



Metabolomics of microRNAs in cardiovascular events in patients with obesity: a systematic review

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Abstract

Introduction: In the metabolomics scenario of obesity and cardiovascular disease, epitranscriptomics establishes a novel mechanism of post-transcriptional RNA regulation. There is growing evidence supporting the role of intra- and extracellular microRNAs (miRNAs) as determinants of cross-talk between adipose tissue, liver, skeletal muscle, and other organs, triggering paracrine communication between different tissues. **Objective:** To describe, through a systematic literature review, the main approaches to metabolomics of microRNAs and exosomes in cardiovascular disease in obese patients. **Methods:** The systematic review guidelines of the PRISMA Platform were followed. The search was conducted from March to May 2025 across the Web of Science, Scopus, Embase, PubMed, ScienceDirect, Scielo, and Google Scholar databases. Study quality was based on the GRADE instrument, and risk of bias was analyzed according to the Cochrane tool. **Results and Conclusion:** A total of 121 articles were found. A total of 18 articles were fully evaluated, and 9 were included and developed in this systematic review. Considering the Cochrane risk of bias tool, the overall assessment resulted in 32 studies with a high risk of bias and 21 studies that did not meet the GRADE and AMSTAR-2 criteria. Most studies presented

homogeneity in their results, with $X^2=91.4\%>50\%$. It was concluded that the decrease in circulating miR-19 levels during dietary interventions for weight loss was associated with a significant reduction in the risk of atherosclerotic cardiovascular disease. Epicardial adipose tissue-derived miRNAs exert paracrine effects on the human heart. Epicardial adipose tissue-derived miR-92a-3p is associated with improved clinical outcomes and is a therapeutic target for the prevention and treatment of obesity-related heart disease. An increased profile of plasma miR-126-3p was identified in hypertensive patients with albuminuria. The Mediterranean diet better modulates endothelial function compared to a low-fat diet. Therefore, the potential of microRNAs, particularly miR-133b and miR-126, is postulated as diagnostic biomarkers to distinguish patients with ST-segment elevation from those with non-ischemic chest discomfort.

Keywords: Cardiovascular diseases. Nutrology. Obesity. Diabetes mellitus. Metabolomics. MicroRNAs.

Introduction

In the metabolomics landscape of obesity and cardiovascular disease, epitranscriptomics establishes a novel mechanism of post-transcriptional RNA

regulation, highlighting the regulation of RNA function in the progression of health or disease. RNA methylation is the most common type of RNA modification, accounting for 60% of all RNA modifications [1].

The epigenetic RNA modification, N6-methyladenosine (m6A), is considered the most prevalent mRNA transcriptional modification. More than 7,000 mRNAs in mammalian cells are modified by m6A, and m6A is estimated to exist in 0.1–0.4% of adenosines [2,3]. In addition to mRNA, m6A also occurs in rRNA, tRNA, small nuclear RNAs, microRNAs (miRNAs or miRs), and long noncoding RNAs [4–6]. m6A is reversibly and dynamically regulated by methyltransferases and demethylases. Studies have reported the emerging roles of m6A in the development of cardiovascular disease (CVD) [7–11].

In this context, obesity and type 2 diabetes mellitus (T2DM) are considered major risk factors for the development of cardiovascular disease (CVD). There is growing evidence supporting the role of intracellular and extracellular microRNAs (miRNAs) as determinants of cross-talk between adipose tissue, liver, skeletal muscle, and other organs, triggering paracrine communication between different tissues. miRNAs can be considered risk factors for CVD due to their correlation with cardiovascular events and, in particular, may be related to the most prominent risk factors [12]. MicroRNAs (miRNAs) are known to be small, non-coding RNA molecules with a powerful ability to regulate gene expression post-transcriptionally, highlighting the potential of miRNAs as new targets for CVD prevention. For example, the microRNA-19 (miR-19) family, composed of miR-19a and miR-19b [13].

