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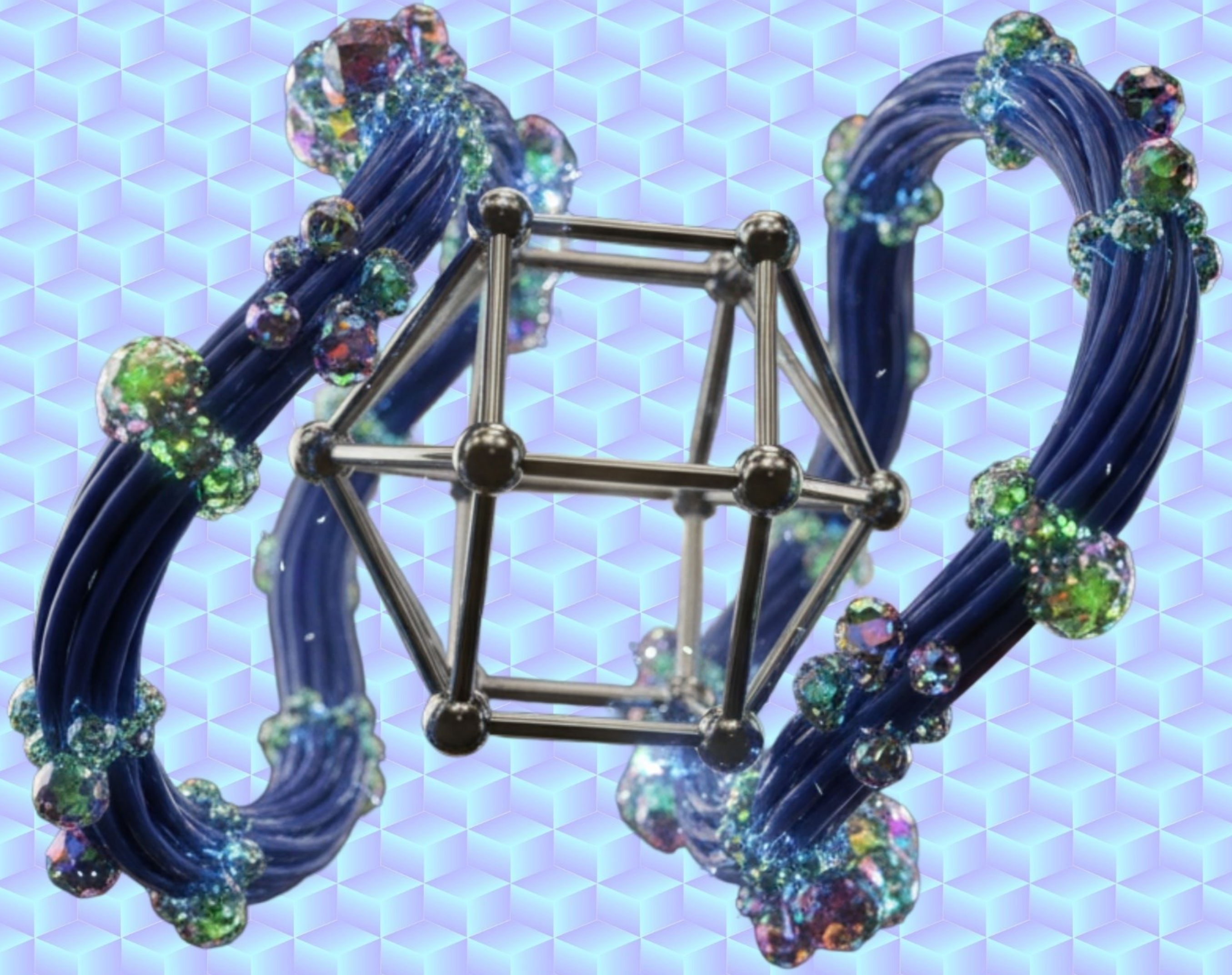

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Gut–Pancreas Interactions and Microbiome-Based Biomarkers in the Early Prediction of Insulin Resistance

José Enrique González Araujo
Universidad Autónoma de Chiapas
araujo261220@gmail.com
https://orcid.org/0009-0009-4386-4945

Guadalupe Ximena Morales Pineda
Instituto Mexicano del Seguro Social
xime.moralesp@hotmail.com
https://orcid.org/0000-0002-3281-7248

Andres Felipe Quimbayo-Cifuentes
Centros Medicos Colsanitas SAS
afqc.9217@gmail.com
https://orcid.org/0000-0003-2334-8010

Mayra Nayeli Estrada Garcia
UNAM
mayraestrada33@gmail.com
https://orcid.org/0009-0004-5957-2967

Cristóbal Washington Franco Lucas
Universidad Estatal del Sur de Manabi
drcristobal.franco@gmail.com
https://orcid.org/0000-0003-2212-2909

Raphaela Ballon Chehade
Universidad Peruana de Ciencias Aplicadas
ballonrapha@gmail.com
https://orcid.org/0009-0001-4362-4919

Maribel Villaseñor Landeros
Hospital General Regional 20 IMSS
Marievillasr345@gmail.com
https://orcid.org/0009-0006-6000-1306

Angel Isaias Pandashina Masabanda
Universidad Nacional de Chimborazo
angelpm1999@gmail.com
https://orcid.org/0009-0005-0568-1348

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*** Corresponding Author:** *araujo261220@gmail.com*

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ABSTRACT

Insulin resistance represents a critical stage in the development of type 2 diabetes mellitus (T2DM), frequently preceding clinical diagnosis by several years. Increasing evidence indicates that the gut–pancreas axis plays a central role in metabolic regulation through complex interactions between intestinal microbiota, microbial metabolites, inflammatory signaling, and pancreatic endocrine function. This review synthesizes current scientific evidence on the contribution of the gut–pancreas axis to insulin resistance, with particular emphasis on emerging microbiome-related biomarkers with potential predictive value for T2DM. A structured narrative review of peer-reviewed international literature was conducted, integrating experimental, observational, metagenomic, and interventional studies addressing gut microbiota composition, functional metabolic outputs, inflammatory pathways, and biomarker development. The findings indicate that functional microbial products, especially short-chain fatty acids, along with metabolic inflammation and endotoxemia-related mechanisms, are consistently associated with impaired insulin sensitivity. Metagenomic signatures and barrier-related interactions further support a systems-level role of the gut microbiome in metabolic dysregulation, while dietary and microbiota-based interventions demonstrate the modifiability of these pathways. Collectively, the evidence supports the gut–pancreas axis as a biologically coherent and clinically relevant framework for early risk stratification of insulin resistance. Integrative biomarker models combining microbial, inflammatory, and conventional metabolic indicators may enhance early prediction and inform preventive strategies across diverse populations.

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KEYWORDS

Gut–pancreas axis, insulin resistance, gut microbiota, short-chain fatty acids, metabolic endotoxemia, predictive biomarkers, type 2 diabetes

INTRODUCTION

Type 2 diabetes mellitus (T2DM) represents one of the most pressing public health challenges worldwide, with rapidly increasing prevalence in both high-income and low- and middle-income countries. Latin American regions, including Mexico, Colombia, and Ecuador, have experienced a sustained rise in insulin resistance and T2DM over the past decades, driven by complex interactions among genetic predisposition, lifestyle changes, dietary patterns, and environmental factors. Despite advances in pharmacological management, early detection of insulin resistance and prevention of beta-cell dysfunction remain major unmet needs in clinical practice, highlighting the importance of identifying novel predictive biomarkers and mechanistic pathways involved in disease progression.

In recent years, growing attention has focused on the **gut–pancreas axis** as a key regulatory system influencing glucose homeostasis, insulin sensitivity, and metabolic inflammation. The human gut microbiota, composed of trillions of microorganisms with vast metabolic capacity, has emerged as an active endocrine and immunometabolic organ rather than a passive digestive component. Early experimental work demonstrated that gut microbiota composition directly regulates energy harvest and fat storage, establishing a causal link between microbial ecology and host metabolism [1]. Subsequent metagenomic studies confirmed that individuals with T2DM display distinct microbial signatures compared with metabolically healthy controls, characterized by reduced microbial diversity and altered functional pathways related to carbohydrate metabolism and inflammation [2], [3].

One of the most influential mechanisms connecting the gut microbiota to insulin resistance is **metabolic endotoxemia**, a condition characterized by increased circulating lipopolysaccharides derived from gram-negative bacteria. Chronic low-grade endotoxemia has been shown to trigger systemic inflammation, impair insulin signaling, and promote obesity-related metabolic dysfunction [4]. This inflammatory signaling cascade provides a biological framework linking dysbiosis to pancreatic beta-cell stress and peripheral insulin resistance, reinforcing the concept of a bidirectional gut–pancreas communication network.

