Heritage Journal of Health Sciences and Research
Volume 1, Issue 2, July–December 2026 | Open Access | Peer Reviewed
Das A. Heritage J Health Sci Res. 2026;1(2):28-31
Received: 15-09-2026 | Accepted: 10-10-2026 | Published: 06-11-2026
Research Article | Heritage J Health Sci Res

Exploring the Role of Gut Microbiome Diversity in the Development of Metabolic Disorders: A Clinical and Molecular Perspective

Dr. Arjun Das [1*]
[1] Department of Medical Biotechnology, Institute of Biomedical Research, Visakhapatnam, India

Abstract

Reduced gut microbiome diversity is consistently associated with obesity, type 2 diabetes (T2D), non-alcoholic fatty liver disease (NAFLD) and cardiovascular disease, and animal and human transfer studies indicate that this relationship is partly causal. The human gut harbours roughly 38 trillion bacterial cells encoding more than 150 times as many genes as the human genome, making it a metabolic organ in its own right. This review synthesises clinical and molecular evidence on how microbial community structure shapes host metabolism. We examine four principal mechanisms: altered energy harvest and short-chain fatty acid (SCFA) signalling, metabolic endotoxaemia driven by lipopolysaccharide (LPS) and intestinal barrier failure, disrupted bile acid signalling through FXR and TGR5 receptors, and the production of pro-atherogenic metabolites such as trimethylamine N-oxide (TMAO). We then review clinical findings across the major metabolic disorders and evaluate emerging interventions, including dietary fibre, probiotics and next-generation probiotics such as *Akkermansia muciniphila*, faecal microbiota transplantation (FMT) and drug–microbiome interactions. Finally, we discuss methodological limitations and the prospects for microbiome-informed precision medicine.

Keywords: gut microbiome, dysbiosis, alpha diversity, obesity, type 2 diabetes, NAFLD, short-chain fatty acids, metabolic endotoxaemia, bile acids, TMAO

Introduction

Metabolic disorders now rank among the leading causes of morbidity and mortality worldwide. Obesity affects over a billion people, and T2D, NAFLD and atherosclerotic cardiovascular disease frequently cluster together as components of metabolic syndrome. Genetics, caloric excess and physical inactivity explain much of this burden, yet they do not fully account for the wide variation in disease risk between individuals with similar lifestyles.

Over the past two decades, the gut microbiome has emerged as an important missing variable. Early work by Ley and colleagues[1] showed that genetically obese *ob/ob* mice carried a different ratio of Firmicutes to Bacteroidetes than their lean littermates. Turnbaugh et al.[2] then demonstrated that the obese microbiome harvested more energy from the diet and that this trait could be transferred to germ-free mice. These findings shifted the microbiome from a passive bystander to an active participant in host metabolism.

Subsequent large-scale metagenomic projects, including MetaHIT and the Human Microbiome Project, revealed that *diversity* itself, rather than any single organism, is a key marker of metabolic health. This paper reviews the clinical and molecular evidence linking microbial diversity to metabolic disease, with the aim of clarifying what is known, what remains uncertain, and how this knowledge may be translated into therapy.

Gut Microbiome Composition and Diversity

The adult gut microbiota is dominated by two bacterial phyla, Bacillota (formerly Firmicutes) and Bacteroidota (formerly Bacteroidetes), with smaller contributions from Actinomycetota, Pseudomonadota and Verrucomicrobiota. Archaea, fungi and bacteriophages complete the ecosystem. Community composition is shaped by mode of birth, infant feeding, diet, antibiotic exposure, geography and age.

Microbial diversity is usually described at two levels. **Alpha diversity** measures richness and evenness within one individual, commonly using the Shannon index or observed species counts. **Beta diversity** measures how different two communities are from each other, using metrics such as Bray–Curtis dissimilarity or UniFrac distance. Profiling relies on 16S rRNA gene sequencing for taxonomic surveys and shotgun metagenomics for species-level and functional resolution.

A healthy microbiome is not defined by one fixed composition. Instead, it is characterised by high diversity, functional redundancy and resilience, meaning the community can resist and recover from disturbances. Le Chatelier et al.[6] studied 292 Danish adults and found that about 23% had low bacterial gene richness. These “low gene count” individuals showed greater overall adiposity, insulin resistance, dyslipidaemia and a more pronounced inflammatory phenotype than high gene count individuals. Low diversity therefore appears to mark a fragile ecosystem that is less able to support metabolic homeostasis.

