Major roles of the gut microbiota and microRNAs in cardiovascular disease events: a systematic review

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Abstract

Introduction: Gut microbiota (GM) is an essential mediator in the health of GM and has been identified as the origin of several diseases by influencing cell signaling and T cell receptor pathways in the central nervous system. Several microRNAs participate in signaling networks through GM intervention. The interaction between GM and miRNAs plays a crucial role in vascular dysfunction. GM can metabolize L-carnitine, choline, and phosphatidylcholine and produce vascular-toxic metabolites such as trimethylamine-N-oxide (TMAO), which is associated with the atherosclerotic process. Nutrology and dietary therapy represent important strategies, especially with the use of plant-derived miRNAs to modify GM. Objective: To carry out a systematic review to highlight the main roles of the gut microbiota and microRNAs in cardiovascular disease events. Methods: The present study followed a concise systematic review model (PRISMA). The literary search process was carried out from March to May 2023 and was developed based on Scopus, PubMed, Science Direct, Scielo, and Google Scholar, using scientific articles from 2002 to 2022. The low quality of evidence was attributed to reports of cases, editorials, and brief communications, according to the GRADE instrument. The risk of bias was analyzed according to the Cochrane instrument. Results and Conclusion: The total of 126 studies were found for eligibility analysis, and then 42 of the 64 total studies were selected for this systematic review. According to the GRADE instrument, most studies showed homogeneity in their results, with $X^2$ =88.7%>50%. It was concluded that the gut microbiota can be influenced by diet, genetics, and environmental factors. Changes in the microbial population can lead to multiple diseases, including cardiovascular disease. miRNAs have been known as important regulators of several biological functions, and are also involved in the pathogenesis of cardiovascular diseases. There is evidence that disturbances in the gut microbiota and derived metabolites impair the development of atherosclerotic cardiovascular disease. Studies have shown that YRNAs belonging to extracellular vesicles and their fragments play important roles in the initiation, progression, and diagnosis of atherosclerosis.

Keywords: Gut microbiota. Cardiovascular diseases. microRNAs. Nutrology.

Introduction

Gut microbiota (GM) is an essential mediator in health and disease, relating to various organs and systems of the body, including the brain, lungs, liver, bones, cardiovascular system, and others. As an example, GM-derived metabolites such as shortchain fatty acid butyrate (SCFA) bind GM and modulate physiology. Furthermore, GM has been identified as the origin of several diseases by influencing related cell signaling pathways such as the WNT/beta-catenin pathway in colorectal cancer and T cell receptor signaling in the central nervous system. Furthermore, several microRNAs participate in signaling networks through GM intervention. The interaction between GM and microRNAs (miRNAs) plays a crucial role in vascular dysfunction and hepatocellular carcinoma [1,2]. Furthermore, GM composition is influenced by host genetics and environmental factors. Recent studies have
shown that GM is not just a passive participant in our health, but can also actively regulate our functions through genes, proteins, and metabolites [3-6]. Dysbiosis can lead to various diseases, not only gastrointestinal but also disorders of the lung, brain, heart, and immune system [7-9]. Dysbiosis plays an important role in cardiovascular diseases (CVD), mainly by activating a pro-inflammatory state in the body and favoring the atherosclerotic process [10,11].

In this context, GM can metabolize L-carnitine, choline, and phosphatidylcholine and produce vascular-toxic metabolites, such as trimethylamine-N-oxide (TMAO), which is associated with the atherosclerotic process [12]. A continuous inflammatory state in the gut can facilitate the transit of bacteria and their metabolites into the bloodstream, thus maintaining chronic inflammation and favoring the development of atherosclerotic plaques, increasing the risk of coronary heart disease, stroke, and other acute complications [11,13].

In this sense, miRNAs are regulators in the processes of gene expression in the host and are linked to specific bacteria [14]. They enter bacterial cells by endocytosis, influencing the GM by stimulating or inhibiting the expansion of certain bacterial species [15-17]. In the miRNAs-gut microbiota connection, miRNAs have effects on intestinal cell proliferation and differentiation, gut architecture, and barrier function [18]. Some studies have shown that GM can have an impact on miRNAs, modulating gene expression in the host [14,19].

