International Journal of Research in Medical Sciences
Pandian S et al. Int J Res Med Sci. 2025 Oct;13(10):4518-4526
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012
DOI: https://dx.doi.org/10.18203/2320-6012.ijrms20253215

Review Article

The gut-vascular axis in diabetes: exploring impaired blood flow, cardiovascular disease, and peripheral arterial complications

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Received: 29 June 2025
Revised: 02 August 2025
Accepted: 02 September 2025

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ABSTRACT

The gut-vascular axis-a dynamic, bidirectional interface between the gut microbiota and vascular system-has emerged as a pivotal regulator of metabolic homeostasis and cardiovascular health, especially in the context of type 2 diabetes mellitus (T2DM). This comprehensive review delineates how microbial dysbiosis, compromised intestinal barrier function, and microbial metabolite imbalances contribute to chronic inflammation, endothelial dysfunction, and vascular complications such as atherosclerosis, coronary artery disease (CAD), and peripheral arterial disease (PAD). Key microbial metabolites such as short-chain fatty acids (SCFAs), trimethylamine-N-oxide (TMAO), and secondary bile acids influence insulin resistance and vascular remodeling. The manuscript also highlights the indirect modulatory roles of SGLT2 inhibitors and GLP-1 receptor agonists on gut microbial dynamics and vascular integrity. Current evidence underscores significant inter-individual variability in microbiota profiles, necessitating personalized therapeutic strategies. Despite compelling preclinical data, translational research in human cohorts remains limited. The review further explores cutting-edge microbiome-based therapeutic strategies, including probiotics, fecal microbiota transplantation (FMT), and engineered microbial therapeutics, while identifying critical research gaps in the development of microbiota-targeted interventions for diabetic vascular disease. Overall, the gut-vascular axis is positioned as a promising frontier in precision medicine for metabolic and cardiovascular complications in diabetes.

Keywords: Gut microbiota, Gut-vascular axis, Type 2 diabetes mellitus, Endothelial dysfunction, Short-chain fatty acids, Trimethylamine-N-oxide, Microbial dysbiosis, Intestinal permeability, Cardiovascular complications, Microbiome-targeted therapy

INTRODUCTION

The gut-vascular axis describes the dynamic bidirectional interplay between the gut and vascular systems. This interaction is primarily mediated by the gut microbiota, intestinal barrier integrity, and systemic signaling pathways of the host. The gut microbiome plays a pivotal role in regulating host vascular and metabolic functions, with implications for chronic diseases, including diabetes and cardiovascular disease (CVD).[1]

A healthy gut microbiome is defined by high microbial diversity, stability, and a balanced ratio of major bacterial phyla, especially *Firmicutes* and *Bacteroidetes*. It is

enriched with beneficial genera, such as *Bifidobacterium*, *Lactobacillus*, *Faecalibacterium*, and *Akkermansia*, which are instrumental in maintaining intestinal barrier integrity, regulating immune homeostasis, and producing critical microbial metabolites, especially SCFAs, such as acetate, propionate, and butyrate.[1,2] These SCFAs exhibit vasoprotective, anti-inflammatory, and metabolic-regulating effects, largely by enhancing endothelial nitric oxide (NO) production, suppressing oxidative stress, and modulating inflammatory pathways.[2,3]

In contrast, gut dysbiosis-marked by reduced microbial diversity, proliferation of pro-inflammatory taxa (e.g., *Enterobacteriaceae*, *Clostridium difficile*), and diminished SCFA-producing bacteria-is associated with increased intestinal permeability or "leaky gut." This allows for the translocation of microbe-derived endotoxins, such as lipopolysaccharide (LPS), into the systemic circulation, leading to metabolic endotoxemia, a driver of chronic low-grade inflammation, endothelial dysfunction, and insulin resistance, all of which contribute significantly to macrovascular and microvascular complications, particularly in individuals with diabetes.[1,4]

In T2DM, especially under conditions of poor glycemic control and metabolic syndrome, intestinal permeability is often increased, further facilitating the translocation of LPS into the bloodstream. This endotoxemia triggers systemic inflammation and contributes to vascular injury, atherogenesis, and dysregulation of lipid metabolism. Compromised NO signaling exacerbates microvascular dysfunction, a hallmark of diabetic vascular pathology.[3,5]