Molecular Mechanisms Linking Dysbiosis to Metabolic Disease

Energy harvest and short-chain fatty acids

Gut bacteria ferment dietary fibre that human enzymes cannot digest, producing the SCFAs acetate, propionate and butyrate. SCFAs supply roughly 5–10% of daily energy needs and act as signalling molecules. They bind the G-protein-coupled receptors GPR41 (FFAR3) and GPR43 (FFAR2) on enteroendocrine L-cells, stimulating release of glucagon-like peptide-1 (GLP-1) and peptide YY (PYY). These hormones enhance insulin secretion, slow gastric emptying and promote satiety.

Butyrate is the main fuel for colonocytes and strengthens the epithelial barrier by upregulating tight junction proteins. Propionate contributes to intestinal gluconeogenesis, which signals satiety through a gut–brain neural circuit. Low-diversity microbiomes are often depleted of butyrate producers such as *Faecalibacterium*

prausnitzii, *Roseburia* and *Eubacterium rectale*. Paradoxically, an obesity-associated microbiome may still extract more total calories from food, as Turnbaugh et al.[2] showed, so the SCFA balance and context matter more than total output.

Metabolic endotoxaemia and the leaky gut

Lipopolysaccharide is a component of the outer membrane of Gram-negative bacteria. Cani et al.[3] showed that a high-fat diet raised plasma LPS two- to three-fold in mice, a state they termed *metabolic endotoxaemia*. Infusing LPS at similar levels reproduced weight gain, insulin resistance and hepatic fat accumulation.

Mechanistically, dysbiosis and dietary fat reduce mucus thickness and tight junction integrity. LPS then crosses the epithelium, often carried within chylomicrons, and activates Toll-like receptor 4 (TLR4) with its co-receptor CD14 on macrophages and adipocytes. This triggers NF-κB and JNK signalling and releases TNF-α and IL-6. These cytokines impair insulin receptor substrate (IRS-1) phosphorylation, producing the low-grade chronic inflammation that underlies insulin resistance.

Bile acid signalling

Primary bile acids synthesised in the liver are converted by gut bacteria into secondary bile acids through deconjugation by bile salt hydrolases and 7α-dehydroxylation. Bile acids act as hormones through two main receptors. The nuclear receptor FXR regulates bile acid synthesis, lipid metabolism and glucose homeostasis in the liver and intestine. The membrane receptor TGR5 stimulates GLP-1 secretion and increases energy expenditure in brown adipose tissue. Dysbiosis alters the size and composition of the bile acid pool, disturbing both pathways and contributing to hepatic steatosis and impaired glucose control.

Microbial metabolites: TMAO, BCAAs and imidazole propionate

Some microbial metabolites are directly harmful. Gut bacteria convert dietary choline, phosphatidylcholine and L-carnitine (abundant in red meat and eggs) into trimethylamine, which the liver oxidises to TMAO. Koeth et al.[9] linked elevated TMAO to accelerated atherosclerosis and higher cardiovascular event risk. Pedersen et al.[14] found that *Prevotella copri* and *Bacteroides vulgatus* drive elevated circulating branched-chain amino acids (BCAAs), which correlate with insulin resistance. Koh et al.[17] identified imidazole propionate, a microbial histidine metabolite, as a molecule that directly impairs insulin signalling via mTORC1.

Table 1: Summary of mechanisms

Mechanism	Key molecules	Host target	Metabolic effect
SCFA signalling	Acetate, propionate, butyrate	GPR41, GPR43; colonocytes	GLP-1/PYY release, satiety, barrier integrity
Metabolic endotoxaemia	LPS	TLR4/CD14, NF-κB	Chronic inflammation, insulin resistance
Bile acid signalling	Secondary bile acids	FXR, TGR5	Glucose and lipid regulation, energy expenditure
Harmful metabolites	TMAO, BCAAs, imidazole propionate	Platelets, endothelium, mTORC1	Atherosclerosis, impaired insulin signalling

Clinical Evidence Across Metabolic Disorders

Obesity

Human studies broadly confirm reduced alpha diversity in obesity, although the Firmicutes-to-Bacteroidetes ratio has proven an inconsistent marker across cohorts. The most compelling causal evidence comes from Ridaura et al.[8], who colonised germ-free mice with faecal microbiota from human twin pairs discordant for obesity. Mice receiving the obese twin's microbiota gained more fat mass. When the two groups were co-housed, bacteria from the lean donor invaded the obese-donor mice and prevented weight gain, but only when the animals ate a low-fat, high-fibre diet.

Type 2 diabetes

Metagenome-wide association studies in Chinese[4] and European[7] cohorts found that T2D is associated with a depletion of butyrate-producing bacteria and an enrichment of opportunistic pathogens and oxidative-stress pathways. A major confounder was later identified: metformin. Forslund et al.[11] and Wu et al.[15] showed that metformin itself reshapes the microbiome, increasing *Escherichia* and *Akkermansia* and SCFA production. Transferring metformin-altered microbiota to germ-free mice improved glucose tolerance, suggesting that part of the drug's effect is microbially mediated.

