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Influence of the Microbiome on Coronary Artery Disease Pathogenesis

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Abstract

Coronary artery disease (CAD) remains one of the leading causes of morbidity and mortality worldwide, driven by atherosclerosis, systemic inflammation, and endothelial dysfunction. Despite advances in treatment, its global impact underscores the need for new preventive and therapeutic strategies. Emerging evidence points to the gut microbiota as a key modulator of CAD pathogenesis, influencing lipid metabolism, immune responses, and vascular integrity. This review explores the biochemical mechanisms linking gut microbiota to CAD, focusing on metabolites such as trimethylamine-N-oxide (TMAO), which promotes cholesterol deposition and inflammation, and short-chain fatty acids (SCFAs), which exert protective effects by enhancing gut barrier function and regulating inflammation and lipid metabolism. It also addresses how lifestyle- and diet-induced dysbiosis exacerbates CAD risk and highlights potential interventions targeting gut microbiota—including prebiotics, probiotics, postbiotics, and fecal microbiota transplantation. By incorporating microbiota profiling into clinical practice, personalized treatment strategies may improve cardiovascular outcomes. This review emphasizes the importance of further research into the gut-heart axis to advance precision medicine in the fight against CAD.

Keywords: Gut microbiome, Coronary artery disease (CAD), Endothelial dysfunction.

1. Introduction

Coronary artery disease (CAD) is a significant cause of death for men and women around the world (Brown et al., 2023; *Coronary Artery Disease*, n.d.; Manuals, 2014). About 5% of people worldwide above the age of 20 years had CAD in 2024 which were responsible for over 350,000 deaths in 2022 alone. This is at a global scale (Di Cesare et al., 2024). CAD is characterized by the gradual narrowing of the arteries by plaque formation and accumulation, leading to atherosclerosis. Hypercholesterolemia and other etiologies disrupt the endothelium such that the low-density lipoprotein (LDL) cholesterol infiltrates the arterial wall, creating yellow-white fatty streaks (Gimbrone & García-Cardeña, 2016). The ensuing massive lipid accumulation causes an inflammatory response (Kong et al., 2022; "Lipid Scavenging Macrophages and Inflammation," 2022; Tall & Yvan-Charvet, 2015; van Dierendonck et al., 2022). As macrophages respond to lipid accumulation, they begin engulfing low-density lipoprotein (LDL), which transforms them into foam cells. These foam cells continue to absorb increasing amounts of oxidized LDL, leading to their buildup in the intimal layer of the artery. This accumulation contributes significantly to plaque formation (Ganesan et al., 2018). To stabilize the plaque, smooth muscle cells form a fibrous cap, resulting in stenosis. In the context of coronary artery disease (CAD), stenosis specifically means the narrowing of the coronary arteries due to the buildup of plaque (atherosclerosis). This narrowing restricts blood flow to the heart muscle, which can lead to chest pain (angina), shortness of breath, or even heart attacks.(Doran et al., 2008; Harman & Jørgensen, 2019; Linton et al., 2019; *Website*, n.d.-a, *Website*, n.d.-b). The formation of plaque can eventually lead to a stroke and myocardial infarction. The risk of plaque build-up leading to stenosis is linked to alcohol use, smoking, and a diet high in fat (Kiechl et al., 1998; Mukamal, 2006; Waksman et al., n.d.). In addition to these risk factors, evidence has demonstrated

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that the gut microbiome may worsen or attenuate atherosclerotic disease ("Impact of Diet on Human Gut Microbiome and Disease Risk," 2021; Tang et al., 2017; Trøseid et al., 2020). The structure and composition of the gut microbiome—primarily made up of five major bacterial phyla: Bacteroidetes, *Firmicutes*, *Actinobacteria*, *Proteobacteria*, and *Verrucomicrobia*—play a critical role in influencing atherosclerotic risk by regulating immune responses, metabolism, and inflammation. (Belizário & Napolitano, 2015; Hou et al., 2022; Rinninella et al., 2019).

In this review, the terms are defined and used as follows to ensure clarity. Microbiota refers to the community of microorganisms—including bacteria, viruses, fungi, and archaea—that inhabit a specific environment, such as the human gut. Microbiome encompasses not only these microorganisms but also their genetic material, metabolic byproducts, and surrounding environmental conditions. Gut bacteria refers specifically to the bacterial component of the gut microbiota. While these terms are related, they are not interchangeable and will be used with these distinctions in mind throughout the manuscript.

