FROM GUT TO PLAQUE: GUT MICROBIOME'S IMPACT ON ATHEROSCLEROSIS DEVELOPMENT AND PROGRESSION. LITERATURE REVIEW

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Abstract

Background. Atherosclerosis remains the leading cause of cardiovascular mortality worldwide. This review examines the emerging role of the gut microbiome in atherosclerosis pathogenesis. Recent advances in sequencing technologies have enabled deeper examination of complex interactions between intestinal microbial communities and cardiovascular health.

Methods. This review followed MOOSE guidelines, searching PubMed, Scopus, Web of Science, and Embase databases through March 2024. Search terms included "gut microbiome," "atherosclerosis," and related concepts. Studies examining relationships between gut microbiome composition and AS were included, with data extracted using standardized forms and organized into four categories for qualitative synthesis.

Results. Research reveals atherosclerosis patients exhibit reduced bacterial diversity and altered Firmicutes to Bacteroidetes ratios. Specific taxonomic signatures include increased Enterobacteriaceae and decreased butyrate-producing bacteria. Key microbial metabolites influence atherosclerosis development: short-chain fatty acids demonstrate anti-inflammatory properties; trimethylamine-N-oxide enhances macrophage cholesterol accumulation; bile acids modulate lipid metabolism; and lipopolysaccharides trigger inflammatory cascades involved in plaque formation.

Conclusion. Understanding gut microbiome contributions to atherosclerosis pathogenesis offers new possibilities for prevention and treatment through microbiota modulation or targeting specific microbial metabolites, representing a paradigm shift toward personalized approaches considering interactions between genetics, environment, and microbiome.

Introduction

Atherosclerosis (AS), a chronic inflammatory disease characterized by plaque accumulation in arterial walls, remains the leading cause of cardiovascular morbidity and mortality worldwide. Among various cardiovascular diseases, ischemic heart disease resulting from atherosclerotic plaque rupture accounts for 42.5% of mortality, and the death rate related to cardiovascular diseases due to coronary atherosclerosis (CAS) continues to rise steadily, comprising more than 30% of all fatalities.[1] Each year, AS claims millions of human lives – significantly more than cancer, pneumonia, diabetes, and many other diseases, including the COVID-19 pandemic. The development of post-COVID complications in the form of thrombosis and increased mortality particularly heightens the relevance of this problem. Consequently, this disease has been termed the "Pandemic of the 21st century".[2] Traditionally, researchers and clinicians have focused on risk factors such as dyslipidemia, hypertension, diabetes, and smoking.[1-3] However, over the past decade, a growing body of evidence has emphasized the human microbiome's significant role in the development and progression of this disease.[1,4,5,6]

The human microbiome, consisting of trillions of microorganisms inhabiting various body sites, has become a key factor in maintaining health and developing diseases.[7,8] The intestinal microbiome, containing the largest and most diverse

microbial community in the human body, influences numerous physiological processes, including metabolism, immune function, and inflammation – all involved in the pathogenesis of AS.[4,9,10]

Recent advances in sequencing technologies and bioinformatics have allowed researchers to more deeply examine the complex interactions between the gut microbiome and human physiology.[11,12] These studies have revealed intricate connections between microbial composition, metabolic activity, and atherosclerosis development.[4,9,13] The intestinal microbiota has been found to influence various stages of atherosclerosis, from initial endothelial dysfunction to plaque formation and rupture.[4]

The aim of this review article is to analyze the current state of knowledge regarding the role of the microbiome in AS development. Data on the mechanisms by which gut microbiota influences disease development and progression, key microbial metabolites involved in this process, contribute to the assessment of potential microbiome-based therapeutic approaches, and lead to future directions and challenges in this rapidly developing field of science.

Methods

Study Design and Search Strategy. We conducted this review following the MOOSE guidelines for meta-analyses of observational studies. Our literature search covered PubMed, Scopus, Web of Science, and Embase databases from their inception through March 2024. We used these search terms: "gut microbiome," "gut microbiota," "intestinal microbiome," "intestinal microbiota," "atherosclerosis," "atherosclerotic cardiovascular disease," "coronary artery disease," "carotid atherosclerosis," "plaque," and "cardiovascular disease" in various combinations. We also manually searched reference lists of retrieved articles to identify additional relevant studies.

