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Review Article | Cardiovascular diseases

Role of microorganism in cardiovascular diseases: a comprehensive review

Aroop Mohanty[1], Parul Singh[2], Ankita Kabi[3], Amogh Verma[4], Ranjit Sah[5,6*]

[1] Department of Microbiology, Allindia Institute of Medical Sciences, Gorakhpur, India.
[2] Department of Microbiology, All India Institute of Medical Sciences, Gorakhpur, India.
[3] Department of Anaesthesia and Critical Care, Allindia Institute of Medical Sciences, Gorakhpur, India.
[4] Rama Medical College Hospital and Research Centre, Hapur, India.
[5] Department of Microbiology, Tribhuvan University Teaching Hospital Institute of Medicine, Maharajgunj, Kathmandu, Nepal. [6]Department of Microbiology, Dr. D. Y. Patil Medical College, Hospital and Research Centre, Dr. D. Y. Patil Vidyapeeth, Pune, India

Correspondence: ranjitsah@iom.edu.np

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Evidence in Context

Prior Evidence: Cardiovascular disease (CVD) is a major global health issue. Over the past decade, the gut microbiota's role in human metabolism, immunity, and diseases, including coronary artery disease (CAD), has been recognized. The relationship between gut microorganisms and cardiovascular risk, particularly from the metabolism of a protein-rich diet, remains debated.

Evidence added by this study: This comprehensive review highlights the significant microorganisms associated with CVD, such as Staphylococcus aureus and Streptococcus viridans. It delves into the mechanisms by which gut microbiota influences CVD, emphasizing the role of microbial-associated metabolites. Advanced diagnostic techniques, like next-generation sequencing, have enhanced the detection of microorganisms in heart diseases, paving the way for potential therapeutic interventions.

To view Article

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.

Objectives: This review seeks to elucidate the relationship between gut microorganisms and the development and progression of CVD.

Method: 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, or disruption of the gut microbiota, has been linked to increased inflammation and the development 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 plays a pivotal role 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.*

Introduction

Cardiovascular disease (CVD) remains a significant global health concern, responsible for a large number of deaths each year [1]. Despite significant advancements in cardiovascular treatment, conditions such as heart failure, stroke, myocardial infarction and myocarditis continue to increase in prevalence. These diseases, along with others like peripheral vascular disease impose a substantial burden on public health.

Over the past decade, there has been a growing realization of the crucial role played by the gut microbiota, the microbial community residing in our gastrointestinal tract, in human metabolism, immunity, and disease processes, including coronary artery disease (CAD). The potential role of alterations in the gut microbiota and their impact on the progression of CVD and cardiometabolic diseases has been widely acknowledged. While the effects of the gut microbiota's metabolism of a protein-rich diet have been extensively studied, the association between these microorganisms and cardiovascular risk remains a topic of debate. The complex ecology of the gut microbiota and its biochemical influences and metabolic functionality has attracted the attention of clinicians and researchers. This review aims to explore the link between gut microorganisms and CVD.

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]. Furthermore, slow-growing or intracellular microorganisms like *Staphylococcus aureus*, *Streptococcus equi*, *Streptococcus oralis* and *Bartonella quintana*, can also contribute to BCNE [4, 5].

Numerous infectious agents have been identified as potential contributors to atherosclerosis, including *Helicobacter pylori*, *Cytomegalovirus*, *Hepatitis C virus*, *Chlamydia pneumoniae,* and *Porphyromonas gingivalis* [6]. Intriguingly, a study conducted by Mitra et al. revealed differences in the microbiota composition between symptomatic and asymptomatic atherosclerotic plaques. Asymptomatic plaques exhibited an increased abundance of microbial families associated with the host microbiome, such as Porphyromonadaceae, Bacteroidaceae, Micrococcaceae, and Streptococcaceae [7]. In contrast, symptomatic atherosclerotic plaques displayed a higher prevalence of pathogenic microbial families, including Helicobacteraceae, Neisseriaceae, and Thiotrichaceae [7].

