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Major microRNAs and regulation of gut microbiota in patients with obesity: a systematic review

Renan Francisco Merloto[1*], Bruna Rocha Soares[1]

[1] Zelos Institute. Street: Francisco José Ferreira Sampaio, n°50 – Sala 405, Edifício INC 50, Itu Novo Centro-Itu, São Paulo, Brazil.

*Corresponding author: Dr. Renan Francisco Merloto.
Zelos Institute. Street: Francisco José Ferreira Sampaio, n°50 – Sala 405, Edifício INC 50, Itu Novo Centro-Itu, São Paulo, Brazil. Zip Code: 13303-536
E-mail: renan.merloto@gmail.com
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Abstract

Introduction: Obesity represents a pandemic represented as a chronic, long-term imbalance between calorie intake and energy expenditure. MicroRNAs (miRNAs) stand out. They are a class of small non-coding RNAs that regulate gene expression, and changes in their expression and functions have been associated with many diseases, including metabolic disorders and obesity. **Objective:** It was to present the main considerations and results of clinical studies on the relationship between obesity, gut microbiota, and microRNAs in inflammatory and immunological processes through a systematic review. **Methods:** The PRISMA Platform systematic review rules were followed. The search was carried out from August to September 2023 in the Web of Science, Scopus, PubMed, Science Direct, Scielo, and Google Scholar databases. The quality of the studies was based on the GRADE instrument and the risk of bias was analyzed according to the Cochrane instrument. **Results and Conclusion:** A total of 121 articles were found, and 44 articles were evaluated in full and 30 were included and developed in the present systematic review study. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 22 studies with a high risk of bias and 21 studies that did not meet GRADE and AMSTAR-2. Most studies showed homogeneity in their results, with X^2=77.5%>50%. It was concluded that microRNAs regulate gene expression in adipose tissue, impact the regulation of metabolism and energy homeostasis, and regulate adipogenesis signaling pathways in white, beige, and brown adipose tissue. For example, microRNA (miR-143) promotes brown adipose tissue thermogenesis and inhibits white adipose tissue adipogenesis. Some miRNAs have been implicated in the control of body weight gain, glucose homeostasis, insulin resistance, and lipid metabolism, with crosstalk with the gut microbiota. Furthermore, an association was found between *B. eggerthi* abundance, miR-183-5p expression, and adiponectin levels. Expression of miR-15a-5p was found to be associated with *H. parainfluenzae* abundance and insulin levels.

Keywords: Obesity. Gut microbiota. MicroRNAs. Inflammatory processes.

Introduction

Obesity represents a pandemic represented as a long-term chronic imbalance between calorie intake and energy expenditure, which causes serious comorbidities [1-3]. Obesity is the result of complex and incompletely understood pathological processes, resulting from a crosstalk between environmental factors, genetic susceptibility, and epigenetic mechanisms, resulting in more than 2.0 billion overweight and obese people worldwide [1].

In this scenario, microRNAs (miRNAs) stand out, which are a class of small non-coding RNAs that regulate gene expression [4-6]. These molecules have recognized roles in the regulation of various biological processes, regulating the expression of more than 70% of protein-coding genes, and changes in their expression and functions have been associated with many diseases, including metabolic disorders and obesity [7,8].

Furthermore, host miRNAs contribute to the regulation of the gut microbiota, or the gut microbiota affects the host through the induction of miRNA expression [9]. Evidence suggests that miRNAs produced by host intestinal epithelial cells (IECs) participate in the formation of the gut microbiota and affect bacterial growth. These miRNAs target bacterial mRNA and then the host controls the gut microbiota through degradation of bacterial mRNA or inhibition of translation [10].

Also, the gut microbiota regulates miRNA expression in IEC subtypes and this regulation can alter intestinal homeostasis [11]. In this sense, it has been demonstrated that the expression of some miRNAs is different between IEC subtypes and the difference depends on microbial patterns [12]. Thus, studies provide clues that the gut microbiota regulates host gene expression through modulation of the host miRNA signature and that host metabolism can be influenced by this interaction. Therefore, miRNAs appear to play an important role in host-microbe interactions and can be considered molecular targets for the development of new antimicrobial therapies. However, little is known about the interactions between miRNAs and the host microbiome in the context of obesity [3].

In this context, metabolic disorders are characterized by the inability to use and/or store energy properly. There is growing concern about the dysregulation of miRNAs in metabolic diseases. Recent data show the potential involvement of miRNAs in metabolic diseases, particularly obesity and type 2 diabetes [13].

Added to this, obesity is associated with chronic low-grade inflammation in adipose tissue. The resident immune microenvironment is not only responsible for maintaining homeostasis in adipose tissue but also plays a crucial role in combating obesity and its comorbidities. Increasing evidence suggests that obesity promotes the activation of resident T cells and macrophages. MicroRNAs contribute to the maintenance of the immune response and obesity in adipose tissue. Resident T cells, macrophages, and adipocytes secrete various miRNAs and communicate with other cells to create a potential effect on metabolic organ crosstalk. Resident macrophages and T cell-associated miRNAs have a prominent role in regulating obesity by targeting diverse signaling pathways [14].

