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REVIEW ARTICLE

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Management of enteral/parenteral therapy in patients with obesity in the light of exosomes/microRNAs: a systematic review

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Abstract

Introduction: Alteration in the homeostasis of the intestinal microbiota is related to the prevalence of obesity, which could reach up to 57.8% of the adult world population by 2030. Likewise, the global incidence rate of type 2 diabetes, which represents 90-95 % of all diabetes cases. Extracellular vesicles (exosomes and microRNAs) have emerged as main vehicles for intercellular and intermolecular communication, including those established between the intestinal microbiota and mammals. Providing adequate nutritional therapy with essential nutrients can help mitigate the consequences of the catabolic response. **Objective:** It was to bring together the main considerations of enteral/parenteral nutritional therapy in patients with obesity, highlighting the management of inflammatory and metabolic processes through exosomes and microRNAs. **Methods:** The PRISMA Platform systematic review rules were followed. The search was carried out from August to October 2023 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:** 118 articles were found. A total of 44 articles were evaluated in full and 39 were included in this systematic review. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 12 studies with a high risk of bias and 22 studies that did not meet GRADE. Most studies showed homogeneity in their results, with X^2 =52.5%>50%. It was concluded that exosomes and miRNAs, through enteral/parenteral nutritional therapy, are involved in the control of weight gain, glucose homeostasis, and lipid metabolism. Some clinical studies have shown that enteral nutritional therapy is effective and safe before bariatric surgery, with ketogenic enteral nutrition leading to better clinical outcomes than hypocaloric enteral nutritional protocols in glycemic and lipid profiles to satisfy better regulation of exosomes. and microRNAs, mainly from the intestinal microbiota, for the control of inflammatory and metabolic processes.

Keywords: Enteral/parenteral nutritional therapy. Obesity. Intestinal microbiota. Exosomes. MicroRNAs.

Introduction

Alteration of intestinal microbiota homeostasis, commonly known as dysbiosis, has been associated with numerous diseases, such as colorectal cancer, inflammatory bowel disease, cardiovascular diseases, neurological disorders, autoimmune diseases, obesity, and diabetes **[1,2]**. In particular, the prevalence of obesity is increasing dramatically and it is estimated that around 57.8% of the global adult population will be overweight or obese by 2030 **[3]**. Likewise, the global incidence rate of type 2 diabetes, which accounts for 90-95% of all diabetes cases **[3]**.

In recent years, extracellular vesicles (exosomes and microRNAs) have emerged as major vehicles for intercellular and intermolecular communication, including those established between the gut microbiota and mammals **[4-6]**, and have the potential ability to regulate cellular function in an autocrine manner. or paracrine, even more so when the focus is on obese patients undergoing nutritional therapy. Thus, patients with obesity admitted to the intensive care unit (ICU)

suffer from acute critical illness, with great catabolic stress, which can result in severe muscle loss and prolonged impaired functional results. Providing adequate nutritional therapy with essential nutrients can help mitigate the consequences of the catabolic response. However, identifying the appropriate timing, amount, and routes of nutritional support remains a challenge in the ICU **[7]**.

In this sense, nutritional therapy limits the risk of energy or protein deficit, which has been associated in previous retrospective studies with poor outcomes, such as prolonged ICU and hospital stays, prolonged durations of mechanical ventilation, and a higher incidence of infectious complications, especially in patients with obesity **[8-11]**. The risk of complications is even greater in patients identified as having high nutritional risk upon admission to the ICU **[10]**. However, recent randomized clinical trials and meta-analyses have failed to demonstrate any benefit of adapting nutritional guidelines during the first weeks of ICU on the outcomes studied **[12-15]**.

In this regard, international guidelines recommend the early introduction of hypocaloric enteral nutrition within the first 48 hours, except in cases of uncontrolled shock, hypoxemia, or acidosis **[16-18]**. The justification for these recommendations is based on the results of a meta-analysis that reports the benefit of early enteral nutrition in reducing the incidence of infectious complications, as it regulates the release of microRNAs to modulate various gene expressions, as well as helping to adjust cells regulatory T (Tregs) that contribute to the control of infections **[17]**.

