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# GUT MICROBIOTA AS A THERAPEUTIC TARGET IN OBESITY AND TYPE 2 DIABETES MELLITUS

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**Keywords:**

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**ABSTRACT:** Obesity and type 2 diabetes mellitus (T2DM) are increasing worldwide, and gut microbial features are repeatedly associated with adiposity, insulin resistance and low-grade inflammation. This structured narrative review evaluates whether those associations support therapeutic use. PubMed/MEDLINE, Google Scholar, Clinical Trials.gov and authoritative regulatory or guideline sources were searched for English-language literature published from January 2004 to 17 July 2026. Evidence was classified as experimental, observational, randomized clinical trial or systematic review/meta-analysis. Animal studies support mechanisms involving intestinal permeability, short-chain fatty acids, bile-acid signalling and host-microbial co-metabolism, but these findings cannot be assumed to produce clinical benefit. In humans, dietary fibre and selected prebiotic, probiotic or synbiotic products may produce small, heterogeneous improvements in glycaemia or adiposity. Preparation-specific trials of *Akkermansia muciniphila* are promising, particularly for pasteurized products, but live, pasteurized and protein-based preparations are not interchangeable and none is an approved treatment for obesity or T2DM. Fecal microbiota transplantation remains experimental for metabolic disease because engraftment is variable, metabolic outcomes are inconsistent and infection-transmission risk requires rigorous donor screening. Microbiota changes after bariatric surgery, metformin, acarbose or berberine may contribute to response but do not replace their established direct mechanisms. Microbiota-directed strategies should therefore be regarded as adjunctive or investigational, with future trials requiring strain or product identification, dose standardization, adequate power, longer follow-up and clinically meaningful endpoints.

**INTRODUCTION:** Obesity and T2DM now impose a major clinical and economic burden. In 2022, approximately 2.5 billion adults were overweight and 890 million were living with obesity; about 43% of adults were overweight and 16% had obesity [1].

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The International Diabetes Federation estimated that 589 million adults aged 20-79 years were living with diabetes in 2024 (11.1% of this age group), with a projected increase to 853 million by 2050; diabetes was associated with about 3.4 million deaths and more than US$1 trillion in health expenditure in 2024 [2].

These conditions frequently coexist and increase cardiovascular, renal, hepatic and other complications, creating a need for effective prevention and treatment without overstating unproven alternatives. The human gut microbiota comprises bacteria, archaea, viruses and fungi

whose collective gene content and metabolic functions interact with diet, medications and host physiology. Current estimates place bacterial and human cell numbers in the same order of magnitude, while metagenomic catalogues reveal a microbial gene repertoire much larger than the human genome [3, 4]. The Human Microbiome Project and later studies established roles in nutrient transformation, vitamin production, xenobiotic metabolism, colonization resistance and mucosal immune development [5, 6].

Early mouse studies reported increased microbial energy-harvesting capacity with obesity, and small human studies popularized the Firmicutes-to-Bacteroidetes ratio [7, 8]. This ratio is not a consistent diagnostic marker across populations. Transferring microbiota from obesity-discordant twins to germ-free mice transmitted aspects of the donor phenotype, supporting biological plausibility under controlled experimental conditions [9]. In humans, lower microbial gene richness has been associated with adiposity and inflammation, and metagenome-wide association studies have identified altered microbial functions in T2DM [10, 11, 12]. These human findings are primarily associative: diet, geography, medication, disease duration and bowel transit can influence both the microbiome and metabolic phenotype [13].

A central interpretive problem is therefore the gap between association, experimental causation and clinical utility. Animal models can isolate mechanisms but do not reproduce the heterogeneity, drug exposure or long-term outcomes of human obesity and T2DM. Observational studies may identify biomarkers but cannot establish that changing a taxon will change disease. Randomized trials provide more direct evidence, yet many microbiota interventions are small, short and based on surrogate endpoints. This review addresses that gap by integrating evidence according to study design; distinguishing live, pasteurized and protein-based microbial preparations; comparing major human trials by strain or product, dose and duration; and separating microbiota-mediated hypotheses from established drug or surgical mechanisms. Recent 2025-2026 clinical and regulatory evidence is incorporated to clarify what is ready for adjunctive use and what remains investigational.

