



REVIEW ARTICLE

Nutrological therapy and control of inflammatory processes and metabolic disorders in patients with obesity: a systematic review

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Abstract

Introduction: Obesity establishes a long-term chronic imbalance between calorie intake and energy expenditure, which causes serious comorbidities. MicroRNAs stand out, which are a class of small noncoding RNAs that regulate gene expression. Changes in their expression and functions have been associated with several diseases, including metabolic disorders and obesity. Enteral and parenteral nutrition therapy functions as an important regulator of microRNAs against inflammatory and metabolic processes. Objective: It was to carry out a systematic review of the main approaches to enteral and parenteral nutrition therapy in patients with obesity, to regulate the gene expression of microRNAs to mitigate inflammatory processes and metabolic disorders. Methods: The PRISMA Platform systematic review rules were followed. The search was carried out from August to September 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 117 articles were found. A total of 41 articles were evaluated in full and 30 were included in this systematic review. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 20 studies with a high risk of bias and 24 studies that did not meet GRADE. Most studies showed homogeneity in their results, with $X^2 = 75.2\% > 50\%$. It was concluded that studies accumulate evidence that circulating miRNAs are associated with obesity. Some microRNAs have been implicated in the control of body weight gain, glucose homeostasis, insulin resistance, and lipid metabolism. In this sense, enteral feeding is an effective and safe treatment before bariatric surgery, with ketogenic enteral nutrition leading to better clinical results than hypocaloric enteral nutritional protocols in glycemic and lipid profiles. A diverse range of nutritional interventions are effective in treating obesity and its comorbidities, mainly through nutrotherapy triggers on microRNAs.

Keywords: Enteral nutrition therapy. Parenteral nutrition therapy. Obesity. MicroRNAs.

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Obesity establishes a chronic long-term imbalance between calorie intake and energy expenditure, which causes severe comorbidities **[1,2]**. 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 people with overweight and obesity in the world **[1]**. In this scenario, 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 regulating 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]**. 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 by degrading bacterial mRNA or inhibiting translation **[10-13]**.

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 play a prominent role in regulating obesity by targeting multiple signaling pathways [14].

In this context, enteral and parenteral nutrition therapy is critical for the treatment of obesity, as it acts as triggers to modulate gene expression through microRNAs and, downstream, helps regulate inflammatory and meta-inflammatory processes in patients with obesity. 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 by

variety of additional mechanisms, а including facilitating diet adherence. Low-calorie diets, compared with higher-calorie diets, reliably induced greater weight loss in the short term (<6 months), with this benefit deteriorating in the long term (>12 months). Few significant long-term differences in weight loss were observed for diets with varying macronutrient composition, although some regimens short-term advantages showed (e.q., lowcarbohydrate versus low-fat) [15].

Therefore, the present study performed a systematic review of the main approaches of enteral and parenteral nutrition therapy in patients with obesity, in order to regulate the gene expression of microRNAs to mitigate inflammatory processes and metabolic disorders.

Methods

Study Design

The present study followed an 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: 08/23/2024. The AMSTAR 2 (Assessing the methodological quality of systematic reviews) standards were also followed. Available at: https://amstar.ca/. Accessed on: 08/23/2024.

Research Strategy and Search Sources

The literature search process was carried out from August to September 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 (DeCS /MeSH Terms) were used *Enteral nutrition therapy. Parenteral nutrition therapy. Obesity. MicroRNAs*, and using the Boolean "and" between the MeSH terms and "or" between the historical discoveries.

Study Quality and Risk of Bias

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. 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 117 articles were found and submitted to eligibility analysis, and then 30 final studies were selected to compose the results of this systematic review from the total of 31 references that were included in this study. The listed studies presented 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 =75.2%>50%. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 20 studies with a high risk of bias and 24 studies that did not meet GRADE and AMSTAR-2.



Source: Own authorship.

Nutrological Therapy, Obesity and Metabolic Syndrome

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]**.

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 several metabolic processes **[18]**.

In addition, studies have accumulated 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]**. 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 **[25]**. 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 **[26,27]**.

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 intestinal bacteria that metabolizes phenolic acids, which are considered beneficial for human health [26]. 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 bacterium was found to be underrepresented after sleeve gastrectomy surgery [27]. Given these findings of nutritherapy activation of microRNAs, according to the new ESPEN Standard Operating Procedures, the previous guidelines for providing the best medical nutrition therapy to sick patients have been updated. 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, which 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 toward the best evidence-based therapy [28].

Furthermore, 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 are effective in treating obesity and its comorbidities, mainly through microRNA-based nutrotherapy triggers. Although



interventions based on caloric restriction are effective in promoting weight loss, longterm adherence to behavioral changes may be better supported through alternative interventions based on dietary patterns, food quality, and mindfulness **[29]**.

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 **[30]**.

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 (HEN) protocols in obese patients who were 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 four-week follow-up. Furthermore, clinical parameters were assessed by blood tests, and patients were asked to report any side effects daily using a self-administered questionnaire. Compared with baseline, BMI, WC, WC, and NC were significantly reduced in both study groups (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 [31].

Conclusion

It was concluded that studies accumulate evidence that circulating miRNAs are associated with obesity.

Some miRNAs have been implicated in the control of body weight gain, glucose homeostasis, insulin resistance, and lipid metabolism. In this sense, enteral nutrition is an effective and safe treatment before bariatric surgery, with ketogenic enteral nutrition leading to better clinical outcomes than hypocaloric enteral nutritional protocols in glycemic and lipid profiles. A diverse range of nutritional interventions are effective in the treatment of obesity and its comorbidities, mainly through nutrotherapy triggers on microRNAs.

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Conflict of Interest

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