Disruption of the overall state of gut microbiota, known as dysbiosis, has been linked to increased inflammation, which is closely associated with the development of atherosclerosis [8]. Recent evidence has also connected alterations in gut microbiota and its metabolites to hypertension and vascular dysfunction [9, 10]. Specific microbial species, such as *Escherichia coli, Klebsiella pneumoniae*, and *Streptococcus viridans*, have been implicated in heart failure [11]. Another study demonstrated that patients with symptomatic stroke and transient ischemic attack exhibited an altered gut microbiota with an increased presence of opportunistic pathogens like Enterobacter, Megasphaera, Oscillibacter, and Desulfovibrio [12].

Furthermore, the gut microbiota can significantly influence blood lipid composition, which in turn can impact the development of coronary artery disease [13,14,15].

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

Blood-borne parasites, such as *Borrelia burgdorferi*, *Ehrlichia* species, and *Babesia* species, have also been linked to myocarditis [10].

Additionally, certain fungal species, notably *Aspergillus fumigatus*, *A. flavus*, and *A. nidulans*, have been frequently implicated in heart diseases [11].

Mechanisms of gut microbiome induction in cardiovascular disease

The gut microbiome serves as an endocrine organ, producing bioactive metabolites that can impact host physiology. Dysbiosis, which refers to changes in the composition of the gut microbiome associated with disease, has been linked to conditions such as atherosclerosis, hypertension, heart failure, chronic kidney disease, obesity, and type 2 diabetes [16]. Alterations in the gut microbiota can have significant effects on the regulation of host biochemistry and metabolism. Understanding the interplay between gut microflora, the inflammasome, the innate immune system, bile acids, and gut permeability can potentially inform preventive strategies against cardiovascular disease and shed light on the role of microorganisms in the pathogenesis of autoimmune diseases [17, 18, 19, 20, 21, 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]. By converting common nutrients into metabolites, the resident microflora in the intestinal tract can act as filters for dietary components. Specific microbial-associated metabolites such as trimethylamine-N-oxide (TMAO), short-chain fatty acids (SCFAs), and secondary bile acids have been implicated in influencing the development of cardiovascular disease [23]. Lower gut microbial diversity has been associated with elevated levels of white blood cells and C-reactive protein (hsCRP), whereas higher loads of gut microorganisms are inversely correlated with various markers of low-grade inflammation, including hsCRP and interleukin-6 (IL-6) [24,25,26,27].

Extensive research utilizing advanced technologies has provided substantial insights into the impact of gut bacteria on the

Development of cardiovascular disease (CVD) [28,29,30]. One study demonstrated that gut bacteria, specifically *Escherichia coli,* can convert dietary products like L-carnitine and phosphatidylcholine into trimethylamine (TMA), which is further metabolized in the liver to form trimethylamine-N-oxide (TMAO). This conversion promotes atherosclerosis and cardiovascular diseases [30,31,32,33,34]. Additionally, an elevated level of the gut bacterium *Collinsella* has been observed in the carotid artery of patients with symptomatic atherosclerosis. Conversely, certain probiotics such as *Lactobacillus rhamnosus* GR-1, *Bifidobacterium infantis*, and *Methanomassiliicoccus luminyensis* B10 have shown effectiveness in treating heart failure in mouse models, further emphasizing the central role of gut microflora in CVD development [35].

Periodontal pathogens, including *Porphyromonas gingivalis*, *Prevotella intermedia*, and *Fusobacterium nucleatum*, have been found to exacerbate high-fat diet-induced systolic and diastolic arterial pressure in diabetic mice, contributing to the development of cardiovascular complications. Lipopolysaccharide (LPS) derived from *P. gingivalis* has been implicated in inflammation-induced CVD through the promotion of oxidative stress (increased reactive oxygen species) and mitochondrial dysfunction [36,37]. Furthermore, an intriguing study utilizing a mouse model has shed light on the mechanisms by which microorganisms can modulate pathogenic inflammation in the heart and influence novel innate immune responses [38,39].