Eligibility Criteria. We included studies that: examined relationships between gut microbiome composition or microbial metabolites and atherosclerosis; compared atherosclerosis patients with healthy controls; were published in English with full text available; and had clear methodology and outcomes related to atherosclerosis. We excluded case reports, conference abstracts, letters, commentaries, methodologically unclear studies, animal studies without clinical validation, and studies focusing only on cardiovascular outcomes without direct atherosclerosis assessment.

Data Extraction and Quality Assessment. We extracted data using a standardized form. We collected information on authors, publication year, study design, sample size, population details, microbiome assessment methods, bacterial taxa or metabolites studied, main findings, and statistical approaches.

Data Synthesis and Analysis. We performed a qualitative synthesis, organizing findings into four categories: microbial diversity and composition changes in atherosclerosis; key microbial metabolites in atherosclerosis pathogenesis;- mechanisms connecting gut microbiota to atherosclerosis; and potential therapeutic approaches targeting the gut microbiome. For studies with similar outcomes, we summarized the consistency and direction of associations.

Results

Microbial Diversity and Composition. The human gut microbiome represents a complex ecosystem consisting of bacteria, archaea, viruses, and eukaryotic microbes.[14] The integrity of the intestinal barrier plays an important role in preventing pathogens and toxins from entering the bloodstream, which can influence disease development.[15,16] The microbiome participates in maintaining the integrity of tight junctions between intestinal epithelial cells, thereby regulating intestinal permeability; certain taxa stimulate mucin production that strengthens the intestinal barrier; and microbial metabolites can affect the expression of genes responsible for the barrier function of the intestine.[16,17]

In the context of AS, studies have shown significant differences in the composition of gut microbiota between people with and without this disease.[17,18,19]

According to research, there is a reduction in bacterial diversity, particularly in patients with AS compared to healthy individuals.[13,20] In a mouse study, *Chan et al.* demonstrated decreased bacterial diversity in atherosclerosis, as well as a correlation between this phenomenon

and plaque size and cholesterol levels.[21] This reduction in diversity is associated with the loss of beneficial microbes and overgrowth of potentially pathogenic species. Moreover, according to available research, various microorganisms inhabit the atherosclerotic plaque itself, including *Streptococcus, Pseudomonas, Klebsiella, Veillonella spp.,* and *Chlamydia pneumonia*.[22,23]

Thus, the taxonomic composition of the gut microbiome in AS undergoes significant changes. Patients with AS exhibit an altered ratio of the two dominant bacterial phyla, Firmicutes and Bacteroidetes.[24,25] Although the exact consequences of this phenomenon are still debated, this change is believed to affect host metabolism and inflammation. According to *Szabo et al.,* a higher ratio of Firmicutes to Bacteroidetes was recorded in the group with high values of intima-media thickness.[26] There is also evidence that the amount of Bacteroides and Prevotella in the intestine has prognostic value for this disease.[27,28]

Some bacterial genera are consistently associated with AS. Patients with atherosclerosis show increased amounts of *Enterobacteriaceae, Collinsella, Streptococcaceae*, and *Klebsiella,* and decreased levels of *Roseburia, Eubacterium,* and *Ruminococcaceae spp.*; it should be noted that the latter bacteria are butyrate-producing.[29,30] According to data, *Akkermansia muciniphila* provides protection against atherosclerosis by improving the barrier function of the intestinal epithelium, suppressing the inflammatory process induced by endotoxemia.[31,32] *Chen et al.,* as a result of their research, suggested that,[33] and *Lactobacillales* could be used as predictors of coronary AS.[33] According to a recent study by *Li et al.,* bacteria of the genus *Oscillibacter* are associated with cholesterol reduction. The authors found that this taxon has the ability to metabolize cholesterol, which may help maintain lipid balance.[34]

Despite variations in specific taxa, functional analysis often reveals similarities in metabolic pathways, emphasizing the importance of microbial function rather than simply the presence of specific species.