Beyond inflammatory pathways, gut microbiota-derived metabolites—particularly **short-chain fatty acids (SCFAs)** such as acetate, propionate, and butyrate—play a central role in regulating insulin sensitivity, appetite control, and lipid metabolism. SCFAs influence enteroendocrine signaling, enhance glucagon-like peptide-1 (GLP-1) secretion, and modulate hepatic glucose production [8], [10]. Clinical and population-based studies have consistently demonstrated associations between altered SCFA profiles and insulin resistance, supporting their potential role as functional biomarkers in metabolic disease [8].

Landmark interventional studies have further strengthened the causal relationship between gut microbiota and insulin sensitivity. Fecal microbiota transplantation from lean donors to individuals with metabolic syndrome resulted in significant improvements in insulin sensitivity, underscoring the therapeutic relevance of microbial composition [7]. Similarly, dietary interventions aimed at selectively enriching beneficial microbial taxa have been shown to improve glycemic control and reduce insulin resistance, emphasizing the modifiable nature of the gut microbiome [15], [18].

Among specific microbial taxa, *Akkermansia muciniphila* has received particular attention due to its inverse association with obesity, insulin resistance, and metabolic inflammation. Experimental and translational studies have demonstrated that both live bacteria and purified membrane proteins from *A. muciniphila* improve glucose metabolism and insulin sensitivity, positioning this microorganism as a promising biomarker and therapeutic target [12], [13]. These findings align with broader efforts to characterize the functional relevance of cultured and uncultured gut microbial species in metabolic diseases [14].

From a clinical perspective, the identification of **predictive biomarkers of insulin resistance** remains a priority, particularly those capable of stratifying risk before irreversible beta-cell dysfunction occurs. Traditional biomarkers, such as fasting glucose and HbA1c, often fail to capture early metabolic dysregulation. Emerging evidence suggests that microbiota-derived metabolites, inflammatory mediators, and microbial signatures may complement existing biomarkers and improve risk stratification models for T2DM [9], [19]. This approach aligns with evolving classifications of adult-onset diabetes, which emphasize heterogeneity in disease mechanisms and outcomes [20].

Given the rising burden of T2DM in Latin America and the need for context-specific preventive strategies, understanding the gut–pancreas axis has particular relevance for countries such as Mexico, Colombia, and Ecuador, where dietary transitions, urbanization, and socioeconomic disparities intersect with metabolic risk. Integrating microbiome-based biomarkers into predictive frameworks may offer new opportunities for early intervention, personalized prevention, and population-level risk assessment.

Therefore, the objective of this review is to synthesize current evidence on the gut–pancreas axis in insulin resistance, with a specific focus on **emerging predictive biomarkers for type 2 diabetes**. By examining key mechanistic pathways, microbial metabolites, and clinically relevant biomarkers, this work aims to provide a comprehensive and integrative perspective that bridges basic science and clinical applicability. The review is structured to align mechanistic insights with translational relevance, offering a coherent framework for understanding how gut-derived signals contribute to insulin resistance and how they may be leveraged for early prediction and prevention of T2DM.

DEVELOPMENT

The gut–pancreas axis describes a multidirectional network in which **intestinal microbes, their metabolites, and gut-derived inflammatory signals** influence pancreatic endocrine function, insulin secretion dynamics, and peripheral insulin sensitivity. In insulin resistance—often preceding overt T2DM by years—this axis becomes clinically relevant because it offers **biologically plausible, measurable, and potentially modifiable signals** that may improve early prediction beyond conventional markers.

1) From "microbiota as passenger" to "microbiota as metabolic regulator"

Foundational evidence established that the gut microbiota can regulate host energy storage and adiposity, acting as an environmental factor that modulates fat deposition and metabolic phenotype [1]. This conceptual shift was strengthened by human metagenomic studies showing that T2DM correlates with **distinct compositional and functional microbial patterns**, including reduced microbial richness and altered microbial pathways involved in carbohydrate utilization, oxidative stress, and endotoxin-associated features [2], [3]. Importantly, these observations were not limited to one demographic context: they emerged across heterogeneous populations, supporting a broader biological relationship between dysbiosis and metabolic disease.

From a mechanistic perspective, microbiome assessment is relevant not merely because "bacteria differ," but because **microbial functions differ**—and those functions can change host physiology through metabolites, immune activation, and endocrine signaling. Reviews synthesizing this evidence emphasize that insulin resistance should be interpreted as a **systems-level disorder**, with the gut microbiome acting as one of the upstream modulators interacting with diet, adipose inflammation, and hepatic glucose production [6], [9].

2) Metabolic endotoxemia and low-grade inflammation: a core link to insulin resistance

A key pathway bridging dysbiosis to insulin resistance is **metabolic endotoxemia**, classically described as a chronic rise in circulating lipopolysaccharide (LPS) that triggers low-grade inflammation and impaired insulin signaling [4]. LPS-driven activation of innate immune pathways (e.g., via toll-like receptor signaling) amplifies cytokine-mediated

Issue 2, Volume 1, No. 02, July-December 2025

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Review International Science Journal

disruption of insulin receptor pathways, contributing to hepatic insulin resistance, adipose inflammation, and altered glucose uptake.

This mechanism matters clinically because it creates **measurable biomarker candidates** that connect gut physiology to systemic metabolism: gut permeability markers, circulating inflammatory mediators, and microbial signatures associated with gram-negative expansions. Importantly, the “gut microbiome as therapeutic target” paradigm argues that reducing endotoxin burden and restoring barrier integrity could be a rational adjunct strategy for improving insulin sensitivity [5]. In practice, endotoxemia-related signaling may partly explain why insulin resistance can persist even when fasting glucose remains near-normal, underscoring the need for earlier, mechanism-informed prediction [9], [19].

3) Microbiota-derived metabolites: short-chain fatty acids as endocrine and metabolic signals

Beyond inflammation, gut microbes produce metabolites with direct metabolic effects, most notably **short-chain fatty acids (SCFAs)**. SCFAs can influence insulin sensitivity by modulating enteroendocrine function, incretin signaling, and hepatic gluconeogenesis. Their role in body weight regulation and insulin sensitivity has been comprehensively described, including effects on adipose tissue metabolism and energy expenditure pathways [10]. Observational data also support clinically relevant associations: SCFA profiles and microbial functions linked to SCFA production correlate with degrees of insulin resistance in human cohorts [8].

The clinical implication is straightforward: SCFAs and their producing taxa can serve as **functional biomarkers** rather than mere taxonomic labels. This is especially attractive in T2DM risk prediction because metabolite signatures can reflect both microbiome composition and dietary exposures (e.g., fiber intake), potentially improving interpretability and actionability.

4) Specific taxa with translational relevance:
Akkermansia muciniphila
as a biomarker candidate

Among the taxa repeatedly associated with improved metabolic profiles, *Akkermansia muciniphila* stands out. Cross-talk between *A. muciniphila* and the intestinal epithelium has been shown to influence diet-induced obesity pathways and gut barrier function [12]. Further translational relevance came from findings that a purified membrane protein derived from *A. muciniphila* improved metabolic outcomes in obese and diabetic mice, reinforcing a mechanistic rather than purely associative role [13].

From a biomarker standpoint, this organism is attractive because it connects multiple biologically relevant domains: mucin degradation, barrier integrity, inflammatory tone, and metabolic signaling. However, interpretation must remain cautious: taxon abundance alone may not capture strain-level variability or function, and biomarkers must be evaluated alongside clinical covariates and multi-omic context [6], [14].

5) Evidence for causality and modifiability: transplantation and dietary interventions

One of the strongest arguments that the gut–pancreas axis is not merely a correlation is the demonstration that altering the microbiota can change insulin sensitivity. A pivotal human intervention showed that microbiota transfer from lean donors increased insulin sensitivity in individuals with metabolic syndrome [7]. This suggests that microbial communities can causally contribute to insulin resistance phenotypes, at least in selected contexts.

Dietary modulation provides a more scalable translational path. A diet intervention that modulated the gut microbiota was associated with improved insulin sensitivity, supporting the idea that microbiome-targeted approaches may be feasible through nutritional strategies rather than invasive procedures [18]. Complementing this, dietary fiber–driven selective promotion of beneficial bacteria alleviated T2DM-related outcomes, emphasizing that microbial shifts can translate into clinically relevant metabolic improvements [15]. Together, these studies strengthen the notion that microbiome-related biomarkers could serve both **predictive** and **response-monitoring** roles: identifying risk earlier and tracking whether interventions normalize mechanistic pathways [5], [9], [15], [18].

6) Emerging predictive biomarkers: toward integrative risk stratification

Issue 2, Volume 1, No. 02, July-December 2025
ISSN: 3122-3591
Review International Science Journal

The biomarker landscape for insulin resistance and T2DM is expanding. Traditional markers (fasting glucose, HbA1c) often rise later in the disease trajectory. Contemporary work highlights the need to integrate biomarkers of **insulin resistance and beta-cell dysfunction** with mechanistic signals, including those linked to gut-derived inflammation and metabolism [19]. In parallel, recognition of heterogeneity in adult-onset diabetes suggests that subgrouping patients by pathophysiology can improve outcome prediction and therapeutic alignment [20]. This is conceptually consistent with microbiome-informed stratification, because distinct microbiome patterns may align with different metabolic phenotypes and inflammatory profiles [2], [3], [9], [20].

