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Gut microbiota and insulin resistance - mechanisms and clinical evidence: A review of biological mechanisms, as well as observational and interventional evidence

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ABSTRACT

Background: Changes in the composition and function of the gut microbiota are associated with metabolic disorders, including lowered insulin sensitivity. Simple insulin resistance indices, such as HOMA-IR and TyG, are commonly used in population studies. *Objective*: A synthetic presentation of the evidence linking the gut microbiota with insulin resistance, as well as a discussion of biological mechanisms and clinical implications. *Methods*: This is a narrative review that includes observational and cohort studies, mechanistic studies, and microbiota-modulating interventions (e.g., supplementation, fecal transplants, and dietary interventions). Studies investigating the relationships between the microbiota profile, metabolome, and HOMA-IR and TyG values were included. *Results*: Various studies have shown a consistent association between specific changes in the microbiome and higher HOMA-IR and TyG values. Research has also suggested that microbial metabolites can cause insulin resistance, disrupted gut barrier function, and/or endotoxemia. Preliminary microbiota-modulating interventions show improvements in metabolic parameters; however, most trials are small and short-term. *Conclusions*: An integrated analysis of insulin resistance and its connections to the microbiota and metabolome can help clarify mechanisms and identify possible therapeutic targets. Further long-term studies are needed.

Keywords: gut microbiota; insulin resistance; HOMA-IR; TyG index; metabolomics; fecal microbiota transplantation.

1. INTRODUCTION

Insulin resistance, a metabolic disorder associated with type 2 diabetes and metabolic syndrome, is characterized by an inadequate tissue response to insulin that results in elevated levels of insulin in the blood, disturbances in carbohydrate

metabolism, increased risk for developing cardiovascular disease (Lee et al., 2023; Peplies et al., 2016; Simental-Mendía et al., 2008; Taheri et al., 2020) and multiple factors contributing to the risk include visceral obesity, chronic inflammation, poor nutrition, and family history of this disorder (Al-Mrabeh, 2020). The processes underlying these phenomena, however, remain incompletely understood (Crudele et al., 2023; Peplies et al., 2016; Salas-Salvadó et al., 2011).

As research develops, there is growing evidence that gut microbiota influence metabolism through the production of short-chain fatty acids and other bioactive elements found in food. The gut microbiota interacts with the immune system and plays an important role in maintaining the integrity of the intestinal barrier. Gut microbiota also modulate gut-liver signalling, which plays an important role in lipid metabolism and glucose metabolism. There are differences in how microbiota function that are related, but not yet understood, to overweight or obese people and reduced insulin sensitivity (Crudele et al., 2023; Deng et al., 2022; Tilg et al., 2020). The research suggests that a diet high in endotoxins (such as lipopolysaccharide) can trigger an inflammatory response that ultimately leads to insulin resistance (Cani et al., 2008). Some interventions modulating the microbiota — nutritional modifications, probiotic therapy, or fecal microbiota transplantation (FMT) — have optimized metabolic parameters in selected studies. However, their results remain heterogeneous (Chambers et al., 2019; Depommier et al., 2019; Vrieze et al., 2012).

