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Blood microbiome and cardiometabolic disease: insights, therapeutic strategies, and future directions

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Cardiometabolic diseases (CMDs), particularly cardiovascular disease (CVD), type 2 diabetes mellitus (T2DM), and chronic kidney disease (CKD), emerged as primary contributors to global morbidity and mortality. In addition to traditional factors, recent studies demonstrated that blood microbiomes may also promote the development or progression of these CMDs. Traditionally, blood was considered sterile; however, the notion of blood as a sterile environment has been challenged by findings demonstrating the presence of a microbiome in both healthy and disease states. Although there has been a tremendous expansion in human microbiome research, with hundreds of projects underway globally the blood microbiome has not received the same level of attention as its gut and oral counterparts. The circulating microbiome is an emerging trend that has drawn a high level of interest in the biomedical field, given its potential to generate predictive biomarkers and the means to screen for potential pathogens. This comprehensive review explores the latest advancements in blood microbiome research, emphasizing biomarker identification, diagnostic tools, treatment modalities, and prevention in CMDs. We also delve into existing challenges and present a future-oriented treatment strategy using advanced methods. Deciphering the blood microbiome's role in disease could lead to the classification of patient subgroups, enabling precision microbiota-based therapies.

KEYWORDS

CMDS, blood microbiome, dysbiosis, biomarkers, therapeutics

Introduction

Cardiometabolic disorders (CMDs), including type 2 diabetes mellitus (T2DM), chronic kidney disease (CKD), and CVD represent a major global health challenge characterized by their rising prevalence and profound social and economic burdens (Ralston and Nugent, 2019). The global burden of cardiometabolic disorders is substantial, with an estimated 523 million individuals affected by CVD (Fuster), 422 million by T2DM (Zhou et al., 2016), and 847 million by CKD (Jager et al., 2019). By 2030, the global economic burden of cardiometabolic diseases is projected to reach approximately US$6.3 trillion, effectively doubling current costs (Arena et al., 2015). These diseases are driven by a complex interplay of genetic, behavioral, and environmental factors, including genetic predispositions, sedentary lifestyles, poor dietary habits, and environmental exposures such as air pollution (Ralston and Nugent, 2019). In recent years, the gut microbiota has emerged as a key player in the pathogenesis of numerous diseases, with extensive research elucidating its role in modulating metabolic, immune, and inflammatory pathways (Velmurugan et al., 2020). These staggering figures highlight the widespread prevalence of these conditions and their significant impact on global health, emphasizing the critical need for effective management and intervention strategies. In this study, we aim to comprehensively characterize the composition and diversity of the blood microbiome in patients with CMD. Additionally, we provide a focused discussion on the potential mechanisms through which the blood microbiome may influence the pathogenesis and progression of CMD, offering insights into its role in disease development.

Nearly 70% of medical decision-making relies on laboratory findings, underscoring the critical role of diagnostic testing in clinical practice. Key laboratory results, such as biochemistry and hematology profiles, are often available on the day of hospital admission, providing essential insights into a patient's health status and guiding immediate therapeutic interventions (Bissonnette and Bergeron, 2010). These tests serve as foundational tools for diagnosing conditions, monitoring disease progression, and tailoring treatment strategies, highlighting their indispensable value in modern healthcare. Triggering microbiome analysis is critical for enabling timely clinical decisions and interventions, particularly within the first 6 hours of sepsis presentation, to effectively reduce morbidity and mortality. Rapid identification of microbial profiles and their associated pathogenic mechanisms can guide targeted antimicrobial therapy and personalized treatment strategies, improving patient outcomes. Integrating microbiome analysis into early sepsis management protocols represents a promising approach to enhancing the precision and efficacy of care in this life-threatening condition (Kumar et al., 2006). Although blood has traditionally been considered a sterile environment, recent advances in high-throughput sequencing technologies have challenged this notion, revealing the presence of a low-abundance but diverse blood microbiome even in healthy individuals (Tan et al., 2023). In 2001, Nikkari and colleagues were among the first to detect bacterial DNA in the blood, challenging the long-held notion of blood sterility (Nikkari et al., 2001). This finding was further supported by Moriyama et al., who confirmed the presence of a blood microbiome in healthy individuals (Moriyama et al., 2008). Additionally, Castillo et al. investigated the interactions between the blood microbiome and other human microbiomes, shedding light on its potential systemic role (Castillo et al., 2019). In recent years, research has increasingly focused on elucidating the composition and functional significance of the blood microbiome and its association with human health and disease. Emerging evidence suggests that the blood microbiome may contribute to the development and progression of various conditions, including T2DM, colorectal cancer, inflammatory bowel diseases (IBD), hypertension, myocardial infarction (MI), coronary heart disease, kidney complications, and HIV infection (Potgieter et al., 2015; Amar et al., 2019; Shah et al., 2019; Søby et al., 2020; Gedgaudas et al., 2022; Khan et al., 2022a; Guo et al., 2023; Jagare et al., 2023; Sampaio et al., 2023). These findings underscore the importance of further exploring the blood microbiome as a potential biomarker and therapeutic target in a wide range of diseases.