Main Metabolic Functions of the Gut Microbiota. The gut microbiome plays a crucial role in various metabolic processes that may influence the development of AS.[35] Bacterial taxa in the intestine participate in the metabolism of food components, including carbohydrates, proteins, and lipids.[36,37] Their metabolic activity can produce both beneficial and potentially harmful compounds affecting cardiovascular health.[1,5] Microbial products activate TLRs on immune cells, leading to the production of pro-inflammatory cytokines that play a role in atherosclerotic plaque development;[38] furthermore, the microbiome affects the balance between T-cells with pro- and anti-inflammatory phenotypes, which may determine AS progression.[15,39]

SCF As. A key element in the microbiome's influence on atherosclerosis development is the production of short-chain fatty acids (SCFAs).[40] Certain bacteria ferment dietary fiber to produce SCFAs such as butyrate, acetate, and propionate. These substances, especially butyrate, support intestinal health by nourishing colonocytes and maintaining epithelial integrity.[41,42,43] This explains the anti-inflammatory properties of SCFAs, as well as their role in improving lipid metabolism and insulin sensitivity.[43] These effects are explained by SCFAs' ability to bind to membrane GPCR receptors and affect intracellular enzymes of enterocytes.[44,45] Entering the bloodstream, SCFAs exert their action by interacting with specific receptors GPR43, GPR41, GPR109A, and GPR91 (succinate receptor 1 (SUCNR1)), thereby affecting various organs and systems including the cardiovascular system,[46] influencing the energy potential of cells[45] and reducing the secretion of IL-6 and IL-8.[47] Moreover, SCFAs significantly influence atherosclerosis development by regulating Treg cell formation and inhibiting histone deacetylase (HDAC) activity.[47,48] *Tian et al.* noted butyrate's role in positively affecting endothelial function by reducing damage caused by IL-1ß through the PPARδ/miR-181b signaling pathway. Butyrate restores endothelium-dependent relaxation, reduces ROS levels, and NOX2 expression in endothelial cells.[49]

The effect of SCFAs on fat metabolism and cholesterol formation has been

studied. Haghikia et al., in a mouse model of atherosclerosis, demonstrated that propionate reduced total cholesterol levels and prevented disease development by blocking cholesterol transport in the intestine and increasing IL-10 and Treg cell levels, positively affecting the intestinal immune system.[49] In a recent study, *Pagonas et al.* showed the prognostic significance of propionate in relation to coronary atherosclerosis.[50] Thus, SCFAs demonstrate diverse effects on AS development, which may change at different stages of the disease. This field of science is very promising; however, further research on the role and interactions of SCFAs is necessary for a more complete understanding and effective application in atherosclerosis treatment.

TMAO. Accumulated evidence indicates that intestinal bacteria can metabolize dietary choline and L-carnitine to form trimethylamine (TMA), which is further converted to trimethylamine-N-oxide (TMAO) in the liver through the enzyme Flavin-containing monooxygenase 3 (FMO3).[51,52] In turn, TMAO is associated with the development of numerous diseases, including AS. TMAO levels in the body depend on factors such as diet, gut microflora, kidney function, and hepatic enzyme activity.[51] TMAO's actions in AS development include: enhancing cholesterol accumulation in macrophages, foam cell formation, platelet activation with increased thrombosis risk, and disruption of reverse cholesterol transport.[53] Additionally, it reduces the activity of liver enzymes responsible for bile acid synthesis (Cyp7a1 and Cyp27a1),[54,55] as well as bile acid transporters (Oatp1, Oatp4, Ntcp, Mrp2).[54] This leads to disruption of bile acid-related metabolic pathways, exacerbating atherosclerosis. The FMO3 enzyme level is regulated through the farnesoid X receptor (FXR), which plays a key role in controlling bile acid metabolism and TMAO production as mentioned earlier.[55] Accumulated research has identified several gut bacteria capable of producing TMA, thereby increasing blood TMAO levels. These bacteria include representatives of the *Firmicutes* and *Actinobacteria phyla*: *Acinetobacter, Serratia, Escherichia coli, Streptococcus sanguinis, Desulfovibrio-alaskensis, Desulfovibriodesulfuricans, Citrobacter, Klebsiella pneumoniae, Providencia, Shigella*, and *Achiomobacter.*[56,57] Many of these bacteria play a crucial role in AS development. It should be noted that research focused on developing strategies to reduce TMAO levels,[58,59] including dietary interventions, probiotics, and FMO3 inhibitors,[57,60,61] is currently relevant.