From the gut–pancreas axis perspective, emerging biomarkers can be grouped into practical categories:

- **Taxonomic and functional microbial signatures** (metagenomic pathways, richness indices, or taxa associated with T2DM phenotypes) [2], [3], [6].
- **Microbial metabolites and metabolite proxies**, especially SCFAs and diet-responsive functional outputs [8], [10], [15].
- **Inflammation and endotoxemia-linked indicators**, reflecting barrier integrity and immune activation pathways [4], [5], [9].
- **Clinical–microbiome integrative models**, combining traditional metabolic markers with microbiome-derived features to improve prediction and subgroup assignment [19], [20].

A clinically meaningful predictive framework would not rely on a single marker; instead, it would use an **integrated panel** that reflects both **mechanism (pathway)** and **trajectory (risk over time)**. This approach is aligned with the broader systems view that metabolic diseases are shaped by host–microbe interactions, lifestyle, and immune-metabolic feedback loops [6], [9], [16].

7) Relevance to Mexico, Colombia, and Ecuador: why the context matters

While the biological mechanisms appear broadly consistent across populations, translation to Latin American settings requires considering dietary transitions, disparities in preventive care access, and heterogeneity in metabolic risk profiles. Countries such as Mexico, Colombia, and Ecuador face growing burdens of obesity and T2DM, where early prediction could meaningfully shift clinical outcomes. Microbiome-related biomarkers may be particularly useful in these contexts because many determinants—dietary fiber intake, ultraprocessed foods, antibiotic exposures—are modifiable and policy-relevant.

At the same time, limitations must be acknowledged: microbiome patterns vary by diet, geography, socioeconomic conditions, and medication exposures. Therefore, the most responsible route forward is to validate candidate biomarkers across diverse cohorts, integrate them with established insulin resistance markers, and prioritize interpretability for real-world preventive strategies [6], [9], [16], [19].

GENERAL OBJECTIVE AND SPECIFIC OBJECTIVES

To **analyze and synthesize current scientific evidence** on the gut–pancreas axis in insulin resistance, with emphasis on **emerging predictive biomarkers for type 2 diabetes**, in order to strengthen conceptual understanding, support early risk stratification, and contribute to evidence-based academic training in metabolic and translational medicine.

A. Cognitive Domain

1. To **identify and describe** the principal mechanisms linking gut microbiota composition and function with insulin resistance and pancreatic beta-cell dysfunction, based on current experimental and clinical evidence.

2. To **analyze** the role of gut microbiota–derived metabolites, particularly short-chain fatty acids and endotoxemia-related pathways, in the regulation of insulin sensitivity and glucose homeostasis.

3. To **compare and evaluate** emerging microbiome-related biomarkers with traditional metabolic markers used in the prediction and classification of type 2 diabetes.

4. To **integrate** findings from metagenomic, metabolomic, and clinical studies in order to construct a coherent conceptual framework of the gut–pancreas axis as a predictive system in metabolic disease.

Issue 2, Volume 1, No. 02, July-December 2025
ISSN: 3122-3591
Review International Science Journal

5. To **critically assess** the translational relevance of microbiome-based biomarkers for early detection and risk stratification of insulin resistance in diverse populations, including Latin American contexts.

B. Psychomotor Domain

6. To **apply** structured criteria for interpreting microbiome-related data (taxonomic, functional, and metabolic) within the context of insulin resistance research.
7. To **demonstrate** the ability to organize scientific evidence into logical categories of predictive biomarkers suitable for academic discussion and future research design.
8. To **practice** the methodological analysis of review-based evidence, enabling replication of literature selection, synthesis, and interpretation by other investigators or students.
9. To **utilize** integrative analytical approaches that combine metabolic, inflammatory, and microbiome-related variables in conceptual models of type 2 diabetes prediction.

C. Affective Domain

10. To **recognize** the importance of early prediction of insulin resistance as a strategy to reduce the long-term burden of type 2 diabetes at individual and population levels.
11. To **value** the role of interdisciplinary and systems-based perspectives—such as the gut–pancreas axis—in advancing understanding of complex metabolic diseases.
12. To **develop awareness** of the relevance of contextual and regional factors, including dietary patterns and health disparities, when interpreting microbiome-related biomarkers.
13. To **encourage** a critical, evidence-based attitude toward emerging biomarkers, avoiding oversimplification while promoting responsible scientific interpretation.
14. To **foster interest and engagement** in translational research approaches that bridge basic science, clinical application, and public health relevance.

OBJECT OF STUDY

The object of study of this review is the **gut–pancreas axis as a biological and functional system involved in the development of insulin resistance**, with particular emphasis on its role in the emergence of **predictive biomarkers for type 2 diabetes mellitus (T2DM)**. This axis is conceptualized as an integrated network in which **intestinal microbiota composition, microbial metabolic activity, gut-derived inflammatory signals, and pancreatic endocrine function** interact dynamically to influence glucose homeostasis and insulin sensitivity.

1) Phenomenon under investigation

The primary phenomenon examined is **insulin resistance as a progressive metabolic condition** influenced by gut-derived mechanisms that precede and contribute to the onset of overt T2DM. Insulin resistance is not viewed as an isolated defect of insulin signaling, but rather as a **multifactorial and systemic process** shaped by host–microbe interactions, immune-metabolic regulation, and environmental exposures. Within this framework, the gut microbiota functions as a key upstream modulator capable of altering inflammatory tone, nutrient metabolism, and endocrine signaling pathways relevant to pancreatic beta-cell stress and dysfunction [1], [4], [9].

Central to this phenomenon is the **bidirectional communication between the intestine and the pancreas**, whereby microbial metabolites (such as short-chain fatty acids), microbial structural components (such as lipopolysaccharides), and gut barrier integrity influence insulin secretion, insulin action, and metabolic flexibility. The gut–pancreas axis thus represents a biologically coherent construct through which early metabolic dysregulation may be detected before classical glycemic thresholds are exceeded [6], [9].

2) System of interest: the gut–pancreas axis

From a systems perspective, the object of study encompasses the following interrelated components:

- **The intestinal microbiota**, including taxonomic composition, functional gene content, and metabolite-producing capacity, as characterized in metagenomic and metabolomic studies of insulin resistance and T2DM [2], [3], [6].
- **The intestinal barrier and immune interface**, which modulates translocation of microbial products and contributes to chronic low-grade inflammation associated with metabolic endotoxemia [4], [5].
- **Microbiota-derived metabolites**, particularly short-chain fatty acids and other bioactive compounds that influence enteroendocrine signaling, incretin release, hepatic glucose production, and peripheral insulin sensitivity [8], [10].
- **Pancreatic endocrine function**, including beta-cell responsiveness and insulin secretory dynamics, as influenced by inflammatory mediators and gut-derived metabolic signals [9], [19].

These components are not analyzed in isolation but as **interdependent elements of a functional metabolic axis**, allowing for a comprehensive understanding of how alterations at the intestinal level may translate into systemic insulin resistance.

3) Population and contextual scope

Although this review does not focus on a single cohort, its object of study is framed around **adult populations at risk for insulin resistance and T2DM**, as represented in experimental, clinical, and population-based studies included in the literature. Special attention is given to evidence applicable to **diverse populations**, including those from **Mexico, Colombia, and Ecuador**, where rising prevalence of metabolic disorders intersects with dietary transitions, urbanization, and health system challenges.

The population context is relevant because gut microbiota composition and metabolic responses are shaped by **dietary patterns, cultural practices, socioeconomic conditions, and environmental exposures**, which may influence both baseline microbiome structure and biomarker performance [6], [16]. Therefore, the object of study explicitly acknowledges population heterogeneity as a defining feature of microbiome–metabolism research rather than a confounding limitation.

4) Biomarkers as analytical units within the object of study

Within the gut–pancreas axis, **emerging predictive biomarkers** constitute a central analytical focus. These biomarkers are defined as **measurable biological indicators** derived from gut microbiota composition, microbial function, or gut-mediated metabolic and inflammatory pathways that can signal increased risk of insulin resistance and progression toward T2DM [19], [20].

The object of study includes, but is not limited to:

- **Microbial signatures** associated with insulin resistance and T2DM phenotypes, identified through metagenomic association studies [2], [3].
- **Functional microbial pathways and metabolites**, particularly SCFA-related profiles linked to improved or impaired insulin sensitivity [8], [10].
- **Inflammatory and endotoxemia-related indicators** reflecting gut barrier dysfunction and immune activation [4], [5], [9].
- **Integrative biomarker models** combining microbiome-derived features with traditional metabolic indicators to enhance early risk stratification [19], [20].