Sequencing technologies have unveiled novel biomarkers like the blood microbiome, advancing disease diagnosis and prevention. Moving beyond traditional culture-based methods, modern molecular techniques such as 16S rRNA sequencing, qPCR, and shotgun metagenomics have confirmed the presence of a blood microbiome in healthy individuals. These tools enable precise characterization of microbial communities, offering new insights into their role in health and disease and their potential as diagnostic and therapeutic targets (Tan et al., 2023). It is crucial to acknowledge the limitations in study design, including small sample sizes, limited taxonomic resolution, methodological variability, and the difficulty in differentiating cell-free microbial DNA from viable microbial cells. Additionally, environmental contamination remains a common challenge that can confound results. Addressing these limitations is essential for ensuring the accuracy and reliability of blood microbiome research and its translation into clinical applications (Castillo et al., 2019; Berg et al., 2020). To ensure an accurate definition of the blood microbiome, it is critical to minimize microbial DNA contamination by adhering to strict aseptic techniques during sample collection and implementing thorough disinfection of the skin puncture site (Doern et al., 2019). DNA sequencing methods are susceptible to contamination from microbial DNA present in laboratory reagents and kits (Salter et al., 2014), a challenge further amplified by the low microbial biomass and high host DNA background in blood samples, which increases the noise-to-signal ratio (Glassing et al., 2016). However, evidence indicates that contamination alone cannot fully account for the observed microbial signals; instead, the blood microbiome is thought to originate, at least in part, from microbial translocation from sites such as the gut (Castillo et al., 2019). Despite significant advancements, the biology of the blood microbiome remains poorly understood, particularly its functional interactions with human health and disease. Further research is needed to elucidate its role and potential as a diagnostic or therapeutic target.

In this review, we examine the latest advancements in understanding the composition and role of the blood microbiome

in human health and disease, supported by specific disease-related insights. We delve into the identification of blood-based biomarkers, address methodological and interpretative challenges, and explore innovative therapeutic strategies enabled by cutting-edge technologies. Furthermore, we propose future research directions aimed at elucidating the functional mechanisms of the blood microbiome, emphasizing an integrative approach to unravel its complex interactions and potential clinical applications.

Blood microbiome dysbiosis in CMDs

Our understanding of the role of the microbiota in human health and disease is built on epidemiological, observational, molecular, and animal-modeling experiments. The microbiota plays an important role in human health and disease. Healthy individuals' blood microbiome composition and diversity are largely overlooked (Païssé et al., 2016; Castillo et al., 2019; Tsafarova et al., 2023; Di Gloria et al., 2024). The major blood phyla with their respective roles are summarized in Table 1. Emerging evidence highlights the association between dysbiosis in the human blood microbiome and the pathogenesis of various diseases, including chronic kidney disease, diabetes mellitus, and cardiovascular disease (Figure 1).

Blood microbiome alteration in chronic kidney disease

Chronic kidney disease is a growing healthcare burden affecting about 13.4% of the population worldwide (Guo et al., 2025). In the last few decades, CKD patients have steadily increased. In adults, hypertension and diabetes are the leading causes of CKD, while congenital anomalies of the kidney and urogenital tract account for the majority of CKD etiologies in children. In children, CKD affects neurocognitive abilities, school performance, growth, quality of life, and the cost of medical care (Wehedy et al., 2022). CKD is associated with the development of severe health conditions like cardiovascular diseases, neurological complications, adverse pregnancy outcomes, and hyperkalemia. Factors contributing to CKD progression include activation of the renin-angiotensin-aldosterone system, proteinuria, chronic inflammation, and repetitive acute kidney injury (Wehedy et al., 2022). In addition, existing evidence showed an association between gut dysbiosis, inflammation, and CKD (Evenepoel et al., 2017). Gut dysbiosis disrupting intestinal barrier function in CKD permits the translocation of gut-derived toxins, bacterial products, and intact bacteria into the circulation, resulting in inflammation (Vaziri et al., 2016). This circulating microbiome in CKD is indirectly evidenced by higher levels of endotoxins, LPS levels, and gut uremic toxins measured in the blood (Andersen et al., 2017).

A previous study has shown higher levels of *Legionella, Serratia, Yersinia, Acinetobacter, Pseudomonas, Lysobacter, Hyphomicrobium, Bacillus, Sediminibacterium*, and *Pseudarcicella*, and lower levels of *Stenotrophomonas, Paracoccus, Sphingomonas*, and *Tyzzer* were found in CKD patients (Shah et al., 2019). Demmer et al. reported the association between fewer Proteobacteria levels with subgingival plaque and elevated systemic inflammation, suggesting that the oral microbiome could impact the circulating microbiome in hemodialysis patients (Demmer et al., 2017). Shah et al. examined blood fractions with leukocytes, revealed different microbes than cell-free blood, and showed a strong negative correlation between glomerular filtration and higher circulating Proteobacteria in CKD patients (Shah et al., 2021). Another study found higher levels of *Staphylococcus* and *Streptococcus* and predominant *Legionella* and *Enhydrobacter* in the blood of kidney patients (Shah et al., 2021). Intriguingly, most of the blood bacteria in CKD patients are not typical urinary tract commensals, suggesting that disturbances in urinary mucosa may not contribute to the dysbiotic blood microbiome (Perez-Carrasco et al., 2021). Sumida et al. used 16S rRNA sequencing and ITS analysis to compare the circulating microbiome in hemodialysis patients and healthy individuals. They found elevated Actinobacteria and reduced Proteobacteria levels in patients who died from cardiovascular events, with these microbial changes significantly correlated to Nrf2, a key regulator of antioxidative responses. This correlation persisted across demographic and clinical factors and was linked to a slight increase in cardiovascular mortality risk. By focusing on the "cell-free"

TABLE 1 The predominant bacterial phyla in the human blood.