In recent years, increasing studies have demonstrated the imbalanced expression of miR-19 in the blood, heart, and vessels with cardiac development and CVD risk in humans and animals. Furthermore, circulating miRNAs are subject to dietary and behavioral modulations (such as sleep and physical activity) and subsequently regulate important cardiovascular pathways involved in lipid metabolism, endothelial function, cardiac hypertrophy, and fibrosis [12,13]. Furthermore, studies accumulated over the last two decades have revealed the role of miRNAs in important pathobiological events observed in the hearts of patients with diabetes and myocardial infarction, including cardiomyocyte death, angiogenesis, inflammatory response, myocardial remodeling, and myocardial lipotoxicity [14].

In addition, the scientific literature shows that obesity is the main cause of obstructive sleep apnea (OSA) and a significant risk factor for atherosclerosis.

The role of exosomes in this process has attracted considerable attention. Exosomes are extracellular vesicles (EVs) released by various cells and mediate cell-to-cell communication, transporting miRNAs, proteins, mRNAs, DNA, or lipids to target cells, thereby modulating the functions of target cells and tissues. Intermittent hypoxia in OSA alters the exosomal transporter in the circulation and promotes endothelial cell permeability and dysfunction, which have been associated with the pathogenesis of atherosclerosis [15].

In cases of hyperlipidemia, the roles of microRNAs in modulating macrophage activation, lipid metabolism, and hyperlipidemia are also highlighted. There are potential mechanisms by which microRNAs control lipid metabolism and the risk of cardiometabolic disorders, which may help identify microRNAs as a promising therapeutic target for hyperlipidemia and related cardiovascular diseases [16].

Consequently, the present study aimed to describe, through a systematic literature review, the main approaches to metabolomics of microRNAs and exosomes in cardiovascular diseases in obese patients.

Methods

Study Design

This study followed the international systematic review model, following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) guidelines. Available at: <http://www.prisma-statement.org/?AspxAutoDetectCookieSupport=1>. Accessed on: April 11, 2025. The AMSTAR-2 (Assessing the Methodological Quality of Systematic Reviews) methodological quality standards were also followed. Available at: <https://amstar.ca/>. Accessed on: April 11, 2025.

Data Sources and Search Strategy

The literature search process was conducted from March to April 2025 and developed based on Web of Science, Scopus, Embase, PubMed, Lilacs, Ebsco, Scielo, and Google Scholar, covering scientific articles from various periods to the present day. The following descriptors (DeCS/MeSH Terms) were used "Cardiovascular diseases. Nutrology. Obesity. Diabetes mellitus. Metabolomics. MicroRNAs," and the Boolean "and" between MeSH terms and "or" between historical findings were used.

Study Quality and Risk of Bias

Quality was classified as high, moderate, low, or very low based on the risk of bias, clarity of comparisons, precision, and consistency of analyses.

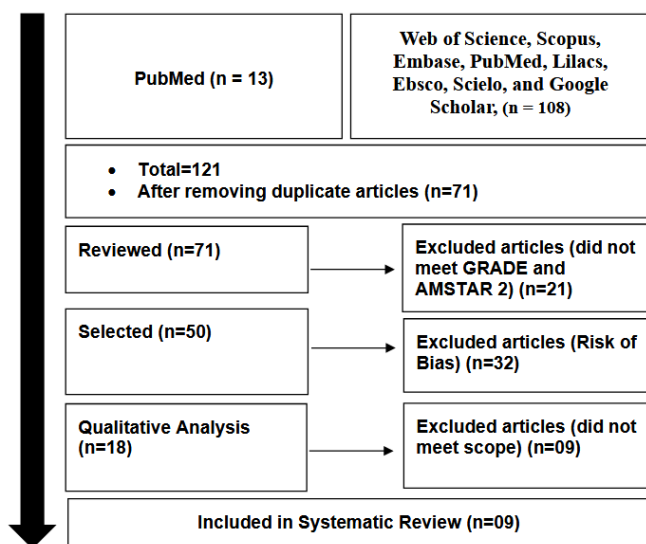
The most prominent articles were systematic reviews or meta-analyses of randomized controlled trials, followed by randomized clinical trials. Low-quality evidence was attributed to case reports, editorials, and brief communications, according to the GRADE instrument. Risk of bias was analyzed according to the Cochrane instrument by analyzing the funnel plot (sample size versus effect size), using Cohen's d test.