## MATERIALS AND METHODS:

**Literature-Search Strategy:** A structured narrative search was conducted in PubMed/MEDLINE, Google Scholar and ClinicalTrials.gov. WHO and International Diabetes Federation sources were used for disease-burden estimates; FDA, European Food Safety Authority and European Commission sources were used for safety and regulatory statements; and current clinical guidelines were used for the clinical perspective. The search period was 01 January 2004 to 17 July 2026, and the final search was performed on 17 July 2026. Seminal pre-2004 reports were not required for the questions addressed.

The core search string was: ("gut microbiota" or "gut microbiome" or "gastrointestinal microbiome") and (obesity or "type 2 diabetes" or "insulin resistance" or "metabolic syndrome") and (probiotic* or prebiotic* or synbiotic* or "dietary fibre" or "dietary fiber" or "short-chain fatty acid*" or "bile acid*" or "*Akkermansia muciniphila*" or "fecal microbiota transplantation" or "faecal microbiota transplantation" or metformin or acarbose or berberine or "bariatric surgery" or pharmacomicrobiomics or postbiotic* or "live biotherapeutic product*"). Focused combinations of the disease terms with each intervention or mechanism were also used. Searches were limited to English-language records.

The inclusion criteria were human randomized trials, prospective or cross-sectional studies, systematic reviews or meta-analyses, and authoritative guidelines or regulatory documents relevant to obesity, T2DM, insulin resistance or metabolic syndrome. Animal and *in-vitro* studies were retained only when they provided mechanistic information that could not be inferred from human trials. The exclusion criteria were duplicate records, non-English reports, conference abstracts without sufficient methods or results, articles unrelated to metabolic outcomes, unverified secondary claims and animal-only studies without clear mechanistic relevance.

The broad PubMed query returned approximately 8,364 records before focused refinement. Titles and abstracts were screened for relevance, followed by full-text or complete abstract assessment of

potentially eligible sources and backward citation checking of major trials and reviews. Because this was a structured narrative review rather than a systematic review or meta-analysis, a PRISMA flow and quantitative risk-of-bias synthesis were not undertaken. Seventy-five sources were retained in the final narrative, including experimental, observational, randomized, meta-analytic, guideline and regulatory evidence. The evidence type and principal limitations were recorded during synthesis. Ethical approval and consent were not required because no new human or animal data were collected.

## RESULTS AND DISCUSSION;

**Evidence Framework: From Mechanism to Therapeutic Outcome:** Evidence is described in four categories. Experimental evidence includes in-vitro systems, germ-free or antibiotic-treated animals and microbial-transfer studies; it can support causality within a model but not clinical efficacy. Observational human evidence identifies associations and potential responders but remains vulnerable to confounding and reverse causation. Randomized clinical trials evaluate an intervention-product combination in a defined population; their results should not be generalized to different strains, doses or preparations. Systematic reviews and meta-analyses increase precision but inherit heterogeneity and product-mixing from the included trials. Accordingly, mechanistic plausibility is not presented here as proof of weight loss, HbA1c reduction or prevention of complications.

**Barrier Dysfunction, Inflammation and Insulin Resistance:** In mice, high-fat feeding and chronic low-dose lipopolysaccharide (LPS) exposure can increase intestinal permeability, inflammatory signalling, adiposity and insulin resistance [14, 15]. These experiments support a model in which microbial products activate Toll-like receptor and nuclear factor-kappa B pathways, with cytokine release and adipose-tissue immune-cell recruitment [16]. However, LPS assays and permeability markers vary substantially in humans. Cross-sectional elevations cannot show whether barrier dysfunction caused metabolic disease or resulted from diet, adiposity or medication. The clinically relevant inference is therefore limited: weight loss and dietary quality may improve barrier-related biology, but no LPS-targeted microbiota product has established efficacy for obesity or T2DM.

***Akkermansia muciniphila*: Preparation-specific Evidence:** *Akkermansia muciniphila* is a mucin-associated bacterium linked with mucus-layer and epithelial signalling. In diet-induced obese mice, live *A. muciniphila* improved barrier-related and metabolic measures [17]. Pasteurization and the purified outer-membrane protein Amuc_1100 also improved several metabolic endpoints in mice, demonstrating that live colonization is not required in that model [18]. Protein-based findings are preclinical and should not be represented as evidence for a marketed protein therapy.