Gut bacteria express various receptors such as Lipopolysaccharide (LPS) and pattern recognition receptors (PRRs), which play a role in stimulating and modulating the host immune response [44]. Several pathways, including the trimethylamine (TMA)/trimethylamine N-oxide (TMAO) pathway, short-chain fatty acids (SCFAs) pathway, and primary and secondary bile acid (BAs) pathways, are known to interact with host endocrine hormones such as ghrelin, leptin, and glucagon-like peptide 1 (GLP-1) [40,41,42].

In terms of linking adaptive immunity to cardiovascular disease (CVD), the glucocorticoid-induced leucine zipper (GILZ) protein has been reported to suppress immune and inflammatory responses, which can contribute to the development of myocardial infarction (MI). This suppression is associated with reduced levels of Th-17 cells and elevated levels of anti-inflammatory cytokine IL-10 positive cells [43]. Cytokines, including interferon-γ, transforming growth factor-β1, and interleukin-1β, also play a role in this process [44].

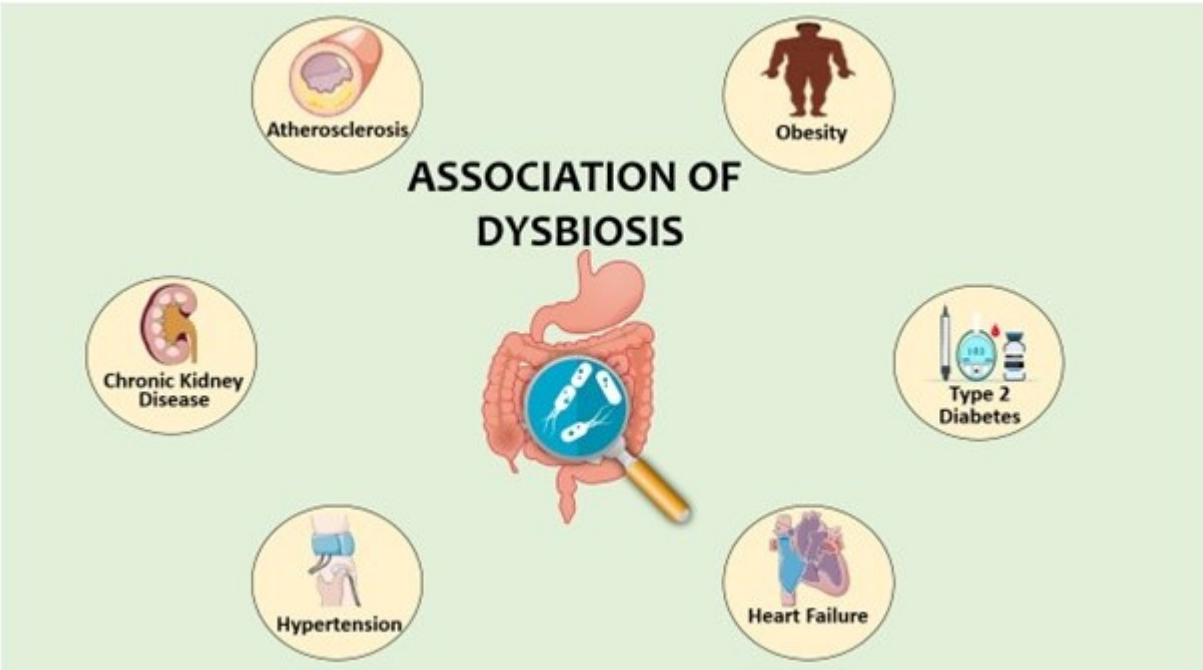

Figure 1: Shows Association of Dysbiosis. Conditions associated with dysbiosis include Atherosclerosis, Obesity, Hypertension (HTN), Chronic Kidney Disease (CKD), Type 2 Diabetes (T2D), and Heart Failure.