Results and Discussion

Summary of Findings

A total of 121 articles were found and submitted for eligibility analysis, with 09 final studies selected to comprise the results of this systematic review. The selected studies were of medium to high quality (Figure 1), considering the level of scientific evidence from studies such as meta-analysis, consensus, randomized clinical trials, prospective, and observational studies. Biases did not compromise the scientific basis of the studies. According to the GRADE instrument, most studies presented homogeneity in their results, with $X^2 = 91.4\% > 50\%$. Considering the Cochrane risk of bias tool, the overall assessment resulted in 32 studies with a high risk of bias and 21 studies that did not meet the GRADE and AMSTAR-2 criteria.

Figure 1. Article selection.

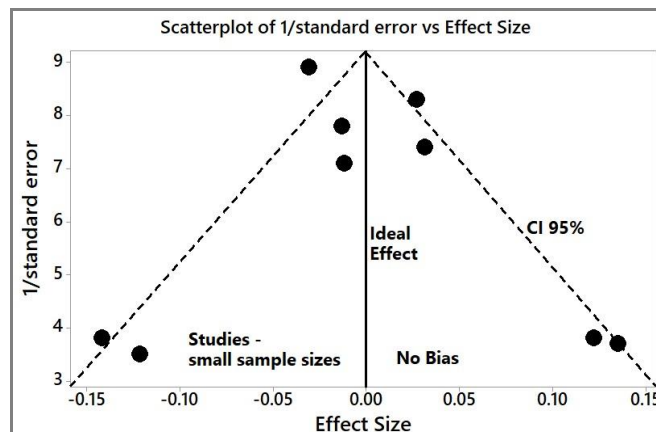


Source: Own Authorship.

Figure 2 presents the results of the risk of bias of the studies using the funnel plot, showing the calculation of the effect size (magnitude of the difference) using Cohen's d test. Precision (sample size) was determined indirectly by the inverse of the standard error (1/Standard Error). This graph displayed symmetrical behavior, suggesting no significant risk of bias, either among studies with small sample sizes

(lower precision), shown at the bottom of the graph, or among studies with large sample sizes, shown at the top.

Figure 2. The symmetrical funnel plot suggests no risk of bias among the small sample size studies shown at the bottom of the graph (n=4). High-confidence and highly recommended studies are shown above the graph (n=5 studies).



Source: Own Authorship.

Major Clinical Findings

Consuming a high-fat, high-calorie diet increases body mass due to excess calories, leading to dysfunctions in glycolipid metabolism and the development of obesity and metabolic syndrome (MS). The metabolic changes induced by overnutrition need to be elucidated. Furthermore, changes in the gut microbiota, intestinal barrier dysfunction, and immune dysregulation induced by a high-fat diet alter intestinal tryptophan and biliary metabolism, which, with concomitant elevations in free fatty acids, promote insulin insensitivity. Immunometabolic changes induce adipose tissue dysfunction, which alters the secretion of adipokines and lipid metabolites that contribute to dyslipidemia, hepatosteatosis, cardiovascular dysfunction, and endocrine dysregulation [17].

In this context, unbalanced adipose expansion enables epigenomic changes mediated by exosomes and microRNAs that affect the pathogenesis of obesity and MS [17]. A review study gathered evidence of aberrant m6A methylation in cardiovascular diseases (CVD), including cardiac hypertrophy, heart failure, arterial aneurysm, vascular calcification, and pulmonary hypertension [18].

