation. Mapping these networks clarifies why dietary patterns, fiber type/amount, fat quality, and polyphenol diversity have system-wide effects: they reprogram microbial metabolic outputs that act as hormones[30].

5. Diet, Lifestyle, and Environmental Modulators of the Microbiome–Metabolism Axis

Diet composition is the strongest, most modifiable determinant of the adult microbiome. High-fiber, minimally processed patterns (Mediterranean, plant-forward) enrich SCFA-producing guilds, increase microbial diversity, and improve HOMA-IR and hepatic fat independent of weight loss. Specific fibers (inulin, GOS, resistant starch) increase butyrate producers and GLP-1; arabinoxylans and β-glucans modulate BA metabolism and LDL-C[31, 32]. Polyphenol-rich foods (berries, cocoa, tea) act as prebiotics, with microbial conversion to bioactive phenolics that reduce inflammation and improve endothelial function. Fat quality matters: replacing saturated with mono-/polyunsaturated fats shifts BA pools and microbial composition, improving insulin sensitivity[33].

Ultra-processed foods (emulsifiers, artificial sweeteners, low fiber) erode mucus, favor facultative anaerobes, and can worsen glycemic responses in susceptible individuals. Some non-nutritive sweeteners alter microbiome functions and glucose tolerance in a person-specific manner; cautious use and monitoring are prudent. Emulsifiers (carboxymethylcellulose, polysorbate-80) can increase permeability and low-grade inflammation in experimental models[34].

Timing and lifestyle layer on composition. Time-restricted feeding and circadian alignment synchronize microbial diurnal oscillations, BA signaling, and host glucose metabolism[34]. Physical activity increases microbial diversity, enriches butyrate producers, and improves SCFA profiles; exercise plus fiber often yields additive benefits. Sleep sufficiency and stress reduction stabilize autonomic and hormonal inputs that shape gut motility and microbial habitats. Medications (metformin, PPIs, antibiotics, statins) also remodel the microbiome; metformin increases *Akkermansia* and SCFA producers and may mediate part of its glycemic benefit via microbial pathways.

Environmental and early-life factors, like birth mode, breastfeeding, antibiotic exposures, and infections, set initial trajectories that affect later metabolic risk. While not modifiable retrospectively, these factors inform risk stratification. Collectively, aligning diet quality, meal timing, activity, sleep, and judicious medication use provides a potent, low-risk strategy to remodel the microbiome–metabolism axis and improve glycemic control.

6. Microbiome-Targeted Therapies: Evidence, Limitations, and Safety

Prebiotics, probiotics, synbiotics: RCTs show that fermentable fibers (inulin, GOS, resistant starch) improve insulin sensitivity, fasting glucose, and inflammatory markers, with effect sizes modest but clinically meaningful when sustained. Probiotics (selected *Bifidobacterium/Lactobacillus* strains) modestly improve HOMA-IR and lipid profiles, though strain and dose specificity are critical[33, 35, 36]. Pasteurized *Akkermansia* and next-generation probiotics are under evaluation; early data suggest safety and small metabolic benefits. Synbiotics (prebiotic + probiotic) may enhance colonization and metabolite production.

Postbiotics: Direct delivery of microbial metabolites or their precursors, e.g., butyrate/tributyrin, propionate, inulin esters can strengthen barrier function and stimulate GLP-1, though GI tolerance and palatability limit dosing[37–39]. BA-modulating agents (sequestrants, FXR/TGR5 modulators) affect glycemia and lipids but require careful safety monitoring (e.g., LDL-C changes, gallbladder effects).

FMT and defined consortia: Lean-donor FMT improves insulin sensitivity in subsets characterized by low baseline diversity or specific microbial signatures, but benefits fade without diet co-intervention. Capsule-based FMT improves safety/logistics but shares durability issues. Stand

CONCLUSION

Obesity and diabetes intersect with the gut microbiome through altered diversity, dysregulated metabolites, and impaired barrier function that amplify inflammation and insulin resistance. Converging evidence implicates SCFA, bile acid, and tryptophan pathways, alongside microbial modulation of incretins and energy harvest. Interventions such as dietary fiber, polyphenols, probiotics, synbiotics, postbiotics, antibiotics, and FMT can shift communities and improve metabolic endpoints, yet durability and safety remain variable. Future progress requires causal, mechanism-rich RCTs, standardized endpoints, and stratification by baseline enterotypes, diet, and host genetics. Integrating multi-omics with precision nutrition and ethical data sharing will translate microbiome science into scalable, equitable strategies for obesity and T2D prevention.

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