Non-alcoholic fatty liver disease

The liver receives about 70% of its blood supply from the gut via the portal vein, so it is the first organ exposed to microbial products. NAFLD, now increasingly termed metabolic dysfunction-associated steatotic liver disease (MASLD), is linked to small intestinal bacterial overgrowth, increased gut permeability and raised LPS levels. Loomba et al.[16] developed a stool-metagenome signature that distinguished advanced fibrosis from mild disease with good accuracy. Some bacteria, such as high-alcohol-producing *Klebsiella pneumoniae*, may even generate endogenous ethanol that drives liver injury[20].

Cardiovascular disease

Elevated plasma TMAO predicts major adverse cardiovascular events independently of traditional risk factors. TMAO enhances platelet reactivity, promotes foam cell formation and impairs reverse cholesterol transport. Dysbiosis-associated inflammation and altered bile acid metabolism further contribute to dyslipidaemia and endothelial dysfunction.

Table 2: Summary of clinical associations

Disorder	Typical microbial changes	Representative study
Obesity	Lower alpha diversity, low gene richness, increased energy harvest	Ridaura et al., 2013
Type 2 diabetes	Fewer butyrate producers, more opportunistic pathogens; metformin confounding	Qin et al., 2012; Forslund et al., 2015

Disorder	Typical microbial changes	Representative study
NAFLD / MASLD	Increased permeability, LPS, Proteobacteria; endogenous ethanol	Loomba et al., 2017
Cardiovascular disease	TMAO-producing taxa, inflammatory profile	Koeth et al., 2013

Therapeutic Interventions Targeting the Microbiome

Diet. Diet is the most powerful and accessible modulator of the microbiome. High-fibre diets rich in fermentable polysaccharides increase SCFA production and diversity, whereas Western diets high in fat, sugar and emulsifiers reduce both. Zhao et al.[18] showed that a high-fibre diet in T2D patients selectively promoted SCFA producers and improved HbA1c. Zeevi et al.[12] found that post-meal glucose responses to identical foods varied widely between people and could be predicted using microbiome data, supporting personalised nutrition.

Probiotics, prebiotics and synbiotics. Conventional probiotics such as *Lactobacillus* and *Bifidobacterium* strains have shown modest and inconsistent metabolic benefits in trials. Prebiotics such as inulin and fructo-oligosaccharides selectively feed beneficial bacteria. Next-generation probiotics are more promising. In a randomised proof-of-concept trial, Depommier et al.[19] found that pasteurised *Akkermansia muciniphila* improved insulin sensitivity and reduced total cholesterol in overweight, insulin-resistant volunteers.

Faecal microbiota transplantation. Vrieze et al.[5] transferred faecal microbiota from lean donors to men with metabolic syndrome and observed improved peripheral insulin sensitivity at six weeks, together with a rise in butyrate-producing bacteria. However, the benefits were transient and varied with the recipient's baseline microbiome, and FMT for metabolic disease remains experimental.

Drug–microbiome interactions. Metformin, acarbose and GLP-1 receptor agonists all alter the microbiome, and the microbiome in turn affects drug metabolism and response. Non-nutritive sweeteners may also matter: Suez et al.[10] reported that saccharin induced glucose intolerance in mice through microbiome changes, and later human work confirmed person-specific effects. Understanding these two-way interactions could improve drug selection and dosing.

Challenges and Future Directions

Despite rapid progress, several obstacles limit clinical translation:

- **Causality versus correlation.** Most human data are cross-sectional. Metabolic disease, diet and medication all change the microbiome, so reverse causation is hard to exclude.
- **Confounding.** Drugs such as metformin and proton pump inhibitors, plus diet, alcohol and stool consistency, strongly shape microbial profiles and must be adjusted for.
- **Methodological variation.** Differences in sample collection, DNA extraction, sequencing platforms and bioinformatic pipelines make cross-study comparison difficult.
- **Population bias.** Most cohorts come from Western, high-income countries. Populations in South Asia, Africa and Latin America, which have distinct diets and rising metabolic disease rates, remain under-studied.
- **Mouse-to-human gaps.** Germ-free mouse models are invaluable but differ from humans in anatomy, diet and immune development.

Future research should prioritise longitudinal cohorts, integrated multi-omics combining metagenomics, metabolomics and host genetics, and machine-learning models that predict individual responses. Engineered bacteria, defined bacterial consortia and postbiotics such as purified microbial metabolites offer more controlled alternatives to FMT. Mendelian randomisation studies can also help separate causal microbial effects from confounded associations.

