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REVIEW ARTICLE

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# Nutritional therapies in patients with obesity in controlling gene expression of microRNAs for reducing inflammatory processes and metabolic disorders: a systematic review

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## Abstract

**Introduction:** In the context of the obesity pandemic, an estimated 3.0 billion patients have excessive reserves of adipose tissue and calories. These patients with excess energy are not classified as overweight or obese. 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, and enteral nutritional therapy is essential for the treatment of obesity, as it works as triggers to modulate gene expression through microRNAs. **Objective:** This study aimed to present the main considerations of enteral nutritional therapy in patients with obesity, in controlling the gene expression of microRNAs in the gut microbiota, adipose tissue, and circulatory systems to reduce inflammatory processes, and metabolic disorders. **Methods:** The systematic review rules of the PRISMA Platform were followed. The research was carried out from May to July 2024 in the 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 127 articles were found. A total of 38 articles were fully evaluated and 17 were included in this systematic review. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 20 studies with high risk of bias and 23 studies that did not meet the GRADE. Most studies showed homogeneity in their results, with $X^2$=73.5% >50%. It was concluded that certain miRNAs have been implicated in the control of body weight gain, glucose homeostasis, insulin resistance and lipid metabolism. A single dose of dietary protein has acute effects on hormonal and metabolic regulation and increases the expression of exosomal miRNA in individuals with obesity and insulin resistance. Enteral feeding is an effective and safe treatment in the regulation of these microRNAs. Ketogenic enteral nutrition may lead to better clinical outcomes than hypocaloric enteral nutritional protocols in glycemic and lipid profiles. A diverse range of nutritional interventions have been shown to be effective in the treatment of obesity and its comorbidities, mainly through the modulation of nutritherapy on microRNAs in adipose tissue, intestinal microbiota and circulatory systems.

**Keywords:** Obesity. Nutritional therapies. Gut microbiota. Inflammation. Metabolic disorders. MicroRNAs.

## Introduction

In the context of the obesity pandemic, it is estimated that 3.0 billion patients have excessive reserves of adipose tissue and calories **[1]**. These patients with excess energy are not classified as overweight or obese. Significant progress has been made in understanding the pathophysiological processes involved in excess adiposity. Adipose tissue is a dynamic organ and metabolically active in the production of hormones, which release a storm of

molecules that incite multiform systemic inflammatory processes **[1,2]**.

In the context of obesity and its comorbidities, microRNAs (miRNAs) stand out, which are a class of small non-coding RNAs that regulate gene expression **[3-6]**. These molecules have recognized roles in the regulation of several biological processes, regulating the expression of more than 70% of protein-coding genes, and alterations in their expression and functions have been associated with many diseases, including metabolic disorders and obesity **[7,8]**.

Also, 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 bacterial mRNA degradation or translation inhibition **[10-13]**.

Besides, 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 potentially affect metabolic organ crosstalk. Resident macrophages and T cell-associated miRNAs play a prominent role in regulating obesity by targeting multiple signaling pathways **[14]**.

Given this, enteral and parenteral nutritional therapy is critical for the treatment of obesity, as it functions as triggers to modulate gene expression through microRNAs and, downstream, helps regulate inflammatory and meta-inflammatory processes in obese patients. Weight loss diets are available that include various permutations of energy restriction, macronutrients, foods, and dietary intake patterns. Caloric restriction is the common pathway to weight reduction, but different diets can induce weight loss through a variety of additional mechanisms, including facilitating diet adherence. Low-calorie diets, compared with higher-calorie diets, reliably induced greater weight loss in the short term (<6 months), with a deterioration of this benefit in the long term (>12 months). Few significant long-term differences in weight loss were observed for diets with varying macronutrient composition, although some diets showed short-term advantages (e.g., low-carbohydrate versus low-fat) **[15]**.

Therefore, the present study presented the main considerations of enteral nutritional therapy in patients with obesity, in the control of gene expression of microRNAs of the gut microbiota, adipose tissue, and circulatory systems for the reduction of inflammatory processes and metabolic disorders.

## Methods

### Study Design

This study followed the international systematic review model, following the PRISMA (preferred reporting items for systematic reviews and meta-analysis) rules. Available at: http://www.prisma-statement.org/?AspxAutoDetectCookieSupport=1. Accessed on: 06/21/2024. The AMSTAR 2 (Assessing the methodological quality of systematic reviews) methodological quality standards were also followed. Available at: https://amstar.ca/. Accessed on: 06/21/2024.

### Search Strategy and Search Sources

The literature search process was carried out from May to July 2024 and developed based on Web of Science, Scopus, PubMed, Lilacs, Ebsco, Scielo, and Google Scholar, covering scientific articles from various periods to the present day. The following descriptors (MeSH Terms) were used: "Obesity. Nutritional therapies. Gut microbiota. Inflammations. Metabolic disorders. MicroRNAs", and using the Boolean "and" between MeSH terms and "or" between historical findings.

### Study Quality and Risk of Bias

The quality was classified as high, moderate, low, or very low regarding the 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.