Phyla	Description
Proteobacteria	Proteobacteria are Gram-negative bacteria that can expand in the blood during dysbiosis, leading to diseases like sepsis and inflammation. An example is *Escherichia coli*, which can cause bacteremia and systemic infections.
Bacteroidetes	This phylum comprises aerobic and anaerobic Gram-negative bacteria, which can occasionally be present in the blood. They are known for breaking down carbohydrates, with their metabolic byproducts influencing host inflammation and immune responses. An example is *Bacteroides fragilis*, which has been linked to bacteremia and systemic inflammation, particularly in pathological conditions.
Actinobacteria	This phylum is primarily composed of Gram-positive bacteria with high guanine and cytosine content. While typically beneficial, such as *Bifidobacterium bifidum* in the gut microbiota, some Actinobacteria can enter the blood under certain conditions, leading to bacteremia or systemic infections, particularly in immunocompromised individuals.
Firmicutes	This phylum comprises Gram-positive bacteria with low guanine and cytosine content. While typically found in the gut, some Firmicutes can enter the blood under certain conditions, causing bacteremia or infections. They are phenotypically diverse, with some capable of forming endospores. An example is *Roseburia hominis*, which, though beneficial in the gut, has been occasionally associated with bloodstream infections in dysbiosis or disease states.

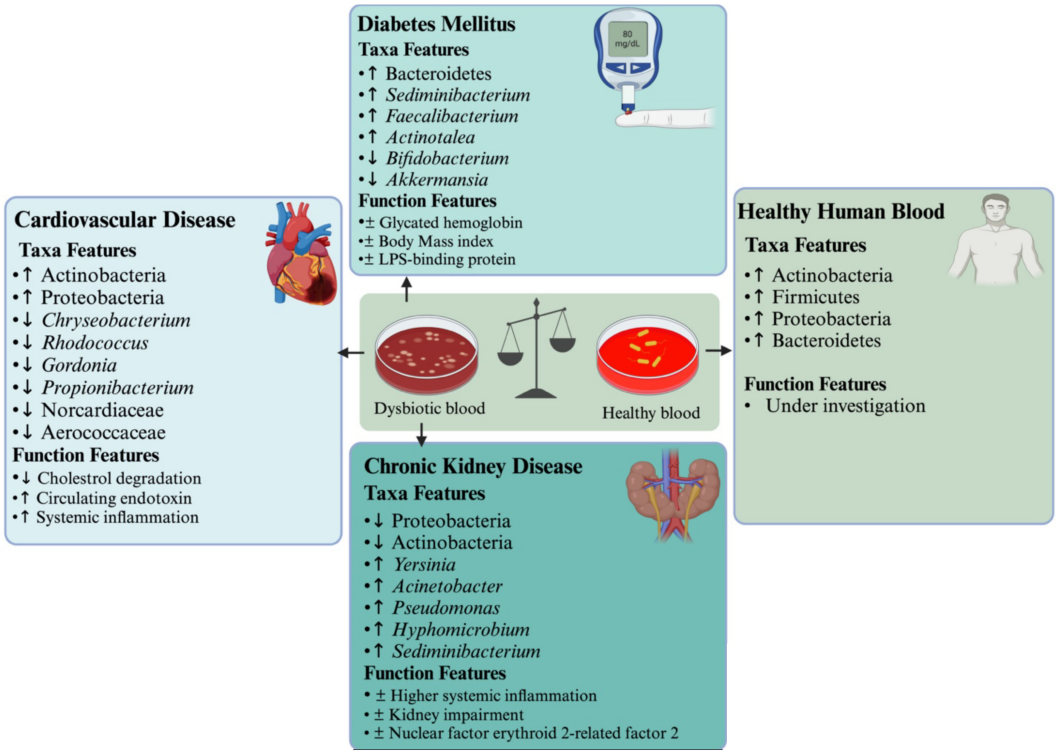

FIGURE 1
Perturbations in the blood microbiome and their association with cardiovascular disease, diabetes, and chronic kidney disease contribute to systemic inflammation and impaired endotoxin clearance. The (↑) symbol indicates higher species abundance, (↓) represents lower species abundance, an asterisk (*) denotes statistical significance, and (±) marks correlation.

circulating microbiome in serum or plasma, the study highlights its direct impact on immune cells and cardiac myocytes, offering a minimally invasive approach for assessing cardiovascular risk in end-stage renal disease (Sumida et al., 2021a). In another study, Sumida et al. reported depleted Proteobacteria levels in CVD patients, alongside elevated *Staphylococcus* genus, suggesting a link between altered microbiome composition and cardiovascular comorbidities in hemodialysis patients (Sumida et al., 2021b).