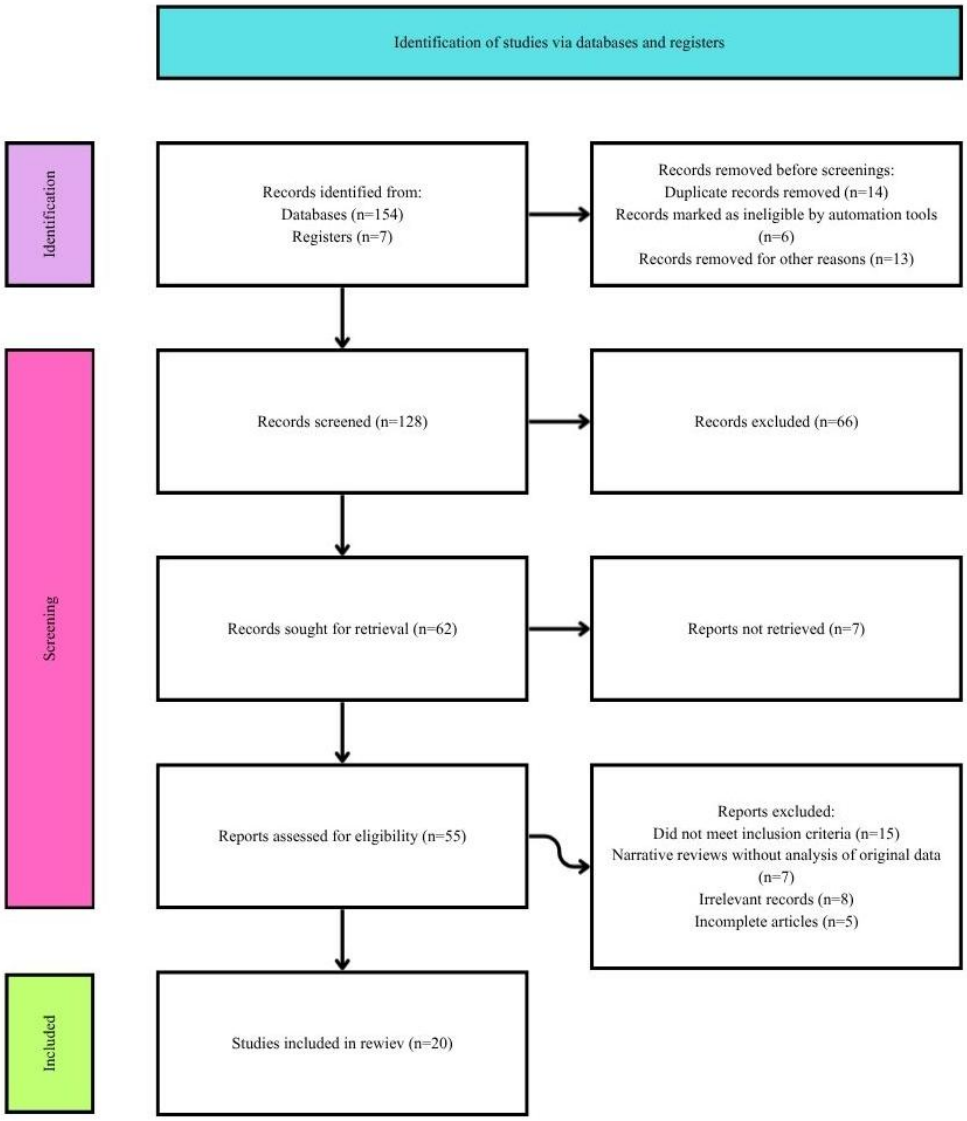

Figure 1. Flow chart

Comparisons of microbiota profiles in individuals with and without type 2 diabetes reveal differences in microbiota composition (Larsen et al., 2010; Zhang et al., 2013). However, it is still unclear which of these changes are causal. Also unknown are the correlations

between specific metabolic microbiota & metabolites & simple insulin resistance indices [homeostasis model assessment of insulin resistance (HOMA-IR)] and triglyceride/glucose index (TyG), and what types of interventions alter these permanently. Most published studies have been either observational or small-sample; thus, it is difficult to conclude the cause of the findings (Chambers et al., 2019; Deng et al., 2022; Vrieze et al., 2012; Zhang et al., 2013).

This review focuses on clinical and translational studies linking the microbiota and metabolome profile with HOMA-IR and TyG, and on evaluating potential biological mechanisms and therapeutic implications.

2. REVIEW METHODS

The review has a narrative and thematic character. It included observational studies, randomized controlled trials, clinical interventions, and translational studies that addressed the relationship of the gut microbiota or metabolome with insulin resistance indices (HOMA-IR, TyG) in adults. We determined that this article would include only studies that met these criteria: reviewed previously published literature (not case reports or reviews that had significant new data), were not studies of children, and reported on metabolic outcomes. We searched the following electronic sources using the years 2000 through June 2025: PubMed, MEDLINE, Embase, Scopus, ScienceDirect, and Web of Science (across its many subdomains) to identify additional articles. We identified other articles relevant to our criteria from the reference lists of key articles across different electronic database sources.