The first randomized proof-of-concept human study enrolled 40 insulin-resistant adults with overweight or obesity; 32 completed three months of daily placebo, live *A. muciniphila* or pasteurized *A. muciniphila* at 1 × 10^10 cells. Pasteurized bacteria improved insulin sensitivity and selected anthropometric or biochemical outcomes compared with placebo, whereas the live preparation did not reproduce every endpoint. The study was exploratory, small and not designed for clinical events [19]. A 2026 trial randomized 90 adults with overweight or obesity who first lost at least 8% of body weight during an eight-week low-energy diet and then received daily pasteurized *A. muciniphila* MucT or placebo for 24 weeks. Mean weight regain was lower with the pasteurized preparation (1.2 ± 0.7 versus 3.2 ± 0.4 kg), with no treatment-related serious adverse event; short follow-up, commercial involvement and the selected post-weight-loss population limit generalization [20].

For live strain AKK-WST01, a 2025 randomized 12-week study in 58 drug-naive adults with overweight or obesity and T2DM reported no significant overall between-group metabolic benefit. Exploratory analyses suggested colonization and metabolic improvement among participants with low baseline abundance, but this subgroup result requires prospective confirmation [21]. Thus, live and pasteurized products cannot be treated as equivalent, and response may depend on baseline ecology. EFSA concluded that a specified pasteurized preparation was safe under defined novel-food conditions, and the European Union authorized pasteurized *A. muciniphila* as a novel

food [22, 23]. Novel-food authorization is not medicinal approval; no live, pasteurized or protein-based *A. muciniphila* product is approved as a treatment for obesity or T2DM.

**Energy Harvest, Diet and Microbial Adaptability:** Germ-free mouse work established that microbial colonization can regulate host fat storage, and microbial-transfer experiments demonstrate that donor communities can modify phenotype in controlled recipients [24, 9]. In humans, diet can alter microbiota composition within days, while longer dietary interventions may improve microbial gene richness together with metabolic markers [25, 26]. The direction of causality remains complex: reduced energy intake and weight loss can change both metabolism and microbiota, and the microbiota change may be a mediator, a marker or both. This supports dietary intervention as standard care with potential microbiome effects, not the use of stool composition as an independent treatment target.

**Short-chain Fatty Acids: Beneficial Pathways and Context-Dependent Effects:** Acetate, propionate and butyrate are produced during microbial fermentation, but they differ in tissue handling and signalling. Butyrate is an important colonocyte fuel and can support epithelial integrity; acetate enters peripheral metabolism; and propionate is substantially utilized by the liver. SCFAs also influence histone deacetylases and receptors such as FFAR2 and FFAR3 [27, 28]. In cellular and animal systems, SCFAs can stimulate GLP-1 and peptide YY and modulate immune function [29]. These mechanisms provide a rationale for fibre-rich diets but do not imply that a higher concentration of every SCFA is always beneficial. Context matters. In a mouse model, acetate participated in a microbiome-brain-beta-cell pathway that promoted hyperphagia and metabolic syndrome [30]. Propionate administration increased glucagon and fatty acid-binding protein 4 and impaired insulin action in experimental systems, with short-term findings also explored in humans [31]. Conversely, controlled delivery of propionate to the colon has reduced weight gain in a separate human trial. Differences in route, dose, compartment, background diet, host phenotype and duration can explain apparently conflicting effects. Fecal SCFA concentrations also reflect production minus absorption and transit, so a high fecal value is not necessarily evidence of high systemic benefit. SCFA-based claims should therefore specify the molecule, delivery site, exposure and population [32]. Other metabolites, including branched-chain amino acids and indole or trimethylamine-related compounds, further complicate a single-metabolite interpretation [33].

**Bile-acid Signalling through FXR and TGR5:** Gut microbes modify the bile-acid pool by deconjugation and conversion of primary to secondary bile acids. These molecules signal through farnesoid X receptor (FXR) and Takeda G-protein-coupled receptor 5 (TGR5), affecting hepatic glucose and lipid pathways, intestinal hormones and energy expenditure [34]. Much mechanistic evidence derives from mice; for example, microbiota-dependent reduction of tauro-beta-muricholic acid alters intestinal FXR signalling, but this bile acid is prominent in mice and the result cannot be directly transferred to humans [35]. TGR5 activation can increase energy expenditure or GLP-1 in experimental models, while FXR effects vary by tissue, bile-acid species and disease stage [36, 37]. The appropriate clinical conclusion is that bile-acid signalling may mediate part of the response to diet, surgery or drugs, not that universal FXR activation, inhibition or TGR5 stimulation will improve every patient.

