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Glycemic Variability and Gut Microbiota Metabolic Patterns: A Novel Perspective on Diabetic Complications

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ABSTRACT

Emerging evidence indicates a critical link between diabetic complications and the interplay of glycemic variability and gut microbiota metabolic activity. This review comprehensively examines the regulatory effects of glycemic fluctuations on the composition and function of the gut microbiota, while elucidating the key mechanisms by which microbial metabolic reprogramming—mediated through short-chain fatty acids, bile acids, and other metabolites—disrupts host metabolic and immune homeostasis, thereby exacerbating diabetic complications. Research demonstrates that glycemic variability not only directly contributes to vascular and neuronal damage but also remodels the gut microbiota's metabolic network, triggering systemic metabolic dysregulation and chronic low-grade inflammation. Building on these findings, we explore novel therapeutic strategies targeting the gut microbiota for the prevention and management of diabetic complications. By adopting a "gut-organ axis" framework, this study unveils the cascade of interactions among glycemic variability, gut microbiota, and metabolic disturbances in the pathogenesis of diabetic complications, offering both theoretical foundations and innovative approaches for clinical intervention.

1 | Introduction

Diabetes mellitus has emerged as one of the most pressing global public health challenges of the 21st century. Recent epidemiological data reveal that the number of individuals with diabetes worldwide has surpassed 537 million, with projections indicating a rise to 783 million by 2045 (Barrea et al. 2025; Moradi Baniasadi et al. 2025). This metabolic disorder not only imposes a substantial disease burden but also contributes to significant morbidity and mortality due to its multisystem complications, including cardiovascular disease, diabetic nephropathy, retinopathy, and peripheral neuropathy (Sedighi et al. 2025). Notably, despite continuous optimization of glycemic control strategies, the incidence of diabetic complications remains persistently high. This clinical conundrum suggests that conventional glycemic markers (e.g., Hemoglobin A1c (HbA1c)) may fail to fully capture the critical pathological mechanisms underlying disease progression. In recent years, growing attention has been directed toward the role of glycemic variability (GV) in diabetic complications (Lucci et al. 2025). Emerging evidence indicates that GV may serve as an independent predictor of microvascular complications, extending beyond its association with long-term glycemic control (Šoupal et al. 2014). Furthermore, acute hyperglycemia exacerbates tissue damage through metabolic

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and hemodynamic pathways similar to chronic hyperglycemia (Marcovecchio et al. 2011), reinforcing the limitations of HbA1c as a standalone assessment. Clinically, GV is quantified through parameters including mean glucose levels, standard deviation (SD), and mean amplitude of glycemic excursions (MAGE), which collectively provide a more comprehensive evaluation of glycemic control (Chen, Chen, et al. 2024; Chen, Shen, et al. 2024; Monnier et al. 2025). A study of 34 type 1 diabetes patients revealed significant correlations between glycemic variability indices and metabolic parameters. The average daily risk range and glycemic instability index showed positive correlations with insulin sensitivity ($\rho = 0.5$ and $\rho = 0.48$, respectively; $p < 0.01$), while hypoglycemia risk metrics demonstrated a negative correlation with maximal epinephrine response during hypoglycemia ($\rho = -0.46$, $p < 0.01$) (Pitsillides et al. 2011). These findings underscore the clinical significance of glycemic fluctuation monitoring, which enables timely identification of potential risks and optimization of therapeutic strategies through comprehensive metabolic assessment.

Recent scientific advances have yielded two breakthrough perspectives in understanding diabetic complications. First, technological innovations in continuous glucose monitoring have demonstrated that glycemic variability represents an independent risk factor for complications, distinct from chronic hyperglycemia. Mechanistic studies reveal that glucose fluctuations contribute directly to end organ damage through oxidative stress induction and endothelial dysfunction (Papachristoforou et al. 2020; Klimontov et al. 2021). Emerging evidence has increasingly elucidated the critical interplay between gut microbiota and diabetes pathogenesis. As the largest microbial ecosystem in humans, the intestinal microbiome not only modulates nutrient metabolism and energy homeostasis, but also significantly influences diabetes development through immunomodulatory mechanisms and inflammatory pathway regulation (Tilg and Moschen 2014; Ma et al. 2019). Current research demonstrates a bidirectional relationship between gut dysbiosis and diabetes mellitus, wherein microbial imbalance contributes to disease pathogenesis while diabetic metabolic derangements exacerbate microbiota alterations—a phenomenon termed the "glucose-microbiota axis" (Li et al. 2018; Wang et al. 2021). Notably, microbial metabolites including short-chain fatty acids (SCFAs) and bile acids (BAs) play pivotal roles in glycemic regulation through multiple physiological pathways (Takeuchi et al. 2024; Tran et al. 2025). Mechanistic studies reveal that SCFAs enhance hepatic glycogen synthesis by stimulating insulin production through both intestinal G-protein-coupled receptor (GPCR) signaling pathways and hepatic AMP-activated protein kinase (AMPK) activation (Tan et al. 2023; Thiruvengadam et al. 2023). Furthermore, BAs modulate glucose homeostasis by promoting the secretion of Glucagon-like peptide-1 (GLP-1) and peptide YY (PYY) from intestinal L cells and pancreatic α cells (Guo et al. 2024). This bidirectional crosstalk between gut microbiota and diabetes not only provides novel insights into disease pathogenesis, but also suggests potential therapeutic avenues for diabetes prevention and complication management through microbial modulation strategies.

This review presents the first systematic integration of glycemic dynamics and gut microbiota metabolic networks in diabetic complications from a multi-scale regulatory perspective. By elucidating how microbial metabolic reprogramming amplifies organ damage induced by glycemic fluctuations, we establish a unified theoretical framework for complication pathogenesis while identifying multiple druggable targets. These findings represent a paradigm shift from conventional glycemic control to precision multi-target intervention strategies, providing both theoretical foundations for microbiome-based therapeutics and actionable insights for complication prevention.

2 | Bibliometric Analysis of Glycemic Variability Research: Current Landscape and Trends

2.1 | Literature Screening and Dataset Construction

Our bibliometric analysis extracted 823 publications from PubMed, including original articles ($n = 491$), reviews ($n = 58$), clinical trials ($n = 19$), case reports ($n = 2$), and other publication types ($n = 253$). The initial dataset spanned publications from 2010 to 2025. After applying a filter to include only publications within the 16-year period (2010–2025), 802 publications remained eligible for analysis (Figure 1A). Following removal of duplicates and rigorous type-specific screening, these 802 publications formed the final curated dataset for subsequent analyses.

2.2 | Publication Trends and Citation Analysis

The annual publication count on glycemic variability research demonstrated consistent growth from 2010 to 2022, peaking in 2021 ($n = 85$) and 2022 ($n = 89$), followed by a modest decline in 2023–2024 (Figure 1A). The mean citation rate per article showed a gradual increase from approximately 1 citation in 2010 to nearly 2 citations by 2018, then entered a downward trajectory approaching zero by 2025 (Figure 1A). This pattern suggests that while research activity has recently tapered, earlier contributions maintain a substantial academic impact in the field.