Prospective cohort studies and experimental models have demonstrated a direct correlation between elevated circulating LPS levels and the severity and instability of atherosclerotic plaques. Notably, patients with ST-elevation myocardial infarction (STEMI) exhibit significantly higher LPS concentrations than those with stable CAD or healthy individuals.[4,6,7] This supports the role of microbial translocation and systemic inflammation in atherosclerotic plaque destabilization, reinforcing the importance of maintaining gut barrier integrity and microbial homeostasis for vascular health.

PATHOPHYSIOLOGICAL MECHANISMS LINKING THE GUT AND VASCULAR HEALTH IN DIABETES

Diabetes mellitus is a multifactorial metabolic disorder that affects multiple organ systems, notably the gastrointestinal and cardiovascular systems. Recent advances underscore the pivotal role of the gut microbiome in regulating vascular health, particularly in T2DM. A critical mechanism involves the disruption of the intestinal barrier, commonly referred to as “leaky gut”and dysbiosis, an imbalance in the gut microbial community. These changes facilitate the translocation of microbial components, such as LPS, into the systemic circulation, which activates inflammatory signaling cascades that impair endothelial function and compromise vascular integrity.[8]

In T2DM, gut microbial alterations are often characterized by a decrease in beneficial commensals, particularly *Faecalibacterium prausnitzii*, a prominent butyrate-producing species integral to maintaining gut homeostasis and anti-inflammatory signaling pathways. A reduced abundance of *F. prausnitzii* has been correlated with intestinal dysfunction and systemic inflammation in diabetic conditions, suggesting a direct link between gut microbial shifts and vascular pathology.[8]

One promising mechanism involves the microbial anti-inflammatory molecules (MAM) secreted by *F. prausnitzii*. These molecules have been demonstrated to reinforce gut barrier function by modulating tight junction proteins, particularly zona occludens-1 (ZO-1). ZO-1 plays a central role in regulating intestinal epithelial permeability, and its upregulation is associated with the restoration of barrier integrity.[1] In preclinical models (e.g., db/db mice, a widely accepted T2DM model), recombinant MAM supplementation significantly improved ZO-1 expression and reestablished intestinal barrier function, highlighting the therapeutic potential of microbial metabolites in mitigating gut-derived inflammation and subsequent vascular injury.[1]

KEY MECHANISMS LINKING GUT DYSBIOSIS TO VASCULAR DYSFUNCTION

Endotoxin translocation and inflammation

The translocation of gut-derived LPS into the circulation is a major driver of chronic low-grade inflammation in diabetes. Elevated systemic LPS levels have been shown to activate toll-like receptor 4 (TLR4) signaling pathways, promoting endothelial dysfunction, increased vascular permeability, and atherogenesis.[1]

Altered microbial metabolites and TMAO elevation

Dysbiosis in diabetes also modifies the profile of microbial metabolites, including an increase in TMAO levels. TMAO has been implicated in the impairment of endothelial function, promotion of vascular stiffness, and enhancement of inflammatory atherosclerotic processes, all of which contribute to the increased cardiovascular risk in individuals with diabetes.[1]

Disruption of NO bioavailability

NO is a key vasodilator that maintains vascular tone and endothelial health. In diabetic dysbiosis, both inflammatory cytokines and harmful microbial metabolites inhibit endothelial NO synthase (eNOS) activity, leading to reduced NO production, vascular stiffness, and an elevated risk of hypertension and arterial dysfunction.[1]

THE GUT-VASCULAR AXIS AND PAD IN DIABETES

The human microbiota encompasses a diverse ecosystem of microorganisms, including bacteria, archaea, viruses (mainly bacteriophages), and eukaryotes (primarily yeasts), that maintain a symbiotic relationship with the host and play a pivotal role in metabolic, immunological, and vascular homeostasis.[9]

T2DM is a rapidly escalating global health concern owing to its growing prevalence and substantial contribution to morbidity and mortality.[10] As of 2019, over 460 million adults worldwide were diagnosed with diabetes, with projections estimating an increase to 783.2 million by 2045.[11] An accumulating body of evidence has highlighted the critical role of the gut microbiota in the pathogenesis of metabolic disorders, such as T2DM.[10]

Hyperglycemia, a central feature of T2DM, is implicated in increased intestinal permeability through glucose transporter 2 (GLUT2)-mediated mechanisms, facilitating the translocation of microbial products, such as LPSs, into the systemic circulation.