Bile Acids. The gut microbiome, specifically bacteria and archaea such as *Methanobrevibacter Smithii, Clostridium,* and *Enterococcus*, in which bile acid hydrolase has been detected,[62] plays a key role in bile acid biotransformation, performing deconjugation, dehydroxylation, and epimerization of primary bile acids. The latter participate in regulating lipid and glucose metabolism through activation of the farnesoid X receptor (FXR) and G-protein-coupled receptor TGR5, modulation of intestinal permeability and inflammation, affecting gut microbiota composition.

Bile acids play a significant role in AS development by affecting receptors that regulate cholesterol metabolism and lipid exchange. These acids influence signaling pathways that control bile acid synthesis, carbohydrate metabolism, as well as immune cell expression and inflammatory processes. These receptors possess both anti-atherosclerotic and pro-atherosclerotic effects.[63] Currently, the nuclear farnesoid X receptor (FXR) and the membrane G-protein-coupled Takeda receptor 5 (TGR5; i.e., bile acid G-protein-coupled receptor 1) are being extensively studied, with the role of these receptors potentially applicable in AS treatment.[64]

Lipopolysaccharides (LPS), a structural element of gram-negative bacteria, is considered by contemporary researchers as a possible factor contributing to atherosclerosis formation—a chronic inflammatory process affecting blood vessels.[65] The molecular mechanism of this phenomenon is associated with the interaction between LPS and the TLR4 receptor located on inflammatory cell membranes, triggering a cascade release of cytokines involved in atherosclerotic plaque formation.[66] Recent scientific works indicate that LPS may accelerate atherosclerotic progression by stimulating cellular senescence

in vascular tissue and enhancing the senescence-associated secretory phenotype (SASP).[67] According to *Wang et al.,* LPS induces macrophage senescence, manifested by morphological changes, secretion of the senescence-associated secretory phenotype (SASP), and DNA damage. This process contributes to lipid accumulation in atherosclerosis and can be prevented through inhibition of the BRD4 protein.[68] This integration of bacterial infection and cellular senescence concepts offers an innovative perspective on atherosclerosis pathogenesis mechanisms. Studies demonstrate that TLR4 signaling pathway activation under LPS influence leads to increased pro-inflammatory gene expression and cytokine synthesis, including interleukin-1ß, interleukin-6, and tumor necrosis factor-α.[66] These inflammatory mediators induce endothelial dysfunction, promote monocyte recruitment to the subendothelial space, and stimulate macrophage transformation into foam cells—key cellular elements of atherosclerotic lesions.[65,67] Furthermore, LPS may disrupt lipid metabolism, increasing hepatic cholesterol synthesis and reducing reverse cholesterol transport efficiency.[10] Interestingly, these effects are particularly pronounced in the presence of other atherosclerosis risk factors, such as hypercholesterolemia and arterial hypertension, indicating complex interactions between various pathogenetic mechanisms. Thus, current scientific data indicate an important role of LPS in atherosclerosis pathogenesis.

In addition to the aforementioned metabolites, it should be noted that current data suggest certain gut microbiome representatives can metabolize dietary polyphenols into bioactive compounds with potential anti-inflammatory and antioxidant properties, which may represent protective mechanisms in AS.[69,70] Moreover, metabolites capable of activating inflammasomes, promoting chronic inflammation and atherogenesis,[71,72] and indoles, tryptophan derivatives with anti-inflammatory properties potentially protecting against AS, are being studied.

Understanding these microbial functions provides insight into potential mechanisms linking the gut microbiome with AS development. This also highlights potential targets for therapeutic interventions based on microbiome modulation, including probiotics,[73] prebiotics,[74] fecal microbiota transplantation,[75] and targeted microbial metabolite modulation.[75]

Discussion

The growing body of evidence reviewed in this article highlights the significant role of the gut microbiome in atherosclerosis pathogenesis through multiple interconnected mechanisms. The evidence points toward a complex relationship between gut microbial dysbiosis and atherosclerotic disease, mediated through various microbial metabolites and inflammatory pathways.[19,29,30]

The consistent finding of reduced bacterial diversity in atherosclerosis patients across multiple studies suggests that microbial richness may be protective against cardiovascular disease. This aligns with broader evidence indicating that higher gut microbiome diversity is generally associated with better health outcomes.[20,23] The mechanisms underlying this relationship likely involve the collective metabolic functions of diverse bacterial communities.