In this scenario, the association between circulating miRNAs and CVD has been widely investigated to discover new possible diagnostic markers [20-23]. The miRNAs-gut microbiota relationship is especially involved in the regulation of epithelial dysfunction [9]. GM can influence RNA genes affiliated with miRNA classes, such as vascular miR-204, miR-108, or miR-181, decreasing or increasing the risk of developing atherosclerosis [24-27].

Still in this aspect, nutrology and dietary therapy represent important strategies, especially with the use of plant-derived miRNAs to modify GM [28,29]. For example, studies in mice have shown that ginger-derived exosomes contain miRNAs that can influence GM by increasing fatty acid metabolism. Wang et al. observed an increase in Bifidobacterium species and SCFA-producing bacteria, reducing body weight, hepatic steatosis, low-grade inflammation, and insulin resistance [29,30]. Probiotics can restore GM balance to the benefit of the host [31]. The role of miRNAs in GM modulation highlighted their possible implication in the molecular mechanism of action of probiotics [15,16].

Therefore, this study aimed to carry out a systematic review to highlight the main functions of the gut microbiota and miRNAs in cardiovascular disease events.

**Methods**

**Study Design**

The present study followed a systematic review model, following the rules of systematic review - PRISMA (Transparent reporting of systematic review and metaanalysis-HTTP: //www.prisma-statement.org/).

**Search Strategy and Search Sources**

The literary search process was carried out from March to May 2023 and was developed based on Scopus, PubMed, Science Direct, Scielo, and Google Scholar, using scientific articles from 2002 to 2022, using the descriptors (MeSH Terms): Gut microbiota. Cardiovascular diseases. microRNAs. Nutrology, and using the Booleans "and" between the MeSH terms and "or" between the historical findings.

**Study Quality and Risk of Bias**

Quality was rated as high, moderate, low, or very low for risk of bias, clarity of comparisons, precision, and consistency of analyses. The most evident highlight was for systematic review articles or meta-analysis of randomized clinical trials, followed by randomized clinical trials. The low quality of evidence was attributed to case reports, editorials, and brief communications, according to the GRADE instrument. The risk of bias was analyzed according to the Cochrane instrument through the analysis of the Funnel Plot (Cohen test (d)).

**Literary Review Results**

**Summary of Findings**

It was found 126 studies that underwent eligibility analysis, and then 42 of the 64 total studies were selected for the present systematic review (Figure 1), considering in the first instance the level of scientific evidence of studies in study types such as meta-analysis, consensus, randomized clinical trial, prospective and observational. The biases did not compromise the scientific basis of the studies. According to the GRADE instrument, most studies showed homogeneity in their results, with $X^2 = 88.7% > 50%$. 
Figure 1. Flowchart showing the article selection process.

Major Clinical Outcomes

GM can be influenced by diet, genetics, and environmental factors. Any change in its composition results in pathophysiological changes that can further influence the evolution of several conditions, including CVD. MicroRNAs interact with GM to modulate host gene expression. Circulating microRNAs are stable against degradation due to their closure in extracellular vesicles [32].

Many studies have highlighted the connection between miRNAs and GM, especially in the case of dysbiosis, which leads to intestinal epithelial barrier dysfunction and inflammatory response [30-32]. MicroRNAs are particularly involved in the regulation of intestinal epithelial cells (IEC) [28-30]. Some studies have shown that fecal miRNAs can influence GM composition. miR-375 plays an important role in the production of the mucus layer in epithelial cells and influences stem cell proliferation in the intestinal epithelium. The suppression of miR-381-3p allows nuclear receptor-related protein-mediated IEC proliferation while gut barrier function is being enhanced [1,2].

Furthermore, GM can produce biologically active metabolites, which can further influence the physiological processes of the host. Changes in the microbial population can lead to multiple diseases, including CVD [22]. Dysbiosis, intestinal inflammation, and altered intestinal barrier can result in high concentrations of bacterial structural elements and microbial metabolites in the circulation, including trimethylamine N-oxide (TMAO) and short-chain fatty acids, which can further favor the evolution of CVD. Low concentrations of microbes that produce butyrate have been associated with heart failure and coronary artery disease [11].

In addition, phenylacetylglutamine has the potential to favor negative cardiovascular phenotypes in hosts, by acting on adrenergic receptors. TMAO is a metabolite often found in Western diets, rich in lecithin, choline, phosphatidylcholine, and carnitine, which predicted cardiovascular risk in some clinical studies and amplified the atherosclerotic process in animal models [33-35].