There exists, however, vast species-level variation and variance in their relative abundance. *Bacteroidetes* and *Firmicutes* are anaerobic and represent over 90% of all bacterial species in a healthy gut ("Alternations of the Gut Microbiota and the Firmicutes/Bacteroidetes Ratio after Biologic Treatment in Inflammatory Bowel Disease," 2024; Magne et al., 2020). The *Firmicutes* to *Bacteroidetes* ratio, however, varies between individuals. This individual variability between people is influenced by factors such as host genetics, use of antibiotics, lifestyle, hygiene, and diet (Murga-Garrido et al., 2021; Pedroza Matute & Iyavoo, 2023; Sokhna & Mu, n.d.). Advances in the sequencing of genomes and bioinformatics have now allowed for the identification, and examination, of these microbes. Also shedding light to the composition and possible role in cardiometabolic disorder pathogenesis (Fernandez-Rhodes et al., 2020; Shah & Newgard, 2015).

The microbiome impacts the integrity of the intestinal mucosal barrier, controls nutrient metabolism and uptake, facilitates immunological tissue maturation, and prevents propagation of pathogenic microorganisms (Choden & Cohen, 2019; Lin & Zhang, 2017). Gut microbiota also modulate host processes through bioactive metabolites that affect distant organs directly or indirectly. The predominant interaction pathways include the trimethylamine (TMA)/trimethylamine N-oxide (TMAO) pathway, short-chain fatty acid (SCFA) pathway, and primary and secondary bile acid (BA) pathways. Secondly, some of them stimulate the parasympathetic nervous system, impacting the control of glucose and other metabolism processes to form metabolic syndrome (Li et al., 2023). In order to be a means of communication between other organs, the signal of gut micro bacteria needs to pass through the intestinal epithelium. The bacteria first sends metabolites, a kind of signal with the epithelial cells. The neuropods of these are associated with the vagus nerve (Chen et al., 2021; *DEFINE_ME*, n.d.; Margolis et al., 2021). This is also associated with the brain generating complete communication. Some gut microbiota signaling molecules are composed of structural elements, e.g., lipopolysaccharides (LPS) and peptidoglycans, that interact with host mucosal surface cells in pattern recognition receptor (PRR) fashion. PRRs detect pathogen-associated molecular patterns (PAMPs), which induce and control the host immune response (Di Vincenzo et al., 2023; Li & Wu, 2021).

Hence, peptidoglycans and LPS can induce multiple downstream signaling cascades via host receptors at the vasculature and epithelial cell interface and also when gut barrier function is disrupted (Wheeler et al., 2023). The gut microbiome significantly contributes to the progression of coronary artery disease (CAD) through the modulation of systemic inflammation, lipid metabolism, and endothelial function through microbiota-derived metabolites such as TMAO, which are important intermediaries in atherosclerosis pathogenesis. To examine the biochemical processes by which the gut microbiome functions to establish the onset of coronary artery disease (CAD) with special reference to microbial metabolites to determine their clinical significance in the development of atherosclerosis, systemic inflammation, and endothelial dysfunction.

While previous research has established the gut microbiome's role in influencing cardiovascular risk, the current study distinguishes itself by synthesizing emerging evidence on the specific mechanisms—particularly the role of microbial metabolites such as TMAO, SCFAs, and secondary bile acids—in CAD pathogenesis. This review not only outlines these pathways but also evaluates their clinical potential for diagnostic and therapeutic applications, emphasizing novel interventions like postbiotics and microbiota profiling for personalized cardiovascular care.

To ensure a comprehensive review, relevant studies were identified through searches of databases such as PubMed, Google Scholar, and ScienceDirect using keywords including "gut microbiome," "coronary artery disease,"

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"TMAO," "SCFAs," "bile acids," and "cardiovascular risk." Inclusion criteria focused on peer-reviewed articles published in English from 2008 to 2024 that discussed microbiota-derived metabolites in the context of CAD pathogenesis or therapy. This approach enabled the synthesis of clinically relevant findings while prioritizing recent mechanistic and translational insights.

2. The Gut-Heart Axis: Elucidating the Association

The gut bacteria send signals to the immune system through the regulation of tolerance and immune activation, which allows the body to respond well to injury and infection. Gut microbes trigger specialized immune cells to activate the immune system to eliminate viral infections (Wiertsema et al., 2021).