2.3 | Analysis of Authors, Institutions, and Journals

A three-factor analysis revealed collaborative networks among authors, institutions, and journals in glycemic variability research. The top five journals publishing on this topic were *Diabetes Technology & Therapeutics* ($n = 57$), *Journal of Diabetes Science and Technology* ($n = 46$), *Diabetes Care* ($n = 32$), *Diabetes Research and Clinical Practice* ($n = 30$), and *Frontiers in Endocrinology* ($n = 24$), demonstrating their scholarly influence in this field (Figure 1B,C). Key contributors included Fendler Wojciech and Kim Chulho, whose work appeared in high-impact journals such as *Diabetes Research and Clinical Practice* and *Diabetology & Metabolic Syndrome* (Figure 1C). Su Jian-bin and Wang Xue-qin also published significant findings in journals including *Scientific Reports* and *Journal of Diabetes Investigation* (Figure 1C,D). Geographically, China led with 30.06% of publications, followed by the United States (11.79%) and Japan (10.78%). Other active contributors included South Korea (8.66%), Italy (5.70%), and India (3.85%) (Figure 1F). This distribution highlights Asia's prominent role in glycemic

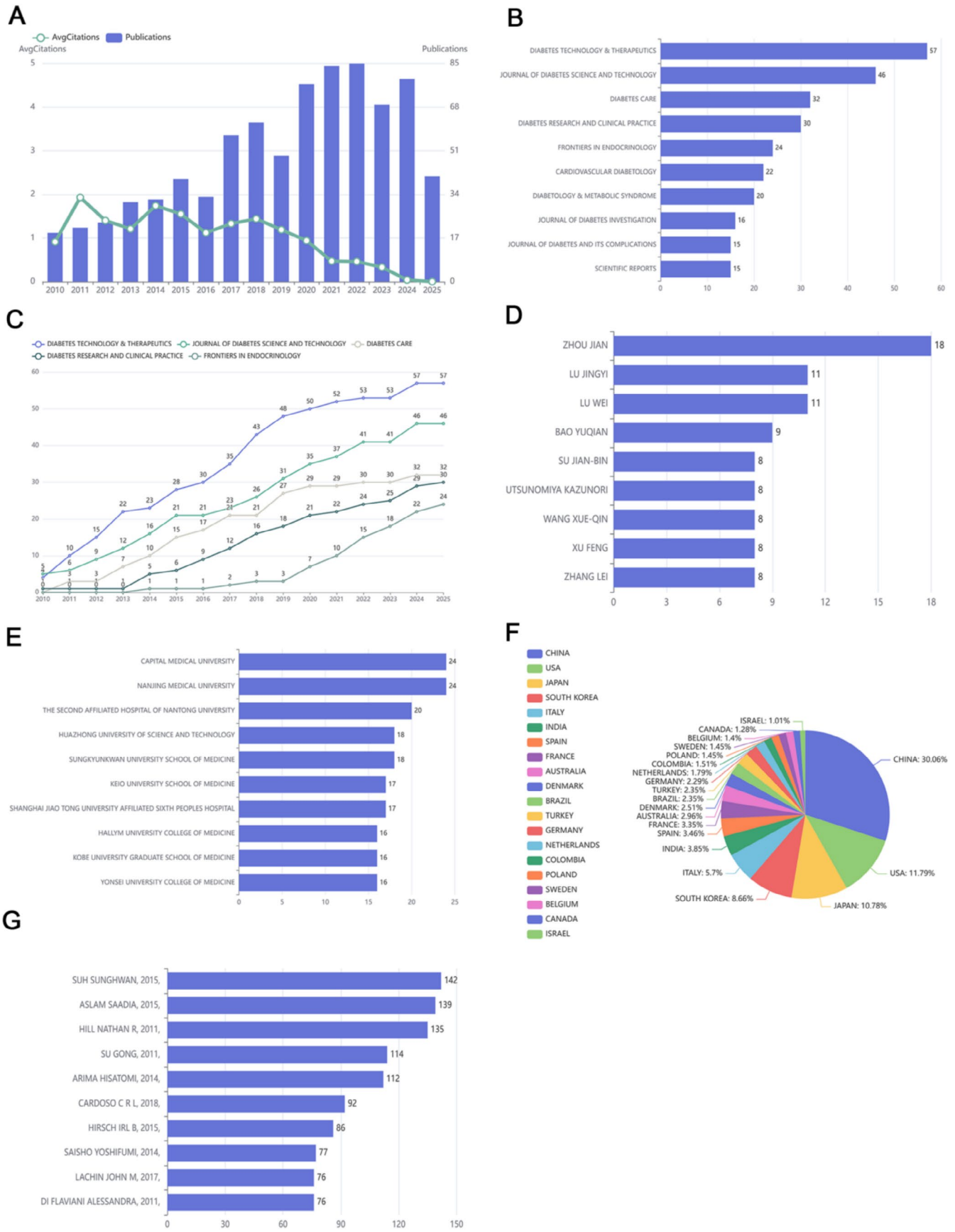

FIGURE 1 | Bibliometric analysis of glycemic variability: (A) Publication trends over the past decade; (B, C) Journals publishing related articles; (D) Authors contributing to the field; (E) Institutions involved in research; (F) Countries with significant contributions; (G) Citation analysis of publications.