We conducted the article selection in two stages: in the first, we evaluated titles and abstracts for compliance with the inclusion criteria; in the second, we analyzed the full texts of the selected papers. We placed each selected piece of literature into distinct thematic groups (i.e., microbiota–HOMA–IR correlations, microbiota-modulating interventions, and translational studies). We then evaluated these data using a qualitative thematic synthesis. We did not conduct a quantitative meta-analysis. The results of the thematic synthesis included the following categories: observational evidence, intervention study results, proposed biological mechanisms, and limitations and gaps in the research demanding further investigation. In the end, we compiled 20 relevant articles that provide the most compelling clinical evidence to support our argument (Figure 1).

3. RESULTS AND DISCUSSION

The Gut Microbiota and Metabolism — Current State of Knowledge

Differences in the Microbiota in Healthy Individuals and Those with Glycemic Disorders

Comparative studies show reproducible changes in the microbiota composition in individuals with glycemic disorders. In many studies, patients with type 2 diabetes had lower microbiota diversity and a lower proportion of bacteria producing short-chain fatty acids (SCFAs). An increase in taxa associated with pro-inflammatory signals was also described. These changes concern both the taxonomic composition and the functional potential of the microbiome (Crudele et al., 2023; Larsen et al., 2010; Zhang et al., 2013).

The decline in microbiota diversity has not been unequivocally established following a review of all studies. There are numerous factors important when evaluating studies examining microbiota diversity, such as methodology, bioinformatics analysis, and sequencing methods. Microbiota changes are known to occur in conjunction with both increased visceral fat and metabolomic alterations in certain cohorts. Therefore, establishing the direction of causation can prove difficult among all variables evaluated (Deng et al., 2022; Zhang et al., 2013).

Mechanisms: Metabolites, Gut Barrier, Inflammation, and Endotoxemia

The impact of gut microbiota on the host's metabolism is partly achieved through the production of metabolites that modulate host metabolism by acting on various systems, including the intestinal barrier. Short-chain fatty acids (butyrate, acetate, and propionate) affect both intestinal cells and the endocrine system. Incretins are regulated by secretion, by their incretin function, and by how they work in both adipose tissue and the liver to support metabolic activity. In addition, insulin sensitivity is a function of the concentration of the biodegradable plate and an individual’s metabolic background (Chambers et al., 2019; Crudele et al., 2023; Pedersen et al., 2016; Tilg et al., 2020).

Dysbiosis can compromise the intestinal barrier's integrity, leading to the translocation of bacterial products (such as lipopolysaccharide, or LPS) into the bloodstream and chronic low-grade inflammation known as metabolic endotoxemia, which is linked to insulin resistance. While it is possible to assess serum LPS levels, there are considerable methodological challenges, and evidence for this link has been variable (Cani et al., 2008; Tilg et al., 2020).

The microbiota may alter the serum metabolome profile. Certain microbial metabolites are correlated with insulin resistance and the development of type 2 diabetes. It has also been shown that functional differences in the microbiome (metabolic pathways) may be equally or more significant than taxonomic changes when metagenomics and metabolomics are studied together (Crudele et al., 2023; Pedersen et al., 2016).

Bidirectional Relationships: Microbiota and Insulin Resistance

The microbiome and our capability to regulate blood sugar levels have a comprehensive relationship with one another. Dysbiosis may lead to or exacerbate metabolic diseases by changing fermentation-derived metabolite production by the microbiota from sugary foods, disrupting the integrity of the gut barrier, and activating an immune response through pro-inflammatory substances. Gut development is usually influenced by metabolic factors, including insulin resistance, visceral obesity (abdominal fat), and changes in bile salt secretion; therefore, other metabolic factors play a role in establishing the community structures and functional attributes of the gut microbiome. However, prospective studies are needed to determine conclusions about the effect (Crudele et al., 2023; Deng et al., 2022; Tilg et al., 2020).