Furthermore, a study compared the effects of GLP-1 analogues (GLP-1RAs), such as liraglutide, semaglutide, dulaglutide, and exenatide, on the regulation of miRNAs in the treatment of T2DM. GLP-1RAs modify the expression of miRNAs involved in endothelial function, sugar metabolism, and

adipogenesis, including, among others, miR-27b, miR-130a, and miR-210. Baseline levels of miR-15a-5p predict weight loss, while higher levels of miR-378-3p and miR-126-3p are associated with better glycemic control and lower HbA1c and FPG levels one year after treatment. miR-375-5p has also been reported as a predictor of HbA1c levels. Liraglutide has a protective effect against pancreatic β -cell apoptosis by downregulating miR-139-5p. MiR-375, highly expressed in pancreatic islets, can be considered a biomarker to assess the cytoprotective action of GLP-1RAs on β -cells. GLP-1RAs also increase β -cell responsiveness by promoting GLP-1 receptor expression through suppression of miR-204. While semaglutide and exenatide reduce systolic and diastolic blood pressure, exenatide did not demonstrate such an effect. The long-acting miR-29b-3p induced by exenatide is necessary for protection against diabetic cardiomyopathy. Liraglutide modulates critical regulators of endothelial cell function and atherosclerosis, including miR-93-5p, miR-26a-5p, and miR-181a-5p. Additionally, the regulation of exosomal miRNAs, such as miR-192, by GLP-1RAs is implicated in the development of fibrosis and inflammation in microcardiovascular outcomes of T2DM [19].

Also, microRNA-19 (miR-19) plays a critical role in cardiac development and CVD. A clinical study included 509 overweight or obese participants from the 24-month weight loss diet intervention study (the POUNDS Lost study) and had available data on circulating miR-19a-3p and miR-19b-3p at baseline and after 6 months. The primary outcome of this analysis was the change in atherosclerotic cardiovascular disease (ASCVD) risk at 6 and 24 months, which estimates the probability of major ASCVD events over 10 years. Secondary outcomes were changes in the components of the ASCVD risk score. Circulating levels of miR-19a-3p and miR-19b-3p decreased significantly during the initial 6-month dietary intervention period. A greater reduction in miR-19a-3p or miR-19b-3p was found to be related to a greater reduction in ASCVD risk over 6 months, regardless of concomitant weight loss. Participants with a greater reduction in miR-19 without sleep disturbance had a greater reduction in ASCVD risk than those with mild/moderate/major sleep disturbance. Furthermore, a change in physical activity significantly modified the associations between change in miR-19 and change in ASCVD risk over 24 months. A greater decrease in miR-19 was significantly associated with a greater reduction in ASCVD risk among participants with increased physical activity, whereas non-significant inverse associations were observed among those without increased physical activity [20].

Authors Carena et al. (2023) [21] explored the

ability of human epicardial adipose tissue (EAT)-derived microRNAs (miRNAs) to regulate myocardial redox state and clinical outcomes. The final prognostic value of the discovered targets was tested in patients undergoing cardiac surgery, followed for 8 years. EAT miR-92a-3p was related to lower oxidative stress in the human myocardium, a finding confirmed by the use of genetic regulators of miR-92a-3p in the human heart and EAT. miR-92a-3p reduced superoxide (O²⁻)-derived nicotinamide adenine dinucleotide phosphate (NADPH) oxidase. High levels of miR-92a-3p in EAT were independently related to a lower risk of adverse cardiovascular events. Therefore, EAT-derived miRNAs exert paracrine effects in the human heart. EAT-derived miR-92a-3p is associated with improved clinical outcomes and is a therapeutic target for the prevention and treatment of obesity-related heart disease.

It is also noteworthy that Martinez-Arroyo et al. (2023) [22] estimated the predictive value of a plasma microRNA signature associated with albuminuria on the incidence of cardiovascular events. A plasma microRNA profile associated with albuminuria was identified in the discovery cohort (n=48), and three microRNAs (miR-126-3p, miR-1260b, and miR-374a-5p) were confirmed in the validation cohort (n=98). Elevated miR-126-3p levels were associated with shorter cardiovascular event-free survival (HR = 1.48, (1.36-1.62), p<0.0001), as well as with combined coronary artery disease and stroke (HR = 2.49, (2.19-2.83), p<0.0001).