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Diagnostic modalities

In the field of microbiology, several advanced techniques and molecular biology tools have proven to be highly valuable in the detection of microorganisms implicated in heart diseases. Molecular methods such as polymerase chain reaction (PCR), 16S rRNA sequencing, and next-generation sequencing (NGS) have demonstrated their effectiveness in directly detecting microbial pathogens associated with cardiovascular diseases, including infective endocarditis [45, 46,47]. These molecular tools offer significant advantages over traditional culture-based methods, particularly in identifying viable but non-culturable pathogenic microorganisms [48,49,50].

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. Metagenomic studies offer a broader, multi-kingdom view, but they also have their limitations. A significant portion of the data, particularly viral data, cannot be assigned a specific function due to a lack of close matches in reference databases [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. Additionally, incorporating innovations such as natural language processing, text mining, taxonomic representations, and standardizing the vocabulary used across the microbiome research field can expedite our comprehension [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 contribute to understanding the complexity between the gut microbiome and cardiovascular health, laying the groundwork for potential therapeutic interventions and preventive strategies

Prospects for the future

Emerging evidence suggests a strong association between the gut microbiome and the incidence of cardiovascular disease (CVD). Research indicates that the microbiota interacts with the host through various pathways, and disruptions in the composition of the gut microbiota or its metabolites may contribute to increased risks 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.

Significant efforts are currently underway to explore the potential applications of microbiota in CVD and other human diseases more broadly. Firstly, there is a shift towards identifying specific strains of microbes, rather than focusing solely on the overall bacterial community, to better understand the contributions of individual microorganisms to disease progression. Secondly, future research may place greater emphasis on investigating microbiome-mediated metabolites and their downstream functional consequences, as current studies primarily focus on microbial composition. 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 understanding the role 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

To gain a comprehensive understanding of the impact of gut microbiota on human health and to develop effective therapeutic interventions for conditions such as hypercholesterolemia and coronary artery disease (CAD), it is crucial to unravel the intricate interplay between various physiological factors that influence gut microbiota and disease development.

- 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).

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

Additional information
No additional information is available for this paper.

Declaration of competing interest
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References

1. Benjamin EJ, Virani SS, Callaway CW, et al. Heart Disease and Stroke Statistics-2018 Update: A Report from the American Heart Association [published correction appears in Circulation. 2018 Mar 20;137(12): e493]. Circulation. 2018;137(12): e67-e492. doi:10.1161/CIR.0000000000000558

2. Muller AM, Fischer A, Katus HA, Kaya Z. Mouse models of autoimmune diseases - autoimmune myocarditis. Curr Pharm Des. 2015;21(18):2498-2512. doi:10.2174/1381612821666150316123711

3. Fournier PE, Gouriet F, Casalta JP, et al. Blood culture-negative endocarditis: Improving the diagnostic yield using new diagnostic tools. Medicine (Baltimore). 2017;96(47):e8392. doi:10.1097/MD.0000000000008392

4. Boudebouch N, Sarih M, Chakib A, et al. Blood Culture-Negative Endocarditis, Morocco. Emerg Infect Dis. 2017;23(11):1908-1909. doi:10.3201/eid2311.161066

5. Brouqui P, Raoult D. Endocarditis due to rare and fastidious bacteria. Clin Microbiol Rev. 2001;14(1):177-207. doi:10.1128/CMR.14.1.177-207.2001

6. Libby P, Egan D, Skarlatos S. Roles of infectious agents in atherosclerosis and restenosis: an assessment of the evidence and need for future research. Circulation. 1997;96(11):4095-4103. doi:10.1161/01.cir.96.11.4095

7. Mitra, S., Drautz-Moses, D.I., Alhede, M. et al. In silico analyses of metagenomes from human atherosclerotic plaque samples. Microbiome 3, 38 (2015). https://doi.org/10.1186/s40168-015-0100-y