Changes in the Firmicutes to Bacteroidetes ratio in atherosclerosis patients represent a taxonomic signature that has been similarly observed in other inflammatory and metabolic conditions, including obesity and diabetes. This suggests common pathways through which gut dysbiosis may contribute to cardiometabolic disorders. While some studies report increased Firmicutes / Bacteroidetes ratios in atherosclerosis, others show opposite findings,[24,25] highlighting the need for more nuanced analyses that focus on specific genera or species rather than phylum-level changes.

The depletion of butyrate-producing bacteriain atherosclerosis patients is particularly significant given butyrate's anti-inflammatory properties and its role in maintaining intestinal barrier integrity. The resulting decrease in butyrate production may promote systemic inflammation and endothelial dysfunction through multiple mechanisms, including reduced Treg cell induction and increased intestinal permeability lead-

ing to endotoxemia.[40,49]

The research on TMAO represents one of the most compelling links between gut microbiota and atherosclerosis, providing a clear mechanistic pathway from dietary components to cardiovascular risk. The identification of specific bacterial taxa capable of producing TMA (the TMAO precursor) offers potential targets for therapeutic interventions. However, strategies aimed at reducing TMAO levels must consider the complex interplay between diet, gut microbiota, and host factors.[51,61]

Bile acids are also cruisal in atherosclerosis development through various receptors regulating lipid and carbohydrate metabolism, and inflammation.[62,64]

The role of LPS in promoting atherosclerosis through TLR4 signaling and cellular senescence represents an intriguing connection between microbial products and vascular aging. This mechanism may explain how gut dysbiosis featuring increased abundance of gram-negative bacteria could accelerate atherosclerotic processes, even in the absence of traditional risk factors.[10,65]

The emerging understanding of gut microbiome contributions to atherosclerosis also emphasizes the need for personalized approaches to cardiovascular disease prevention. Individual variations in diet response, genetic factors influencing host-microbe interactions, and baseline microbiome composition may all impact the effectiveness of microbiome-targeted interventions.

Limitation. The present literature review has several limitations that should be acknowledged. First and foremost, as a literature review, our work is inherently limited by the methodological constraints of narrative synthesis without the rigorous statistical approach of meta-analysis. While we followed MOOSE guidelines for observational studies, a formal meta-analysis or systematic review with quantitative synthesis would provide stronger evidence regarding the associations between gut microbiome alterations and atherosclerosis. Second, the heterogeneity of study designs, populations, and methodologies used across the included studies makes direct comparisons challenging. Finally, cultural and regional dietary patterns significantly influence gut microbiota, which may affect the applicability of observed associations in different geographical contexts.

What's Known? Atherosclerosis remains the leading cause of cardiovascular morbidity and mortality worldwide, with ischemic heart disease from atherosclerotic plaque rupture accounting for 42.5% of mortality. Traditional risk factors include dyslipidemia, hypertension, diabetes, and smoking. Patients with atherosclerosis show reduced gut bacterial diversity and altered ratios of dominant bacterial phyla, particularly *Firmicutes* and *Bacteroidetes*. Key microbial metabolites like TMAO, SCFAs, bile acids, and lipopolysaccharides have been linked to atherosclerosis development through various mechanisms affecting cholesterol metabolism, inflammation, and endothelial function.

What's New? Recent research has revealed the critical role of the gut microbiome in atherosclerosis pathogenesis, with specific bacterial taxa like *Akkermansia muciniphila* showing protective effects and others like *Oscillibacter* demonstrating cholesterol-lowering abilities. Novel therapeutic approaches targeting the microbiome include probiotics, prebiotics, fecal microbiota transplantation, and targeted microbial metabolites, precisely those capable of activating inflammasomes. The emerging understanding of how LPS accelerates atherosclerosis through cellular senescence and the senescence-associated secretory phenotype provides an innovative perspective on disease mechanisms. This paradigm shift in cardiovascular medicine is moving toward more personalized, holistic interventions that consider the complex interactions between human genetics, environmental factors, and the microbiome.

Conclusions

Thus, studying the gut microbiome's contribution to atherosclerosis pathogenesispromotes a deeper understanding of mechanisms underlying this disease's development, opening new possibilities for both prevention strategies and atherosclerosis treatment. Modulation ofgut microbiome or targeting specific microbial metabolites, can

become an approach, which represents a paradigm shift in cardiovascular medicine, moving toward more personalized and holistic interventions that consider the complex interaction between human genetics, environmental factors, and the microbiome.

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