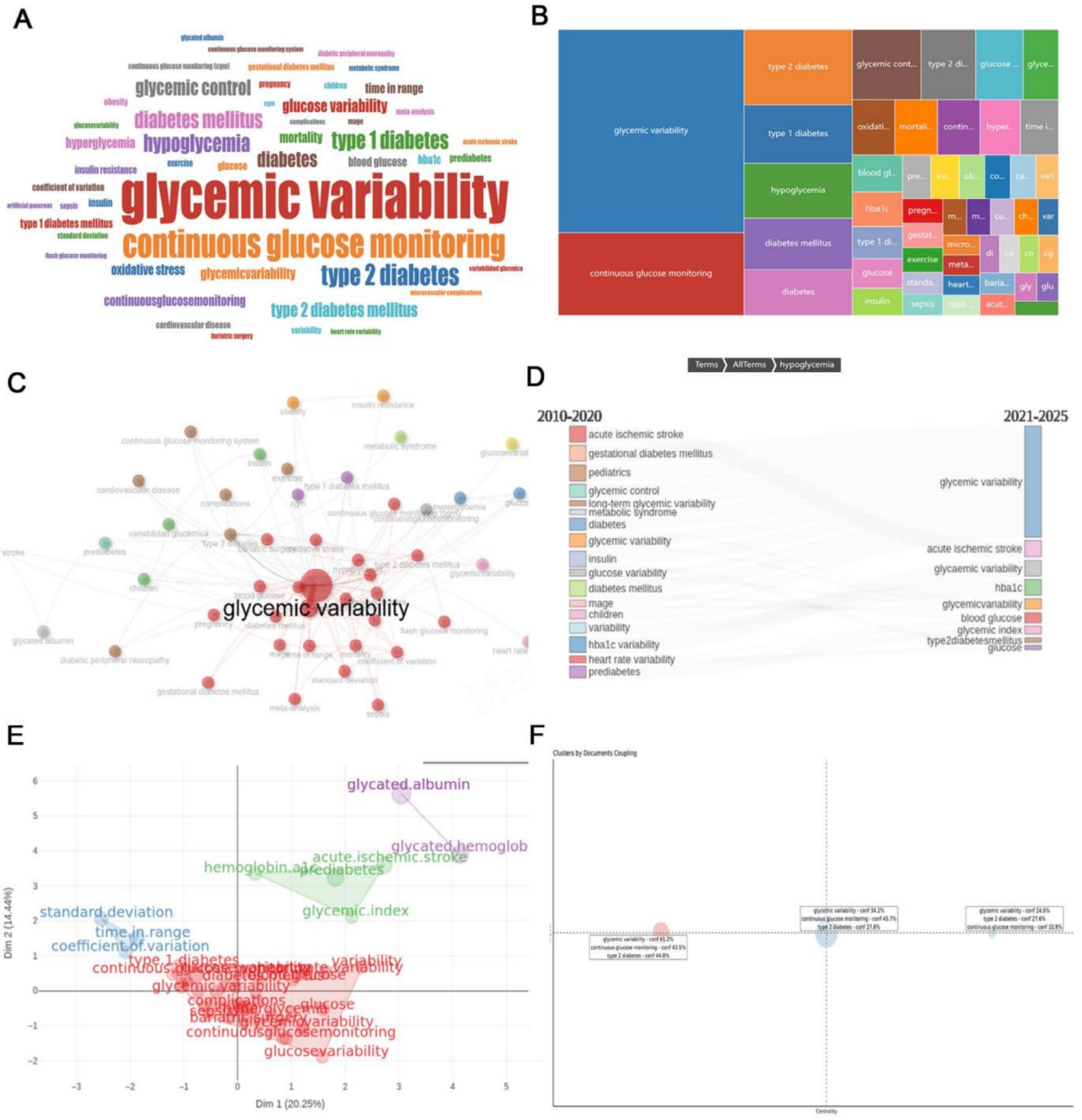

FIGURE 2 | Citation analysis of publications; (A, B) Keyword analysis; (C, D) Topic co-occurrence network and research hotspot analysis; (E, F) Thematic factor and cluster analysis.

variability research, with Western nations following closely. Among the most-cited works, Suh Sunghwan's 2015 publication ranked first with 142 citations, followed by Aslam Saadia (139 citations, 2015) and Hill Nathan R (135 citations, 2011) (Figure 1G).

2.4 | Keyword Analysis and Co-Occurrence Network

The keyword analysis revealed two predominant research themes: "glycemic variability" and "continuous glucose monitoring" (Figure 2A). High frequency terms including "diabetes mellitus," "type 1 diabetes," and "type 2 diabetes" indicated a primary research focus on diabetes classification and management. Additional terms such as "glycemic control," "hypoglycemia," and "hyperglycemia" represented key aspects of glucose regulation, while "obesity," "insulin resistance," and "cardiovascular disease" highlighted important comorbidities and risk factors (Figure 2B). The co-occurrence network analysis positioned "glycemic variability" as the central node, demonstrating strong connections with multiple secondary keywords (Figure 2C). Three distinct research clusters emerged from this network: diabetes-specific investigations

(including type 2 diabetes mellitus and gestational diabetes mellitus), glucose monitoring technologies (continuous and flash glucose monitoring systems), and metabolic comorbidities (obesity, insulin resistance, and cardiovascular disease). Temporal analysis revealed an evolution in research focus—while earlier studies (2010–2020) emphasized clinical contexts such as acute ischemic stroke and pediatric populations, recent investigations (2021–2025) have shifted toward more precise metrics including HbA1c and glucose levels while maintaining emphasis on stroke outcomes (Figure 2D). This progression from broad clinical observations to targeted mechanistic studies reflects the field's maturation toward developing more sophisticated management strategies.

2.5 | Thematic Factor and Cluster Analysis

Thematic factor analysis identified two principal dimensions, accounting for 20.25% and 14.44% of the variance, respectively. The lower-left quadrant featured keywords such as "standard deviation," "time in range," and "type 1 diabetes," reflecting a focus on glycemic control metrics and management strategies, particularly in type 1 diabetes. In contrast, the upper-right quadrant included terms like "glycated albumin," "acute ischemic stroke," and "hemoglobin A1c," highlighting long-term glycemic control and its association with cardiovascular risk (Figure 2E). This suggests that research addresses both short-term glycemic variability and its long-term clinical implications. Coupling cluster analysis revealed three distinct clusters. The first cluster (lower-left) emphasized "glycemic variability," "continuous glucose monitoring," and "type 2 diabetes," with confidence levels of 41.2%, 43.5%, and 44.8%, respectively. A second cluster (central) maintained similar themes but with varying confidence scores (34.2%, 45.7%, and 27.6%), while the third (upper-right) showed weaker associations (24.6%, 27.6%, and 10.9%) (Figure 2F). These findings indicate consistent research priorities with differing degrees of thematic linkage.

3 | Physiological and Pathological Mechanisms of Glycemic Variability

3.1 | Core Regulatory Mechanisms of Glucose Homeostasis

Glucose homeostasis is maintained through the coordinated interplay of neural, endocrine, and metabolic systems, with pancreatic β-cell function serving as the central regulator (Henriques et al. 2025) (Figure 3). Under physiological conditions, postprandial hyperglycemia stimulates pulsatile insulin secretion, facilitating glucose uptake in peripheral tissues, while fasting glucose levels are maintained through glucagon-mediated hepatic glucose output (Kommu et al. 2025; Santos et al. 2025). Aging significantly disrupts this equilibrium: compared to 6-month-old rats, 24-month-old animals exhibit elevated basal glucose levels during the dark phase ($p < 0.01$), attenuated stress-induced glycemic responses (42% reduction in peak glucose elevation), and a strong negative correlation between hippocampal synaptic mitochondrial protein expression and diurnal glucose fluctuations ($r = -0.68$) (Braunstein et al. 2024). This dysregulation is closely linked to oxidative stress. In patients with type 2 diabetes, the MAGE shows strong positive correlations with oxidative stress markers, including 8-isoprostane ($r = 0.82$) and thiobarbituric acid-reactive substances ($r = 0.76$). Furthermore, glycemic variability directly promotes aortic collagen deposition and vascular dysfunction through activation of the reactive oxygen species (ROS)/p38 mitogen-activated protein kinase (MAPK)/runt-related transcription factor 2 (Runx2) signaling pathway (Zhang et al. 2020).

3.2 | Key Determinants of Glycemic Variability and Their Interactions

Glycemic variability arises from dynamic interactions among metabolic characteristics, hormonal regulation, and lifestyle factors (Canelli et al. 2023; Li et al. 2023). Clinical evidence identifies age, prolonged diabetes duration, and BMI > 31 kg/m^2 as independent predictors of glycemic instability (Lytrivi et al. 2025; Ortega et al. 2025). In type 1 diabetes, insulin sensitivity positively correlates with MAGE, while impaired epinephrine response during hypoglycemia significantly increases fluctuation risk (Teixeira et al. 2017). Lifestyle interventions demonstrate measurable effects—high glycemic index diets exacerbate postprandial glucose fluctuations in type 2 diabetes, whereas optimized exercise timing enhances glycemic control. Notably, moderate-intensity exercise initiated 45 min postprandial reduces glucose peaks more effectively than delayed (90-min) exercise (Qi et al. 2025). These findings provide a mechanistic foundation for personalized glucose management strategies.

3.3 | Diabetes Subtype-Specific Glycemic Variability Patterns and Clinical Implications

Type 1 diabetes (T1D) patients exhibit extreme glucose excursions and characteristic "brittle diabetes" patterns due to absolute insulin deficiency and limitations of exogenous insulin replacement therapy, demonstrating significantly greater glycemic variability than type 2 diabetes (T2D) patients (Kuenen, et al. 2011). T2D displays distinct disease-stage dependent patterns: early-stage patients primarily show exaggerated postprandial glucose spikes, while late-stage patients develop increased basal glycemic variability. Large cohort studies confirm that postprandial glucose fluctuations in T2D independently predict cardiovascular event risk (Chen et al. 2010; Lu et al. 2019).

