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REVIEW ARTICLE

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Enteral and parenteral therapy in the regulation of microRNAs to mitigate 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 non-coding 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 January to March 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 =59.2% >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.

Introduction

Obesity establishes a long-term chronic imbalance between calorie intake and energy expenditure, which causes serious 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 overweight and obese people worldwide **[1]**.

In this scenario, microRNAs (miRNAs) stand out, which are a class of small noncoding RNAs that regulate gene expression **[3-6]**. 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 intestinal microbiota, or the intestinal 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 intestinal 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 **[10-13]**.

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]**.

In this context, enteral and parenteral nutrition therapy is fundamental for the treatment of obesity, as it works as triggers to modulate gene expression through microRNAs and, downstream, helps to 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. Calorie restriction is the common route to weight loss, but different diets can induce weight loss through a variety of additional mechanisms, including facilitating adherence to the diet. Low-calorie diets, compared to higher-calorie regimens, reliably induced greater weight loss in the short term (<6 months), with deterioration of this benefit in the long term (>12 months). Few significant long-term differences in weight loss have been observed for diets with varying macronutrient composition, although some regimens have shown short-term advantages (e.g., low-carb versus low-fat) **[15]**.

Therefore, the present study carried 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

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.prisma-statement.org/?AspxAutoDetectCookieSupport=1. Accessed on: 02/20/2024. The methodological quality standards of AMSTAR 2 (Assessing the methodological quality of systematic reviews) were also followed. Available at: https://amstar.ca/. Accessed on: 02/24/2024.

Search Strategy and Sources

The literary search process was carried out from January to March 2024 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 *"Enteral nutrition therapy. Parenteral nutrition therapy. Obesity. MicroRNAs"*, and using the Boolean "and" between the MeSH terms and "or" between historical discoveries.

Study Quality and Risk of Bias

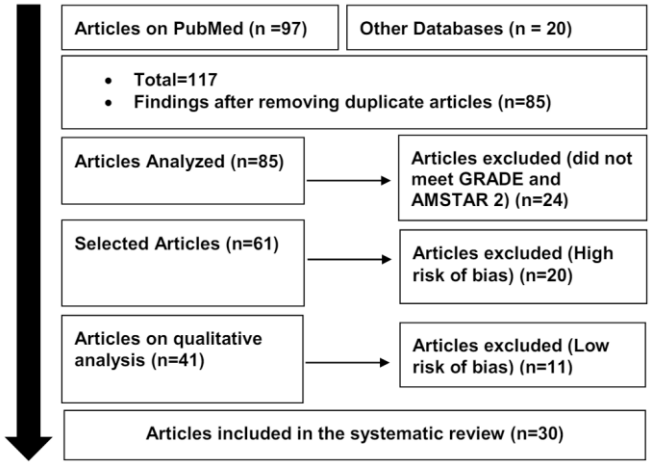
Quality was classified as high, moderate, low, or very low in terms of risk of bias, clarity of comparisons, precision, and consistency of analyses. The most evident emphasis was on systematic review articles or meta-analyses of randomized clinical trials, followed by randomized clinical trials. The 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.

Results and Discussion

Summary of Findings

A total of 117 articles were found that were subjected to eligibility analysis and, subsequently, 30 final studies were selected to compose the results of this systematic review of the total of 31 references that were included in this study. 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=59.2%>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.

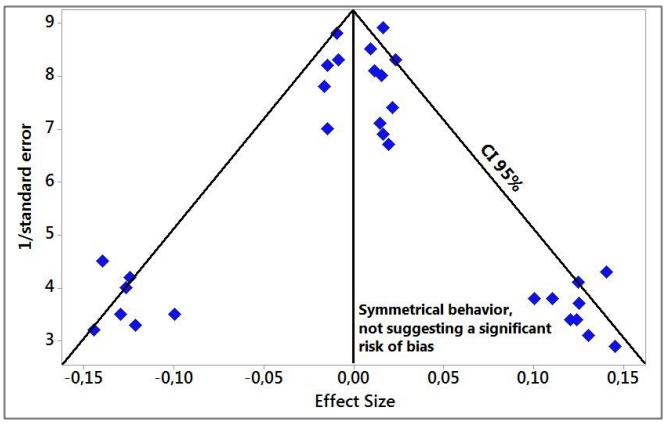
Figure 1. Flowchart - Article selection process.



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 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 graph. High confidence and high recommendation studies are shown above the graph (n= 30 studies).



Source: Own Authorship.

Main Findings - Enteral Therapy, Obesity and microRNAs

In the scenario of enteral and parenteral nutrotherapy, a study showed that microRNAs, according to targeted nutrotherapy 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 in 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]**.

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]**. 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]**.

Also, 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 **[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 bacteria was found to be underrepresented after sleeve gastrectomy surgery **[27]**.

In light of these findings of nutrotherapy activation of microRNAs following the new ESPEN Standard Operating Procedures, previous guidelines for providing the best medical nutritional therapy to sick patients have been updated. These guidelines define who are at-risk patients, 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 administering adequate nutrient supply. It is suggested to better determine the quantity and nature of carbohydrates, fats, and proteins. Special attention is paid 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]**.

Besides, medical nutritional therapy based on the latest scientific evidence should be offered to all patients with obesity as part of obesity treatment interventions. Medical nutritional 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 nutrotherapy triggers on microRNAs. While interventions based on calorie restriction are effective in promoting weight reduction, long-term 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 must be identified early to confirm the indication of nutritional therapy. Monitoring nutritional status in post-bariatric surgery should be considered in the hospital and after discharge, especially after surgery in the upper gastrointestinal tract, as normal oral food intake decreases for several months **[30]**.

Finally, weight loss induced by the ketogenic diet before bariatric surgery has beneficial effects in 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. One study evaluated the clinical impact, efficacy, and safety of ketogenic enteral nutrition (KEN) versus hypocaloric enteral nutrition (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. In addition, clinical parameters were assessed by blood tests, and patients were asked daily to report any side effects using a self-administered questionnaire. Compared to baseline, BMI, WC, WC, and CP 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 fat thickness. aortomesenteric membrane ($p=0.332$), triglyceride levels ($p=0.534$), degree of steatosis ($p=0.616$), and volume of the left hepatic lobe ($p=0.264$). 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 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.

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Conflict of interest

The authors declare no conflict of interest.

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