**TABLE 1: MAJOR MECHANISMS LINKING GUT MICROBIOTA WITH OBESITY AND T2DM, EVIDENCE LEVEL AND THERAPEUTIC INTERPRETATION**

| Mechanism | Evidence supporting the link | Context or limitation | Cautious therapeutic interpretation |
|---|---|---|---|
| Energy harvest | Germ-free and transfer experiments show that microbial communities can alter energy extraction and adiposity [7, 24, 9] | Animal housing, diet and recipient biology differ from human disease; human associations are confounded. | Dietary quality and energy balance remain primary; no universal obesity microbiome is defined. |
| Barrier/LPS | High-fat-fed mouse studies link permeability and LPS signalling with inflammation and insulin resistance [14, 15] | Human LPS and permeability measurements are heterogeneous and often cross-sectional. | Barrier-supportive dietary patterns are reasonable; LPS-directed microbial therapy is unproven. |

| | | | |
|---|---|---|---|
| SCFAs | Cell, animal and human studies support receptor, incretin and epithelial effects [27, 29] | Acetate, propionate and butyrate differ; route, concentration and host state change the effect [30, 31] | Increase fibre through guideline-based diet; avoid assuming that all SCFA increases are beneficial. |
| Bile acids | Microbial bile-acid conversion affects FXR/TGR5 pathways in experimental studies [34, 35] | Tissue-, species- and bile-acid-specific effects limit direct translation. | Bile-acid changes may mediate response but do not establish a stand-alone therapy. |
| A. muciniphila | Mouse mechanisms plus preparation-specific human trials of live or pasteurized products [18, 19, 20, 21] | Strain, viability, dose, baseline abundance and population matter. | Promising investigational/adjunct product class; not an approved obesity or T2DM medicine. |
| Gene richness | Lower richness is associated with adiposity and inflammation; diet-induced improvement can accompany metabolic change [10, 26] | Association does not establish a clinical cutoff or causality. | Not ready as a diagnostic or treatment-selection test. |

FXR, farnesoid X receptor; LPS, lipopolysaccharide; SCFA, short-chain fatty acid; T2DM, type 2 diabetes mellitus; TGR5, Takeda G-protein-coupled receptor 5.

**Prebiotics, Dietary Fibre and Food-Pattern Interventions:** Prebiotics are substrates selectively utilized by host microorganisms that confer a health benefit, whereas not every dietary fibre fulfils this definition [38]. Inulin-type fructans, galacto-oligosaccharides and resistant starch differ in fermentability, dose-response and tolerability. Fibre can support microbial functions and SCFA production, but effects depend on the food matrix, background diet, bowel transit and baseline microbiota [39, 40]. Whole grains, pulses, vegetables, fruits, nuts and seeds also provide nutrients and can improve cardiometabolic health through mechanisms that do not require microbial mediation.

Human trials illustrate this variability. In an exploratory study of women with obesity, inulin-type fructans modified Bifidobacterium and selected metabolic measures, but the study was small and outcome-specific [41]. In 60 adults with overweight, 10 g/day inulin-propionate ester for 24 weeks reduced weight gain and abdominal adiposity compared with inulin control, but this engineered delivery system should not be generalized to all fibre products [42]. Across randomized trials, prebiotic effects on glucose and lipid outcomes are generally modest and heterogeneous [43]. A gradual increase in food-based fibre is usually practical; bloating, pain, diarrhoea or constipation can limit adherence, and patients with complex gastrointestinal disease may need individualized advice.

**Probiotics, Synbiotics and Postbiotics:** A probiotic is a live microorganism that confers a health benefit when administered in an adequate amount. The effect is tied to the identified strain or defined strain combination, dose, delivery matrix and endpoint; it cannot be assigned to an entire genus or species [44]. Product labels should state genus, species and strain, viable count through the end of shelf life, storage conditions, serving size and safety information. Expert criteria also require strain-level characterization, evidence of safety and at least one positive human trial for the claimed benefit [45]. Synbiotics combine live microorganisms and a selectively utilized substrate, with either complementary or synergistic logic [46]. Postbiotics are preparations of inanimate microorganisms and/or their components that confer a health benefit; purified microbial proteins alone are not automatically postbiotics [47].

Meta-analyses suggest statistically significant but clinically limited average effects in T2DM. Earlier analyses found small changes in glucose, adiposity and lipid markers with substantial differences among products [48, 49]. A 2026 meta-analysis of 48 randomized trials reported mean reductions of approximately 7 mg/dL in fasting glucose, 0.34 percentage point in HbA1c and 0.91 in HOMA-IR, but heterogeneity, varying strain combinations and short durations weaken product-level conclusions [50]. These average effects are smaller than those expected from established glucose- or weight-lowering therapies and should not justify replacing indicated medication.