The microbiome activates T-cells that play a crucial role in the adaptive immune system. T cells are activated because their T Cell receptor binds to an antigen fragment so that T cells can recognize and respond to antigens (Lee & Mazmanian, 2010; Shim et al., 2023). The activation releases cytokines which coordinate the immune response. Some of the inflammatory cytokines produced are, interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α). Extended production of these cytokines can result in inflammation-related diseases like CAD. This will create a positive feedback since the cytokines generate more T-cells that secrete more TNF-α and IL-6 to ensure an effective immune response (Chen et al., 2017). Present in the microbiome, lipopolysaccharides (LPS) are produced when gram-negative bacteria undergo death or during shedding of bacteria. LPS binds to immune receptors such as Toll-like receptor 4 (TLR4) present in the gut or blood. Binding initiates a cascade of intracellular signaling that further stimulates immune cells and leads to the development of inflammatory cytokines. When LPS of microbial origin breach the barrier, bacteria gain entry into the blood and cause systemic inflammation. A healthy microbiome maintains a tight barrier that resists leaks of LPS (Kim et al., 2021; Maldonado et al., 2016). Dysbiosis can promote LPS translocation. IL-6 and TNF-α have a direct effect on vascular endothelial cells. TNF-α and IL-6 reduce the bioavailability of nitric oxide, which leads to dysfunctional vasodilation and increased vascular stiffness. IL-6 increases endothelial cell activation, which allows the immune cells to stick to the endothelium allowing the immune cells to move easily through the bloodstream (Didion, 2017). TNF-α increases endothelial permeability and disrupts the integrity of these tight junctions, later leading to leakages of blood vessels.

This IL-6-driven compliance triggers local inflammation and oxidative stress and promotes thrombosis causing vascular dysfunctions and tissue damage (Komarova et al., 2017; "The Blood-Brain Barrier in Alzheimer's Disease," 2017; Wettschureck et al., 2019). Other cytokines involved in this process are interferon gamma (IFN-γ) and Interleukin-17 (IL-17). IFN-γ and IL-17 induce oxidative stress and also stimulate neutrophils further enhancing endothelial permeability and inflammation (Naderi-Meshkin & Setyaningsih, 2024; Qiao et al., 2024). Specifically, the damage to the endothelial glycocalyx leaves the underlying cells vulnerable to further damage. Endothelial dysfunction may then result in atherosclerosis and hypertension. The gut microbiota regulates lipid metabolism through microbial breakdown of food lipids into absorbable components like free fatty acids (Ziółkiewicz et al., 2023). It also produces bioactive compounds like short-chain fatty acids (SCFAs) that contribute to energy balance through regulation of metabolic processes. They are fat storage and energy consumption. Additionally, SCFAs increase insulin sensitivity and regulate glucose metabolism, by inhibiting inflammation (Vinolo et al., 2011). This demonstrates the essential function of the microbiome in the coordination of lipid and carbohydrate metabolism for metabolic health in general.

3. Major Metabolites and Their Functions in CAD with Respect to the Influence on Diet

Dietary and lifestyle influences have a profound effect on gut microbiota and cardiovascular disease, underlining the essential function of gut-derived metabolites in the course of cardiovascular events (Duan et al., 2022). TMAO is a metabolite that is involved in metabolic processes and has been studied for its involvement in human health, especially cardiovascular health. Red meat, eggs, and fish contain high levels of choline and L-carnitine. Gut microbiota in the gut microbiome metabolize these nutrients which leads to the production of TMA . TMA is absorbed where it is transported to the liver. The liver oxidized TMA to TMAO (Gatarek & Kałużna-Czaplińska, 2021; Janeiro

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et al., 2018). TMAO has been associated with cholesterol metabolism dysfunction with increased deposition of cholesterol in the artery wall. A study revealed that an elevated level of TMAO is associated with an increased risk of myocardial infarction (Haghikia et al., 2018). SCFAs are indeed beneficial gut bacteria fermentation products of dietary fibers. Increased microbial diversity by exercise is favorable, and increased SCFA and production of SCFA is associated with lowered blood pressure and inflammation. Acetate, propionate, and butyrate are some of the principal SCFAs, each performing distinct but complementary functions in their function to support health.

SCFAs play a crucial role in immune homeostasis as well as in preventing excessive inflammatory response via an effect on T-regulatory cell differentiation and function. SCFAs are cardioprotective via preventing a decrease in systemic inflammation, improving lipid metabolism, and leading to decreased blood pressure levels (Canani et al., 2011). Secondary bile acids are a group of gut bacterially-derived metabolites from converted primary bile acids. Secondary bile acids also play key functions in many physiological processes, particularly through their interaction with signaling pathways and effect on lipid metabolism. The most important mechanism of action is the modulating action of the farnesoid X receptor (FXR) and TGR5 pathways. FXR is a nuclear receptor involved in regulating biosynthesis of bile acids, lipid metabolism, and glucose homeostasis, and TGR5 is a membrane receptor contributing to energy expenditure as well as anti-inflammatory signaling. Together, the pathways contribute to metabolic equilibrium as well as healthy lipid profiles.