Besides, miRNAs have been known as important regulators of several biological functions, being also involved in the pathogenesis of CVD [33,34]. The most abundant miRNAs in cardiac tissue are miR-1, let-7, miR-133, miR-126-3p, miR-30c, and miR-26a [35], while in arteries the most frequent miRNAs are miR-145, let-7, miR-125b, miR-125a, miR-23 and miR-143 [36-38].

In this scenario, there is evidence of disturbances in GM and derived metabolites that impair the development of atherosclerotic cardiovascular disease (ASCVD). One study analyzed 30 patients for the relationship of GM to coronary artery disease (CAD) and 30 age- and sex-matched healthy controls to identify microbial metabolites associated with CAD, which were then evaluated in an independent population of ASCVD patients and controls ( n=256). Indole-3-propionic acid (IPA), a tryptophan metabolite exclusively derived from microorganisms, was the most down-regulated metabolite in patients with CAD. Circulating IPA was then shown in an independent population to be associated with ASCVD risk. In murine- and human-derived macrophages, IPA administration promoted cholesterol efflux from macrophages to ApoA-I through an undescribed miR-1425p/ABCA1 signaling pathway. Furthermore, the miR-142-5p/ABCA1/reverse cholesterol transport axis in macrophages was dysregulated in CAD patients and correlated with changes in circulating IPA levels [39].

Also, a Mediterranean diet style has been reported to be associated with a lower degree of inflammation biomarkers and a protective role in cardiovascular and cerebrovascular events. We report a new positive association between baseline plasma ceramide concentrations and cardiovascular events and how adherence to a Mediterranean-style diet may influence the potential negative relationship between elevated plasma ceramide concentrations and CVD. Several randomized clinical trials have shown the positive effects of the Mediterranean diet style on various cardiovascular risk factors such as body mass index, waist circumference, blood lipids, blood pressure, inflammatory markers and adhesion molecules, and
diabetes and how these advantages of Mediterranean diets are maintained compared to a low-fat diet. The PREDIMED study showed that the incidence of cardiovascular events was lower among those assigned to a Mediterranean diet supplemented with extra virgin olive oil or nuts than among those assigned to a low-fat diet [40].

In this context, oxidative stress and inflammation interact in the development of diabetic atherosclerosis. Intracellular hyperglycemia promotes the production of mitochondrial reactive oxygen species (ROS), increased formation of intracellular advanced glycation end products, activation of protein kinase C, and increased polyol pathway flux. ROS directly increases the expression of inflammatory and adhesion factors, the formation of oxidized low-density lipoprotein, and insulin resistance, as well as activates the ubiquitin pathway, inhibits the activation of AMP-protein kinase and adiponectin, decreases the activity of endothelial nitric oxide synthase, all accelerating atherosclerosis. Changes in GM composition and changes in microRNA expression that influence the regulation of target genes that occur in diabetes interact with increased ROS and inflammation to promote atherosclerosis [41].

In this sense, finally, it is understood that atherosclerosis is characterized by the accumulation of lipids and chronic inflammation. Studies have shown that YRNAs belonging to extracellular vesicles and their fragments play important roles in the initiation, progression, and diagnosis of atherosclerosis. YsRNA-5p transcripts promote foam cell apoptosis and inflammatory responses by binding to Ro60 in vitro and in vivo. YRNAs can regulate the progression of atherosclerosis by binding to several proteins, including nucleolin, Ro60, La, hnRNPK, hnRNPI, YBX1, and ELAVL1. YRNAs can be derived from miRNAs and piRNAs; in particular, Y4sRNA-3p and Y5sRNA-3p in humans are also called piR-hsa-32167 and piR-hsa-116589, respectively. Furthermore, YRNAs are detectable in blood plasma and YRNA ratios are potential biomarkers for inflammatory diseases, including cardiovascular disease. MicroRNAs have been known as important regulators of several biological functions, and are also involved in the pathogenesis of cardiovascular diseases. There is evidence that disturbances in the gut microbiota and derived metabolites impair the development of atherosclerotic cardiovascular disease. Studies have shown that YRNAs belonging to extracellular vesicles and their fragments play important roles in the initiation, progression, and diagnosis of atherosclerosis.

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