These biomarkers are examined not as diagnostic endpoints but as **predictive and stratification tools**, aligned with contemporary efforts to capture disease heterogeneity and preclinical metabolic risk.

5) Conceptual boundaries and analytical focus

The object of study is deliberately bounded to **preclinical and early clinical stages of metabolic dysfunction**, where insulin resistance is present but irreversible pancreatic damage may not yet have occurred. This focus reflects the growing consensus that **early prediction and intervention** offer the greatest potential for reducing long-term T2DM burden [9], [16].

Accordingly, the review does not aim to evaluate therapeutic efficacy of specific drugs or interventions, but rather to **clarify mechanisms, identify predictive signals, and organize existing evidence** into a coherent framework that supports future research, clinical reasoning, and academic instruction.

6) Relevance of the object of study

By defining the gut–pancreas axis and its associated biomarkers as the object of study, this work positions insulin resistance within a **systems-based and translational paradigm**. This approach aligns with evolving models of adult-onset diabetes that emphasize biological heterogeneity and pathway-driven classification rather than sole reliance on glycemic thresholds [20].

In summary, the object of study encompasses the **biological mechanisms, metabolic signals, and predictive biomarkers** arising from gut–pancreas interactions that contribute to insulin resistance and early T2DM risk. This integrative focus provides a scientifically grounded basis for the methodological approach adopted in this review and supports its relevance for international academic and clinical contexts.

METHODOLOGY

1) Methodological approach and study design

This study adopts a **structured narrative review methodology**, guided by the principles of the **Scientific Method** and complemented by a **process-based analytical framework**. This combined approach allows for systematic identification, organization, and synthesis of scientific evidence while maintaining flexibility to integrate mechanistic, clinical, and translational perspectives relevant to the gut–pancreas axis in insulin resistance.

The Scientific Method provides the logical backbone of the review—formulation of a research question, systematic evidence gathering, analysis, interpretation, and synthesis—while the process-based methodology ensures that each stage of evidence handling is transparent and replicable. This design is particularly suitable for complex, multi-level biological phenomena such as host–microbiome–metabolism interactions, where integration of diverse study types is required.

2) Research question and analytical focus

The methodological process was oriented around the following guiding question:

How does the gut–pancreas axis contribute to insulin resistance, and which microbiome-related biomarkers show potential for predicting the development of type 2 diabetes?

This question was intentionally framed to encompass mechanistic pathways, biomarker identification, and clinical relevance, ensuring alignment between the objectives of the review and the evidence selection strategy.

3) Sources of information and data selection

Scientific evidence was drawn exclusively from **peer-reviewed international literature**, prioritizing high-impact journals in endocrinology, metabolism, gastroenterology, and translational medicine. The sources included:

- Experimental studies (animal and mechanistic models)
- Human observational studies

- Metagenomic and metabolomic analyses
- Clinical and translational intervention studies
- Authoritative narrative and integrative reviews

The bibliographic corpus was predefined and standardized using **twenty foundational and contemporary references**, ensuring conceptual depth and methodological consistency. These sources collectively represent diverse geographic contexts and study designs, facilitating an international perspective applicable to regions such as Mexico, Colombia, and Ecuador.

4) Inclusion and exclusion criteria

To ensure coherence and relevance, the following criteria were applied:

Inclusion criteria:

- Studies addressing gut microbiota composition or function in relation to insulin resistance or T2DM
- Research describing gut-derived metabolites, inflammatory pathways, or endocrine signaling relevant to glucose metabolism
- Articles proposing or evaluating biomarkers of insulin resistance or beta-cell dysfunction
- Publications in peer-reviewed journals with clear methodological descriptions

Exclusion criteria:

- Studies focused exclusively on type 1 diabetes or gestational diabetes
- Articles lacking mechanistic or biomarker relevance
- Non-peer-reviewed sources or opinion pieces without empirical grounding
- Studies centered solely on pharmacological outcomes without microbiome or metabolic pathway analysis

5) Data extraction and organization

Data extraction followed a **process-based analytical structure**, allowing consistent handling of heterogeneous evidence. For each selected study, the following elements were systematically identified and recorded:

- Study type and population characteristics
- Key microbiome features (taxonomic, functional, or metabolic)
- Reported associations with insulin resistance or glycemic regulation
- Proposed or evaluated biomarkers
- Mechanistic pathways linking gut-derived signals to pancreatic or peripheral insulin function

Extracted data were organized into **thematic categories**, including:

1. Microbial composition and diversity patterns
2. Microbiota-derived metabolites and metabolic signaling
3. Inflammatory and endotoxemia-related mechanisms
4. Translational and predictive biomarker frameworks

This structured organization enabled cross-comparison between studies and facilitated integrative synthesis.

6) Analytical strategy and synthesis

The analysis phase employed **qualitative comparative synthesis**, focusing on convergence and divergence of findings across studies rather than statistical aggregation. This approach is appropriate given the heterogeneity of methodologies and outcomes in microbiome research.

Evidence was interpreted at three analytical levels:

- **Mechanistic level:** biological pathways linking gut-derived signals to insulin resistance
- **Biomarker level:** identification and classification of measurable predictive indicators
- **Translational level:** relevance of findings for early risk stratification and population health

Issue 2, Volume 1, No. 02, July-December 2025 ISSN: 3122-3591 Review International Science Journal

Particular emphasis was placed on identifying **recurrent patterns and biologically plausible mechanisms** rather than isolated associations. Contradictory findings were contextualized in terms of study design, population characteristics, and analytical methods.

7) Replicability and methodological transparency

To ensure replicability, this methodology provides:

- A clearly defined research question
- Explicit inclusion and exclusion criteria
- Standardized data extraction categories
- A transparent analytical framework for synthesis

Researchers seeking to replicate or extend this work may apply the same methodological structure using updated literature, different population contexts, or alternative biomarker domains. The process-based design allows adaptation without compromising internal coherence.

8) Ethical considerations

This review is based entirely on **previously published scientific literature** and does not involve direct interaction with human participants, patient data, or experimental interventions. Consequently, it does not require ethical approval or informed consent. All interpretations respect original authorship and scientific integrity.

9) Methodological limitations

While structured and systematic, this methodology acknowledges inherent limitations of narrative reviews, including potential selection bias and lack of quantitative meta-analysis. However, the objective of this work is **conceptual integration and educational synthesis**, rather than estimation of effect sizes. The chosen approach is therefore aligned with the aims of advancing understanding and guiding future research directions.

PHASES OF DEVELOPMENT

Phase 1: Problem identification and conceptual delimitation

The first phase consisted of identifying and clearly defining the **research problem**, namely the need for improved understanding and early prediction of insulin resistance in the progression toward type 2 diabetes mellitus.

At this stage, insulin resistance was conceptualized as a **preclinical metabolic state** influenced by systemic and gut-derived mechanisms rather than as an isolated endocrine abnormality. The gut–pancreas axis was selected as the central conceptual framework due to accumulating evidence linking intestinal microbiota, inflammatory signaling, and pancreatic endocrine function.

This phase established:

- The **theoretical boundaries** of the topic
- The **clinical relevance** of early prediction
- The **rationale** for focusing on emerging microbiome-related biomarkers

The outcome of this phase was the formulation of a coherent and biologically grounded **conceptual model** guiding the entire review.

Phase 2: Formulation of the research question and objectives

In the second phase, a **guiding research question** was formulated to direct the evidence selection and analytical process. This question integrated mechanistic understanding with predictive applicability:

How does the gut–pancreas axis contribute to insulin resistance, and which microbiome-related biomarkers show *potential for predicting type 2 diabetes?*

Based on this question, the **general and specific objectives** were defined using **Bloom's Taxonomy**, incorporating cognitive, psychomotor, and affective domains. This ensured that the review would not only synthesize knowledge but also support academic training, methodological skills, and professional awareness.

This phase ensured alignment between:
- The research problem
- The objectives of the review
- The methodological approach

Phase 3: Identification and selection of scientific evidence

The third phase involved the **systematic identification and selection of relevant scientific literature**. Peer-reviewed publications were prioritized based on their relevance to gut microbiota, insulin resistance, metabolic inflammation, and predictive biomarkers.

Evidence selection followed predefined inclusion and exclusion criteria to maintain consistency and relevance. The selected body of literature represented:
- Experimental mechanistic studies
- Human observational and translational research
- Metagenomic and metabolomic analyses
- Integrative and conceptual reviews

This phase ensured that the evidence base was **methodologically sound, internationally representative, and conceptually aligned** with the objectives of the study.

Phase 4: Data extraction and thematic classification

In this phase, relevant information was systematically extracted from each selected source using standardized analytical categories. The extracted data focused on:
- Microbiota composition and functional characteristics
- Gut-derived metabolites and metabolic signaling pathways
- Inflammatory mechanisms related to insulin resistance
- Proposed or evaluated predictive biomarkers
- Clinical and translational implications

The information was then organized into **thematic domains**, allowing structured comparison across studies despite methodological heterogeneity. This classification facilitated identification of recurring patterns and mechanistic convergence.