Specific trials should be interpreted only for the tested formulation. A six-month multi-strain product in T2DM improved selected insulin-

resistance and inflammatory measures, but the combination does not validate other mixtures [51]. A six-week trial of 300 g/day yogurt containing Lactobacillus acidophilus La-5 and *Bifidobacterium animalis* subsp. lactis Bb-12 (at least 10^6 colony-forming units/g of each) in 60 adults with T2DM reported improved fasting glucose and antioxidant markers; its duration and surrogate endpoints limit conclusions [52]. Product quality is a clinical issue: loss of viability from heat or poor storage, contamination, inaccurate counts and substitution of strains can invalidate efficacy evidence. Common adverse effects are gas and altered stool pattern. Rare bloodstream infection is a concern in severely immunocompromised, critically ill or central-line patients, so selection and monitoring matter.

**Fecal Microbiota Transplantation:**

**Experimental for Metabolic Disease:** FMT transfers a complex donor community and associated metabolites. In 18 men with metabolic syndrome, a single lean-donor intestinal infusion improved insulin sensitivity at six weeks compared with autologous transfer [53]. A later study found that improvement at six weeks was not durable at 18 weeks and depended partly on baseline recipient microbiota [54]. In the FMT-TRIM pilot trial, 24 adults with obesity received weekly oral lean-donor or placebo capsules for six weeks; engraftment occurred, but body weight and major metabolic outcomes did not significantly improve [55]. Another capsule trial demonstrated microbial changes without convincing weight loss [56]. In a 70-participant phase 2 trial, a single oral FMT combined with daily low-fermentable fibre improved HOMA2-IR at six weeks, whereas FMT alone did not establish a consistent metabolic effect [57]. These small trials show biological activity but inconsistent efficacy and uncertain durability.

Current clinical guidance supports fecal microbiota-based therapies for selected recurrent *Clostridioides difficile* infection scenarios, not for obesity or T2DM [58]. FDA-approved fecal microbiota products are indicated to prevent recurrent *C. difficile* infection after antibacterial treatment; their approval does not extend to metabolic disease [59]. Investigational FMT requires robust donor history and laboratory screening for enteric pathogens, multidrug-resistant organisms and relevant viruses; standardized collection and processing; traceability; informed consent; and adverse-event follow-up. Serious infection transmission, including fatal events involving resistant organisms, has been reported [60]. Long-term transfer of unrecognized phenotypes and unpredictable engraftment remain concerns. FMT for obesity or T2DM should therefore occur only in an appropriately approved clinical trial, not routine practice.

**Bariatric Surgery and the Microbiome:** Bariatric or metabolic surgery can produce substantial and durable weight loss and improve T2DM through reduced intake, altered anatomy, nutrient sensing, bile-acid and incretin changes and weight-dependent and weight-independent mechanisms. Human studies show substantial microbiome change after surgery, but microbial composition can remain abnormal and is influenced by diet, anatomy and medication [61].

Transfer of microbiota from gastric-bypass-treated mice reduced adiposity in recipient mice, supporting a contributory mechanism in that model [62]. Long-term human cohort data associate postsurgical microbiome changes with fat-mass regulation but do not prove independent mediation [63]. Clinical eligibility should follow obesity and diabetes guidelines, not a stool profile [64]. It is not currently possible to reproduce the established benefits of surgery by a probiotic or FMT.

**Metformin, Acarbose and Berberine: Direct Actions versus Microbial Mediation:** Metformin lowers glucose through established hepatic and intestinal actions and can also alter the gut environment. In treatment-naive T2DM, randomized and mechanistic human work showed microbiome changes and supported a partial contribution to therapeutic effects [65]. Cross-sectional studies must account for metformin because its microbial signature can be mistaken for a disease signature [66]. Associations with increased *A. muciniphila* or SCFA-producing taxa and changes in bile acids or incretin-related pathways are plausible mediators, not proof that the microbiome is the primary mechanism [67, 68]. Gastrointestinal adverse effects may also involve gut exposure and microbial interactions.

Acarbose directly and reversibly inhibits intestinal alpha-glucosidases and delays carbohydrate absorption. More carbohydrate therefore reaches the colon, secondarily changing fermentation, microbial composition and bile-acid profiles.

