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Role of microorganism in cardiovascular diseases: a comprehensive review

Aroop Mohanty[1†], Parul Singh[1†], Ankita Kabi[2], Amogh Verma[3], Ranjit Sah[4,5*]

[1] Department of Microbiology, All India Institute of Medical Sciences, Gorakhpur, Uttar Pradesh, India.

[2] Department of Anaesthesia and Critical Care, All India Institute of Medical Sciences, Gorakhpur, Uttar Pradesh, India.

[3] Rama Medical College Hospital and Research Centre, Hapur, India.

[4] Department of Microbiology, Tribhuvan University Teaching Hospital Institute of Medicine, Maharajgunj, Kathmandu, Nepal.

[5] Department of Microbiology, Dr. D. Y. Patil Medical College, Hospital and Research Centre, Dr. D. Y. Patil Vidyapeeth, Pune 411018, Maharashtra, India.

**Correspondence:ranjitsah@iom.edu.np*

† Equally contributed

Abstract

Background: Cardiovascular disease (CVD) is a major global health challenge, with increasing prevalence despite advancements in treatment. Recently, the gut microbiota's role in human metabolism, immunity, and disease processes, including CVD, has gained significant attention. This review aims to clarify the connection between gut microorganisms and the initiation and advancement of cardiovascular disease (CVD).

Methods: A comprehensive review was conducted, focusing on the significant microorganisms associated with CVD, the mechanisms through which the gut microbiome influences CVD, and the diagnostic modalities used to detect these microorganisms.

Results: CVD can arise from various infectious and non-infectious agents, with certain microorganisms being implicated in heart failure, atherosclerosis, and other cardiovascular conditions. Dysbiosis, which refers to an imbalance or disturbance in the gut microbiota, is linked with heightened inflammation and onset of atherosclerosis. Advanced molecular biology tools, such as PCR and next-generation sequencing, have proven effective in detecting microbial pathogens associated with CVD. The gut microbiome's interaction with the host occurs through various pathways, and disruptions in its composition or metabolites can contribute to CVD risks.

Conclusion: The gut microbiota has a pivotal part in modulating systemic immune responses and metabolic dysfunctions, contributing to CVD development. Understanding this relationship offers potential therapeutic targets and strategies for preventing and treating CVD. Future research should focus on specific microbial strains, microbiome-mediated metabolites, and personalized interventions to harness the gut microbiota's therapeutic potential.

Keywords: *: cardiovascular disease; gut microbiota; dysbiosis; atherosclerosis; inflammation; microbial pathogens; diagnostic modalities; next-generation sequencing; metabolites; therapeutic interventions.*

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Evidence in Context

- Cardiovascular diseases (CVDs) are a leading global cause of death, affecting economic productivity and life quality.
- Gut microbiota significantly influences metabolism and CVD development.
- Specific microorganisms are linked to diseases like endocarditis and atherosclerosis.
- Changes in gut microbiota impact blood lipid composition and coronary artery disease.
- Advanced PCR and sequencing techniques enhance the identification of CVD-related microorganisms.

To view Article

Introduction

Cardiovascular disease (CVD) continues to be a substantial global health challenge, accounting for a significant number of annual deaths worldwide [1]. Despite significant advancements in cardiovascular treatment, conditions such as heart failure, stroke, myocardial infarction and myocarditis continue to increase in prevalence. They are one of the leading causes of mortality and morbidity across the globe. While CVDs are top ranked cause of mortality and morbidity in the high-income countries, with epidemiological transition in progress, they are also on the rise among the low and low-middle-income countries, thus making them a global crisis. These diseases, along with others like peripheral vascular disease impose a substantial burden on public health. This in turn impacts the quality of life of the population and the country leading to decreased human and economic productivity.

Rising recognition of the critical role played by the gut microbiota, which is the microbial population that resides in our gastrointestinal tract, in human metabolism, immunity, and disease processes, including coronary artery disease (CAD), has taken place over the course of the last 10 years. There has been a substantial increase in awareness of the potential effect of alterations in the gut microbiome and how these changes affect the development of cardiovascular disease (CVD) and cardiometabolic disorders. There has been a significant amount of study conducted on the topic of how the gut microbiome processes a diet that is high in protein; nevertheless, the relationship between these microbes and the risk of cardiovascular disorders is still a matter of debate. The complex ecology of the gut microbiota, in addition to its biochemical impacts and metabolic activities, has piqued the curiosity of academics as well as specialists in the medical field. A connection between gut microbes and cardiovascular disease is the subject of this review.