Therefore, the present study aims to present the main considerations and results of clinical studies on the relationship between obesity, gut microbiota, and microRNAs in inflammatory and immunological processes through a systematic review.

Methods

Study Design

The present study followed the international systematic review model, following the rules of PRISMA (preferred reporting items for systematic reviews and meta-analysis). Available at: http://www.prismastatement.org/?AspxAutoDetectCookieSupport=1. Accessed on: 09/17/2023. The methodological quality standards of AMSTAR-2 (Assessing the methodological quality of systematic reviews) were also followed. Available at: https://amstar.ca/. Accessed on: 09/17/2023.

Data Sources and Research Strategy

The literary search process was carried out from August to September 2023 and was developed based on Web of Science, Scopus, PubMed, Lilacs, Ebsco, Scielo, and Google Scholar, covering scientific articles from various eras to the present. The descriptors (MeSH Terms) were used: *"Obesity. Gut microbiota. microRNAs. Inflammatory processes"*, and using the Boolean "and" between the MeSH terms and "or" between historical discoveries.

Study Quality and Risk of Bias

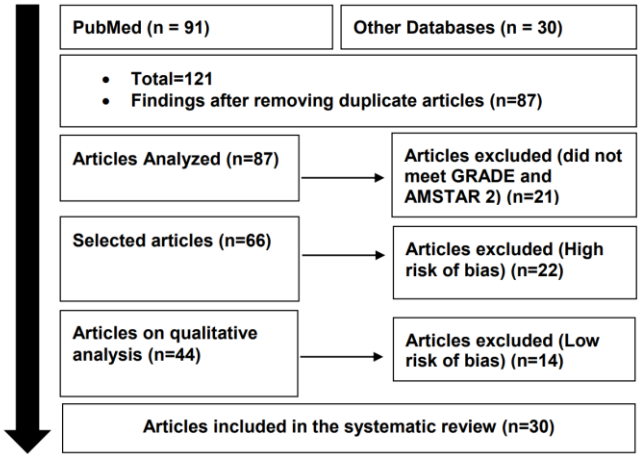
Quality was classified as high, moderate, low, or very low in terms of risk of bias, clarity of comparisons, precision, and consistency of analyses. The most evident emphasis was on systematic review articles or meta-analyses of randomized clinical trials, followed by randomized clinical trials. The 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 by analyzing the Funnel Plot graph (Sample size versus Effect size), using the Cohen test (d).

Results and Discussion

Summary of Findings

A total of 121 articles were found that were subjected to eligibility analysis, with 30 final studies being selected to compose the results of this systematic review. The studies listed were of medium to high quality (Figure 1), considering the level of scientific evidence of studies such as meta-analysis, consensus, randomized clinical, 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=77.5%>50%. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 22 studies with a high risk of bias and 21 studies that did not meet GRADE and AMSTAR-2.

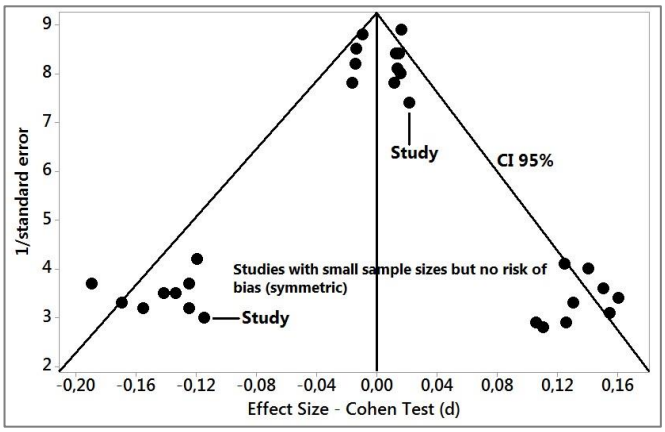
Figure 1. Selection of articles.



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 the Cohen Test (d). Precision (sample size) was determined indirectly by the inverse of the standard error (1/Standard Error). This graph had a symmetrical behavior, not suggesting a significant risk of bias, both between studies with a small sample size (lower precision) that are shown at the bottom of the graph and in studies with a large sample size that are presented at the top.

Figure 2. The symmetric funnel plot suggests no risk of bias among the small sample size studies that are shown at the bottom of the plot. High confidence and high recommendation studies are shown above the graph (n=30 studies).



Source: Own authorship.

Obesity, Gut Microbiota and microRNAs

MicroRNAs hybridize with complementary sequences in mRNA and silence genes by destabilizing the mRNA or preventing mRNA translation. Evidence suggests that microRNAs are not only synthesized endogenously but can also be obtained from dietary sources and that dietary compounds (for example, plant foods, and cow's milk) alter the expression of endogenous microRNA genes. Nutrition alters the expression of endogenous microRNA genes, thus aggravating the effects of nutrition-microRNA interactions on gene regulation and disease diagnosis. MicroRNAs derived from diet and endogenous synthesis have been implicated in physiological and pathological conditions, including those linked to nutrition and metabolism [15].