Special diabetes subtypes reveal important mechanistic insights—sulfonylurea-treated T2D patients demonstrate greater glycemic variability compared to those receiving Dipeptidyl peptidase-4 (DPP-4) inhibitors (Yoo et al. 2015). These differences inform both clinical monitoring approaches and personalized treatment strategies, including closed-loop insulin pump systems for T1D and GLP-1 receptor agonists (RAs) targeting postprandial fluctuations in T2D (Dandona 2017; Umpierrez and Kovatchev 2018).

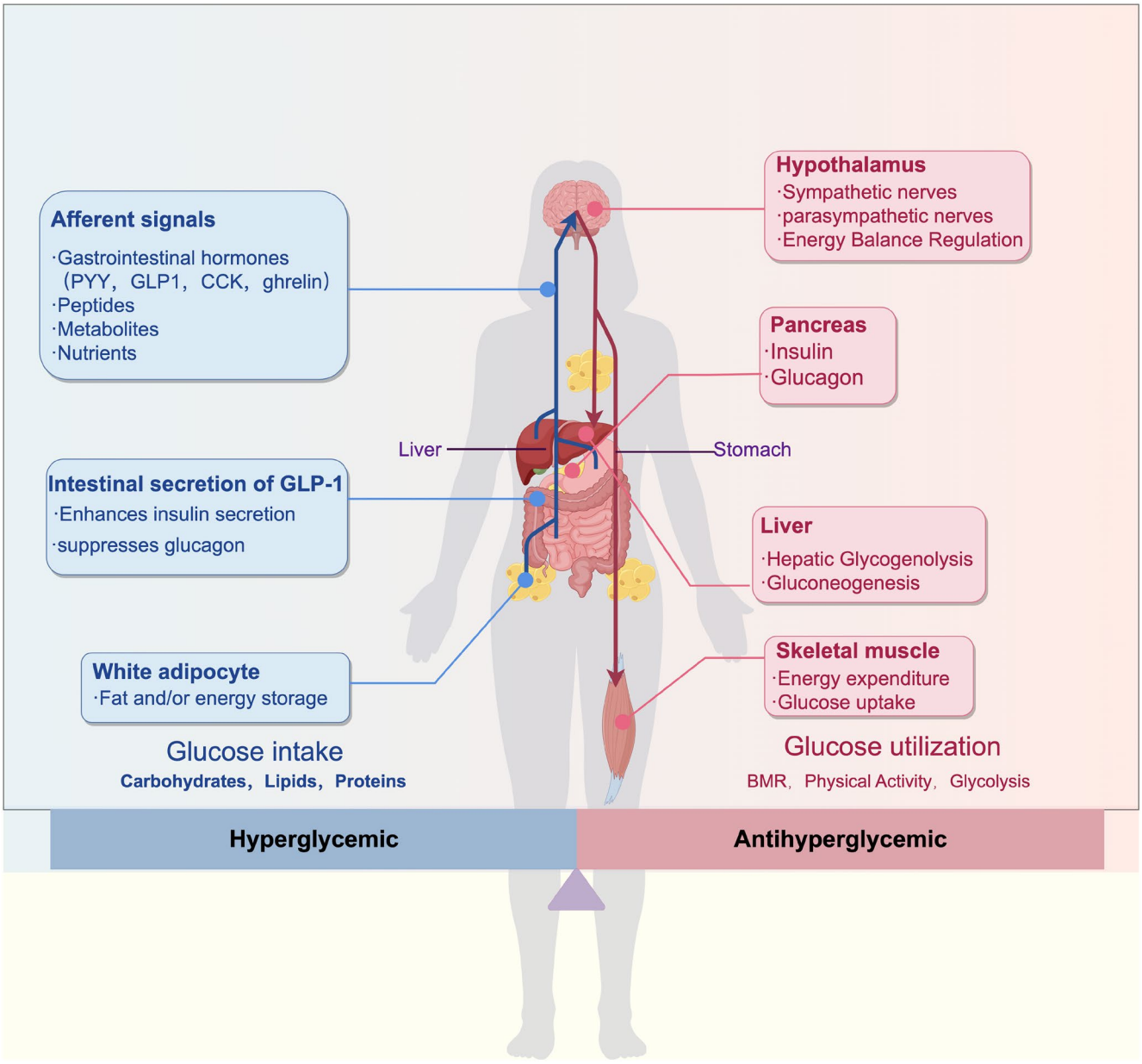

FIGURE 3 | Blood glucose homeostatic regulation mechanism: The diagram uses a human body as the background, labeling various organs and tissues with arrows indicating the pathways of signal transmission and their directions of action.

3.4 | Mechanistic Role of Glycemic Variability in Diabetic Complications

Glycemic variability has been established as an independent risk factor for diabetic complications through multiple synergistic mechanisms. In the skeletal system, clinical studies demonstrate that greater glucose fluctuations in type 2 diabetes correlate significantly with reduced bone mineral density ($\beta = -0.32$, $p < 0.01$) and increased fracture risk (HR = 1.45). This effect is mediated by glucose variability specifically suppressing osteoblast Runx2 expression (58% reduction) while activating osteoclast differentiation signals (Chen, Li, et al. 2025; Chen, Wang, et al. 2025). In cardiovascular complications, animal models reveal that glycemic variability accelerates myocardial fibrosis (2.1-fold increase in collagen deposition) and diastolic dysfunction (0.35 reduction in E/A ratio) more severely than sustained hyperglycemia. This process is driven by sodium-glucose cotransporter 1 (SGLT1) -mediated mitochondrial ROS overproduction (3.8-fold increase) (Wu et al. 2021). Epidemiological evidence for microvascular complications shows that each 1 mmol/L increase in MAGE elevates retinopathy progression risk by 18% (95% CI 1.05–1.32), likely due to oscillating hyperglycemia-induced endothelial apoptosis (2.3-fold increase) and sustained Interleukin-6 (IL-6) secretion (Jung 2015; Klimontov et al. 2021) (Figure 4). Notably, in type 1 diabetes, while the quantitative relationship between glycemic variability and microvascular complications requires larger validation studies, closed-loop insulin systems that reduce glucose fluctuations improve nerve conduction velocity by 23% ($p < 0.05$), underscoring the therapeutic value of variability control (Smith-Palmer et al. 2014). These findings collectively establish