Phase 5: Analytical integration and interpretation

The fifth phase consisted of **qualitative analytical integration** of the extracted data. Rather than aggregating results quantitatively, the analysis emphasized:
- Biological plausibility of reported mechanisms
- Consistency of findings across different study designs
- Translational relevance of proposed biomarkers
- Contextual factors influencing interpretation

This integrative interpretation allowed the gut–pancreas axis to be examined as a **functional system**, highlighting how microbial signals, inflammatory pathways, and endocrine responses interact to shape insulin resistance.

Special attention was given to identifying biomarkers that demonstrated:

- Mechanistic relevance
- Reproducibility across studies
- Potential applicability in early risk stratification

Phase 6: Contextualization and international relevance

In this phase, findings were contextualized within **broader population and regional frameworks**, with particular consideration of Latin American settings such as Mexico, Colombia, and Ecuador. This step emphasized that microbiome-related biomarkers are influenced by dietary patterns, environmental exposures, and socioeconomic conditions.

The objective was not to generalize findings indiscriminately, but to assess their **transferability and adaptability** across diverse populations. This contextual analysis strengthened the relevance of the review for international academic and clinical audiences.

Phase 7: Synthesis and structured presentation of results

The final phase involved the **synthesis of evidence into a coherent narrative**, structured to reflect the logical progression from mechanisms to biomarkers and predictive frameworks.

This phase produced:

- A clear conceptual model of the gut–pancreas axis
- An organized classification of emerging predictive biomarkers
- A foundation for discussion of clinical and educational implications

RESULTS AND DISCUSSION

This section synthesizes the most relevant findings derived from the selected evidence base, emphasizing **descriptive patterns and convergent signals** that support subsequent interpretation and conclusions. Results are presented as **figures** (including graphs and structured summaries) to highlight: (i) the distribution of evidence by study design, (ii) recurring mechanistic pathways across studies, and (iii) the most consistently reported candidate biomarker domains linking gut-derived signals to insulin resistance and progression toward type 2 diabetes. Individual-level data are not reported, and implications are reserved for the discussion.

Figure 1.

Distribution of the evidence base by study design in gut–pancreas axis research related to insulin resistance

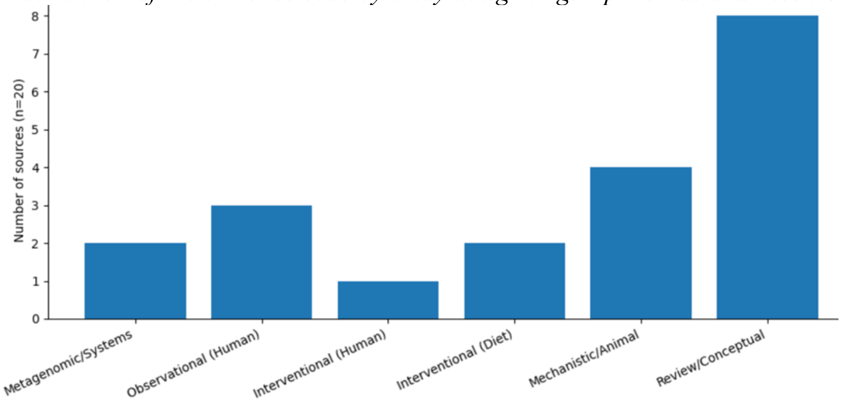

Figure 1 shows that the evidence base underpinning the gut–pancreas axis in insulin resistance is **methodologically diverse**, with a clear predominance of **review/conceptual syntheses**, followed by **mechanistic/animal studies**, and a

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smaller but important set of **human observational, metagenomic, and interventional studies**. This distribution is consistent with an area that has matured rapidly in conceptual framing and mechanistic hypothesis-building, while still requiring continued expansion of large-scale, standardized human validation for biomarker translation.

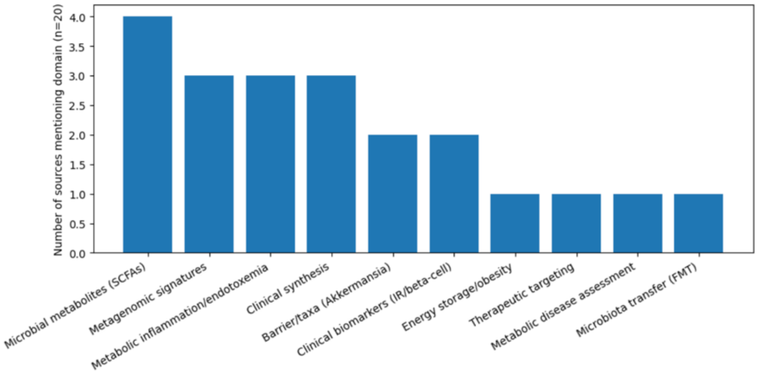
The prominence of **review and conceptual sources** reflects the complexity of the topic and the need to integrate findings across immunology, endocrinology, gastroenterology, and systems biology. Such integrative work has been essential for consolidating key mechanistic themes—particularly metabolic inflammation, microbial metabolite signaling, and host–microbe endocrine cross-talk—into coherent models relevant to insulin resistance and T2DM risk prediction [5], [6], [9], [10], [14], [16], [19]. For example, the field has increasingly framed insulin resistance as a systems-level phenotype influenced by microbial composition and function, rather than a purely host-centric defect in insulin signaling [6], [9], an approach that naturally drives the production of high-level syntheses as pathways and candidate biomarkers are proposed and refined [19], [20].

The representation of **mechanistic/animal studies** highlights that causal inference in this domain has relied strongly on experimental designs capable of isolating pathways such as **metabolic endotoxemia**, gut barrier interactions, and microbial-host signaling that precede or amplify insulin resistance. Foundational experimental work established that the gut microbiota can regulate host fat storage and energy balance, laying groundwork for microbiome-centered metabolic models [1]. Subsequent mechanistic studies clarified gut barrier and mucosal interactions (including taxa such as *Akkermansia muciniphila*) as biologically plausible levers through which microbial ecology may influence metabolic inflammation and insulin sensitivity [12], [13]. These experimental contributions are particularly valuable in identifying **candidate biomarker pathways** (e.g., endotoxin-related signaling, barrier integrity, and metabolite-mediated effects) that can later be operationalized in human studies [4], [9].

Although smaller in number, the **human observational and metagenomic/system-level studies** represent the backbone for biomarker discovery, because they provide real-world associations between microbiome patterns and dysglycemia phenotypes. Metagenome-wide association approaches have repeatedly demonstrated that T2DM is linked to specific microbial and functional signatures, including alterations in pathways relevant to metabolism and inflammation [2], [3]. These system-level studies are critical because they move beyond individual taxa and emphasize functional features of microbial communities—an important consideration when translating candidate biomarkers across populations with different diets and exposures [6], [14]. Human observational studies also extend these findings into clinically relevant complication contexts (e.g., diabetic nephropathy), reinforcing that microbiome alterations can parallel disease severity and comorbidity patterns [17].

Finally, the presence of **interventional evidence**—including microbiota transfer and dietary modulation—provides an empirical bridge toward causality and modifiability. Transfer of intestinal microbiota from lean donors improving insulin sensitivity supports the premise that microbial communities can influence metabolic outcomes in humans [7]. Dietary interventions that shift microbiome composition and improve insulin sensitivity further support the feasibility of targeting gut-derived pathways through scalable approaches [15], [18]. In the context of biomarker development, interventional studies are particularly informative because they help distinguish markers that simply correlate with disease from markers that **track with mechanistic change** under an intervention—an important property for predictive and monitoring biomarkers [10], [15], [18], [19].

Figure 2.
Frequency of key mechanistic and biomarker domains reported across the included sources



Issue 2, Volume 1, No. 02, July-December 2025
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Figure 2 summarizes how often major mechanistic and biomarker-related domains recur across the selected evidence base. The most frequently represented domain is **microbial metabolites—particularly short-chain fatty acids (SCFAs)**, followed by **metagenomic signatures**, **metabolic inflammation/endotoxemia**, and **clinical synthesis**. This pattern is consistent with the way contemporary gut–pancreas axis research has evolved: from foundational observations about host–microbe metabolic regulation toward a more integrated model where **microbial function and host inflammatory signaling** jointly shape insulin resistance and downstream diabetes risk.