Conclusion

Gut microbiome diversity is a meaningful indicator of metabolic health, and its loss contributes to obesity, T2D, NAFLD and cardiovascular disease through defined molecular pathways. These include reduced SCFA signalling, LPS-driven inflammation, disrupted bile acid signalling and the production of harmful metabolites such as TMAO. Transfer experiments in animals and early FMT trials in humans support a partly causal role. Translating this knowledge into routine care will require rigorous longitudinal studies, standardised methods and more diverse study populations. Diet remains the most practical tool available today, while next-generation probiotics and microbiome-guided precision medicine represent promising directions for preventing and treating metabolic disease.

References

1. Ley RE, Bäckhed F, Turnbaugh P, Lozupone CA, Knight RD, Gordon JI. Obesity alters gut microbial ecology. Proc Natl Acad Sci USA. 2005;102(31):11070–11075.
2. Turnbaugh PJ, Ley RE, Mahowald MA, Magrini V, Mardis ER, Gordon JI. An obesity-associated gut microbiome with increased capacity for energy harvest. Nature. 2006;444(7122):1027–1031.
3. Cani PD, Amar J, Iglesias MA, et al. Metabolic endotoxemia initiates obesity and insulin resistance. Diabetes. 2007;56(7):1761–1772.
4. Qin J, Li Y, Cai Z, et al. A metagenome-wide association study of gut microbiota in type 2 diabetes. Nature. 2012;490(7418):55–60.
5. Vrieze A, Van Nood E, Holleman F, et al. Transfer of intestinal microbiota from lean donors increases insulin sensitivity in individuals with metabolic syndrome. Gastroenterology. 2012;143(4):913–916.
6. Le Chatelier E, Nielsen T, Qin J, et al. Richness of human gut microbiome correlates with metabolic markers. Nature. 2013;500(7464):541–546.
7. Karlsson FH, Tremaroli V, Nookaew I, et al. Gut metagenome in European women with normal, impaired and diabetic glucose control. Nature. 2013;498(7452):99–103.
8. Ridaura VK, Faith JJ, Rey FE, et al. Gut microbiota from twins discordant for obesity modulate metabolism in mice. Science. 2013;341(6150):1241214.
9. Koeth RA, Wang Z, Levison BS, et al. Intestinal microbiota metabolism of L-carnitine, a nutrient in red meat, promotes atherosclerosis. Nat Med. 2013;19(5):576–585.
10. Suez J, Korem T, Zeevi D, et al. Artificial sweeteners induce glucose intolerance by altering the gut microbiota. Nature. 2014;514(7521):181–186.
11. Forslund K, Hildebrand F, Nielsen T, et al. Disentangling type 2 diabetes and metformin treatment signatures in the human gut microbiota. Nature. 2015;528(7581):262–266.
12. Zeevi D, Korem T, Zmora N, et al. Personalized nutrition by prediction of glycemic responses. Cell. 2015;163(5):1079–1094.
13. Sender R, Fuchs S, Milo R. Revised estimates for the number of human and bacteria cells in the body. PLoS Biol. 2016;14(8):e1002533.

14. Pedersen HK, Gudmundsdottir V, Nielsen HB, et al. Human gut microbes impact host serum metabolome and insulin sensitivity. Nature. 2016;535(7612):376–381.
15. Wu H, Esteve E, Tremaroli V, et al. Metformin alters the gut microbiome of individuals with treatment-naive type 2 diabetes, contributing to the therapeutic effects of the drug. Nat Med. 2017;23(7):850–858.
16. Loomba R, Seguritan V, Li W, et al. Gut microbiome-based metagenomic signature for non-invasive detection of advanced fibrosis in human nonalcoholic fatty liver disease. Cell Metab. 2017;25(5):1054–1062.
17. Koh A, Molinaro A, Ståhlman M, et al. Microbially produced imidazole propionate impairs insulin signaling through mTORC1. Cell. 2018;175(4):947–961.
18. Zhao L, Zhang F, Ding X, et al. Gut bacteria selectively promoted by dietary fibers alleviate type 2 diabetes. Science. 2018;359(6380):1151–1156.
19. Depommier C, Everard A, Druart C, et al. Supplementation with *Akkermansia muciniphila* in overweight and obese human volunteers: a proof-of-concept exploratory study. Nat Med. 2019;25(7):1096–1103.
20. Yuan J, Chen C, Cui J, et al. Fatty liver disease caused by high-alcohol-producing *Klebsiella pneumoniae*. Cell Metab. 2019;30(4):675–688.