Human stratification data suggest that baseline microbiota may modify response, but glycaemic benefit should not be attributed solely to microbial change [69]. Berberine has direct molecular and intestinal effects as well as microbiota-related hypotheses. Rat studies show microbial remodeling during prevention of diet-induced obesity and insulin resistance but cannot establish human efficacy [70]. In the 409-participant PREMOTE trial, berberine alone or with probiotics lowered HbA1c more than placebo or probiotics alone over 12 weeks; the design, antibiotic run-in and gastrointestinal adverse effects limit attribution of benefit to microbiota mediation [71].

Pharmacomicrobiomic biomarkers are promising for predicting response, but none of these drugs should be selected or withheld on the basis of a commercial stool test.

**TABLE 2: MICROBIOTA-TARGETED INTERVENTIONS: PRODUCT SPECIFICITY, POTENTIAL BENEFIT, LIMITATIONS AND SAFETY**

| Intervention | Product-specific evidence | Potential clinical role | Limitations and safety | Ref. |
|---|---|---|---|---|
| Food-based fibre/prebiotics | Effects differ by substrate and dose; 10 g/day inulin-propionate ester reduced weight gain in one 24-week trial. | Guideline-consistent dietary adjunct; may improve satiety or selected glycaemic markers. | Bloating and altered bowel habit; engineered products cannot be generalized to all fibre. | 42,43 |
| Conventional probiotics | Evidence must match strain, count, matrix, dose and endpoint. | Possible small adjunctive effect on fasting glucose, HbA1c or HOMA-IR. | Heterogeneous trials; viability/storage and contamination; caution in severely immunocompromised or critically ill patients. | 45,50 |
| Synbiotics | Defined microorganism-substrate combinations; complementary and synergistic products are distinct. | Investigational adjunct where the tested combination has human evidence. | Combination-specific; cannot infer superiority over either component. | 46 |
| Pasteurized *A. muciniphila* | Specific preparations studied at 1 × 10^10 cells/day for 3 months or daily after weight loss for 24 weeks. | Promising adjunct/investigational strategy for selected adults. | Small or selected populations; no therapeutic approval for obesity/T2DM. | 19, 20, 22 |
| Live *A. muciniphila* | AKK-WST01 once daily for 12 weeks; no overall benefit, exploratory response at low baseline abundance. | Investigational; potential biomarker-defined response needs confirmation. | Live and pasteurized products are not interchangeable. | 21 |
| FMT | Small RCTs show engraftment with inconsistent, often short-lived insulin-sensitivity effects. | Research intervention only for obesity/T2DM. | Infection transmission, donor screening, durability and regulatory oversight. | 53, 55, 57, 58 |

FMT, fecal microbiota transplantation; HbA1c, glycated haemoglobin; HOMA-IR, homeostatic model assessment of insulin resistance; RCT, randomized controlled trial; T2DM, type 2 diabetes mellitus.

**Biomarkers and Analytical Limitations:** Candidate features include gene richness, butyrate-producing taxa, *A. muciniphila* abundance, microbial pathways, bile-acid profiles and circulating or fecal metabolites.

None has a validated universal clinical cutoff for diagnosing obesity, T2DM or treatment response. Technical variation arises from stool collection, storage, DNA extraction, sequencing platform, bioinformatic pipeline and compositional statistics. Biological variation arises from diet, geography, age, bowel transit, antibiotics and other medication. Repeated association does not make an individual taxon a causal biomarker.

Commercial microbiome reports should therefore not be used to prescribe probiotics, stop medication or determine eligibility for surgery or FMT. Multi-omic markers may be valuable in prospectively validated trials [72, 73].

**TABLE 3: CANDIDATE MICROBIOTA-RELATED BIOMARKERS AND THEIR PRESENT CLINICAL STATUS**

| Candidate marker | Reported evidence | Sources of variability | Present clinical status | Ref. |
|---|---|---|---|---|
| Microbial gene richness | Often lower with adiposity and inflammation; can change with diet. | Population, sequencing and dietary exposure. | Research measure; no diagnostic or treatment cutoff. | 10, 26 |
| Butyrate-producing taxa | Often reduced in T2DM cohorts. | Taxonomic redundancy; production differs from fecal concentration. | Hypothesis-generating; not a stand-alone probiotic prescription marker. | 11, 12 |
| *A. muciniphila* abundance | Associations plus baseline-dependent response signals. | Strain, assay, diet, metformin exposure and baseline abundance. | Not validated for routine treatment selection. | 67, 21, 20 |
| SCFA profile | Mechanistic and intervention links with gut hormones and metabolism. | Molecule, sample compartment, absorption, route and disease state. | Research endpoint; high value is not uniformly beneficial. | 27, 30, 31 |
| Bile-acid profile | Changes after drugs or surgery and links with FXR/TGR5 pathways. | Species, tissue, enterohepatic cycling, drugs and anatomy. | Potential stratification marker; not standard care. | 34, 69 |
| LPS/barrier markers | Experimental link to inflammation and insulin resistance. | Assay performance, meals, obesity and systemic inflammation. | No validated microbiota-treatment threshold. | 14, 16 |

FXR, farnesoid X receptor; LPS, lipopolysaccharide; SCFA, short-chain fatty acid; T2DM, type 2 diabetes mellitus; TGR5, Takeda G-protein-coupled receptor 5.