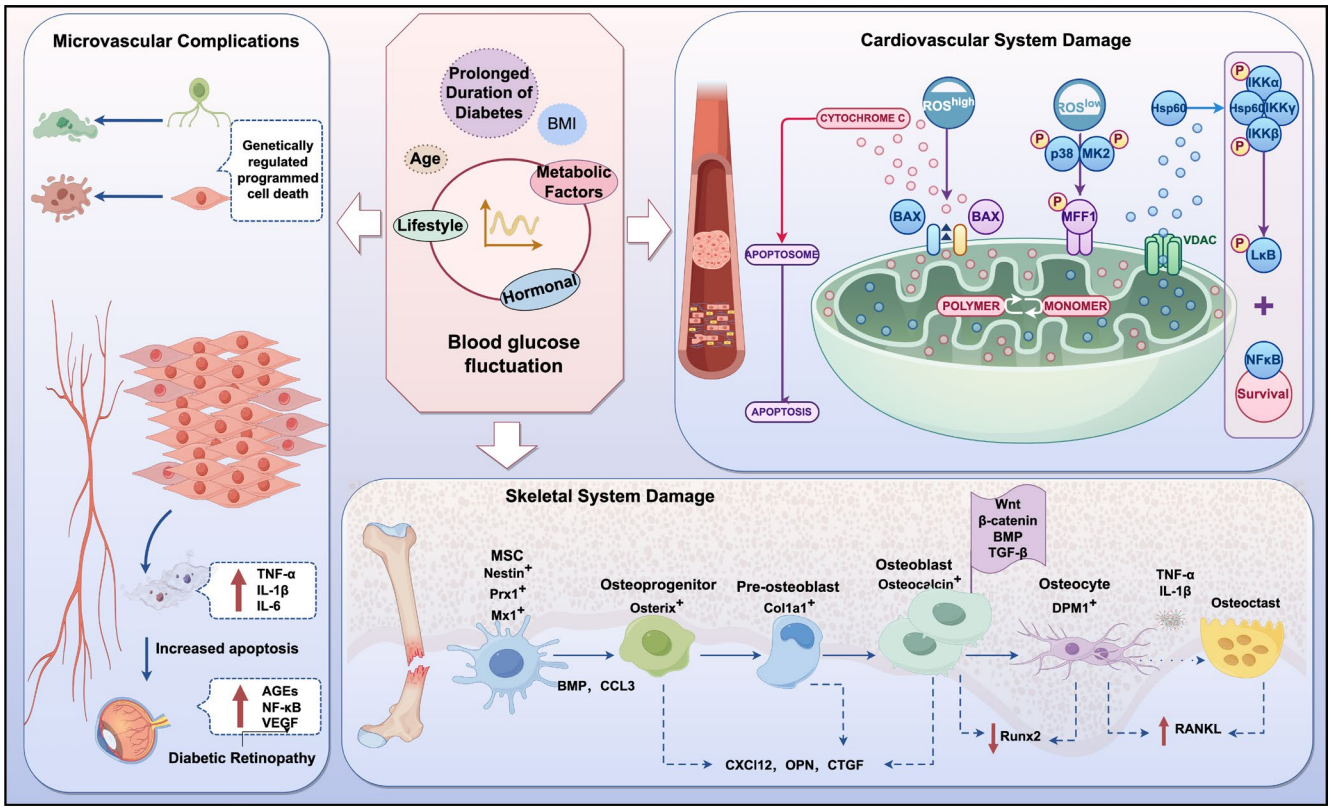

FIGURE 4 | Mechanistic role of glycemic variability in diabetic complications: The diagram is divided into three main sections, describing microvascular complications, cardiovascular system damage, and skeletal system damage.

glycemic variability management as a cornerstone of comprehensive diabetes care and provide a mechanistic basis for targeted interventions (Huang et al. 2023).

4 | Gut Microbiota: A New Perspective on Blood Glucose Fluctuation Research

4.1 | Biological Basis of Gut Microbiota Metabolic Patterns

The gut microbiota, a complex microbial community residing in the human intestinal tract, plays a fundamental role in host metabolism through its diverse biochemical transformations (Wen et al. 2022). These microbial populations metabolize dietary components into bioactive compounds that participate in various physiological processes. A prime example is the fermentation of dietary fibers into SCFAs, including acetate, propionate, and butyrate. Beyond serving as energy substrates for colonic epithelial cells, SCFAs modulate glucose metabolism by stimulating intestinal L-cells to secrete GLP-1 (Darra et al. 2023). The microbiota also mediates the biotransformation of primary BAs into secondary BAs, which regulate lipid metabolism, energy homeostasis, and intestinal barrier function through specific receptor interactions (Lin et al. 2023). Notably, microbial-derived trimethylamine N-oxide (TMAO) has emerged as a risk factor for cardiovascular diseases, highlighting the systemic impact of gut microbial metabolism (Wen et al. 2022; Shuai et al. 2025). Furthermore, bacterial processing of tryptophan yields various indole derivatives that participate in immune regulation and inflammatory responses within the gut microenvironment (Miao et al. 2025; Zhao et al. 2025).

4.2 | Gut Microbiota Metabolic Patterns in Diabetic Complications

Growing evidence implicates gut microbiota dysbiosis as a critical contributor to the pathogenesis of diabetic complications. Patients with diabetes exhibit distinct gut microbial profiles compared to healthy individuals, which may promote intestinal barrier dysfunction, chronic low-grade inflammation, and metabolic endotoxemia (van Olden et al. 2015; Guo et al. 2022). The gut microbiota influences diabetic complications through several interconnected mechanisms. Microbial dysbiosis compromises intestinal barrier integrity, increasing permeability to bacterial endotoxins such as lipopolysaccharide. This triggers systemic inflammation that exacerbates insulin resistance and tissue damage (Sohail et al. 2017; Guo et al. 2022). Microbial metabolites, particularly SCFAs and BAs, play direct roles in metabolic regulation (Parada Venegas et al. 2019; Wang et al. 2019). SCFAs enhance insulin sensitivity and modulate enteroendocrine hormone secretion to improve glucose and lipid homeostasis (Crommen and Simon 2017; Spiljar et al. 2017), while BAs regulate energy metabolism and inflammatory responses through receptor-mediated signaling (Liu, Jin, et al. 2024; Liu, Zhang, et al. 2024; Xu et al. 2024). Furthermore, gut microbiota alterations disrupt immune homeostasis, leading to aberrant immune activation that amplifies inflammatory tissue