Significant microorganisms associated with cardiovascular diseases

CVD can arise from various infectious and non-infectious agents, each with its implications [2]. In cases of endocarditis, where the inner lining of the heart becomes inflamed, a significant proportion (around 70%) are identified as blood culture-negative endocarditis (BCNE) [3].

BCNE is often observed in patients who have previously received antibiotic treatment [4]. Additionally, microorganisms that have a slow growth rate or reside within cells, such as Staphylococcus aureus, Streptococcus equi, Streptococcus oralis, and Bartonella quintana, can play a role in the development of blood culture-negative endocarditis (BCNE) [4,5].

Numerous infectious agents have been identified as potential contributors to atherosclerosis [6]. Remarkably, a study by Mitra et al [7] found that atherosclerotic plaques with symptoms and those without showed different compositions of the microbiome. Microbial groups linked to the host microbiome, including Porphyromonadaceae, Bacteroidaceae, Micrococcaceae, and Streptococcaceae, were more prevalent in asymptomatic plaques [7]. On the other hand, pathogenic microbial groups such as Neisseriaceae, Thiotrichaceae, and Helicobacteraceae were more common in symptomatic atherosclerotic plaques [7]. Thus, the role of microorganisms has been already established in multiple cardiovascular diseases, which reiterates the possible targeting of them in improving CVD-related health.

Dysbiosis, which refers to the disturbance of the general composition of gut microbiota, has been correlated with heightened inflammation, a key factor in the progression of atherosclerosis [8]. Recent evidence has also connected alterations in gut microbiota and its metabolites to increased blood pressure as well as to vascular dysfunction [9,10]. Heart failure is linked to certain types of microorganisms, including Escherichia coli, Klebsiella pneumoniae, and Streptococcus viridans [11]. A further investigation revealed that individuals suffering from symptomatic stroke and transient ischemic attack had a modified gut microbiota characterized by a higher abundance of opportunistic pathogens such as Enterobacter [12].

Furthermore, the gut microbiota can significantly influence blood lipid composition, which in turn can impact the development of coronary artery disease [13-15].

Staphylococcus aureus-induced myocarditis can lead to sepsis (bacterial infection in the bloodstream) and the formation of abscesses in the heart [6].

Mechanisms of gut microbiome induction in cardiovascular disease

When the microbiota in the gut perform the function of an endocrine organ, they produce bioactive substances that can influence the physiology of the host. Atherosclerosis is one of the conditions that has been linked to dysbiosis, which is a term that is used to describe changes in the microbiome of the gut that are associated with sickness [16]. There is the potential for changes in the microbiota of the gut to have a considerable impact on the control of the biochemistry and metabolism of the host. An in-depth comprehension of the interaction among gut microbiota, the inflammasome, the innate immune system, bile acids, and gut permeability has the potential to provide valuable insights into preventative measures against cardiovascular disease and illuminate the involvement of bacteria in the development of autoimmune illnesses [17-22].

Indeed, gut microorganisms play a crucial role in modulating systemic immune responses and metabolic dysfunctions, particularly in individuals with obesity, and contribute to the development of atherosclerosis [23,24]. The indigenous microorganisms present in the gastrointestinal system might function as filters for food components by converting typical nutrients into metabolites. Decreased microbial diversity in the lower gastrointestinal tract is correlated with higher levels of leukocytes and high-sensitivity C-reactive protein (hsCRP). In contrast, larger amounts of gut bacteria have shown a negative association with several markers of mild inflammation, such as hsCRP and interleukin-6 (IL-6) [24-27].

Extensive research utilizing advanced technologies has provided substantial insights into the impact of gut bacteria on the development of cardiovascular disease (CVD) [28-30]. Research has shown that gut bacteria, particularly Escherichia coli, can transform food substances such as L-carnitine and phosphatidylcholine into trimethylamine (TMA). This TMA is then processed in the liver to produce trimethylamine-N-oxide (TMAO). This conversion promotes atherosclerosis and cardiovascular diseases [30-34]. Furthermore, an increased presence of the gut bacterium Collinsella has been detected in the carotid artery of individuals suffering from symptomatic atherosclerosis. On the flip side, specific probiotics like Lactobacillus rhamnosus GR-1 have demonstrated efficacy in managing heart failure in experiments involving mouse models. These findings underscore the significant involvement of gut microflora in the development of cardiovascular disease (CVD) [35].