Secondary bile acids within lipid metabolism play a role in cholesterol clearance as well as triglyceride production (Guzior & Quinn, 2021; Larabi et al., 2023; "Microbial Transformations of Bile Acids and Their Receptors in the Regulation of Metabolic Dysfunction-Associated Steatotic Liver Disease," 2023, "Review on Chronic Metabolic Diseases Surrounding Bile Acids and Gut Microbiota: What We Have Explored so Far," 2024). By modulating the breakdown and recycling of cholesterol, secondary bile acids prevent excessive accumulation of cholesterol that leads to cardiovascular disease. They also modulate the formation of triglycerides by influencing the gut microbiota, which affects fat digestion and the bile acid pool, and by directly acting on lipid metabolism through their receptors, which is essential for regulating lipid homeostasis of the body. Dysregulation of secondary bile acid synthesis is generally caused by gut dysbiosis, which creates metabolic aberration. An abnormal bile acid profile has been implicated with plaque formation in the arteries to contribute to atherosclerosis. This gives a reason for keeping the gut microbiota in the correct manner so as not to cause disturbance to the metabolism of bile acid and therefore avoid the dangers for CVDs. Different kinds of metabolites exist, but their contribution to CAD is conflicting and pivotal (*Cholesterol Metabolism*, n.d.; Daniels et al., 2009; Duan et al., 2022). Evidence from a second meta-analysis also showed that each additional 7 g/d of dietary fiber intake could lower the risk of CVDs by 9% (Fu et al., 2022). Conversely, a high-fat diet encourages the growth of pro-inflammatory microbial strains, suppresses bile acid production, and destroys endothelial integrity, which contributes to CVD. In contrast, fiber-fermented SCFAs play protective roles by inhibiting inflammation, improving lipid metabolic disorder, and maintaining intestinal barrier function, lowering CAD risks. Secondary bile acids also exert positive modulation on lipid metabolism via the FXR and TGR5 pathway in the improvement of cholesterol clearance but with the potential to cause plaque formation under disequilibrium. The findings show the interactive correlations of gut microbiota-derived metabolites with CAD development or prevention. Alcohol use and smoking disturb microbial equilibrium towards more production of harmful metabolites, further contributing to cardiovascular disease risk (Clemente-Suárez et al., 2023; "Dietary Fats and the Gut Microbiota: Their Impacts on Lipid-Induced Metabolic Syndrome," 2022; Wali et al., 2020).

3.1 Therapeutic Approaches Against Gut Microbiota for Heart Disease Prevention

Therapeutic approaches like probiotics, prebiotics and therapy can also prevent heart diseases by altering the gut microbiota. Probiotics consist of live, beneficial bacteria, especially of the *Lactobacillus* and *Bifidobacterium* genera, which reduce inflammation by dampening immune responses. *Lactobacillus* and *Bifidobacterium* produce Th cells, IL-10, and TGF-β which strengthens immune tolerance against pathogens. They also lower the levels of TMAO by suppressing the formation of trimethylamine, a precursor of TMAO, whose levels have been strongly linked with cardiovascular disease in recent years. Moreover, probiotics enhance gut barrier function and lessen endotoxemia and systemic inflammation, which are some of the causal factors of heart disease. On the other hand, prebiotics like inulin

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and resistant starches nourish the beneficial bacteria in the gut, stimulating their growth and activity. These fibers trigger the production of SCFAs like acetate, propionate, and butyrate, which are anti-inflammatory in nature, improve lipid metabolism, and maintain gut barrier function, all of which foster cardiovascular health (Chen et al., 2023; de Vos et al., 2022; He et al., 2019).

Additional therapeutic approaches to prevent CVD include XXX and YYY. Another Treatment is fecal microbiota transplantation (FMT), a treatment that aims to restore microbial balance by transplanting the gut microbiota of healthy donors into recipients.The treatment can re-balance the population of microbes in the gut, hence improving metabolic health and reducing risk factors for CVD, including inflammation and lipid imbalance. Out of the 222 patients who were evaluated at the one-month time point, 200 (90%) had their clostridioides difficile infection (CDI) resolved. Notably, 197 of these 200 patients (98%) achieved this result with just one round of FMT. Additionally, of 112 patients who were still CDI-free at one month and followed up to six months, recurrences developed in only 4 (4%) (Kelly et al., 2021). However, FMT is not free of difficulties, including ethical aspects and the risk of transmission of pathogens. Austere donor screening and universalized protocols are needed to surmount the safety concerns and heterogeneity in results that currently hamper its widespread use (Biazzo & Deidda, 2022; Zhang et al., 2024). To conclude, newer therapies have forged a new way in targeting gut microbiota for cardiovascular well-being. Postbiotics are microbial metabolites such as SCFAs or nonviable bacterial components such as peptides and polysaccharides that mimic live microbes' therapeutic effects without risks. These bioactive substances were found to possess potential anti-inflammatory properties and could be involved in the improvement of gut barrier function, and lipid metabolism. These are specific treatments that could modulate gut microbial activities and prevent heart disease (Hijová, 2024; Maftei et al., 2024; Prajapati et al., 2023).