Observational Evidence

Cross-sectional and Cohort Studies

Cross-sectional studies provide abundant evidence of differences in the microbiota composition between healthy individuals and those with glycemic disorders. However, their interpretation remains limited by the lack of a temporal sequence of events and by confounding factors (diet, medications, age, geography).

Longitudinal cohort studies provide better evidence for determining the order of events than alternative methods. Some results indicate that changes in gut bacteria can occur before or during weight gain and/or before and during the loss of glucose tolerance, while other studies show that changes in gut bacteria and in metabolism occur at the same time (Deng et al., 2022; Larsen et al., 2010; Zhang et al., 2013).

Relationships Between Insulin Resistance Indices and the Microbiota

A large body of studies has shown that insulin resistance indices, such as HOMA-IR, are associated with changes in serum metabolites and microbiota composition. While specific taxa and metabolic pathways may be altered by insulin resistance and microbiome dysfunction, correlation does not equal causation, and the influence of diet, medication use, and/or inflammation will affect both the insulin resistance index (HOMA) and the microbiome (Crudele et al., 2023; Lee et al., 2023; Pedersen et al., 2016).

Longitudinal Results: What Comes First?

Longitudinal studies have provided mixed evidence for the relationship between changes in the microbiota and metabolic parameters. For some groups, changes in the microbiota occurred before any decline in metabolic health, suggesting a potential causal relationship. In other groups, the changes in microbiota were evidence of the other way around and were merely a consequence of weight gain or changes in the metabolome. The directionality of the relationship needs more long-term studies that control for confounding variables and can integrate taxonomic and functional data, such as metagenomics and metabolomics (Deng et al., 2022; Zhang et al., 2013).

Interventional Evidence

Akkermansia muciniphila Supplementation

Early clinical studies have established that including Akkermansia muciniphila as a dietary supplement has an impact on metabolic markers among obese and overweight people, including measurements of how well their bodies use insulin (i.e., insulin sensitivity). It should be noted, however, that although these findings appear promising, they were obtained from relatively small, short-term clinical trials; thus, there is still insufficient scientific evidence to assess the long-term effects of adding A. muciniphila to the diet (Depommier et al., 2019). New research indicates that A. muciniphila and other probiotic and prebiotic foods may provide beneficial metabolic outcomes for humans without using A. muciniphila in combination with other types of pro/prebiotic ingredients or as part of a synbiotic food product (Zhu et al., 2026).

Fecal Microbiota Transplants from Lean Donors (FMT)

In some studies, transplants of microbiota from lean donors to recipients with metabolic syndrome improved insulin sensitivity, suggesting that microbiota composition can affect host metabolism. The effect, however, was sometimes transient and depended on the recipient's diet and other surrounding factors, suggesting the need for consistent protocols and longer observation periods (Vrieze et al., 2012).

Dietary Interventions Affecting Microbiota and Insulin Sensitivity

When SCFA substrates are provided as part of an intervention (e.g., prebiotics, inulin-propionate ester), numerous controlled studies have shown improvements in metabolic parameters and insulin sensitivity. Results depend on the amount of intervention, how long it's used, what else is in the person's diet, and how their specific microbiome responds to it (Chambers et al., 2019).

Metformin — Effect on Microbiota and Role as a Confounding Factor

Metformin itself alters microbiota composition and the metabolomic profile. During pharmacotherapy with this drug, increases in the relative abundance of selected taxa (including Akkermansia and some Enterobacteriaceae), changes in bile acid metabolism, and alterations in intestinal metabolite production are observed. These changes may indirectly alter glucose metabolism and inflammation. For this reason, metformin is a significant confounding factor in interventional and observational studies regarding the microbiota. Interpreting the effects involves controlling for drug use (analysis of untreated subgroups, assessment of changes before and after initiating therapy) (Gao et al., 2024; Petakh et al., 2023).