Periodontal pathogens have been identified as contributors to the exacerbation of both systolic and diastolic arterial pressure in diabetic mice subjected to a high-fat diet. This involvement of periodontal pathogens plays a role in the development of cardiovascular complications. Moreover, lipopolysaccharide (LPS) originating from P. gingivalis has been linked to inflammation-induced cardiovascular disease (CVD) by promoting oxidative stress, as expressed by the rise in the reactive oxygen species levels, and mitochondrial dysfunction [36,37]. Moreover, an interesting study conducted with a mouse model has provided insights into how microorganisms can manipulate pathogenic inflammation within the heart and impact unique innate immune responses [38,39].

Numerous pathways, including the "trimethylamine (TMA)/trimethylamine N-oxide (TMAO)" pathway, the "short-chain fatty acids (SCFAs)" pathway, and the "primary and secondary bile acid (BAs) pathways," are recognized for their interactions with host endocrine hormones [40-42].

Regarding the connection between adaptive immunity and cardiovascular disease (CVD), the glucocorticoid-induced leucine zipper (GILZ) protein has been identified as having a role in suppressing immune and inflammatory reactions, which can contribute to the onset of myocardial infarction (MI). This suppression is linked to decreased levels of Th-17 cells and an increase in anti-inflammatory cytokine IL-10 positive cells [43]. Gut bacteria express a range of receptors, including Lipopolysaccharide (LPS) and pattern recognition receptors (PRRs), which are involved in initiating and regulating the host's immune response [44]. Cytokines such as interferon-γ also participate in this regulatory process [44].

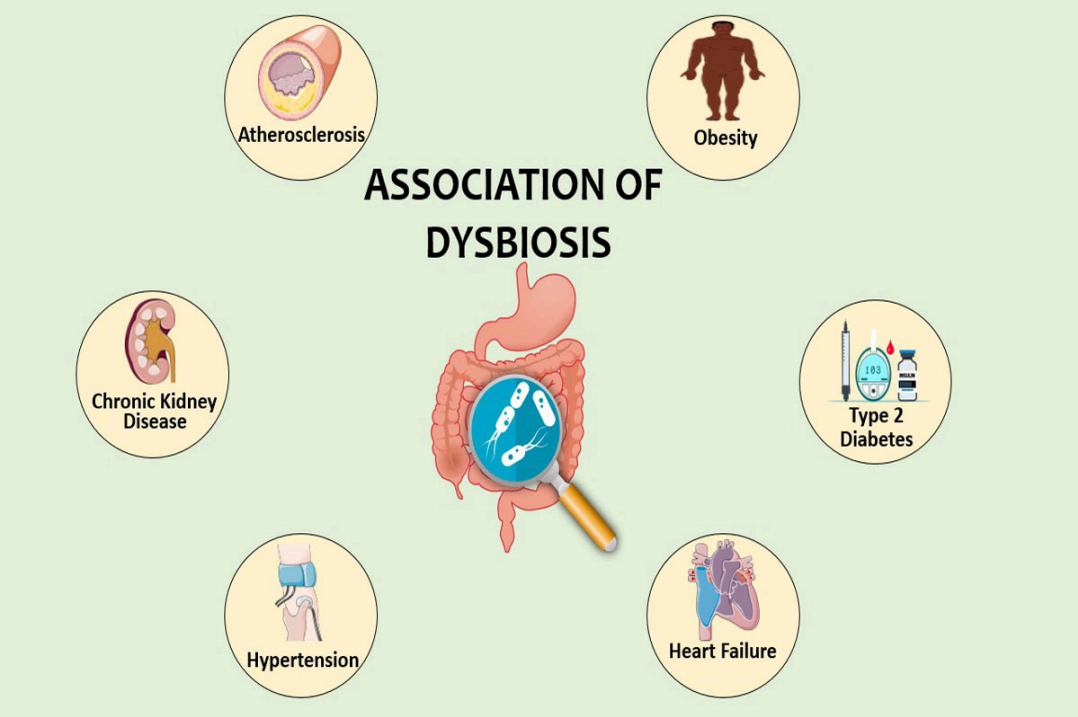

Figure 1: Association of Dysbiosis.

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Diagnostic modalities

In the field of microbiology, advanced techniques and molecular biology tools have been crucial for identifying microorganisms related to heart diseases. Molecular methods such as polymerase chain reaction (PCR) have demonstrated their effectiveness in directly detecting microbial pathogens associated with cardiovascular diseases, including infective endocarditis. These methods have significantly improved our ability to pinpoint the involvement of microorganisms in heart-related illnesses [45-47]. These molecular tools offer notable advantages over conventional culture-based methods, especially in detecting pathogenic microorganisms that may be viable but not cultivable using traditional approaches [48-50].