This phenomenon contributes to chronic low-grade inflammation, immune activation, and metabolic endotoxemia.[10,12]

Furthermore, diabetes mellitus predisposes individuals to macrovascular and microvascular complications, including PAD, retinopathy, and nephropathy, by promoting endothelial dysfunction and vascular inflammation.[13] These complications are exacerbated by gut barrier dysfunction and dysbiosis-induced systemic inflammation.[13]

MECHANISMS OF GUT DYSBIOSIS AND VASCULAR COMPLICATIONS IN DIABETES

Gut dysbiosis, defined as an imbalance between beneficial and pathogenic gut microbiota, manifests in three major patterns: loss of beneficial microbial species, overgrowth of potentially harmful bacteria, and reduced microbial diversity.[14] These disruptions potentiate metabolic endotoxemia, characterized by LPS translocation into the bloodstream, which activates inflammatory pathways, including NF-κB and the NLRP3 inflammasome, thereby inducing insulin resistance and systemic inflammation.[15,16]

In T2DM, dysbiosis is consistently associated with an overrepresentation of opportunistic pathogens and a decline in health-promoting bacteria, such as *Akkermansia muciniphila* and *Bifidobacterium spp*.[17] This dysbiotic state enhances the production of pro-inflammatory cytokines (e.g., TNF-α, IL-6, and IL-1β), increases oxidative stress, and compromises the gut-vascular barrier (GVB), thereby facilitating endothelial dysfunction, a precursor to atherosclerosis and CVD.[18-20]

Among the key microbial metabolites implicated in vascular pathology is TMAO, a hepatic derivative of the gut microbiota metabolism of choline and carnitine. Elevated TMAO levels promote foam cell formation, vascular inflammation, and plaque instability, thereby accelerating atherosclerosis and increasing the risk of myocardial infarction and stroke.[21-23]

Additionally, dysbiosis leads to decreased production of SCFAs, such as butyrate, acetate, and propionate. These metabolites have anti-inflammatory effects, support epithelial integrity, and modulate blood pressure and insulin sensitivity.[24] A reduction in SCFAs further exacerbates endothelial dysfunction and promotes vascular complications.[14]

Alterations in bile acid metabolism, another consequence of dysbiosis, result in the accumulation of cytotoxic bile acids and depletion of protective secondary bile acids, contributing to dyslipidemia, oxidative stress, and atherosclerosis progression.[24]

Moreover, microbiota-derived toxic metabolites, such as phenylacetylglutamine (PAGln), stimulate platelet hyperactivity and thrombosis, further linking dysbiosis to adverse cardiovascular outcomes, including heart failure (HF).[24]

FUTURE PERSPECTIVES IN GUT-VASCULAR AXIS RESEARCH IN DIABETES

Emerging data indicates that diabetes affects the blood microbiota, which is shaped by gut-derived bacteria and their metabolites, thereby influencing insulin resistance and offering fresh diagnostic and therapeutic possibilities.[25] Fermenting indigestible food materials, producing vitamins, and controlling energy metabolism via SCFA generation all depend on the gut microbiota. Disturbances in gut barrier integrity can cause bacterial translocation, influencing host metabolism and distant organ function through compounds obtained from bacteria like SCFA, BA, and TMAO.[26] A major target for therapeutic interventions in diabetes is gut flora, as changes in its lead to metabolic malfunction and inflammation.[27]

Gut microbiota and T1D

The gut microbiota and the occurrence of T1D are strongly correlated, according to Li et al gut microbiota and innate immunity affect T1D development and incidence. T1D prototypes are non-obese diabetic (NOD) mice. NOD mice lacking the MyD88 protein do not develop T1D. MyD88 is necessary for IL-1 and TLR signaling. This impairment alters the distal intestinal microbiome. MyD88-deficient NOD animals protected from diabetes transmitted gut microbiota to wild-type female NOD mice, reducing pancreatitis and autoimmune glycosuria. Bacteroidetes dominate the gut microbiota of preclinical T1D; butyrate-producing bacteria are few, and microbial diversity is low.