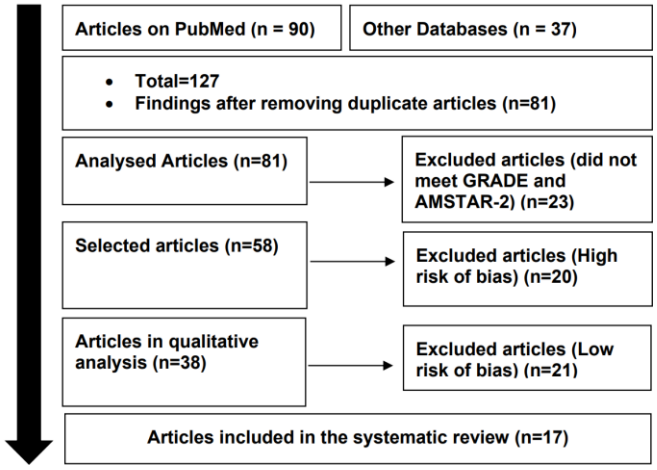
## Results and Discussion

### Summary of Findings

A total of 127 articles were found and submitted to eligibility analysis, and then 17 studies were 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. Biases did not compromise the scientific basis of the studies. According to the GRADE instrument, most studies presented homogeneity in their results, with $X^2$=73.5%>50%. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 20 studies with high risk of bias and 23 studies that did not meet GRADE.

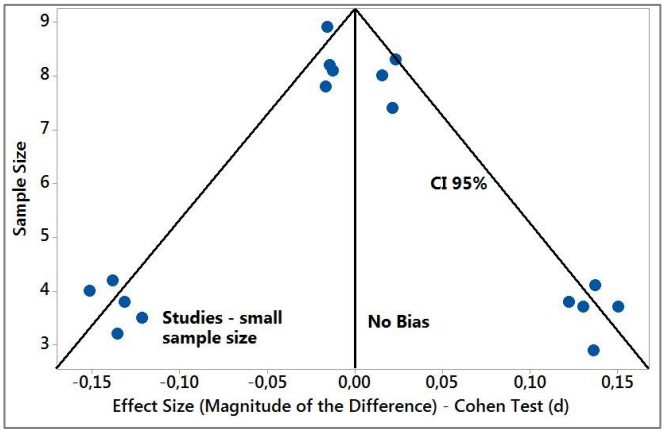
Figure 1. Flowchart - Article selection process.




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 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 among studies with small sample sizes (lower precision) that are shown at the bottom of the graph and in studies with large sample sizes that are shown at the top.

Figure 2. The symmetrical funnel plot does not suggest a risk of bias among the studies with small sample sizes that are shown at the bottom of the graph. Studies with high confidence and high recommendation are shown above the graph (n=17 studies).




Source: Own Authorship.

## Nutritional Therapies and Obesity Treatment

In the context of enteral and parenteral nutrition therapy, a study showed that microRNAs, according to targeted nutrition therapy for patients with obesity, 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 thermogenesis in brown adipose tissue and inhibits adipogenesis in white adipose tissue **[17]**.

A recent study by Hernández-Gómez et al. (2024) **[18]** analyzed the acute effects of protein intake from different food sources on the postprandial metabolic response, amino acid levels, and circulating miRNA expression in adults with obesity and insulin resistance. This clinical trial included adults with obesity and insulin resistance who consumed (1) animal-based protein (AP; calcium caseinate) or (2) plant-based protein (VP; soy protein isolate). Glycemic, insulin, and glucagon responses, amino acid levels, and exosomal microRNAs isolated from plasma were analyzed. After AP intake, the area under the curve (AUC) of insulin ($p = 0.04$) and plasma concentrations of branched-chain amino acids ($p = 0.007$) and gluconeogenic ($p = 0.01$) increased. The effects of different types of proteins on miRNA concentrations were assessed by measuring their circulating levels in plasma. Compared with the baseline, the AP group showed increased circulating levels of miR-27a-3p, miR-29b-3p, and miR-122-5p. Subsequent time-course analyses at 0, 30, and 60 min revealed the same pattern and differences between treatments.

These miRNAs that interact with obesity-associated bacteria regulate the expression of genes involved in several metabolic and obesity-related pathways, such as carbohydrate and lipid metabolism, 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 several metabolic processes **[19]**.

In addition, studies are accumulating evidence that circulating miRNAs are associated with obesity **[20-23]**. Some miRNAs have been implicated in the control of body weight gain, glucose homeostasis, insulin resistance, and lipid metabolism **[24,25]**. miR-21-5p, miR-103a, and miR-221-3p were found to be downregulated in blood samples from individuals with obesity in a meta-analysis study **[26]**. Furthermore, miRNAs that were dysregulated in obesity are associated with several metabolic processes, such as glucose intolerance, maintenance of pancreatic beta cell

mass, adipocyte development and adipose tissue physiology, inflammation pathways, and cardiomyocyte survival **[27,28]**.