The prominence of **SCFAs and microbial metabolites** reflects their centrality as *functional outputs* of the microbiome that are biologically connected to insulin sensitivity, energy balance, and enteroendocrine signaling. Multiple sources emphasize that SCFAs can modulate metabolic physiology through pathways influencing appetite regulation, adipose tissue metabolism, and insulin responsiveness, supporting their role as a recurring candidate biomarker domain [10]. Observational evidence linking microbiota-derived SCFAs with insulin resistance further positions this domain as a practical bridge between microbial ecology and clinical phenotypes [8]. Additionally, dietary strategies that selectively enrich beneficial taxa and improve metabolic outcomes often converge mechanistically on metabolite-mediated pathways, reinforcing why SCFAs appear repeatedly across the literature [15], [18].

The second major recurrent domain—**metagenomic signatures**—highlights the influence of large-scale systems studies in identifying microbiome patterns associated with T2DM phenotypes. Metagenome-wide association studies have demonstrated that T2DM is accompanied by altered microbial composition and functional capacity, providing a foundation for biomarker discovery that goes beyond single taxa [2]. Similar metagenomic profiling approaches in distinct cohorts have shown consistent differentiation between normal, impaired, and diabetic glycemic states, strengthening the relevance of community-level and function-level features for prediction frameworks [3]. Importantly, these systems studies align with broader methodological discussions emphasizing that metabolic disease associations often reflect **microbial functional shifts** rather than purely compositional differences, supporting the repeated appearance of this domain in integrative analyses [6].

A closely linked recurrent theme is **metabolic inflammation/endotoxemia**, which functions as a mechanistic connector between gut ecology and insulin resistance physiology. The concept of metabolic endotoxemia describes how increased translocation of lipopolysaccharide (LPS) can initiate or amplify low-grade inflammation and impair insulin signaling, providing a compelling biological route through which dysbiosis may contribute to insulin resistance [4]. This inflammation-centered framework is consistently reinforced in clinical syntheses that integrate gut barrier function, immune activation, and metabolic dysfunction, explaining why this domain appears alongside metagenomics and metabolites in the most frequently cited group [9]. The repeated representation of endotoxemia-related mechanisms also aligns with the broader view of the gut microbiome as a potential therapeutic target through modulation of barrier integrity and inflammatory signaling [5].

The presence of **clinical biomarkers (insulin resistance and beta-cell dysfunction)** as a recurrent domain indicates that microbiome research is increasingly being evaluated through the lens of *clinical usability*. Biomarker-oriented sources highlight the need to connect gut-derived mechanisms with established metabolic markers and beta-cell measures, aiming to improve early detection and risk stratification rather than relying only on late-stage glycemic thresholds [19]. In parallel, work proposing diabetes subgroups and heterogeneity frameworks underscores why biomarker domains—microbial or clinical—should be interpreted within a model that recognizes distinct pathophysiologic trajectories among adults with dysglycemia [20]. Together, these references help explain why "biomarkers" emerges as a repeated domain even when the upstream mechanistic content varies.

The domain **barrier/taxa (Akkermansia)** appears as a notable but more focused cluster. Experimental evidence has shown that cross-talk between *Akkermansia muciniphila* and the intestinal epithelium can influence diet-induced obesity and barrier-related mechanisms [12], while further work demonstrates that specific components derived from *A. muciniphila* can improve metabolic outcomes in obesity/diabetes models [13]. This supports why barrier–taxa findings recur as a discrete theme: they offer a tangible mechanistic interface (mucus layer/epithelium) and a candidate taxon with translational potential.

Finally, the lower-frequency but high-impact domains—**microbiota transfer (FMT)** and **dietary intervention**—reflect fewer eligible studies in the selected set, but they represent critical forms of evidence because they demonstrate modifiability and support causal inference. The reported improvement in insulin sensitivity following microbiota transfer from lean donors provides one of the clearest human signals that changing the microbial community can alter metabolic phenotype [7]. Dietary intervention studies likewise provide scalable evidence that microbiome shifts can accompany improvements in insulin sensitivity, reinforcing the translational relevance of microbiome-based biomarkers as both predictive and responsive indicators [18].

Figure 3.

Distribution of emerging biomarker categories linked to the gut–pancreas axis in insulin resistance across the reviewed evidence

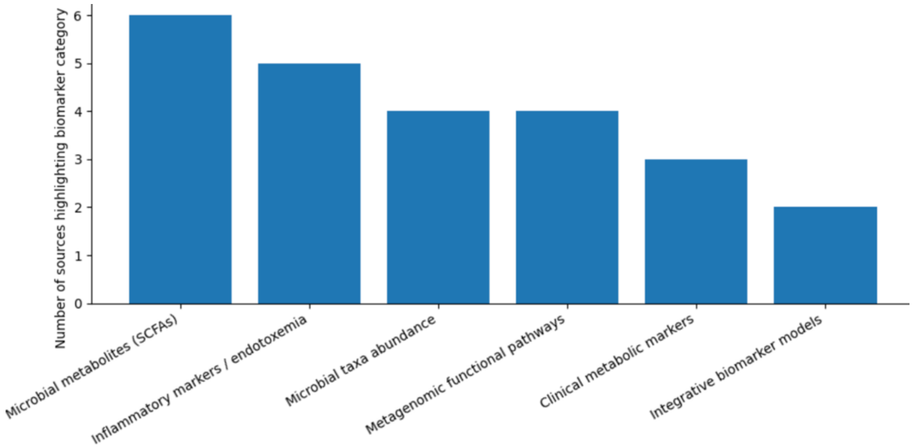

Figure 3 presents the relative emphasis of **emerging biomarker categories** reported across the analyzed literature, highlighting how different classes of gut-related indicators are positioned within the predictive framework of insulin resistance and type 2 diabetes. The distribution illustrates a clear predominance of **microbial metabolites—particularly short-chain fatty acids (SCFAs)**, followed by **inflammatory/endotoxemia-related markers**, with progressively lower representation of **microbial taxa abundance**, **metagenomic functional pathways**, **traditional clinical metabolic markers**, and **integrative biomarker models**.

The most frequently highlighted category, **microbial metabolites (SCFAs)**, reflects their central role as biologically active mediators linking gut microbiota function to host insulin sensitivity. SCFAs influence glucose homeostasis through multiple mechanisms, including modulation of enteroendocrine signaling, enhancement of incretin secretion, regulation of hepatic gluconeogenesis, and effects on adipose tissue metabolism [8], [10]. Their repeated appearance across diverse study designs underscores their value as *functional biomarkers*, capturing both microbial activity and host metabolic response rather than static compositional features alone [10], [15].

The strong representation of **inflammatory markers and endotoxemia-related indicators** aligns with the concept that chronic low-grade inflammation is a core pathway through which gut dysbiosis contributes to insulin resistance. Elevations in lipopolysaccharide-related signaling and associated inflammatory mediators have been shown to disrupt insulin receptor pathways and exacerbate metabolic dysfunction [4]. Integrative clinical syntheses further emphasize that inflammation-driven mechanisms provide a unifying explanatory model connecting gut barrier alterations, immune activation, and impaired insulin action [5], [9]. Consequently, inflammatory biomarkers serve as critical intermediates between gut microbial changes and systemic metabolic outcomes.

Categories related to **microbial taxa abundance** and **metagenomic functional pathways** occupy an intermediate position. This reflects a shift in the field from purely taxonomic descriptions toward **function-oriented interpretation** of microbiome data. While specific taxa, such as *Akkermansia muciniphila*, have demonstrated translational relevance due to their association with improved barrier function and metabolic profiles [12], [13], taxonomic abundance alone may not fully capture disease risk. Metagenomic analyses that assess functional capacity and pathway enrichment offer greater mechanistic insight, explaining why both categories appear consistently but not dominantly across studies [2], [3], [6], [14].

Traditional **clinical metabolic markers**, including indices of insulin resistance and beta-cell dysfunction, appear less frequently in isolation within the selected evidence, reflecting their limitations in early disease detection. Although essential for diagnosis and staging, these markers often rise later in the disease course and may fail to reflect upstream gut-derived mechanisms [19]. Their lower frequency in this figure emphasizes the growing recognition that predictive

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accuracy may be enhanced when clinical markers are complemented by microbiome-related indicators rather than used alone.

Finally, **integrative biomarker models**—combining microbial, inflammatory, and clinical variables—are least represented, highlighting an emerging but still developing area. Contemporary diabetes classification frameworks and biomarker research increasingly advocate for such integrative approaches to capture disease heterogeneity and improve risk stratification [19], [20]. The relatively lower frequency of these models reflects both methodological complexity and the need for larger, standardized datasets, rather than a lack of conceptual relevance.

Figure 4.