The rise in research on the gut microbiome can be credited to the advancement of affordable and efficient next-generation sequencing (NGS) technology, along with the availability of various "omics" data, including human genomic, metabolomics, and proteomic data. The combination of NGS technology and breakthroughs in bioinformatics has transformed the microbiome field, replacing traditional culture-based methods and enabling the analysis of progressively intricate microbiome characteristics. Nonetheless, certain constraints persist. To illustrate, the utilization of 16S rRNA sequencing may result in a limited perspective on bacteria alone, overlooking other essential life forms such as fungi, protozoa, and viruses. Although they provide a more comprehensive, multi-kingdom perspective, metagenomic research is not without limits. A large fraction of the data, especially the viral data, has no near matches in reference databases, making it impossible to attribute a specific purpose to it [48].

To advance our understanding and progress toward establishing causality in the field of microbiome research, it is crucial to build a comprehensive knowledge base that consolidates fragmented information. Furthermore, we may accelerate our understanding by using advancements like text mining, natural language processing, taxonomic representations, and standardizing terminology used in the microbiome research community [49].

Therefore, continued research efforts aimed at improving quality control, methodologies, and pipelines are imperative for the development of comprehensive models that elucidate the dynamics

Of the gut ecosystem of cardiovascular disease on a global scale. These advancements will play a vital role in comprehending the intricate relationship between the gut microbiome and cardiovascular health. They provide a foundation for potential therapeutic interventions and preventive strategies in this field.

Prospects for the future

Current evidence shows a strong correlation of gut microbiome with the incidence of CVD. Research indicates that the microbiota interacts with the host through various pathways, and disruptions in the content of gut microbiota may lead to a rise in the incidence of CVD and related pathological changes. As a result, innovative therapeutic targets and strategies have been developed to leverage the potential of gut microbiota in preventing and treating CVD.

Considerable work is now being done to investigate the possible uses of bacteria in CVD and other human illnesses in general. First, to get a better understanding of the roles that individual microorganisms play in the development of illness, attention is being directed toward identifying particular strains of germs rather than just the bacterial population as a whole. This will enable us towards a targeted approach towards the gut microbiome rather than a blanket approach. Second, as present studies mostly concentrate on microbial composition, future studies may focus more on examining microbiome-mediated metabolites and their downstream functional implications. Thirdly, personalized approaches for modifying the microbiota are of utmost importance and are actively being pursued. This endeavour can be aided by conducting microbiome profiling of individual patients to identify metabolomic biomarkers.

These ongoing advancements in comprehending the part of the gut microbiome in CVD, along with the exploration of specific microorganisms, metabolites, and personalized interventions, hold great promise for the development of effective therapeutic strategies.

Conclusion

Uncovering the complex interactions between different physiological factors that affect gut microbiota and disease development is essential to developing effective therapeutic interventions for conditions like hypercholesterolemia and coronary artery disease (CAD) and to gaining a thorough understanding of the impact of gut microbiota on human health.

- Blood Culture-Negative Endocarditis (BCNE) is heart lining inflammation linked to prior antibiotic use and involving microorganisms like *Staphylococcus aureus*, *Streptococcus species*, and *Bartonella quintana*.
- Infectious Agents (e.g., *Helicobacter pylori*, *Cytomegalovirus*, *Chlamydia pneumoniae*) contribute to atherosclerosis; microbiota variations are observed in symptomatic and asymptomatic plaque cases.
- Gut microbiota imbalance leads to inflammation, hypertension, vascular issues, and atherosclerosis, with specific microbes (e.g., *Escherichia coli*) linked to heart failure.
- Gut microbiota-generated metabolites (TMAO, SCFAs, secondary bile acids) influence cardiovascular disease development.
- Advanced diagnostic tools (PCR, NGS) outperform culture-based methods in identifying cardiovascular disease-related microorganisms.

Supporting information

None

Ethical Considerations

None

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Author contribution statement

Aroop Mohanty: Conceptualization (lead); writing – original draft (lead); formal analysis (lead); writing – review and editing (equal). **Parul Singh**: conceptualization, Software (lead); writing – review and editing (equal). **Ankita Kabi**: Methodology (lead); writing – review and editing (equal). **Amogh Verma**: Methodology (lead); writing – review and editing (equal). **Ranjit Sah**: Conceptualization (lead); writing – original draft (lead); formal analysis (lead); writing – review and editing (equal).

All authors attest they meet the ICMJE criteria for authorship and gave final approval for submission.

Data availability statement

Data included in article/supp. material/referenced in article.

Additional information

No additional information is available for this paper.

Declaration of competing interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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