Additionally, Merino-Ribas et al. observed significant alterations in the genera levels, including *Cutibacterium, Pajaroellobacter, Devosia, Hyphomicrobium*, and *Pelomonas* in the CKD peritoneal dialysis patients with and without vascular calcification. The study has also shown the association between vascular calcification and an increased risk of all-cause mortality in CKD peritoneal dialysis patients, highlighting the potential role of microbial composition as a factor linked to vascular calcification and mortality risk in patients (Merino-Ribas et al., 2022). Patients at a higher mortality risk showed changes in *Eubacterium eligens* in the gut and the presence of the *Devosia* genus in the blood. Despite no disparities in uremic toxins, intestinal translocation markers, and inflammatory parameters between CKD-peritoneal dialysis patients with and without vascular calcification, soluble CD14 (sCD14), a nonspecific marker of monocyte activation, positively correlated with the severity of vascular calcification (Merino-Ribas et al., 2022). Hence, the gut *Eubacterium eligens* group, blood *Devosia*, and circulating sCD14 merit further exploration as potential biomarkers for vascular calcification, CVD, and CKD. Simões-Silva and colleagues explored the intricate world of peritoneal bacteria, pitting it against counterparts in various body regions, with blood emerging as the closest contender. Despite this close resemblance, their compelling results underscored substantial distinctions between peritoneal and blood bacteria (Simoes-Silva et al., 2020). In another study, Simões-Silva proposed that bloodstream bacteria primarily stem from the dysbiotic gut microbiome in end-stage renal disease, and hemodialysis, to some extent, exacerbates microinflammation by promoting gut microbiota translocation due to impaired gut barrier function (Simoes-Silva et al., 2018). Recently, Sampaio et al. investigated kidney transplant recipients (KTRs) and found evidence supporting the existence of a circulating microbiome that differs from the profiles of the gut and oral microbiomes. This circulating microbiome is characterized by a limited number of operational taxonomic units, representing a shared microbiome. Notably, the blood of KTRs contains a distinctive, relatively low-abundance microbiome, with a dominant of Proteobacteria and Firmicutes (Sampaio et al., 2023). The blood microbiome is now a hot topic. Hence, its composition and leveraging technological advancements are crucial for enhancing our understanding of the blood microbiome and its role in the development of kidney and other human-related diseases.

Blood microbiome alteration in type 2 diabetes mellitus

Type 2 diabetes mellitus is a metabolic disorder characterized by abnormally high blood glucose levels resulting essentially from the resistance of body cells to the effect of insulin (Sedighi et al., 2017). Diabetes is described by a state of chronic low-grade inflammation with abnormal expression and production of multiple inflammatory cytokines such as interleukins and tumor necrosis factor (Dandona et al., 2004). The prevalence of T2DM has reached epidemic proportions worldwide (Sedighi et al., 2017). Recent WHO statistics state that the number of individuals with T2DM around the world was approximately 382 million in 2013, and it is projected to be more than 590 million by 2035 year (Upadhyaya and Banerjee, 2015). In addition, 85% of premature deaths from metabolic syndromes happen in developing countries, of which about 80% are associated with diabetes (Upadhyaya and Banerjee, 2015). Based on WHO reports, T2DM is anticipated to be the seventh leading cause of death by 2030. T2DM is the consequence of a complex interaction between different degrees of genetic susceptibility and environmental factors such as stress, diet, and infections (Sedighi et al., 2017). Circulating microbiota refers to a complex community of microorganisms present in the blood of humans and other animals, primarily associated with immune system modulation and inflammation, as well as potential contributions to certain pathological conditions.

A previous D.E.S.I.R. cohort study has shown a higher 16S rDNA concentration in those who eventually developed T2DM and abdominal adiposity (Amar et al., 2011). A prospective cohort study with primarily Chinese volunteers uncovered the predictive value of the blood genus *Bacteroides* for T2DM (Qiu et al., 2019). *Bacteroides* is a probiotic that is available in the human intestine, yet when it drifts to other parts of the body, it can become pathogenic, causing infections in the mouth, nervous system, and bloodstream (Amar et al., 2011). The enrichment of *Bacteroides* observed in both T2DM and control groups, with a higher prevalence in T2DM, highlights its potential role in T2DM pathology. However, the mechanisms by which *Bacteroides* contribute to the development or progression of T2DM remain poorly understood. Given its dual role as a gut commensal and a potential systemic pathogen, further research is needed to elucidate the mechanisms through which *Bacteroides* influence systemic inflammation and contribute to T2DM pathology.

Subsequent analysis revealed a 28% elevation in gut microbiome levels among diabetes patients compared to a 4% level in healthy individuals, with T2DM patients exhibiting increased gram-positive bacteria, including the *Atopobium cluster* and *Clostridium coccoides*, similar to type 1 diabetes (T1D) (Sato et al., 2014). Another study has shown a higher abundance of Proteobacteria in the blood of patients with T1D (Yuan et al., 2024). A European study has revealed the association between elevated blood sugar and insulin levels with higher levels of blood bacterial DNA (D'Aquila et al., 2021). Donath et al. revealed significant correlations among glycated hemoglobin, body mass index, inflammatory markers, and LPS-binding protein, highlighting a clear association between diabetes and the blood microbiome, with notably elevated levels of the LPS-binding protein in patients with T2DM (Donath et al., 2019). Ghaemi et al. found that patients with diabetes had higher levels of *Ralstonia* spp. compared to non-diabetics and observed higher Proteobacteria in T2DM than in those without diabetes. Genus-level variations were observed in the gut microbiome, blood plasma, and cellular levels. In diabetic patients, *Akkermansia, Bifidobacterium*, and *Faecalibacterium* decreased in leukocytes, while the pre-diabetic group exhibited higher levels of *Lactobacillus, E. coli*, and *Bacteroides fragilis* genera compared to healthy individuals; all these bacteria were elevated in the T2DM group (Ghaemi et al., 2021). Moreover, a recent study found no significant differences at the phyla levels, however, the genera, including *Aquabacterium, Xanthomonas*, and *Pseudonocardia*, were depleted, while genera, e.g., *Sediminibacterium*, *Pseudoclavibacter, Alishewanella*, and *Actinotalea* were enriched in the patient with T2DM compared to the healthy group (Qiu et al., 2019). The involvement of the phylum Proteobacteria and the genus *Sediminibacterium* in the pathophysiology of T2DM remains insufficiently characterized. Future research should emphasize longitudinal investigations to establish causality, multi-omics approaches to integrate functional genomics with metabolomics, and validation studies in larger, diverse cohorts to enhance the generalizability of findings.