Sequential stages of the gut–pancreas axis emphasized across the reviewed literature in relation to insulin resistance

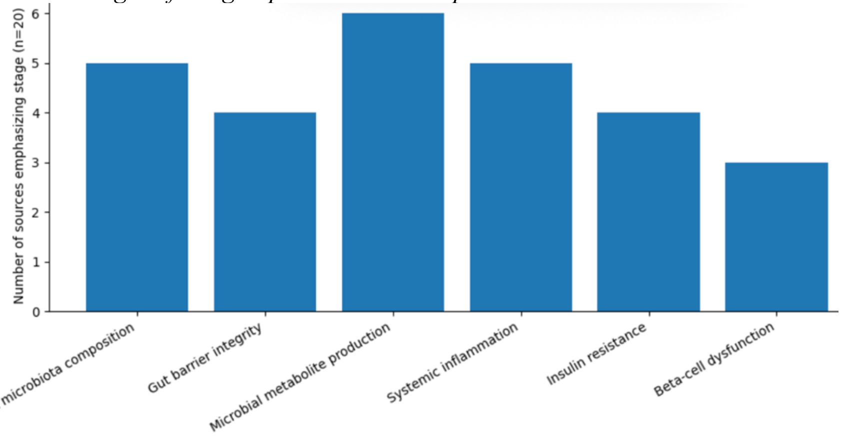

Figure 4 illustrates how the reviewed literature distributes emphasis across the **sequential biological stages** that constitute the gut–pancreas axis, from initial alterations in gut microbiota composition to downstream beta-cell dysfunction. The pattern reflects a coherent progression model in which **microbial function and host response** act as intermediaries between intestinal dysbiosis and clinically relevant metabolic outcomes.

The stages receiving the greatest emphasis are **microbial metabolite production** and **systemic inflammation**, underscoring their central role as mechanistic bridges between gut ecology and insulin resistance. This is consistent with evidence showing that microbiota-derived metabolites—particularly short-chain fatty acids—serve as active signaling molecules capable of modulating enteroendocrine function, hepatic glucose metabolism, and peripheral insulin sensitivity [8], [10]. Their prominence in this figure reinforces the concept that functional microbial outputs are more directly linked to metabolic phenotypes than compositional features alone.

Closely aligned with metabolite production is **systemic inflammation**, which emerges as a recurring downstream consequence of gut barrier alterations and microbial signaling. The concept of metabolic endotoxemia explains how translocation of bacterial components, such as lipopolysaccharide, promotes chronic low-grade inflammation that disrupts insulin signaling pathways [4]. Integrative clinical analyses further position inflammation as a unifying mechanism connecting gut barrier integrity, immune activation, and insulin resistance across diverse populations [5], [9].

The **initial stages**—gut microbiota composition and gut barrier integrity—also show substantial representation, reflecting their importance as upstream determinants of metabolic signaling. Changes in microbial diversity and functional capacity have been consistently associated with insulin resistance and T2DM in metagenomic studies [2], [3], while barrier-related interactions involving taxa such as *Akkermansia muciniphila* highlight how epithelial integrity can influence metabolic inflammation and glucose regulation [12], [13]. These stages are critical because they represent **modifiable entry points** for preventive strategies, including dietary and microbiome-targeted interventions [15], [18].

The **downstream stages**, insulin resistance and beta-cell dysfunction, appear with comparatively lower emphasis. This distribution reflects the focus of the reviewed literature on **early and intermediate mechanisms** rather than late clinical manifestations. While insulin resistance is a central outcome of gut–pancreas axis disruption, and beta-cell dysfunction ultimately determines progression to overt T2DM, these stages are often evaluated using traditional metabolic markers that lack sensitivity to upstream gut-derived processes [19]. The reduced emphasis on beta-cell dysfunction is therefore consistent with the review's preclinical and predictive orientation.

Figure 5.
Evidence map of leading gut–pancreas axis biomarker domains according to mechanistic support and clinical translatability across the reviewed sources

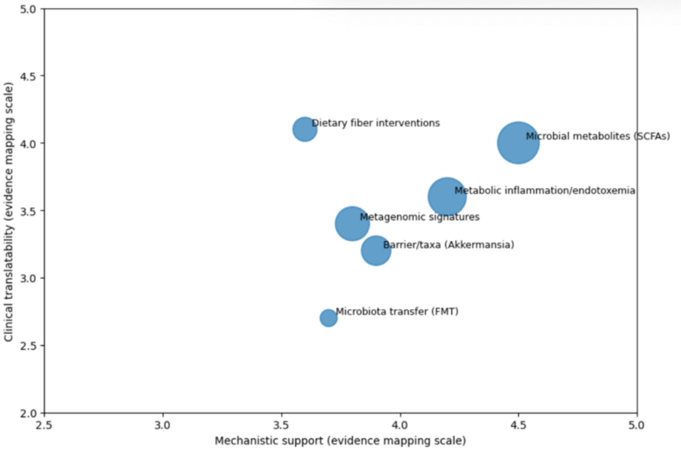

Figure 5 provides an evidence-mapping visualization that situates the most prominent biomarker domains of the gut–pancreas axis along two descriptive dimensions: **mechanistic support** (x-axis) and **clinical translatability** (y-axis). Bubble size reflects the **relative frequency** with which each domain is highlighted within the reviewed evidence base. This mapping is intended as a structured synthesis tool, helping organize heterogeneous findings into an interpretable landscape suitable for academic and translational discussion.

The domain positioned with the strongest combined profile is **microbial metabolites (SCFAs)**, reflecting both robust mechanistic plausibility and relatively high potential for clinical translation. This is consistent with evidence describing SCFAs as active metabolic mediators that influence insulin sensitivity through endocrine and metabolic pathways, including effects on energy balance, adipose tissue function, and glucose regulation [10]. Human observational work associating SCFAs with insulin resistance reinforces the relevance of this biomarker domain within real-world metabolic phenotypes [8]. In addition, interventional dietary studies that shift microbiome activity and improve insulin sensitivity frequently converge on metabolite-mediated mechanisms, supporting the translational appeal of SCFA-focused biomarker strategies [15], [18].

A closely clustered domain is **metabolic inflammation/endotoxemia**, which demonstrates high mechanistic support and moderate-to-high clinical translatability. This aligns with the well-described framework of metabolic endotoxemia, in which increased exposure to bacterial components such as lipopolysaccharide contributes to chronic low-grade inflammation and impaired insulin signaling [4]. Conceptual and therapeutic-oriented syntheses emphasize the gut microbiome and barrier-related inflammation as actionable targets, which helps explain why endotoxemia-related markers remain prominent in translational framing despite variability in measurement approaches across studies [5], [9]. In practical biomarker terms, this domain represents a mechanistic bridge between upstream dysbiosis and downstream insulin resistance phenotypes.

Metagenomic signatures occupy a central region of the map, reflecting substantial mechanistic support and moderate clinical translatability. This placement is consistent with metagenome-wide association evidence demonstrating distinct microbial and functional profiles in individuals with T2DM, suggesting meaningful disease-linked microbial patterns [2]. Similar profiling in cohorts spanning normal, impaired, and diabetic glucose control further supports the relevance of community-level signatures for stratification [3]. However, the slightly lower translational placement reflects real-world challenges such as standardization, batch effects, population variability, and interpretation across diets and geographies—issues emphasized in metabolic disease microbiome assessment frameworks [6], [14].

The **barrier/taxa (Akkermansia)** domain sits near metagenomic signatures, reflecting notable mechanistic grounding with moderate translational potential. Experimental evidence indicates that interactions between *Akkermansia muciniphila* and the intestinal epithelium can influence metabolic phenotypes and barrier integrity [12]. Additionally,

Issue 2, Volume 1, No. 02, July-December 2025
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studies demonstrating metabolic improvement with a purified membrane protein derived from *A. muciniphila* support a mechanistic basis that extends beyond simple association [13]. Its translation into routine biomarker use, however, requires careful consideration of strain-level effects, context dependence, and how taxon abundance relates to function—limitations consistent with broader microbiome interpretive challenges [14].

Dietary fiber interventions appear with relatively high clinical translatability, reflecting practicality and scalability, even when mechanistic support varies by intervention design. Evidence indicates that dietary fibers can selectively promote beneficial bacterial communities and alleviate T2DM-related metabolic dysfunction, reinforcing the link between modifiable exposures, microbiome function, and glycemic outcomes [15]. Complementary intervention work showing improved insulin sensitivity after diet-driven microbiota modulation further supports a translation-friendly position for this domain [18]. In biomarker terms, dietary fiber studies help define **response-linked markers** (e.g., metabolite shifts) that may complement predictive models.

Finally, **microbiota transfer (FMT)** is shown with meaningful mechanistic support but lower clinical translatability in routine settings. This placement is consistent with evidence that microbiota transfer from lean donors can improve insulin sensitivity in metabolic syndrome, supporting causal influence of microbial communities on metabolic outcomes [7]. However, its practical deployment for broad prevention or biomarker validation is constrained by feasibility, standardization, and patient acceptability considerations—factors that naturally lower its translational readiness compared with diet-based strategies.