In addition, an interaction between BMI levels, *B. eggerthii* abundance, and the expression of three miRNAs (miR-130b-3p, miR-185-5p, and miR-21-5p) was observed. *B. eggerthii* is one of the gut bacteria that metabolizes phenolic acids, which are considered beneficial for human health **[27]**. In a recent study, the abundance of *B. eggerthii* was significantly higher in children with obesity and correlated positively with body fat percentage but negatively with insoluble fiber intake in Mexican children. Conversely, this bacterium was found to be underrepresented after sleeve gastrectomy surgery **[28]**.

In light of these findings on the activation of microRNAs by nutritherapy, the previous guidelines for providing the best medical nutrition therapy to sick patients have been updated according to the new ESPEN Standard Operating Procedures. These guidelines define who are the patients at risk, how to assess the nutritional status of an ICU patient, how to define the amount of energy to provide, the route to choose and how to adapt according to the different clinical conditions. It also describes when to start and how to progress in the administration of adequate nutrient supply. It is suggested to better determine the amount and nature of carbohydrates, fats and proteins. Special attention is given to glutamine and omega-3 fatty acids. Specific conditions frequently seen in intensive care, such as patients with obesity, are discussed to guide the physician towards the best evidence-based therapy **[29]**.

Also, medical nutrition therapy based on the latest scientific evidence should be offered to all patients with obesity as part of obesity treatment interventions. Medical nutrition therapy aims to achieve positive health outcomes, not just weight changes. A diverse range of nutritional interventions have been shown to be effective in treating obesity and its comorbidities, mainly through nutrotherapy triggers on microRNAs. Although interventions based on caloric restriction are effective in promoting weight loss, long-term adherence to behavioral changes may be better supported through alternative interventions based on dietary patterns, food quality, and mindfulness **[30]**.

Malnutrition, even in overweight or obese patients, is often underestimated. Patients at metabolic risk should be identified early to confirm the indication for nutritional therapy. Monitoring of nutritional status in the post-bariatric surgery period should be considered in the hospital and after discharge, especially after upper gastrointestinal surgery, since normal oral food intake decreases for several months **[31]**.

Finally, weight loss induced by the ketogenic diet before bariatric surgery has beneficial effects on reducing liver volume, metabolic profile, and intra- and postoperative complications. However, these beneficial effects may be limited by poor adherence to the diet. A potential solution in patients with poor adherence to the prescribed diet could be represented by enteral nutrition strategies. A study evaluated the clinical impact, efficacy and safety of ketogenic enteral nutrition (KEN) versus hypocaloric enteral nutritional protocols (HEN) in obese patient candidates for bariatric surgery. A total of 31 patients with KEN were compared to 29 patients with HEN through a 1:1 randomization. Body weight (BW), body mass index (BMI), waist circumference (WC), hip circumference (HC) and neck circumference (NC) were assessed at baseline and at four-week follow-up. In addition, clinical parameters were assessed by blood tests, and patients were asked to report any side effects daily through a self-administered questionnaire. Compared to baseline, BMI, WC, WC and NC were significantly reduced in both groups studied ($p<0.001$). However, no significant difference was observed between the KEN and HEN groups in terms of weight loss ($p = 0.559$), BMI ($p = 0.383$), WC ($p = 0.779$) and WC ($p = 0.559$). Furthermore, a significant improvement in the general clinical status was found in both groups. However, a statistically significant difference was found in terms of blood glucose, insulin, HOMA index, total cholesterol, low-density lipoprotein, apolipoprotein A1 and apolipoprotein B, while no significant difference was found between the KEN and HEN groups in terms of aortomesenteric fat thickness ($p = 0.332$), triglyceride levels ($p = 0.534$), degree of steatosis ($p = 0.616$) and left hepatic lobe volume ($p = 0.264$). Furthermore, KEN and HEN treatments were well tolerated and no major side effects were recorded **[32]**.

## Conclusion

It was concluded that certain miRNAs have been implicated in the control of body weight gain, glucose homeostasis, insulin resistance, and lipid metabolism. A single dose of dietary protein has acute effects on hormonal and metabolic regulation and increases the expression of exosomal miRNA in individuals with obesity and insulin resistance. Enteral feeding is an effective and safe treatment for regulating these microRNAs. Ketogenic enteral nutrition may lead to better clinical outcomes than hypocaloric enteral nutritional protocols in glycemic and lipid profiles. A diverse range of nutritional interventions is effective in the treatment of obesity and its comorbidities, mainly through the modulation of nutritherapy on microRNAs in

adipose tissue, intestinal microbiota, and circulatory systems.

## CRediT

Author contributions: **Conceptualization -** Suzana Viana de Moura Batalha; **Data curation -** Suzana Viana de Moura Batalha; **Formal Analysis -** Suzana Viana de Moura Batalha; **Investigation -** Suzana Viana de Moura Batalha; **Methodology -** Suzana Viana de Moura Batalha; **Project administration -** Suzana Viana de Moura Batalha; **Supervision -** Suzana Viana de Moura Batalha; **Writing - original draft -** Suzana Viana de Moura Batalha; **Writing-review & editing-** Suzana Viana de Moura Batalha.

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## 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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