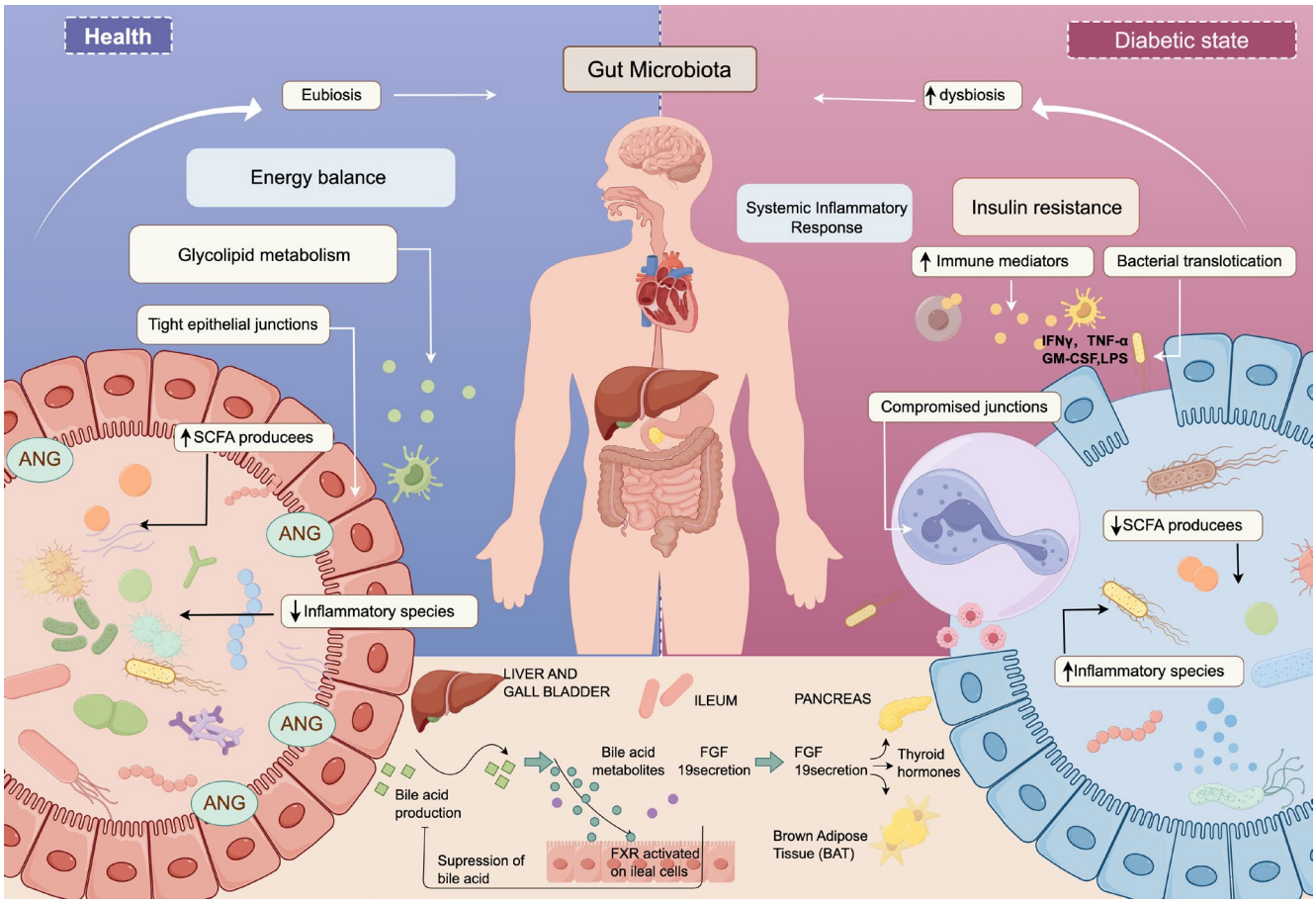

FIGURE 5 | Metabolic patterns of intestinal flora in normal and diabetic states: The left side describes the normal gut microbiota metabolic pattern, while the right side describes the state of diabetes, where gut microbiota dysbiosis is a key factor in the pathogenesis of diabetic complications. The lower part of the image illustrates BA metabolism and its impact on multiple organ systems.

injury (Alvarez-Vieites et al. 2020; Chen, Chen, et al. 2024; Chen, Shen, et al. 2024). Targeting microbial composition may represent a therapeutic strategy to restore immune balance and alleviate complications (Udayappan et al. 2014; Lundgrin and Hatipoglu 2025) (Figure 5).

As discussed previously, glycemic variability significantly contributes to diabetic complications. An important unanswered question is whether glucose fluctuations reciprocally alter gut microbial metabolism, thereby creating a vicious cycle that accelerates disease progression. This potential bidirectional relationship merits further investigation.

4.3 | Bidirectional Interaction Between Glycemic Variability and Gut Microbiota Metabolism

Emerging evidence reveals a complex reciprocal relationship between glycemic fluctuations and gut microbial ecology. Clinical and preclinical studies demonstrate that oscillating glucose levels significantly alter gut microbiota composition and functionality. Hyperglycemic conditions modify intestinal microenvironmental parameters including pH and redox potential, creating selective pressures that reshape microbial communities (Darra et al. 2023; Zong et al. 2024). In diabetic murine models, glycemic variability correlates with reduced microbial diversity, characterized by depletion of beneficial taxa (e.g., *Bifidobacterium, Lactobacillus*) and expansion of potentially pathogenic Enterobacteriaceae (Guo et al. 2024). Conversely, gut microbiota and their metabolic byproducts actively modulate glycemic responses. Microbial-derived SCFAs stimulate G protein-coupled receptors (GPCRs) on enteroendocrine cells, enhancing GLP-1 secretion to promote insulin release and glucose homeostasis (Zhang et al. 2019). Dietary fibers like pectin undergo microbial fermentation to yield SCFAs and secondary BAs, which coordinate glucose regulation through multiple pathways (Elshahed et al. 2021; Yin et al. 2024). Beyond direct metabolic regulation, gut microbiota indirectly influence glycemic variability through modulation of intestinal barrier integrity, systemic inflammation, and immune homeostasis (Jiang et al. 2025; Zheng et al. 2025). These findings collectively suggest that glycemic fluctuations and gut microbial metabolism engage in continuous crosstalk, potentially establishing a vicious cycle in diabetes progression. Further investigation is warranted to elucidate the temporal dynamics and therapeutic implications of this bidirectional relationship.

These findings reveal a sophisticated bidirectional regulatory network between glycemic variability and gut microbiota, where metabolic perturbations may establish a self-perpetuating cycle of "glucose dysregulation-microbial dysbiosis-metabolic