The immune system's responses are regulated by SCFAs like acetate and butyrate, which lower autoimmune T cells and increase regulatory T cells. SCFA supplementation reduces disease development in animal models. Although gut microbiota composition has changed, FMT has not reduced T1D incidence. *Akkermansia muciniphila* may be a protective probiotic. In mice, *E. coli* LPSs inhibit innate immune responses and reduce T1D. T1D-prone newborns have lower microbial diversity and elevated inflammatory bacterial communities in their gut microbiome. Animal studies reveal microbiota-mediated immune regulation, but human research is scarce, requiring microbiome-targeted T1D therapies. In animal models, *E. coli* LPSs decrease innate immune responses and lower T1D incidence; however, *Bacteroides dorei* LPS does not. Intraperitoneal *E. coli* LPS improved autoimmune responses in T1D mice, while oral treatment in NOD mice increased local immunity. After seroconversion, genetically predisposed T1D infants have decreased alpha diversity and increased inflammatory bacterial communities in their gut microbiota. After islet autoantibodies develop, Bacteroidetes dominate the gut microbiota in preclinical T1D, reducing stability and diversity. Islet autoimmunity, indicated by persistent islet antigen autoantibodies in early childhood, precedes T1D development, supporting the gut microbiota's role in disease pathogenesis.[28]

Gut microbiota and vascular health in diabetes

The gut microbiota maintains vascular health and metabolic equilibrium, affecting diabetes pathogenesis. The gut microbiome composition of people with T1D is altered, with opportunistic pathogens (*Clostridiales*, *Oscillibacter*, *Bacteroides*) increasing and beneficial butyrate-producing bacteria (*Bifidobacteria*, *Roseburia*, *Alistipes*) decreasing. Impaired gut barrier integrity is linked to these microbial alterations, resulting in metabolic dysfunction, systemic inflammation, and increased intestinal permeability. Hyperglycemia, a major cause of diabetic complications, is connected to microbiome dysbiosis, especially *D. formicigenerans*, which degrades mucin and increases gut permeability. Microbial imbalances that increase inflammation contribute to microvascular and macrovascular problems such as diabetic nephropathy and CVD.

Reduced butyrate impairs mucosal integrity and immune regulation, whereas increased TMAO from microbial metabolism of dietary phosphatidylcholine causes endothelial dysfunction and atherogenesis. Disease duration and glycemic variability are linked to *Ruminococcaceae*, a family involved in lipid metabolism and inflammation, which may raise cardiovascular risk. The gut microbiome modulates vascular health by producing bioactive metabolites such as SCFAs, secondary bile acids, and TMAO, which affect systemic metabolism.[29,30]

According to Velmurugan et al dysbiosis in the gut and blood bacteria contributes to vascular problems. Microbial translocation caused by gut barrier breakdown induces systemic inflammation and endothelial dysfunction. Microbial metabolites like TMAO and SCFAs affect vascular health; TMAO promotes atherosclerosis, while SCFA deficiency reduces endothelial function. Microvascular (nephropathy, retinopathy) and macrovascular (atherosclerosis, CAD) problems are accelerated by persistent hyperglycemia and microbiota-driven inflammation. Emerging potential indicators and therapeutic targets for enhancing vascular health in diabetes are the blood bacteria and their metabolites.[25,30,31]

Gut dysbiosis and CVDs

Changes in gut microbiota in individuals with HF are associated with worse outcomes and higher inflammation. Notably, they have lower levels of butyrate-producing bacteria such as *Lachnospiraceae* and *Faecalibacterium*, which are linked to gut homeostasis and overall health. In the intestinal biofilms of HF patients, earlier research found enrichment of *Eubacterium rectale* and *Faecalibacterium*; however, contradictory results point to methodological variations.