4. Discussion

Gut microbiota–derived metabolites have emerged as significant regulators of coronary artery disease.The proatherogenic trimethylamine N-oxide (TMAO) is significantly elevated in CVD patients and has been identified as an independent predictor of future major adverse cardiovascular events (Intestinal Microbial Metabolism of Phosphatidylcholine and Cardiovascular Risk) (Mizoe, 2015). Mechanistic studies demonstrate that TMAO atherogenesis is through the promotion of macrophage foam cell formation – in part by inhibiting cholesterol efflux from macrophages – and by endothelial dysfunction caused by oxidative stress and inflammation (Kim et al., 2019; Li et al., 2016)). On the other hand, beneficial short-chain fatty acids (SCFAs) such as butyrate and propionate are reduced in CAD patients (Association of plasma propionate concentration with coronary artery disease in a large cross-sectional study | Frontiers), and their elevated levels have anti-atherosclerotic effects that involve reducing circulating cholesterol, enhancing endothelial nitric oxide bioavailability, and weakening systemic inflammatory responses. Likewise, secondary bile acids (i.e. deoxycholic and lithocholic acid) activate the farnesoid X receptor (FXR) and G protein-coupled bile acid receptor TGR5, which modulate glucose and lipid homeostasis and are anti-inflammatory; dual agonism of FXR/TGR5 in animal models improves metabolic profiles considerably and reduces vascular inflammation, with a concomitant decrease in the formation of atherosclerotic plaque. (Tang & Xia, 2020). In spite of these observations, significant uncertainty and variability characterize the microbiome–CAD relationship.

Not all cohorts report a consistent association between TMAO and cardiovascular risk – one cohort found no difference in plasma TMAO between CAD patients and controls, for example – and adjustment for dietary or renal function variables will weaken the observed risk, questioning whether TMAO is a causal factor in CAD or merely a marker of poor diet and metabolic dysfunction (Cristiani et al., 2021). Also, attempts at gut microbiota intervention have had mixed success: clinical trials of fecal microbiota transplantation or pre/probiotics have on average not lowered TMAO or inflammation significantly, and no large study has yet demonstrated benefit on cardiovascular outcomes due presumably to huge inter-individual microbiome heterogeneity and residual confounding effects (Thomas et al., 2021). These results emphasize the constraints of the present translation of microbiome modulation into cardiovascular therapy and the need for further well-controlled studies to tease out causality and optimize microbiota-targeted intervention.

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5. Conclusion

This review underscores the emerging role of the gut microbiome as a critical modulator of coronary artery disease (CAD), with microbial metabolites—particularly trimethylamine-N-oxide (TMAO), short-chain fatty acids (SCFAs), and secondary bile acids—serving as key intermediaries in influencing lipid metabolism, endothelial function, and systemic inflammation. These metabolites reveal distinct patterns of either risk promotion or cardiovascular protection, offering a molecular basis for understanding CAD progression beyond traditional risk factors. From a clinical standpoint, these findings suggest that microbiota profiling could become a valuable tool in assessing individual risk and guiding personalized prevention strategies. Incorporating gut-targeted interventions such as specific probiotics, prebiotics, and postbiotics into existing treatment protocols may enhance therapeutic outcomes, particularly for patients with comorbidities like diabetes, obesity, or metabolic syndrome. Additionally, the ability to modulate gut-derived metabolites through dietary patterns reinforces the role of nutritional counseling as a cornerstone of cardiovascular care. For policymakers and public health officials, these insights open the door to integrating microbiome-based considerations into dietary guidelines and national cardiovascular disease prevention programs. Promoting fiber-rich diets, reducing consumption of red meat and processed foods, and encouraging gut-friendly lifestyle habits could have broad-reaching effects on population health. As the field moves forward, the translation of microbiome science into routine clinical practice and public health policy represents a promising frontier in the fight against CAD—shifting the paradigm from reactive treatment to proactive, systems-level disease prevention.

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