Blood microbiome alteration in cardiovascular diseases

The relationship between the blood microbiome and CVD has emerged as a prominent area of research, highlighting the critical role of the microbiome in systemic health. However, significant gaps remain in our understanding of the precise mechanisms and the multifactorial nature of these interactions. A previous study has shown that depletion in blood bacterial DNA content and enrichment in the Proteobacteria levels in the blood microbiology predicts long-term cardiovascular prognosis (Amar et al., 2013). Building on this, another study conducted a year later further reported a higher abundance of the phyla Actinobacteria and Proteobacteria in patients with CVD compared to the control group (Dinakaran et al., 2014), reinforcing the potential role of these microbial shifts in cardiovascular health. Amar et al. (2013) reported significant reductions in cholesterol-degrading bacterial families and genera (e.g., Norcardiaceae, Aerococcaceae, *Gordonia*, *Propionibacterium*, *Chryseobacterium*, and *Rhodococcus*) in patients with myocardial infarction compared to healthy individuals (Amar et al., 2019). Liberale et al. (2020) found elevated levels of the gut commensal bacterium Escherichia coli, specifically Escherichia coli lipopolysaccharides, in the blood of coronary thrombosis patients (Liberale et al., 2020). The Escherichia coli lipopolysaccharides strain was linked to disease pathology, including low-grade endotoxemia, proinflammatory cytokine release, elevated soluble P-selectin (indicating platelet activation), and zonulin, a marker of gut permeability (Carnevale et al., 2020). The link between *Escherichia coli* lipopolysaccharides and zonulin indicates the

strain's potential role in enabling bacterial translocation from the gut to the bloodstream. Consistent with the findings of Amar et al. (2013) and Dinakaran et al. (2014), we observed a higher abundance of the phyla Proteobacteria and Actinobacteria in MI patients compared to healthy individuals (Khan et al., 2022a). In another study, we analyzed the blood microbiome composition of healthy controls, acute MI patients, and chronic MI patients, finding a higher abundance of Proteobacteria in acute MI patients compared to chronic MI patients and controls (Khan et al., 2022b). Lawrence et al. reported that *Kokuria, Pseudomonadota*, and *Enhydrobacter* from the Actinobacteria were significantly associated with cardiovascular mortality risk, including an inverse correlation between *Enhydrobacter* and CVD mortality risk (Lawrence et al., 2022). Furthermore, a recent study reported an enrichment of Gammaproteobacteria, Proteobacteria, Ralstonia pickettii, Ralstonia, Burkholderiaceae, and Burkholderiales in the unstable angina group. In contrast, the AMI group exhibited a higher abundance of Bacteroidales, Bacteroidia, Bacteroidota, Clostridia, and Firmicutes (Chen et al., 2024). These findings suggest that elevated levels of Proteobacteria are associated with CVD, as Proteobacteria produce lipopolysaccharides (LPS), which play a critical role in the pathogenesis of CVD (Lin et al., 2020). LPS can induce inflammation indirectly by generating molecular patterns associated with non-microbial risk factors and directly through microbial-associated molecular patterns (MAMPs) (Bonhomme et al., 2024). LPS might also contribute to endotoxemia, which drives the development of inflammatory conditions such as obesity, liver dysfunction, and CVD (Sciarra et al., 2023).

In a recent study integrating blood microbiome and metabolomics, we found reduced AMP, L-leucine, and L-arginine levels in the mTOR pathway in MI patients compared to healthy controls (Khan et al., 2025). AMP regulates cellular energy balance by activating AMPK to inhibit mTOR signaling. Its downregulation may impair energy sensing, leading to unchecked mTOR activity despite energy deficits (Khan et al., 2025). This aberrant signaling can result in excessive energy consumption, ultimately driving cellular energy depletion and apoptosis. L-leucine activates mTORC1, which is crucial for protein synthesis and cardiac repair. Its reduction weakens mTORC1 signaling, leading to muscle atrophy and impaired recovery. Similarly, L-arginine, essential for nitric oxide synthesis and mTOR signaling, supports blood flow and cellular repair. Its depletion increases oxidative stress, and endothelial dysfunction, and hinders tissue recovery, exacerbating cellular damage (Khan et al., 2025). These findings enhance cardiovascular research by uncovering microbiome-metabolome interactions with implications for immunology, metabolism, and microbiology. By linking basic and translational science, they support personalized diagnostics and therapies. Future studies should focus on longitudinal designs, multi-omics integration, and diverse cohort validation to establish causality and improve generalizability.