TMAO is a powerful predictor of HF outcomes, linked to congestion and left atrial stress, whereas changes in the secondary-to-primary bile acid ratio in HF patients may contribute to metabolic dysfunction.

Additionally, HF shares microbiota-derived uremic toxins (indoxyl sulfate, p-cresyl sulfate) with chronic kidney disease (CKD), which increases cardiovascular risk. Targeting bile acid pathways (e.g., ursodeoxycholic acid) has shown potential in limited studies.[32-34]

FUTURE RESEARCH DIRECTIONS

High-throughput sequencing and metabolomics may identify microbial fingerprints linked to atherosclerosis in people with diabetes who have vascular problems, enabling more accurate diagnoses.[27,30,35] Understanding how microbial byproducts like TMAO and SCFAs affect vascular inflammation, insulin sensitivity, and endothelial function could improve treatments.[26] Because microbial populations differ, precision medicine targeting specific microbial dynamics must be studied across age, race, and gender groups.[25,30] Statins and β-blockers may lower IHD risk by restoring gut bacterial burden. Additionally, gut microbiome characteristics may help diagnose IHD in metabolically matched controls.[36] Interprofessional collaboration among systems biology, microbiology, cardiology, and endocrinology is essential. Integrating AI and machine learning with genomics technologies (e.g., metagenomics, transcriptomics, proteomics, metabolomics) may help identify microbial signatures linked to vascular dysfunction and develop personalized treatment plans (Table 1).[33,37]

Table 1: Summarizes key findings, limitations, and future directions in gut-vascular axis research related to diabetes, highlighting the importance of interdisciplinary collaboration and the need for advanced research methodologies.

Headings	Important findings	Limitations	Future directions	References
Vision for the future	The gut microbiota has a crucial role in vascular inflammation and insulin resistance, leading to diabetic problems.	Current research mostly relies on observational studies, making causal inferences challenging	Conduct longitudinal and interventional research to determine the causal relationship between gut microbiota changes and vascular problems in diabetes.	41 and 42
	SCFAs produced by gut bacteria, have been demonstrated to improve glucose metabolism and vascular function.	The exact processes by which SCFAs achieve these benefits are unknown.	Investigate the molecular processes via which SCFAs affect vascular health and glucose metabolism.	43
Interdisciplinary opportunities	Integrating cardiology, endocrinology, and microbiome research can provide a thorough understanding of the gut-vascular connections in diabetes.	Interdisciplinary studies are complex and require substantial coordination among diverse research teams.	Establish collaborative frameworks and funding opportunities to support interdisciplinary research initiatives.	41 and 42
	Advanced technologies like metabolomics and genomics can uncover novel pathways by which gut microbiota affect vascular health in diabetes.	High-throughput technologies generate vast amounts of data, posing challenges in data integration and interpretation.	Develop robust bioinformatics tools and standardized protocols to manage and analyze complex datasets.	43
Call to action	There is a pressing need for clinical trials focusing on microbiome-based diagnostics and interventions to assess their efficacy in preventing and treating vascular complications in diabetes.	The generalizability of clinical trial results may be impacted by individual microbiome variability.	Create tailored medical strategies that take into consideration the variations in each person's microbiome to improve the effectiveness of treatment.	41 and 42
	It is imperative that regulatory rules change to facilitate the creation and application of treatments based on the microbiome.	The particular difficulties presented by microbiome-based treatments might not be sufficiently addressed by the regulatory frameworks in place now.	Collaborate with regulatory organizations to create policies that will enable the safe and efficient application of microbiome research to clinical settings.	41 and 42

PRECISION MEDICINE AND FUTURE INTERVENTIONS

Promising microbiome-targeted interventions include:

Probiotics and prebiotics

Certain strains (e.g., *Lactobacillus*, *Saccharomyces boulardii*) may reduce inflammation and enhance cardiovascular function. Strains like *Bifidobacterium breve*, *Bifidobacterium infantis*, *Bifidobacterium longum*, *Lactobacillus acidophilus*, *Lactobacillus fermentum*, *Lactobacillus plantarum 299v*, and *Lactobacillus rhamnosus GR-1* have demonstrated benefits in conditions such as T2DM, Alzheimer's disease, colorectal cancer, and CVDs. Clinical evidence, however, remains inconsistent, with conflicting results on butyrate's role in tumor growth and concerns about probiotic translocation in immunocompromised patients. Randomized controlled trials also lack sufficient safety data to establish long-term benefits and risks.[32-34]

FMT

FMT is emerging as a potential treatment for gut dysbiosis in diabetes, but clinical trials are needed to assess its efficacy in metabolic and vascular health. Through fecal transfer from healthy donors, FMT restores intestinal microbial balance. It has cure rates near 90% and was approved by the FDA in 2013 for recurrent *Clostridium difficile* infections; capsule-based FMT has comparable success. Its potential in neurological diseases, diabetes, cancer, and ulcerative colitis is under investigation.

Proposed mechanisms include pathogen clearance, immune modulation, and metabolite restoration. Though generally safe, concerns such as infection risks and donor scarcity necessitate further research and personalized approaches.[26,38]

Microbial enzyme inhibitors

Targeting microbial production of TMAO may offer a safer and more effective method to lower vascular disease risk.[32-34]

Diabetes and the oral microbiota

Through oral-fecal transfer, the oral microbiota influences gut composition. Patients with T2DM exhibit distinct oral microbiome changes, with potential contributions to systemic inflammation. Diabetes alters oral bacterial makeup, increasing susceptibility to periodontal disease and tooth loss. Understanding the oral-gut axis may shed light on diabetes progression and complications.[28]

Engineering gut bacteria for therapy

Advances in genetic engineering have enabled therapeutic modifications of gut bacteria. *Lactococcus lactis* has been used in T1D and oral mucositis treatment, while engineered *Lactobacillus jannaschii* reduces HIV infection. *Salmonella* and *Clostridium* have been employed in cancer therapy to deliver ssgenes, cytokines/ antitumor agents. Bacterial secretion systems and CRISPR technologies further expand their therapeutic utility.

Drug-microbiota interactions

Gut microbiota significantly affects drug absorption, metabolism, and efficacy. They influence bioavailability of drugs such as aspirin, amiodarone, metformin, and digoxin. For instance, *E. lentum* alters digoxin metabolism, while *E. coli* β-glucuronidases convert irinotecan into toxic compounds. Understanding these interactions is essential for optimizing personalized therapy.[23,38-40]

BRIDGING RESEARCH AND CLINICAL PRACTICE

Despite promising findings, major knowledge gaps persist: Identifying microbial bioactive compounds that directly impact vascular health.[13] Establishing causal links between dysbiosis and vascular disease.[37] Exploring genetic and epigenetic host-microbiota relationships, and creating standardized microbiome analysis protocols to enhance study reproducibility.[13] Since most current research offers only snapshot views of the microbiome, longitudinal studies are essential to track changes in gut composition during treatment and disease progression (Table 2).[34,37]

Table 2: Summary of studies investigating the gut-vascular axis and its impact on diabetes, cardiovascular, and metabolic health (2017-2025).

Study	Condition	Intervention	Sample (Human)	Key findings
Kootte et al[44]	Metabolic syndrome, obesity	FMT	38	Results showed a decrease in HbA1c levels and increased insulin sensitivity among the subjects.
Smits et al[45]	Metabolic syndrome	FMT	20	Stool microbiome resembled vegan donors after allogenic FMT
Sata et al[46]	Diabetes mellitus	Probiotics (Lactobacillus casei)	70	Results reported an increase in *Lactobacillus* levels and a decrease in total systemic bacteria levels.
Roshanravan et al[47]	Diabetes mellitus	Butyrate + prebiotics	60	Results showed an increase in *A. muciniphila* and microRNA-375, whereas levels of Kruppel-like factor 5 decreased.
Allegretti et al[48]	Obesity	FMT	22	Decrease in taurocholic acid and an altered microbiome towards lean donor profile were noted.
Horvath et al[49]	Obesity, diabetes mellitus	Probiotics + prebiotics	26	Results reported a decrease in Hip circumference, Zonulin and LP(a). Quality of life improved among subjects.
Oraphruek et al[50]	Obesity	Multispecies synbiotic	63	An increase in antioxidant capacity and decrease in malondialdehyde, and *Firmicutes/Bacteroidetes* ratio were noted.
De la Cuesta-Zuluaga et al[51]	Diabetes	Metformin	112	Study found an increase in the levels of *A. muciniphila, Butyrivibrio, Bifidobacterium bifidum* and *Megasphaera*.
Tsai et al[52]	Diabetes	Liraglutide	52	Increase in *Bacteroides dorei* and *Roseburia inulinivorans* were noticed. The levels of *Ruminococcaceae* sp. decreased.
Niu et al[53]	Diabetes	Metformin + Liraglutide	32	Results showed decreased levels of *Blautia, Dialister* and an altered microbiota.