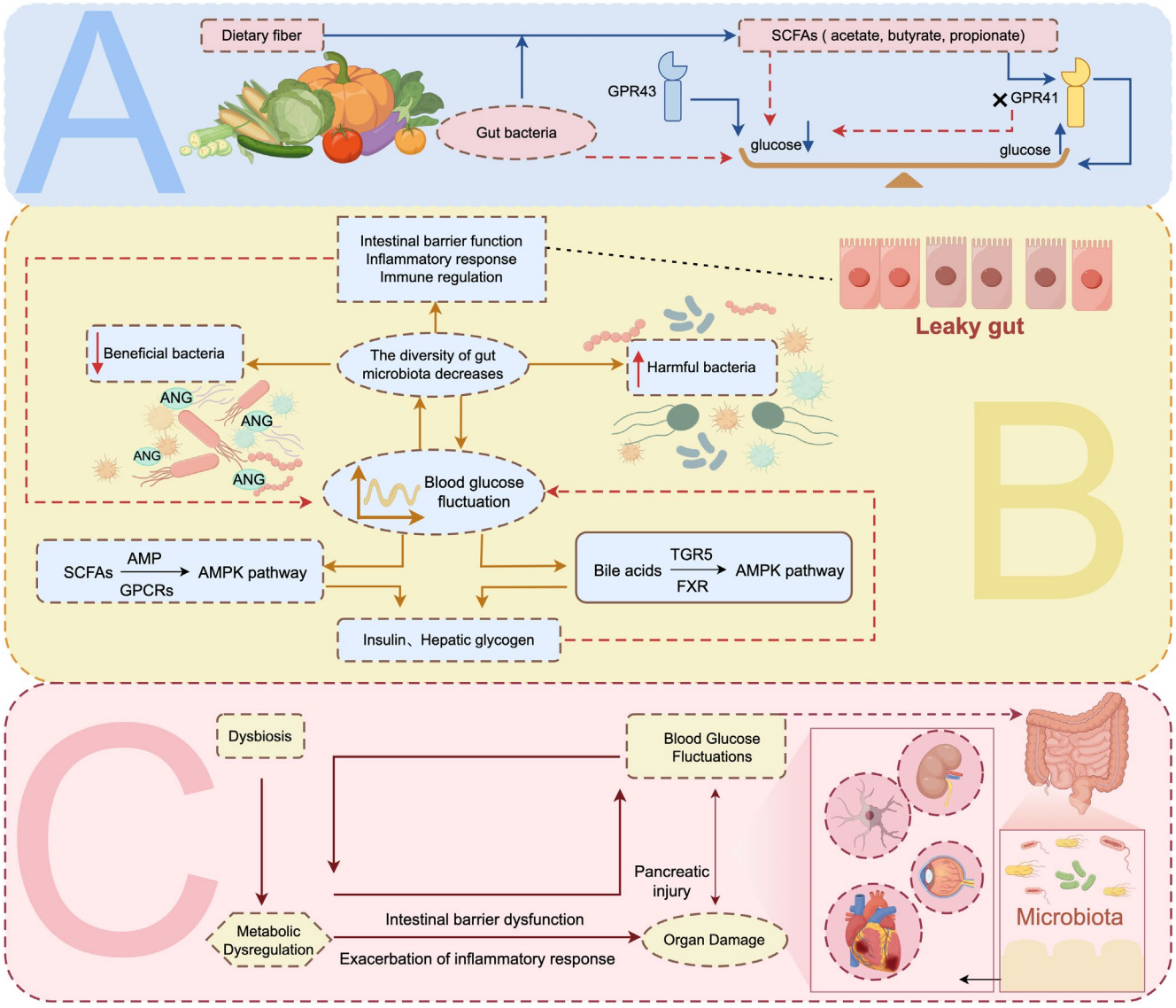

FIGURE 6 | Bidirectional interaction between glycemic variability and gut microbiota metabolism: (A) Dietary fiber is fermented by gut bacteria to produce SCFAs like acetate, butyrate, and propionate. G protein-coupled receptor 43 (GPR43) receptors lower blood glucose, while G protein-coupled receptor 41 (GPR41) may raise it; (B) Blood glucose fluctuations affect the stability of gut microbiota and BA metabolism, leading to imbalances in intestinal barrier integrity, systemic inflammation, and immune homeostasis, which indirectly influence blood glucose fluctuations; (C) Glucose dysregulation-microbial dysbiosis-metabolic dysfunction-end organ damage.

dysfunction-end organ damage." This vicious cycle likely represents a fundamental mechanism driving the progression of diabetic complications, offering novel insights into disease pathogenesis. While this association remains underexplored in diabetes research, the underlying mechanisms may provide explanatory power for key pathological features including insulin resistance and chronic inflammation—hallmarks of diabetic complications. Our synthesis of current evidence positions gut microbial metabolic patterns as central players in complication development, moving beyond the conventional glucocentric paradigm. Notably, microbial metabolites (e.g., butyrate, secondary BAs) demonstrate dual functionality: directly modulating host metabolism while potentially influencing target organ function through epigenetic regulation. Future investigations should prioritize exploring microbial metabolic interventions (e.g., targeted probiotics, dietary fibers) for their potential to simultaneously ameliorate glycemic variability and prevent complications. Such approaches could inform precision medicine strategies for diabetes management. Elucidation of these mechanisms promises to open new avenues for both early prevention and targeted therapy of diabetic complications, potentially revolutionizing clinical approaches to this pervasive metabolic disorder (Figure 6).

5 | Therapeutic Approaches for Glycemic Variability and Gut Microbiota Dysregulation

5.1 | Pharmacological and Non-Pharmacological Strategies for Glycemic Control

Effective management of blood glucose fluctuations is a critical intervention for preventing diabetes complications, with existing approaches encompassing both pharmacological and non-pharmacological therapies (Kovatchev 2012). The

efficacy of various antidiabetic medications in regulating glucose fluctuations varies significantly. DPP-4 inhibitors, exemplified by vildagliptin, reduce postprandial glucose fluctuations by enhancing endogenous GLP-1 activity (Chen et al. 2019). A comparative study involving 24 type 2 diabetes patients demonstrated that vildagliptin could reduce mean A1c equivalent (MAGE) by approximately 20% compared to glibenclamide. It also significantly elevated active GLP-1 levels and inhibited glucagon secretion, though the MAGE reduction was not statistically significant (He et al. 2013). The combination therapy of glucagon-like peptide-1 (GLP-1) RAs with basal insulin provides a more effective glucose management strategy for type 2 diabetes patients, particularly suitable for those requiring stable glucose fluctuations (Lin et al. 2022). SGLT2 inhibitors (SGLT2i) increase urinary glucose excretion and lower blood glucose levels by inhibiting the SGLT2 transporter in the proximal renal tubule without insulin dependence (Sakai et al. 2025). These medications demonstrate dual therapeutic advantages through promoting glucose excretion (glycosuria) and improving glucose fluctuations (Zhang et al. 2025). Currently, combination therapy with GV and metformin is more effective than monotherapy for patients undergoing lifestyle interventions or those already using metformin, without inducing hypoglycemia (Park et al. 2022). GV is associated with increased mortality in critically ill patients. Even in cases of mild hyperglycemia, clinical outcomes with smaller glucose fluctuations are superior to those achieved through strict glycemic control with larger fluctuations. Insulin infusion remains the gold standard for managing stress-induced hyperglycemia in critically ill patients. Optimized insulin therapy, particularly through continuous subcutaneous insulin infusion (CSII) compared to multiple daily injections, demonstrates superior glycemic stability. A study involving 80 critically ill patients revealed that insulin infusion therapy (IIT) significantly reduced GV. Using the Continuous Overlapping Net Glycemic Action (CONGA) metric, which measures glycemic variability over time, GV decreased by 0.65 (95% CI [−1.16, −0.14], $p = 0.01$) without increasing the incidence of severe hypoglycemia. Compared to the insulin sliding scale (ISS), the IIT group required correction for hypoglycemia at a rate of 2.77% ($p = 0.38$), down from 6.8%. Further research indicates that IIT shows significant advantages in reducing glycemic variability, though its impact on improving survival rates in critically ill patients requires validation through larger-scale studies (Almagthali et al. 2024).

Non-pharmacological approaches center on dietary modification and exercise interventions. Strategic carbohydrate management coupled with increased dietary fiber intake effectively mitigates glucose fluctuations. Exercise regimens incorporating combined aerobic and resistance training show measurable impact. This was demonstrated by a study of 50 type 2 diabetes patients showing significant reductions in sensor glucose standard deviation (SDSG) and CV after 1 week of supervised training (Liu, Jin, et al. 2024; Liu, Zhang, et al. 2024). A study involving 252 participants found that regular physical activity (PA) and adherence to the Mediterranean diet (MeDi) independently improved glycemic control and clinical outcomes in patients with T2DM (Radić et al. 2025).

5.2 | Microbiota-Targeted Interventions in Diabetes Management

Emerging evidence highlights gut microbiota modulation as a promising therapeutic strategy for diabetes, with current approaches encompassing dietary modifications, probiotic/prebiotic supplementation, and fecal microbiota transplantation (FMT) (Fernández-Ruiz 2021; Chen, Li, et al. 2025; Chen, Wang, et al. 2025). Dietary intervention represents a fundamental approach, with fiber-rich diets demonstrating particular efficacy in promoting beneficial bacterial growth and enhancing SCFA production (Akanyibah et al. 2025; Zhou et al. 2025). Clinical observations confirm that oat bran, inulin, and other fiber-rich substrates significantly alter microbial metabolic patterns, increasing SCFA generation and consequently improving glycemic control (Dell'Olio et al. 2024). Probiotic administration directly modifies gut microbial composition, with studies demonstrating that *Bifidobacterium* supplementation enhances intestinal barrier function, reduces inflammatory markers, and improves glucose metabolism in diabetic models (Guo et al. 2024). Prebiotics such as fructooligosaccharides selectively stimulate beneficial bacterial proliferation, with documented effects on ameliorating insulin resistance through microbial ecosystem modulation (Zhang et al. 2022). While FMT shows therapeutic potential in restoring microbial homeostasis for diabetes management, its clinical application remains constrained by technical challenges and safety considerations (Su et al. 2025; Yan et al. 2025). This intervention requires further standardization and rigorous evaluation before widespread implementation (Kraithong et al. 2025).