Underlying mechanisms of CMDs

Herein, we briefly explored the mechanisms underlying CKD, T2DM, and CVD, as shown in Figure 2. Microbiome dysbiosis has been implicated in the pathogenesis of CKD through mechanisms involving microbial metabolites and systemic inflammation (Noce et al., 2022). Dysbiosis often leads to an overabundance of bacteria producing trimethylamine N-oxide (TMAO), a metabolite derived from dietary choline and carnitine (Valenbreder et al., 2023). Elevated TMAO levels promote oxidative stress and inflammation in renal tissues, contributing to endothelial dysfunction and fibrosis (Florea et al., 2024). Additionally, microbial translocation of lipopolysaccharides (LPS) from gram-negative bacteria into the bloodstream can trigger immune activation, further exacerbating kidney damage (Wang et al., 2023). These processes impair renal

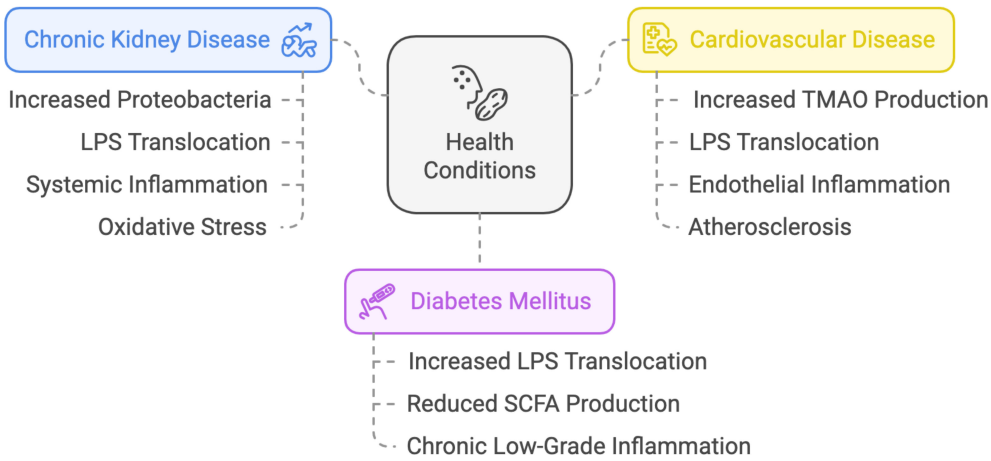

FIGURE 2
Mechanistic insights into chronic kidney disease, diabetes, and cardiovascular disease.

filtration and function, leading to the accumulation of uremic toxins and a progressive decline in kidney health (Lim et al., 2021). The interplay between dysbiosis, TMAO, and inflammation highlights the blood microbiome's role in CKD progression.

In addition, the blood microbiome influences diabetes mellitus through mechanisms that disrupt metabolic homeostasis and promote insulin resistance. Dysbiosis often results in increased levels of LPS, a component of gram-negative bacterial cell walls, which enters the bloodstream and triggers chronic low-grade inflammation (Di Vincenzo et al., 2024). This inflammation impairs insulin signaling pathways in peripheral tissues, leading to insulin resistance and hyperglycemia (Chen et al., 2015). Furthermore, dysbiosis can alter the production of short-chain fatty acids (SCFAs), which play a role in regulating glucose metabolism and insulin secretion. Reduced SCFA levels exacerbate pancreatic beta-cell dysfunction, further compromising glucose regulation (Rekha et al., 2024). The combined effects of inflammation, insulin resistance, and beta-cell dysfunction underscore the contribution of blood microbiome dysbiosis to the development and progression of DM.

Subsequently, blood microbiome dysbiosis contributes to CVD through pathways involving microbial metabolites, endothelial dysfunction, and systemic inflammation. Elevated levels of TMAO, produced by gut microbiota from dietary precursors, are strongly associated with atherosclerosis and plaque formation (Zhu et al., 2020). TMAO promotes endothelial inflammation, foam cell formation, and platelet hyperreactivity, all of which accelerate atherosclerotic progression (Oktaviono et al., 2023). Additionally, dysbiosis can lead to increased LPS translocation into the bloodstream, triggering systemic inflammation and oxidative stress, further damaging vascular tissues (Violi et al., 2023). These processes result in endothelial dysfunction, arterial stiffness, and increased risk of myocardial infarction or stroke (Tuttolomondo et al., 2020). The role of microbiomes in modulating TMAO and inflammation highlights its significance in CVD pathogenesis.

Factors affecting blood microbiome composition

Variability in the blood microbiome may be attributed to a combination of host-related, environmental, and methodological factors, as shown in Figure 3. Host-specific characteristics, such as genetic background, age, immune status, and underlying health conditions, including disease severity and treatment histories, play a significant role in shaping microbial profiles (Alanazi et al., 2024). Additionally, environmental and demographic factors, such as geographic location and lifestyle differences, further contribute to this variability by influencing microbial exposure and colonization dynamics (Parizadeh and Arrieta, 2023). Methodological inconsistencies across studies, including variations in sample collection protocols, DNA extraction techniques, sequencing platforms, and bioinformatics pipelines, can also introduce technical biases, affecting the detection, quantification, and characterization of microbial communities. These methodological disparities, coupled with the heterogeneity of studied populations, may impact the reproducibility and comparability of findings, underscoring the need for standardized approaches in blood microbiome research (Mancin et al., 2024). Temporal fluctuations, driven by changes in health status, treatment regimens, or external exposures (Karwowska et al., 2024), further