Continued.

Study	Condition	Intervention	Sample (Human)	Key findings
Akshay et al[54]	Cardiovascular health	Gut-cardiac axis analysis	Review	Gut microbiota influences cardiac health via inflammation and metabolites.
Rajan et al[55]	CVD, diabetes	Gut-brain-immune axis	Review	Gut dysbiosis alters glucose metabolism, increasing cardiovascular risk.
Pieralice et al[56]	Diabetes, CVD	Lifestyle intervention	Review	Bone-vascular axis contributes to CVD in diabetes.
Zarębska et al[57]	CVD	Gut microbiota analysis	Review	SCFAs and gut dysbiosis linked to atherosclerosis.
Kaur[58]	CKD, vascular calcification	Gut microbiota, vascular calcification	Review	Gut dysbiosis contributes to vascular and bone disease in CKD.
Rodrigues et al[59]	CKD, vascular calcification	Gut-bone-vascular axis analysis	Review	Gut dysbiosis linked to vascular calcification and bone disease.
Stamenic et al[60]	Diabetes, heart disease	Cohort study	1810	Gut microbiome diversity linked to metabolic syndrome and obesity.
Engelen et al[61]	Type 2 diabetes	Cohort study	9,808	Diabetes significantly increases risk of cardiovascular events.
Balint et al[35]	Diabetes, vascular damage	Gut-derived metabolites	90	Certain gut-derived metabolites correlate with endothelial dysfunction.

This table presents key research findings on the gut-vascular axis, highlighting the role of gut microbiota, FMT, probiotics, prebiotics, and pharmacological interventions in metabolic and cardiovascular health. Studies include randomized controlled trials, cohort studies, and reviews examining their effects on insulin sensitivity, vascular function, gut microbiome composition, and cardiovascular risk factors in individuals with diabetes, obesity, and related conditions.

CONCLUSION

This review convincingly establishes the gut-vascular axis as a key mechanistic and therapeutic link between gut microbiota dysbiosis and vascular complications in diabetes. Through a well-curated synthesis of preclinical models, human cohort studies, and emerging microbial biomarkers, it elucidates how microbial translocation, endotoxemia, and metabolite imbalances (e.g., SCFAs and TMAO) precipitate endothelial dysfunction and atherosclerosis in diabetic individuals. By integrating current knowledge on gut-derived inflammation, microbial metabolites, and host-microbe interactions, the manuscript highlights promising interventions such as SCFA augmentation, TMAO modulation, and the restoration of microbial balance via next-generation probiotics and FMT. The inclusion of host-specific and therapy-induced modulation (e.g., via SGLT2 inhibitors and GLP-1 agonists) enriches its translational relevance. However, the manuscript appropriately acknowledges existing limitations in human clinical data, strain-specific microbial responses, and the need for multi-omics-driven, longitudinal trials. Future research should prioritize personalized microbiota profiling and interventional validation to translate these insights into viable clinical strategies for preventing and treating diabetic vascular disease.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

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Cite this article as: Pandian S, Yathindra MR, Shrivastava V, Prystupa Y. The gut-vascular axis in diabetes: exploring impaired blood flow, cardiovascular disease, and peripheral arterial complications. Int J Res Med Sci 2025;13:4518-26.