Limitations of Interventional Evidence

There are several limitations to this review, including the sample size of trials being small, short post-intervention follow-up periods, heterogeneity in types of interventions (for example, different FMT protocols and methods of supplying Akkermansia), and several confounding variables, including diet, medications, and other things that may affect the composition of microbiota or the data obtained from measuring metabolomics. The absence of standardized approaches in metagenomics and metabolomics hinders effective comparison between studies. There is still room for improvement in the types of research being conducted and ultimately how results can be compared. Studies moving forward should include larger-scale, randomized clinical trials, as well as long-term data collection with controlled confounding factors (Cani et al., 2008; Depommier et al., 2019; Gao et al., 2024; Petakh et al., 2023; Vrieze et al., 2012; Zhu et al., 2026).

Data Integration — Possible Mechanisms and Models

How Insulin Resistance Indices Connect with the Microbiota and Metabolome

The presence of microbially associated taxonomic and metabolomic signatures indicates that distinct microbiota can give rise to a range of circulating metabolites in serum, including those linked to insulin resistance. Thus, there are plausible microbiome functional pathways that may contribute to the link between microbiota composition and insulin resistance, such as pathways associated with the production of short-chain fatty acids, the metabolism of amino acids with an aromatic side chain, and other functional pathways (Crudele et al., 2023; Pedersen et al., 2016).

Proposed Mediational Models

The proposed explanations for how microbiota affects insulin resistance include: (1) the metabolite model, where the type of microbiota affects the metabolome, which in turn will affect the degree of insulin resistance. (2) The gut barrier model – dysbiosis causes a change to the gut barrier, resulting in excess levels of endotoxin becoming present from the leakage of the intestines. It is thought that this leads to inflammation, which contributes to insulin resistance. (3) The bidirectional model – both insulin resistance and metabolic changes influence the internal environment of the gut, thus further affecting your microbiota. None of these models is mutually exclusive; they can all occur together (Crudele et al., 2023; Deng et al., 2022; Pedersen et al., 2016; Tilg et al., 2020).

Consistency of Data from Observational, Mechanistic, and Interventional Studies

The observational, mechanistic, and interventional data all provide additional evidence; however, the lack of consistency across these three types most likely stems from differences in methods and social forces. Having access to multiple levels of data (i.e., taxonomy,

metagenomics, metabolomics, and clinical phenotype) combined with the use of standardized analytical methods will enable greater verification of mediational models (Crudele et al., 2023; Deng et al., 2022; Pedersen et al., 2016; Zygmunt et al., 2025).

A Synthetic Summary of the Most Important Findings

There is a growing consensus that the gut microbiota participates in regulating glucose metabolism and insulin sensitivity through metabolites, modulation of the gut barrier, and its impact on inflammation. At the same time, the results are heterogeneous, and evidence of causality requires further longitudinal and interventional studies (Depommier et al., 2019; Larsen et al., 2010; Pedersen et al., 2016; Tilg et al., 2020; Vrieze et al., 2012).

Strengths and Weaknesses of the Available Studies

The use of both metagenomic and metabolomic technologies in research and the collaboration on interventional studies demonstrate some of the field's positive aspects. Conversely, there are numerous negative aspects to this area, including small sample sizes, short post-intervention follow-up periods, potential confounding variables from diet and medications (especially metformin), and the possibility of publication bias. One of the greatest limitations in this field is the lack of standardization among microbiome analysis techniques. Multiple methods for DNA extraction and analysis exist, all of which create challenges to comparing research across studies (Crudele et al., 2023; Deng et al., 2022; Gao et al., 2024; Petakh et al., 2023).

Main Knowledge Gaps

Some of the critical areas that currently fall short include: the examination of long-term, properly designed intervention studies, insufficient understanding of how these interventions might function within human populations, and insufficient integration of functional data with taxonomic (i.e., organism) data. Additionally, there is a need for standardized methods to measure LPS and other endotoxemia-related markers (Cani et al., 2008; Deng et al., 2022; Tilg et al., 2020).

Clinical and Scientific Significance

Understanding the role of the microbiota could lead to new preventive and therapeutic methods for glycemic disorders, including targeted dietary, probiotic, or microbiota interventions. However, current evidence does not yet support widespread clinical implementation without further confirmation (Chambers et al., 2019; Depommier et al., 2019; Vrieze et al., 2012).