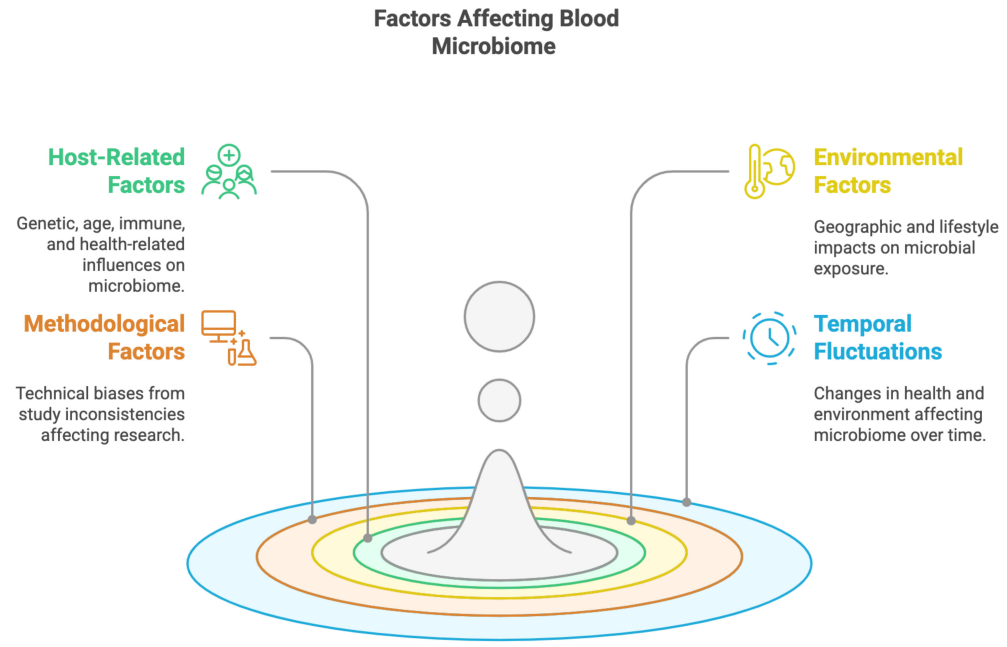

FIGURE 3
Factors affecting blood microbiome composition.

complicate the interpretation of microbial profiles, highlighting the multifaceted nature of factors influencing the blood microbiome.

To enhance the reliability and reproducibility of blood microbiome research, we advocate for standardized methodologies across studies. This includes harmonizing protocols for sample collection, storage, DNA extraction, sequencing, and bioinformatics analysis to minimize technical variability. Rigorous quality control measures, such as the use of negative and positive controls, are essential to mitigate contamination and ensure data accuracy. Collaborative efforts, including large-scale consortia and shared databases, should facilitate data integration from diverse studies, enabling robust meta-analyses and cross-validation. Advanced computational approaches—such as machine learning, multi-omics integration, single-cell sequencing, metatranscriptomics, and metabolomics can further enhance microbial characterization, improve disease prediction, and refine diagnostic and therapeutic strategies. By promoting standardization, fostering collaboration, and leveraging cutting-edge analytical tools, we aim to establish a more comprehensive understanding of the blood microbiome's role in health and disease, ultimately unlocking its potential as a diagnostic and therapeutic target in personalized medicine.

Blood microbiota-based therapeutics and future interventions

Blood acts as a liquid medium carrying the elements necessary for host life. In recent years, the concept of human blood microbiota has been developed, and this has caused serious debates as it may shelve the idea that "blood is a sterile environment" that has been in existence for years. Although there are different hypotheses that the blood microbiota originates from the gut microbiota, its origin is not clearly understood because it contains different phyla (Castillo et al., 2019). The concept of human blood microbiota and its potential therapeutic implications represents a groundbreaking advancement in medicine. If the blood microbiome is confirmed as a key factor in health and disease, it could unlock a range of innovative treatment strategies with transformative clinical implications (Almeida et al., 2022). For instance, (i). In today's medicine, where fecal microbiota transplantation is being considered for treatment, blood transplantation is much more easily feasible. (ii). Potential therapies include targeted probiotic formulations designed to modulate blood microbiota, microbial metabolite-based treatments utilizing postbiotics, and immunomodulation strategies to regulate cytokine production and enhance immune responses. (iii). Dietary and lifestyle interventions, including nutraceuticals and lifestyle modifications, could support a healthy blood microbiota. Advanced diagnostic tools for microbiota profiling and real-time monitoring could enable early disease detection and personalized interventions. (iv). Antimicrobial therapies, such as selective antimicrobials and phage therapy, could eliminate harmful microbes while preserving beneficial ones. (v). Personalized blood microbiota transplants, both autologous and allogeneic, could restore microbial balance, while CRISPR-based microbial engineering may enable gene editing to enhance beneficial properties or reduce pathogenicity. (vi). Nanotechnology-based delivery systems, such as targeted drug delivery and microbial carriers, could ensure precise therapeutic applications, making blood