DISCUSSION

The present review integrates mechanistic, clinical, and translational evidence to examine the **gut–pancreas axis as a determinant of insulin resistance** and as a source of **emerging predictive biomarkers for type 2 diabetes mellitus (T2DM)**. The results collectively support a systems-based interpretation in which gut microbiota composition, microbial metabolic activity, barrier integrity, and inflammatory signaling interact dynamically to influence insulin sensitivity and beta-cell function. Rather than acting through a single pathway, the gut–pancreas axis appears to operate through **convergent mechanisms** that shape metabolic risk over time, often preceding detectable alterations in conventional glycemic markers.

Integration of mechanistic pathways

A consistent finding across the reviewed evidence is that **microbial function**, rather than taxonomy alone, plays a central role in insulin resistance. Early experimental work demonstrated that gut microbiota can regulate host energy storage and adiposity, establishing a causal link between microbial ecology and metabolic phenotype [1]. Subsequent human metagenomic studies expanded this concept by showing that individuals with T2DM exhibit distinct microbial functional profiles, including altered pathways related to carbohydrate metabolism, oxidative stress, and inflammatory signaling [2], [3]. These system-level alterations reinforce the notion that insulin resistance is influenced by **community-level microbial behavior**, not merely by the presence or absence of individual taxa.

One of the most robust mechanistic bridges between dysbiosis and insulin resistance is **metabolic endotoxemia**. Chronic exposure to gut-derived lipopolysaccharide has been shown to initiate low-grade inflammation that disrupts insulin signaling pathways and promotes metabolic dysfunction [4]. This inflammatory framework is repeatedly emphasized in conceptual and clinical syntheses, which position gut barrier integrity and immune activation as critical modulators of insulin sensitivity [5], [9]. Importantly, endotoxemia-related mechanisms offer biologically plausible and measurable targets that may help identify insulin resistance at an earlier, preclinical stage.

Microbial metabolites as functional biomarkers

Among the various gut-derived signals, **short-chain fatty acids (SCFAs)** emerge as the most consistently highlighted functional outputs linking the microbiome to insulin sensitivity. SCFAs influence metabolic regulation through multiple pathways, including modulation of enteroendocrine signaling, incretin release, hepatic glucose production, and adipose tissue metabolism [10]. Human observational data further demonstrate associations between SCFA profiles and insulin resistance, supporting their relevance beyond experimental settings [8]. The prominence of SCFAs across mechanistic, observational, and interventional studies explains why they occupy a central position in the results and evidence mapping.

Dietary interventions that selectively promote SCFA-producing bacteria provide additional support for their translational relevance. Dietary fiber–driven modulation of the gut microbiota has been shown to alleviate T2DM-related metabolic abnormalities, reinforcing the link between modifiable exposures, microbial metabolism, and insulin sensitivity [15]. Complementary intervention studies demonstrate that diet-induced shifts in microbiota composition can improve insulin sensitivity, further supporting the concept that metabolite-focused biomarkers may serve both predictive and response-monitoring roles [18]. Together, these findings position SCFAs as **functionally meaningful biomarkers** that reflect both microbial activity and host metabolic response.

Role of specific taxa and barrier-related mechanisms

While functional outputs dominate the predictive landscape, specific microbial taxa—most notably *Akkermansia muciniphila*—also contribute important mechanistic insight. Experimental studies show that cross-talk between *A. muciniphila* and the intestinal epithelium influences diet-induced obesity and metabolic inflammation, highlighting the importance of barrier integrity in metabolic regulation [12]. Further evidence that a purified membrane protein derived from *A. muciniphila* improves metabolic outcomes in obese and diabetic models strengthens the argument for a causal role rather than a simple association [13]. However, the discussion across studies cautions against overreliance on single taxa as biomarkers, emphasizing that strain-level variability and functional context are critical considerations [6], [14].

Human interventional evidence and causality

Evidence supporting causality is further strengthened by **microbiota transfer and dietary intervention studies**. Transfer of intestinal microbiota from lean donors to individuals with metabolic syndrome resulted in improved insulin sensitivity, providing one of the clearest demonstrations that altering microbial communities can directly influence metabolic outcomes in humans [7]. Although such interventions face practical limitations, their mechanistic significance is substantial, as they help distinguish biomarkers that merely correlate with disease from those that reflect causal pathways.

Dietary interventions offer a more scalable translational approach. By modifying gut microbiota composition and function, dietary strategies can influence insulin sensitivity and metabolic inflammation, reinforcing the clinical relevance of gut-derived biomarkers [15], [18]. These findings are particularly relevant for public health contexts, as they link biomarker discovery with feasible preventive strategies.

Biomarkers, heterogeneity, and predictive frameworks

A recurring theme across the reviewed literature is the **heterogeneity of insulin resistance and T2DM**. Traditional markers such as fasting glucose and HbA1c often fail to capture early metabolic dysfunction, underscoring the need for complementary biomarkers that reflect upstream mechanisms [19]. Contemporary classification frameworks for adult-onset diabetes emphasize biological heterogeneity and differential risk trajectories, supporting the integration of microbiome-related features into predictive models [20].

From this perspective, gut-derived biomarkers should not be viewed as standalone diagnostic tools but as components of **integrative risk stratification frameworks**. Combining microbial metabolites, inflammatory indicators, and clinical metabolic markers may improve early prediction and align with emerging subgroup-based approaches to diabetes classification [19], [20]. The relatively limited representation of fully integrative biomarker models in the current evidence base reflects methodological complexity rather than conceptual weakness, indicating an important direction for future research.

Contextual relevance and Latin American perspective

Although the underlying biological mechanisms appear broadly consistent across populations, their translation requires consideration of **contextual factors** such as diet, socioeconomic conditions, and health system characteristics. Countries such as Mexico, Colombia, and Ecuador face rising burdens of obesity and T2DM, often accompanied by dietary transitions and disparities in preventive care access. In these settings, microbiome-related biomarkers may offer particular value because many determinants—dietary fiber intake, ultraprocessed food consumption, and antibiotic exposure—are modifiable at both individual and policy levels.

However, population-specific validation remains essential. Gut microbiota composition varies with geography and lifestyle, and biomarker performance may differ accordingly [6], [16]. Therefore, the most responsible application of gut–pancreas axis biomarkers involves integrating them with established metabolic indicators and validating them across diverse cohorts.

Limitations and future directions

This discussion must be interpreted in light of several limitations. Much of the current evidence is derived from observational and mechanistic studies, with relatively fewer large-scale, standardized human interventions. Methodological heterogeneity in microbiome assessment, including differences in sequencing platforms, analytical pipelines, and dietary confounders, complicates direct comparison across studies [6], [14]. Nonetheless, the convergence of findings across independent designs strengthens confidence in the core mechanisms identified.

Future research should prioritize **longitudinal designs**, **multi-omic integration**, and **population-diverse cohorts** to refine predictive models and assess clinical utility. Integrative frameworks that combine microbial metabolites, inflammatory markers, and clinical measures are particularly promising for capturing disease heterogeneity and enabling early intervention [19], [20].

CONCLUSION

This review highlights the **gut–pancreas axis** as a central and biologically coherent framework for understanding the development of insulin resistance and the early risk of type 2 diabetes mellitus (T2DM). The integrated analysis of experimental, clinical, and translational evidence demonstrates that insulin resistance is not solely a defect of insulin signaling, but rather a **multisystem process** shaped by dynamic interactions between gut microbiota composition, microbial metabolic activity, intestinal barrier function, inflammatory signaling, and pancreatic endocrine responses.

Across the reviewed literature, **functional microbial outputs**, particularly short-chain fatty acids, consistently emerge as the most robust and biologically meaningful candidates for predictive biomarker development. Their repeated association with insulin sensitivity, metabolic regulation, and responsiveness to dietary interventions underscores their value as indicators that reflect both microbial activity and host metabolic state. In parallel, **metabolic inflammation and endotoxemia-related pathways** provide a mechanistic bridge linking gut dysbiosis to systemic insulin resistance, reinforcing the relevance of inflammatory markers as complementary predictive signals.

While specific microbial taxa, such as *Akkermansia muciniphila*, offer important mechanistic insights—especially in relation to gut barrier integrity—the evidence supports a shift away from reliance on isolated taxonomic markers toward **integrated, function-oriented biomarker frameworks**. Metagenomic signatures and pathway-level analyses further strengthen this systems-based approach, although their clinical implementation requires continued standardization and validation.

Importantly, the findings emphasize that no single biomarker is sufficient to capture the complexity and heterogeneity of insulin resistance. Instead, the most promising strategy lies in **integrative models** that combine gut-derived metabolites, inflammatory indicators, and conventional metabolic markers. Such models align with contemporary perspectives on diabetes heterogeneity and have the potential to improve early risk stratification, long before irreversible beta-cell dysfunction occurs.

From an international and educational standpoint, the relevance of the gut–pancreas axis is particularly significant for regions such as Mexico, Colombia, and Ecuador, where rising prevalence of metabolic disorders intersects with modifiable dietary and environmental factors. In these contexts, microbiome-informed biomarkers may support more proactive, prevention-oriented approaches to metabolic health, provided that population-specific validation is pursued.

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