Directions for Future Research

Research priorities include: (1) large, randomized, long-term interventional trials with medication and diet intervention; (2) studies using the latest profiling methodologies (metagenomics, metatranscriptomics, and metabolomics); (3) mechanistic studies allowing identification of the mediator(s) through which microbiota exert their effects; (4) the establishment of appropriate analytical measurement standards and FMT protocols; (5) the consideration of metformin and other medications, when designing studies. The key findings are mentioned in Table 1.

In future studies, it is also worth using causal methods, such as Mendelian randomization. Such an approach allows a more precise determination of the direction of the relationship between the microbiota and insulin resistance (Crudele et al., 2023; Deng et al., 2022; Gao et al., 2024; Pedersen et al., 2016; Petakh et al., 2023; Zygmunt et al., 2025).

Table 1. Microbiome Interventions and Metabolic Outcomes: Key Trials and Findings.

Study / Intervention	Design	Main outcomes (metric and value)	Key microbiome	Major limitations	Source
Akkermansia muciniphila (pasteurized)	RCT, randomized, double-blind pilot	Insulin sensitivity +28.6% vs placebo; fasting insulin −34.1%	Benefits observed with pasteurized form; no large taxonomic shifts	Small sample; short follow-up; need long-term data	Depommier et al., 2019

Fecal microbiota transplantation (from lean donors)	Randomized allogenic vs autologous infusion	Rate of glucose disappearance 26.2 → 45.3 μmol·kg^{-1}·min^{-1} (6 weeks); effects often transient	Increased butyrate-producing taxa in responders; circulating metabolite changes	Short-lived effect; recipient diet modifies outcome; heterogeneous FMT protocols	Vrieze et al., 2012
Prebiotics / inulin-propionate ester (IPE)	Randomized, double-blind, cross-over	HOMA-2: 1.23±0.17 (IPE) vs 1.59±0.17 (control), p=0.001	Increased propionate delivery; changes in metabolome and inflammatory markers	Small N; short intervention; diet-dependent effects	Chambers et al., 2019
Translational metabolomic analyses	Metagenomics + metabolomics (translational)	Correlations of BCAAs and other metabolites with higher HOMA-IR/TyG	BCAA biosynthesis linked to Prevotella copri, Bacteroides vulgatus; LPS-related pathways implicated	Methodological heterogeneity; needs validation and replication	Pedersen et. al., 2016
Cross-sectional studies	Cross-sectional analyses	Repeated correlations of HOMA-IR/TyG with dysbiosis	Lower α-diversity; fewer SCFA-producing bacteria; increased pro-inflammatory taxa	No temporal sequence; many confounders (diet, medications, geography)	Larsen et. al., 2010; Zhang, 2013
Longitudinal cohorts	Prospective, repeated measures	Identification of taxa associated with HOMA-IR; mixed evidence on directionality	Associations with butyrate-producing pathways (e.g., PWY-5022)	Mixed results; need integration of metagenomics and metabolomics	Deng et al., 2022
Metformin — confounding effect	Prospective cohorts; systematic review	Metabolic improvements; decline in α-diversity by 3 months	Increased *Akkermansia*; shifts in SCFA-producing taxa; functional pathway changes	Metformin is a strong confounder; analyze subgroups off medication	Gao et al., 2024; Petakh et al., 2023

4. CONCLUSION

The gut microbiota influences the host's metabolism through the production of metabolites, modulation of the intestinal barrier, and induction of inflammatory states. The relationships between the gut microbiota and insulin resistance are complex and bidirectional. Early research shows evidence of therapeutic benefit; however, the data are often inconsistent in quality and methodology. Future studies need to have larger sample sizes, be longer, and use a standardized approach that includes both taxonomy and function.

Additionally, controlling confounding variables (e.g., diet, metformin) will also be important in future studies. The results of such studies could enable the formulation of targeted preventive and clinical strategies in glycemic disorders.

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Data and materials availability
All data associated with this study will be available based on the reasonable request to corresponding author.

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