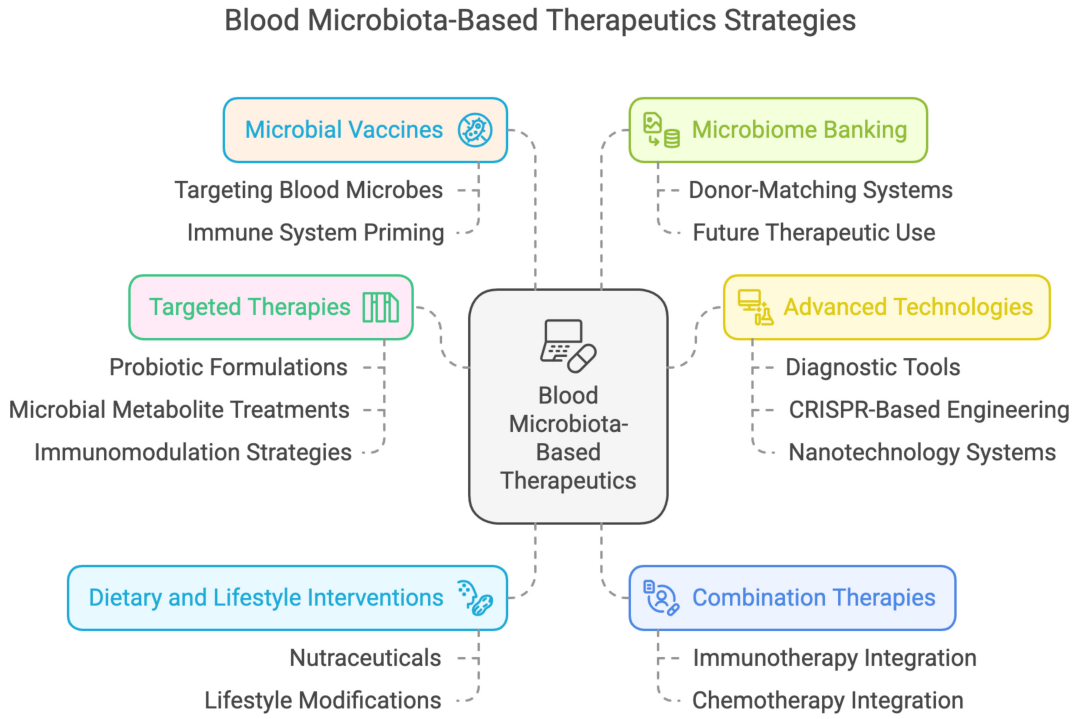

FIGURE 4
Blood microbiota-based therapeutics strategies and future interventions.

microbiota manipulation a promising avenue for future medicine. (vii). Combination therapies offer a multi-modal approach by integrating blood microbiota modulation with treatments like immunotherapy, chemotherapy, or antibiotics to enhance efficacy. A holistic strategy also considers the interplay between blood and gut microbiota for comprehensive health benefits. (viii) Microbial vaccines could target harmful blood microbes, preventing their colonization and priming the immune system for improved responses to infections and cancers. (ix). Additionally, microbiome banking could enable the preservation of healthy blood microbiota samples for future therapeutic use, with donor-matching systems optimizing transplantation outcomes (Figure 4).

Limitations and future research directions

Microbiome research highlights the integral role of coexisting microbes in human biology, challenging the notion of human blood sterility. Rare microbial entry into the bloodstream can trigger severe complications, including sepsis and septic shock (Hotchkiss et al., 2016). Controversy persists among researchers on whether the blood hosts a core microbiome or whether these microbes disseminate from other body niches like the gut, mouth, and skin. For instance, Tan and colleagues have lately been unable to identify the microbiome in healthy human blood. They contradicted the hypothesis of a structured blood microbiome by detecting 117 random microbial species in healthy human blood, most of which originated from different body regions and some of which demonstrated evidence of replication outside the bloodstream (Tan et al., 2023). Although studies have begun to uncover the blood microbiome composition and its mechanisms by which blood microbiome promotes the development and progression of diverse human diseases, however, there are many details remain unknown. Some of the most important unanswered questions that remained include: Why do some healthy individuals have microbes in their blood while others do not, and what is the underlying mechanism for this phenomenon? How do microbes in the blood "deceive" the immune system and live in harmony with the immune system? What is the specific role of bacteria in the onset of a particular disease? What are the advantages and disadvantages of the blood microbes? The blood microbiome in the blood of the diseased population is much higher than that of the healthy population. Is it related to immunity?

Multiple human microbiome studies actively correlate disease states with the structure of the blood microbial community. Interpreting the significance of these cross-sectional studies is challenging due to numerous confounding variables in patient populations. Factors such as structural variations, standardized procedures, incomplete microbial databases, contamination concerns, limited reference databases, unquantified metabolome read-outs, the necessity for functional characterization, and the need for longitudinal studies complicate the analysis. Fortunately, many of these issues can be addressed by conducting intervention studies, standardized protocols, decontamination, improved sequencing technologies, larger sample sizes, rigorous study designs, and strain identification. Further research is necessary to understand the correlation between specific blood bacteria, certain diseases, and their underlying mechanisms.

Conclusions

Different viewpoints exist on the presence of microbiome in the blood of healthy individuals and its association with various human diseases. Some authors support the concept of a healthy blood microbiome, while others suggest that the microbiome disseminates into the blood from other body sites, especially the gut and oral niches. However, it is undeniable that over the past decade, multiple studies have detailed blood microbiome composition and diversity, revealing their association with human health and diseases. Current understanding recognizes the presence of microbes in the blood, emphasizing the complexity of detection and caution needed when associating their genetic material with live bacteria. Observing shifts in the blood microbiome in diabetes, CKD, and CVD suggests their potential role in disease development. Crucial for establishing the blood microbiome as viable biomarkers and innovative therapeutic targets is future research on microbial translocation and physiological mechanisms, with significant implications for healthcare and disease management.

Author contributions

IkK: Conceptualization, Data curation, Investigation, Writing – original draft. ImK: Data curation, Writing – review & editing. AB: Investigation, Writing – review & editing. YX: Data curation, Investigation, Validation, Writing – review & editing. PX: Data curation, Investigation, Writing – review & editing. XX: Conceptualization, Funding acquisition, Supervision, Writing – review & editing. LZ: Conceptualization, Supervision, Validation, Visualization, Writing – review & editing.

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