**TABLE 4: COMPARATIVE SUMMARY OF MAJOR HUMAN CLINICAL STUDIES OF MICROBIOTA-DIRECTED METABOLIC INTERVENTIONS**

| Study/ population | Intervention/ product | Dose | Duration | Sample | Metabolic endpoints | Principal findings | Main limitations |
|---|---|---|---|---|---|---|---|
| Depommier *et al*., overweight/obesity with insulin resistance | Live or pasteurized *A. muciniphila* vs placebo | 1 × 10^10 cells/day | 3 months | 40 randomized; 32 completed | Insulin sensitivity, weight, lipids, safety | Pasteurized product improved insulin sensitivity and selected measures; live product did not reproduce all effects [19] | Exploratory, small, short, surrogate endpoints. |
| Mount *et al*., after ≥8% diet-induced weight loss | Pasteurized *A. muciniphila* MucT vs placebo | Daily trial formulation | 24 weeks after 8-week low-energy diet | 90 randomized | Weight regain, body composition, safety | Mean regain 1.2 ± 0.7 vs 3.2 ± 0.4 kg; no related serious adverse event [20] | Selected responders to initial diet; short maintenance; commercial involvement. |
| Zhang *et al.*, drug-naive T2DM with overweight/obesity | Live *A. muciniphila* AKK-WST01 vs placebo | Once-daily trial formulation | 12 weeks | 58 randomized | Glycaemia, insulin resistance, adiposity, colonization | No significant overall between-group benefit; exploratory improvement in low-baseline subgroup [21] | Small; subgroup finding; strain dose not stated in abstract. |
| Chambers *et al.*, adults with overweight | Inulin-propionate ester vs inulin control | 10 g/day | 24 weeks | 60 randomized | Weight gain, adiposity, appetite | Reduced weight gain and intra-abdominal fat accumulation [42] | Single centre; targeted compound not equivalent to usual food fibre. |
| Ejtahed *et al.*, adults with T2DM | Yogurt with L. acidophilus La-5 + *B. animalis* subsp. lactis | 300 g/day; ≥10^6 CFU/g of each strain | 6 weeks | 60 randomized | Fasting glucose, HbA1c, antioxidant markers | Improved fasting glucose and antioxidant status; no basis for class-wide claims [52] | Short; surrogate endpoints; yogurt matrix. |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | Bb-12 | | | | | | |
| Vrieze *et al.*, men with metabolic syndrome | Lean-donor vs autologous intestinal microbiota transfer | Single duodenal infusion | 6 weeks | 18 randomized | Peripheral/hepatic insulin sensitivity | Lean-donor transfer increased insulin sensitivity at 6 weeks [53] | Very small, men only, invasive route, uncertain durability. |
| Yu *et al.* FMT-TRIM, adults with obesity | Lean-donor FMT capsules vs placebo | Weekly oral capsules | 6 weeks; follow-up to 12 weeks | 24 randomized | Weight, insulin sensitivity, composition | Engraftment without significant improvement in major metabolic outcomes [55] | Pilot size, short follow-up, donor/product variability. |
| Mocanu *et al.*, severe obesity/metabolic syndrome | Oral FMT ± low-fermentable fibre | Single FMT; fibre daily | 6 weeks | 70 randomized | HOMA2-IR and microbial engraftment | Only FMT plus low-fermentable fibre improved HOMA2-IR at 6 weeks [57] | Short, surrogate endpoint; combined intervention limits attribution. |
| PREMOTE, newly diagnosed T2DM | Berberine, probiotics, combination or placebo after antibiotic run-in | Protocol-defined oral products | 12 weeks | 409 randomized | HbA1c, lipids, microbiome, adverse events | Berberine arms lowered HbA1c; probiotics alone did not establish comparable benefit [71] | Antibiotic run-in; GI adverse effects; direct vs microbial effects cannot be separated. |

CFU, colony-forming units; FMT, fecal microbiota transplantation; GI, gastrointestinal; HbA1c, glycated haemoglobin; HOMA2-IR, updated homeostatic model assessment of insulin resistance; T2DM, type 2 diabetes mellitus. Where a complete cell dose was not available in the accessible report, the wording is deliberately limited to the published regimen.