8. Chistiakov DA, Bobryshev YV, Kozarov E, Sobenin IA, Orekhov AN. Role of gut microbiota in the modulation of atherosclerosis-associated immune response. Front Microbiol. 2015;6:671. Published 2015 Jun 30. doi:10.3389/fmicb.2015.00671

9. Kim S, Goel R, Kumar A, et al. Imbalance of gut microbiome and intestinal epithelial barrier dysfunction in patients with high blood pressure. Clin Sci (Lond). 2018;132(6):701-718. Published 2018 Mar 30. doi:10.1042/CS20180087

10. Karbach SH, Schönfelder T, Brandão I, et al. Gut Microbiota Promote Angiotensin II-Induced Arterial Hypertension and Vascular Dysfunction. J Am Heart Assoc. 2016;5(9):e003698. Published 2016 Aug 30. doi:10.1161/JAHA.116.003698

11. Tang WH, Kitai T, Hazen SL. Gut Microbiota in Cardiovascular Health and Disease. Circ Res. 2017;120(7):1183-1196. doi:10.1161/CIRCRESAHA.117.309715

12. Yin J, Liao SX, He Y, et al. Dysbiosis of Gut Microbiota With Reduced Trimethylamine-N-Oxide Level in Patients With Large-Artery Atherosclerotic Stroke or Transient Ischemic Attack. J Am Heart Assoc. 2015;4(11):e002699. Published 2015 Nov 23. doi:10.1161/JAHA.115.002699

13. Fu J, Bonder MJ, Cenit MC, et al. The Gut Microbiome Contributes to a Substantial Proportion of the Variation in Blood Lipids. Circ Res. 2015;117(9):817-824. doi:10.1161/CIRCRESAHA.115.306807

14. Clemente JC, Ursell LK, Parfrey LW, Knight R. The impact of the gut microbiota on human health: an integrative view. Cell. 2012;148(6):1258-1270. doi:10.1016/j.cell.2012.01.035

15. Tremaroli V, Bäckhed F. Functional interactions between the gut microbiota and host metabolism. Nature. 2012;489(7415):242-249. doi:10.1038/nature11552

16. Yamashiro K, Tanaka R, Urabe T, et al. Gut dysbiosis is associated with metabolism and systemic inflammation in patients with ischemic stroke [published correction appears in PLoS One. 2017 Apr 13;12 (4):e0176062]. PLoS One. 2017;12(2):e0171521. Published 2017 Feb 6. doi:10.1371/journal.pone.0171521

17. Barin JG, Talor MV, Diny NL, et al. Regulation of autoimmune myocarditis by host responses to the microbiome. Exp Mol Pathol. 2017;103(2):141-152. doi:10.1016/j.yexmp.2017.08.003

18. Tripathi A, Xu ZZ, Xue J, et al. Intermittent Hypoxia and Hypercapnia Reproducibly Change the Gut Microbiome and Metabolome across Rodent Model Systems. mSystems. 2019;4(2):e00058-19. Published 2019 Apr 30. doi:10.1128/mSystems.00058-19

19. Xu M, Liu PP, Li H. Innate Immune Signaling and Its Role in Metabolic and Cardiovascular Diseases. Physiol Rev. 2019;99(1):893-948. doi:10.1152/physrev.00065.2017

20. Adamczyk-Sowa M, Medrek A, Madej P, Michlicka W, Dobrakowski P. Does the Gut Microbiota Influence Immunity and Inflammation in Multiple Sclerosis Pathophysiology?. J Immunol Res. 2017;2017:7904821. doi:10.1155/2017/7904821

21. Tang WH, Kitai T, Hazen SL. Gut Microbiota in Cardiovascular Health and Disease. Circ Res. 2017;120(7):1183-1196. doi:10.1161/CIRCRESAHA.117.309715

22. Levy M, Thaiss CA, Zeevi D, et al. Microbiota-Modulated Metabolites Shape the Intestinal Microenvironment by Regulating NLRP6 Inflammasome Signaling. Cell. 2015;163(6):1428-1443. doi:10.1016/j.cell.2015.10.048