5.3 | Integrated Therapeutic Approaches for Diabetes and Its Complications

Emerging evidence underscores the critical role of glycemic variability in diabetes progression through its modulation of gut microbiota metabolic reprogramming. This mechanistic insight necessitates a paradigm shift in treatment strategies, where optimal glycemic control must be coupled with microbiota stabilization for maximal therapeutic efficacy (Ebrahimi et al. 2024). Pharmacologically, combination therapies leveraging complementary mechanisms demonstrate synergistic benefits (Nyambuya et al. 2020; Ma et al. 2024). GLP-1 RAs exemplify this dual action, exhibiting not only glucose-lowering effects but also microbiota-modulating properties via intestinal hormone regulation and barrier function enhancement (Chu et al. 2025; Verma et al. 2025). Clinical data reveal significant microbial composition changes in type 2 diabetes patients following 48-week dulaglutide treatment, suggesting microbiota-mediated glycemic benefits (Liang et al. 2024). Metformin represents another multifaceted agent, with proven capabilities in both glycemic control and microbiota modulation. Beyond its primary antidiabetic action, metformin increases beneficial bacterial abundance, thereby improving gut microbial ecology (Sun et al. 2018). These findings highlight the therapeutic advantage of agents that simultaneously target glycemic stability and microbial homeostasis.

FMT demonstrates considerable therapeutic potential, with preclinical studies confirming its efficacy in restoring

microbial diversity and ameliorating metabolic endotoxemia in diabetic models (Suez et al. 2018; Zikou et al. 2024; Qin, Fan, et al. 2025; Qin, Zheng, et al. 2025). Multi-omics analyses integrating 16S rRNA sequencing, metagenomics, and metabolomics reveal substantial interindividual variability in gut microbial composition and metabolic patterns among diabetes patients (Peng et al. 2019; Qin, Fan, et al. 2025; Qin, Zheng, et al. 2025), providing a scientific foundation for personalized intervention strategies. We propose a novel precision probiotic therapy framework targeting specific microbial consortia involved in SCFA production and BA metabolism. This approach achieves dual improvement in glycemic variability and systemic inflammation by strategically modulating microbial networks. Such targeted interventions may disrupt the vicious cycle of "hyperglycemia-dysbiosis-metabolic dysfunction," representing a paradigm shift in diabetes therapeutics. The development of predictive microbial-metabolic signatures will be crucial for standardizing personalized microbiota-based interventions. Future research should focus on establishing response biomarkers to optimize both glycemic control and complication prevention, while maintaining cost-effectiveness in clinical implementation.

6 | Outlook

6.1 | Development of Personalized Glycemic Variability Monitoring

Technological innovations and personalized medicine approaches are converging to transform glycemic control strategies. Recent advances in noninvasive glucose monitoring have yielded novel wearable devices incorporating microneedle arrays and wireless transmission, demonstrating both high accuracy and biocompatibility (Tong et al. 2025). Concurrently, artificial intelligence has revolutionized glucose management, with reinforcement learning algorithms optimizing insulin regimens by analyzing large-scale glycemic data to improve time-in-range (TIR) metrics (Dénes-Fazakas et al. 2024). Precision medicine applications now enable genotype-guided pharmacotherapy, particularly in monogenic diabetes where genetic profiling directs optimal drug selection (Elk and Iwuchukwu 2017; Foddha et al. 2025). Lifestyle interventions have similarly evolved toward personalization, with body composition analysis (including visceral adipose tissue and mid-thigh muscle area) informing targeted exercise protocols that more effectively mitigate glycemic excursions in type 2 diabetes (Liu, Jin, et al. 2024; Liu, Zhang, et al. 2024). The integration of these technological and clinical advances provides a multidimensional framework for precision glycemic management, ushering in an era of intelligent, individualized diabetes care.

6.2 | Glycemic Variability and Gut Microbiota: Research Challenges and Future Directions

The causal relationship between glycemic variability and gut microbiota remains contentious, with bidirectional mechanisms incompletely understood. Current evidence suggests hyperglycemia alters the intestinal microenvironment (e.g., osmotic pressure, inflammation), suppressing beneficial bacteria (e.g., *Bifidobacterium*, *Lactobacillus*) while promoting pathogenic colonization (e.g., Enterobacteriaceae), thereby compromising gut barrier function and exacerbating metabolic dysregulation. Conversely, emerging hypotheses posit that microbial dysbiosis may initiate glycemic fluctuations via endotoxemia, chronic low-grade inflammation, and insulin resistance. Key limitations include reliance on cross-sectional data and animal models, which obscure temporal causality, alongside confounding variables like host genetics and dietary interventions. Future studies should employ longitudinal cohorts, interventional trials (e.g., microbiota transplantation or targeted glycemic control), and causal inference methods (e.g., Mendelian randomization) to delineate directional relationships and molecular interaction networks.

6.3 | Future Directions in Glycemic Variability and Gut Microbiota Research

Advancements in multi-omics technologies and dynamic monitoring systems are driving three fundamental paradigm shifts in this field: First, *dynamic interaction mapping* will emerge through synchronized continuous glucose monitoring (CGM) and real-time microbial metabolite profiling (e.g., SCFAs, secondary BAs), enabling spatiotemporal resolution of host-microbiome crosstalk. Second, *precision modulation strategies* will evolve by leveraging host-microbial co-metabolic signatures (e.g., personalized metagenomic and metabolic phenotypes) to develop targeted probiotic/prebiotic formulations, bacteriophage therapies, and chrono-optimized antidiabetic drug regimens. Third, *convergence science approaches* will integrate organoid models, gut-on-a-chip microfluidics, and machine learning-derived biomarker networks from high-dimensional datasets, facilitating diabetes endotyping and novel therapeutic targeting.

These transformative approaches promise to resolve existing mechanistic controversies while accelerating clinical translation of "gut-glycemic axis" interventions—shifting the therapeutic paradigm from symptomatic management to etiology-targeted treatment.

7 | Conclusion

Through systematic review and in-depth analysis, this study reveals the complex interaction between blood glucose fluctuations and gut microbiota metabolic activities in the development of diabetes complications. The research demonstrates that blood glucose fluctuations not only directly induce vascular and neural damage, but also trigger systemic metabolic disorders and chronic inflammation by reshaping the metabolic network of gut microbiota, thereby accelerating the progression of diabetes complications. Based on the "gut-organ axis" theoretical framework, this paper systematically elucidates the cascade mechanism linking blood glucose fluctuations, gut microbiota dysregulation, metabolic disorders, and organ damage. These findings provide new theoretical support and potential therapeutic pathways for the prevention and clinical management of diabetes complications. Future research should focus on developing personalized blood glucose monitoring technologies, conducting in-depth analysis of molecular mechanisms underlying

blood glucose fluctuations–gut microbiota interactions, and designing targeted comprehensive intervention strategies to offer more precise and effective treatment options for diabetes patients.

Author Contributions

Yongjie Xu, Di Chen, and Wei Pan contributed to the study's conceptualization, methodology, and original draft preparation; Huiru Yang, Yiqiong Zhang, and Mi Liu were responsible for data curation, formal analysis, and visualization; Changyudong Huang, Yinxue Zhong, and Haizhi Li conducted the investigation and provided resources; Liying Zhu and Chengcheng Li performed validation and reviewed and edited the manuscript; Rui Yan supervised the project, administered its execution, and acquired funding. All authors read and approved the final manuscript. Yongjie Xu is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Ethics Statement

As this is a review article, no ethical approval was required, as the study did not involve human or animal participants.

Consent

All authors have provided their explicit consent for the publication of this manuscript.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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