Cione et al. (2024) [23] identified increased circulating expression of hsa-miR-604, hsa-miR-652-5p, and hsa-miR-4451, as well as reduced expression of hsa-miR-3140-3p, hsa-miR-550a-5p, and hsa-miR-363-3p in both familial hypercholesterolemia groups (homozygous and heterozygous) compared with healthy individuals. Higher levels of hsa-miR-1183, hsa-miR-1185-1-3p, hsa-miR-122-5p, hsa-miR-19a-3p, hsa-miR-345-3p, and hsa-miR-34c-5p were detected in heterozygous familial hypercholesterolemia compared to homozygous familial hypercholesterolemia compared to healthy individuals. Most of the upregulated miRNAs primarily affected genes related to cardiac myofibrillogenesis, cholesterol synthesis, RNA editing for apolipoprotein B, and were associated with LDL cholesterol levels. In contrast, downregulated miRNAs primarily affected genes related to plasma biomarkers for coronary artery disease, lipid metabolism, cell adhesion and migration, genetic predictors of type 2 diabetes, and cholesterol metabolism. Rapid diagnosis of ST-segment elevation myocardial infarction is essential for initiating timely treatment. MicroRNAs have recently emerged as biomarkers in cardiovascular diseases. In this regard, the authors evaluated the

discriminatory capacity of serum microRNAs in identifying an ischemic origin in patients presenting with chest discomfort. The study included 98 participants (78 with ST-segment elevation and 20 with non-ischemic chest discomfort). Significant differences in the expression levels of miR-133b, miR-126, and miR-155 (but not miR-1, miR-208, and miR-208b) were observed between the groups. miR-133b and miR-155 exhibited 97% and 93% sensitivity in identifying patients with ST-segment elevation, respectively. miR-126 demonstrated a specificity of 90% in identifying patients with ST-segment elevation [24].

Finally, the CORonary Diet Intervention with Olive Oil and Cardiovascular PREvention (CORDIOPREV) study was an ongoing prospective, randomized, single-blind, controlled clinical trial involving 1,002 patients with coronary artery disease (CAD), whose primary objective was to compare the effect of two healthy dietary patterns (low-fat diet versus Mediterranean diet) on the incidence of cardiovascular events through modulation of microRNAs. Of the total participants, 805 completed the endothelial function study at baseline and were randomized to follow a Mediterranean diet (35% fat, 22% monounsaturated fatty acids [MUFAs], and <50% carbohydrates) or a low-fat diet (28% fat, 12% MUFAs, and >55% carbohydrates), with endothelial function measurements repeated after 1 year. Lower intracellular production of reactive oxygen species (ROS), cell apoptosis and senescence, and greater cell proliferation and angiogenesis were observed between groups after the Mediterranean diet compared to the low-fat diet. Each dietary intervention was associated with distinct changes in epigenetic and proteomic factors that modulate the biological process associated with endothelial dysfunction [25].

Conclusion

It was concluded that the decrease in circulating miR-19 levels during dietary interventions for weight loss was associated with a significant reduction in the risk of atherosclerotic cardiovascular disease. Epicardial adipose tissue-derived miRNAs exert paracrine effects on the human heart. Epicardial adipose tissue-derived miR-92a-3p is associated with improved clinical outcomes and is a therapeutic target for the prevention and treatment of obesity-related heart disease. An increased plasma miR-126-3p profile was identified in hypertensive patients with albuminuria. The Mediterranean diet better modulates endothelial function compared to a low-fat diet. Therefore, the potential of microRNAs, particularly miR-133b and miR-126, is postulated as diagnostic biomarkers to distinguish patients with ST-segment elevation from

those with non-ischemic chest discomfort.

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Informed Consent

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Data Sharing Statement

No additional data are available.

Conflict of Interest

The authors declare no conflict of interest.

Similarity Check

It was applied by Ithenticate®.

Application of Artificial Intelligence (AI)

Not applicable.

Peer Review Process

It was performed.

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