In this sense, a study showed that microRNAs regulate gene expression in adipose tissue, impact the regulation of metabolism and energy homeostasis, regulate adipogenesis signaling pathways in white, beige, and brown adipose tissue, and act on the transcription and differentiation of adipocytes (mesenchymal stem cells) [16]. In 2023, it was identified that microRNA (miR-143) also promotes brown adipose tissue thermogenesis and inhibits white adipose tissue adipogenesis [17].

One study found 26 miRNAs differentially expressed in the plasma of individuals with obesity compared to normal-weight individuals. Furthermore, the expression of 14 miRNAs (miR-107, miR-103a-3p, miR-142-5p, miR-222-3p, miR-221-3p, miR-183-5p, miR-183-5p, miR - 130b-3p, miR-15a-5p, miR-33a-5p, miR-210-3p, miR-144-3p, miR-185-5p, miR-130a-3p and miR-21-5p) has been linked to relative abundance of 4 bacterial species that also differed significantly between cases and controls (*D. longicatena, B. intestinihominis, B. eggerthii* and *H. parainfluenzae*) [3].

These miRNAs that interact with bacteria associated with obesity regulate the expression of genes that participate in several metabolic and obesity-related pathways, such as carbohydrate and lipid metabolism, and endocrine and inflammatory signaling pathways. Most miRNAs do not regulate a specific or individual target gene but rather modulate the expression of a large number of genes, demonstrating their importance in the regulation of various metabolic processes [18].

Furthermore, studies accumulate evidence that circulating miRNAs are associated with obesity [19-22]. Some miRNAs have been implicated in the control of body weight gain, glucose homeostasis, insulin resistance, and lipid metabolism [23,24]. Thus, miR-21-5p, miR-103a and miR-221-3p were found downregulated in blood samples from individuals with obesity in a meta-analysis study [25]. Furthermore, miRNAs that were dysregulated in obesity are associated with various metabolic processes such as glucose intolerance, maintenance of pancreatic beta cell mass, adipocyte development and adipose tissue physiology, inflammation pathways, and cardiomyocyte survival [26,27].

Furthermore, an interaction was observed between BMI levels, *B. eggerthii* abundance, and the expression of three miRNAs (miR-130b-3p, miR-185-5p, and miR-21-5p). *B. eggerthii* is one of the intestinal bacteria that metabolizes phenolic acids, considered beneficial for human health [28]. In a recent study, *B. eggerthii* abundance was significantly higher in children with obesity and correlated positively with body fat percentage but negatively with insoluble fiber intake in Mexican children. On the other hand, this bacteria was found to be underrepresented after sleeve gastrectomy surgery [29].

Still in this reasoning, of the three miRNAs associated with the abundance of *B. eggerthii* and BMI levels, miR-185-5p and miR-21-5p were also correlated with the abundance of *D. longicatena*. Furthermore, miR-185-5p has been described to be involved in oxidative stress, obesity, and diabetes mellitus in many studies [30]. MiR-185-5p has been identified as a regulator of de novo cholesterol biosynthesis and low-density lipoprotein uptake [23].

Added to this, an association was found between *B. eggerthi* abundance, miR-183-5p expression, and adiponectin levels. Previous findings demonstrated that miR-183 can contribute to adipocyte differentiation, adipogenesis, and fat cell development [24]. Both gain-of-function and loss-of-function assays showed that miR-183 promoted 3T3-L1 adipocyte differentiation, lipid accumulation, and adipogenesis by increasing the expressions of peroxisome proliferator-activated receptor gamma (PPARγ), alpha-binding protein to the CCAAT enhancer (C /EBPα), adiponectin and fatty acid synthase (FAS) [30].

Expression of miR-15a-5p was found to be associated with *H. parainfluenzae* abundance and insulin levels. miR-15a positively regulates insulin biosynthesis by inhibiting the expression of the endogenous uncoupling protein 2 (UCP2) gene, leading to higher ATP levels in islets and improving glucose-stimulated insulin secretion. Furthermore, circulating levels of miR-15a were found to be downregulated before the onset of type 2 DM (T2DM) and also in individuals with incident T2DM compared to controls [3,4].

Although a hypothesis-based approach was taken, selecting only miRNAs previously associated with obesity or metabolism makes type I or type II errors due to multiple comparisons possible. Although there are limitations in the current data, the patterns already discovered are important for understanding the contribution of miRNAs and gut microbiota in obesity [3].

Conclusion

It was concluded that microRNAs regulate gene expression in adipose tissue, impact the regulation of metabolism and energy homeostasis, and regulate adipogenesis signaling pathways in white, beige, and brown adipose tissue. For example, microRNA (miR-143) promotes brown adipose tissue thermogenesis and inhibits white adipose tissue adipogenesis. Some miRNAs have been implicated in the control of body weight gain, glucose homeostasis, insulin resistance, and lipid metabolism, with crosstalk with the gut microbiota. Furthermore, an association was found between *B. eggerthi* abundance, miR-183-5p expression, and adiponectin levels. Expression of miR-15a-5p was found to be associated with *H. parainfluenzae* abundance and insulin levels.

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Not applicable.

Ethical Approval

Not applicable.

Informed consent

Not applicable.

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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®.

Peer Review Process

It was performed.

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