23. Hooper LV, Littman DR, Macpherson AJ. Interactions between the microbiota and the immune system. Science. 2012;336(6086):1268-1273. doi:10.1126/science.1223490

24. Bäckhed F, Ding H, Wang T, et al. The gut microbiota as an environmental factor that regulates fat storage. Proc Natl Acad Sci U S A. 2004;101(44):15718-15723. doi:10.1073/pnas.0407076101

25. Gabriel CL, Ferguson JF. Gut Microbiota and Microbial Metabolism in Early Risk of Cardiometabolic Disease. Circ Res. 2023;132(12):1674-1691. doi:10.1161/CIRCRESAHA.123.322055

26. Buford TW. (Dis)Trust your gut: the gut microbiome in age-related inflammation, health, and disease. Microbiome. 2017;5(1):80. Published 2017 Jul 14. doi:10.1186/s40168-017-0296-0

27. Schiattarella GG, Sannino A, Esposito G, Perrino C. Diagnostics and therapeutic implications of gut microbiota alterations in cardiometabolic diseases. Trends Cardiovasc Med. 2019;29(3):141-147. doi:10.1016/j.tcm.2018.08.003

28. Serino M, Blasco-Baque V, Nicolas S, Burcelin R. Far from the eyes, close to the heart: dysbiosis of gut microbiota and cardiovascular consequences. Curr Cardiol Rep. 2014;16(11):540. doi:10.1007/s11886-014-0540-1

29. Qin J, Li R, Raes J, et al. A human gut microbial gene catalogue established by metagenomic sequencing. Nature. 2010;464(7285):59-65. doi:10.1038/nature08821

30. Cotillard A, Kennedy SP, Kong LC, et al. Dietary intervention impact on gut microbial gene richness [published correction appears in Nature. 2013 Oct 24;502(7472)580]. Nature. 2013;500(7464):585-588. doi:10.1038/nature12480

31. Bullon P, Cordero MD, Quiles JL, Morillo JM, del Carmen Ramirez-Tortosa M, Battino M. Mitochondrial dysfunction promoted by Porphyromonas gingivalis lipopolysaccharide as a possible link between cardiovascular disease and periodontitis. Free Radic Biol Med. 2011;50(10):1336-1343. doi:10.1016/j.freeradbiomed.2011.02.018

32. Kowaltowski AJ, de Souza-Pinto NC, Castilho RF, Vercesi AE. Mitochondria and reactive oxygen species. Free Radic Biol Med. 2009;47(4):333-343. doi:10.1016/j.freeradbiomed.2009.05.00433.

33. Ramirez-Tortosa MC, Quiles JL, Battino M, et al. Periodontitis is associated with altered plasma fatty acids and cardiovascular risk markers. Nutr Metab Cardiovasc Dis. 2010;20(2):133-139. doi:10.1016/j.numecd.2009.03.003

34. Kuo LC, Polson AM, Kang T. Associations between periodontal diseases and systemic diseases: a review of the inter-relationships and interactions with diabetes, respiratory diseases, cardiovascular diseases and osteoporosis. Public Health. 2008;122(4):417-433. doi:10.1016/j.puhe.2007.07.004

35. Gan XT, Ettinger G, Huang CX, et al. Probiotic administration attenuates myocardial hypertrophy and heart failure after myocardial infarction in the rat. Circ Heart Fail. 2014;7(3):491-499. doi:10.1161/CIRCHEARTFAILURE.113.000978

36. Shi L, Ji Y, Zhao S, et al. Crosstalk between reactive oxygen species and Dynamin-related protein 1 in periodontitis. Free Radic Biol Med. 2021;172:19-32. doi:10.1016/j.freeradbiomed.2021.05.031