**Cautious Clinical Perspective:** Current evidence does not support a prescriptive microbiome-treatment algorithm. Clinical management should follow established guidelines: nutritionally adequate dietary intervention, physical activity, sleep and behavioural support; evidence-based glucose- and weight-lowering medicines selected for glycaemic, cardiovascular, kidney and weight goals; and metabolic surgery for eligible patients [64, 74]. A diverse, fibre-rich dietary pattern may be recommended for its overall health value and can influence microbial function. A named probiotic or synbiotic may be considered only as an adjunct when its exact formulation has relevant human evidence, quality documentation and acceptable safety. Expected benefits should be described as small and uncertain. Clinicians should review gastrointestinal disease, immune status, central venous access, recent antibiotics and concurrent medicines before recommending a live microbial supplement. Product identity, viable count at end of shelf life, storage, batch quality, adverse effects and stop criteria should be documented. Weight, waist circumference, HbA1c, glucose, lipids, medication use and patient-reported tolerability are more clinically meaningful than a change in relative abundance. FMT, engineered organisms and unapproved live biotherapeutic products should remain within regulated research. No routine stool sequencing panel currently determines which diet, probiotic, drug or surgical procedure a patient should receive.

**Safety, Regulation and Implementation Limits:** The safety profile depends on the intervention. Food-based fibre commonly causes dose-related bloating and stool changes. Live probiotics require accurate identification and manufacturing controls; sporadic invasive infections are most relevant in vulnerable hosts. Postbiotics and pasteurized preparations avoid replication but still require product-specific toxicology and efficacy data. Novel-food authorization addresses defined conditions of food use and does not establish treatment efficacy. FMT carries the broadest biological exposure and requires donor screening, traceability and infection surveillance [45, 22, 60]. Antibiotic exposure, proton-pump inhibitors, metformin and other drugs can alter microbiota and confound both research and clinical interpretation. Probiotics do not necessarily restore an individual's pre-antibiotic community and, in one controlled study, delayed mucosal reconstitution compared with spontaneous recovery [75].

Long-term ecological effects, horizontal gene transfer, antimicrobial resistance and durability require monitoring for next-generation products. Regulatory terminology should be precise: food or supplement, novel food, live biotherapeutic product, biologic and approved medicine are not interchangeable categories.

**Emerging and Investigational Directions:** Artificial-intelligence models that integrate diet, metagenomics, metabolomics and clinical data may help generate response predictions, but they require external validation, transparent performance reporting and protection against demographic or geographic bias. Engineered microbes, defined consortia and metabolite-delivery systems may improve product control, yet containment, gene stability and long-term safety remain unresolved. Postbiotics may offer greater storage stability than live products, although benefits must be demonstrated for each preparation. Personalized microbiota therapy based on baseline abundance, functional genes or metabolite profiles is biologically plausible and supported by exploratory responder analyses, but it remains investigational. Future trials should preregister strain or product identity, genome-level characterization, dose, viability or inactivation method, storage, diet and medication control, colonization or exposure, adverse events and clinically meaningful outcomes. Longer studies should compare any microbiota adjunct with contemporary standard care and determine whether effects persist after treatment.

**CONCLUSION:** Gut microbial functions are biologically connected with intestinal barrier integrity, inflammation, SCFAs, bile acids, appetite signals and drug exposure. The strongest human evidence supports a cautious conclusion: food-based fibre and certain defined prebiotic, probiotic or synbiotic products can be useful adjuncts, but average improvements in weight or glycaemia are generally small and heterogeneous. Preparation-specific trials of pasteurized *A. muciniphila* are encouraging, whereas live-strain results are not uniformly positive and protein-based evidence remains preclinical. FMT produces engraftment but has inconsistent and often transient metabolic effects, carries infection-transmission risk and is experimental for obesity and T2DM. Microbiota changes after metabolic surgery, metformin, acarbose and berberine may contribute to response but do not independently explain their established clinical effects. Standard lifestyle, pharmacological and surgical care should remain primary. Progress will require adequately powered, longer randomized trials with defined strain or product, dose, manufacturing quality, safety surveillance, hard metabolic endpoints and prospective validation of responder biomarkers.

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