37. Zaja I, Bai X, Liu Y, et al. Cdk1, PKCδ and calcineurin-mediated Drp1 pathway contributes to mitochondrial fission-induced cardiomyocyte death. Biochem Biophys Res Commun. 2014;453(4):710-721. doi:10.1016/j.bbrc.2014.09.144

38. Barin JG, Tobias LD, Peterson DA. The microbiome and autoimmune disease: Report from a Noel R. Rose Colloquium. Clin Immunol. 2015;159(2):183-188. doi:10.1016/j.clim.2015.05.009

39. Barin JG, Čiháková D. Control of inflammatory heart disease by CD4+ T cells. Ann N Y Acad Sci. 2013;1285:80-96. doi:10.1111/nyas.12134

40. De Vadder F, Kovatcheva-Datchary P, Goncalves D, et al. Microbiota-generated metabolites promote metabolic benefits via gut-brain neural circuits. Cell. 2014;156(1-2):84-96. doi:10.1016/j.cell.2013.12.016

41. Schwiertz A, Taras D, Schäfer K, et al. Microbiota and SCFA in lean and overweight healthy subjects. Obesity (Silver Spring). 2010;18(1):190-195. doi:10.1038/oby.2009.167

42. Tolhurst G, Heffron H, Lam YS, et al. Short-chain fatty acids stimulate glucagon-like peptide-1 secretion via the G-protein-coupled receptor FFAR2. Diabetes. 2012;61(2):364-371. doi:10.2337/db11-1019

43. Baban B, Yin L, Qin X, Liu JY, Shi X, Mozaffari MS. The role of GILZ in modulation of adaptive immunity in a murine model of myocardial infarction. Exp Mol Pathol. 2017;102(3):408-414. doi:10.1016/j.yexmp.2017.05.002

44. McLaren JE, Michael DR, Ashlin TG, Ramji DP. Cytokines, macrophage lipid metabolism and foam cells: implications for cardiovascular disease therapy. Prog Lipid Res. 2011;50(4):331-347. doi:10.1016/j.plipres.2011.04.002

45. Brouqui P, Raoult D. New insight into the diagnosis of fastidious bacterial endocarditis. FEMS Immunol Med Microbiol. 2006;47(1):1-13. doi:10.1111/j.1574-695X.2006.00054.x

46. Brinkman CL, Vergidis P, Uhl JR, et al. PCR-electrospray ionization mass spectrometry for direct detection of pathogens and antimicrobial resistance from heart valves in patients with infective endocarditis. J Clin Microbiol. 2013;51(7):2040-2046. doi:10.1128/JCM.00304-13

47. Hasman H, Saputra D, Sicheritz-Ponten T, et al. Rapid whole-genome sequencing for detection and characterization of microorganisms directly from clinical samples [published correction appears in J Clin Microbiol. 2014 Aug;52(8):3136]. J Clin Microbiol. 2014;52(1):139-146. doi:10.1128/JCM.02452-13

48. Cheng J, Hu H, Fang W, et al. Detection of pathogens from resected heart valves of patients with infective endocarditis by next-generation sequencing. Int J Infect Dis. 2019;83:148-153. doi:10.1016/j.ijid.2019.03.007

49. Peeters B, Herijgers P, Beuselinck K, et al. Added diagnostic value and impact on antimicrobial therapy of 16S rRNA PCR and amplicon sequencing on resected heart valves in infective endocarditis: a prospective cohort study. Clin Microbiol Infect. 2017;23(11):888.e1-888.e5. doi:10.1016/j.cmi.2017.06.008

50. Mohanty, A., Singh T, S., Kabi, A., Gupta, P., Gupta, P., & Kumar, P. (2017, November 1). BACTERIOLOGICAL PROFILE AND ANTIBIOTIC SENSITIVITY PATTERN OF HOSPITALACQUIRED SEPTICEMIA IN A TERTIARY CARE HOSPITAL IN NORTH EAST INDIA. Asian Journal of Pharmaceutical and Clinical Research, 10(11), 186. https://doi.org/10.22159/ajpcr.2017.v10i11.20554