In line with this, the most recent meta-analysis, conducted by the Cochrane group, including seven randomized controlled trials published between 1993 and 2012, also reported "very low-quality evidence" in favor of early or late enteral nutrition in ICU patients **[19]**. Furthermore, early initiation with rapid achievement of the energy goal has not demonstrated a significant benefit and may even cause harm. Furthermore, in a recent study by Ortiz-Reyes et al., early enteral nutrition showed no benefit compared to late enteral in ventilated patients receiving vasopressor or inotropic therapies after adjustment for disease severity **[20]**. Finally, some concerns have recently emerged about the possible increased risk of digestive complications such as mesenteric ischemia associated with early enteral feeding **[21-23]**.

In this context, 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 **[24-26]**.

Thus, 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 reduction, but different diets can induce weight loss through several additional mechanisms, including facilitating adherence to the diet **[27]**.

Therefore, this study sought to bring together the main considerations of enteral/parenteral nutritional therapy in patients with obesity, highlighting the management of inflammatory and metabolic processes through exosomes and microRNAs.

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: 10/17/2023. The methodological quality standards of AMSTAR 2 (Assessing the methodological quality of systematic reviews) were also followed. Available at: https://amstar.ca/. Accessed on: 10/17/2023.

Search Strategy and Search Sources

The literary search process was carried out from August to October 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: "Enteral/parenteral nutritional therapy. Obesity. Intestinal microbiota. Exosomes. MicroRNAs" (Enteral/parenteral nutritional therapy. Obesity. Gut microbiota. Exosomes. 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-

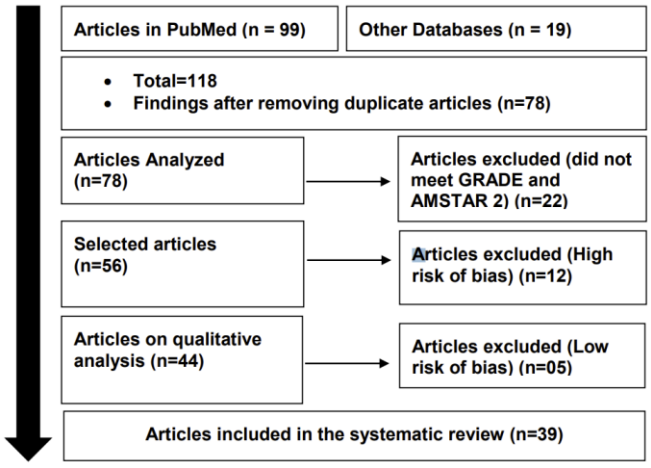
analyses of randomized clinical trials, followed by randomized clinical trials. The low quality of evidence was attributed to case reports, editorials, and brief communications, according to the GRADE instrument. The risk of bias was analyzed according to the Cochrane instrument by analyzing the Funnel Plot graph (Sample size versus Effect size), using the Cohen test (d).

Results and Discussion

Summary of Findings

A total of 118 articles were found that were subjected to eligibility analysis and, subsequently, 39 references 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. The 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=52.5%>50%. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 12 studies with a high risk of bias and 22 studies that did not meet GRADE and AMSTAR-2.

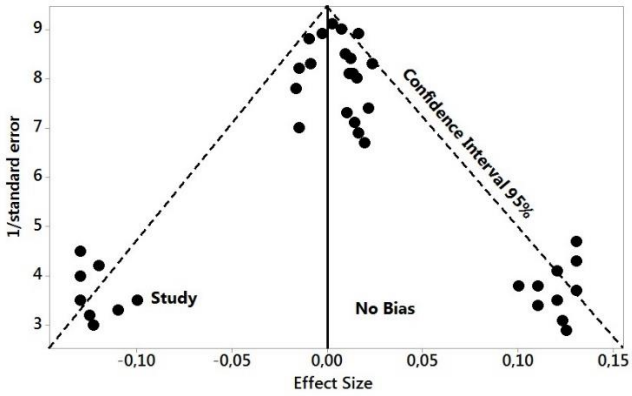
Figure 1. Flowchart - Article selection process.



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 plot. High confidence and high recommendation studies are shown above the graph (n= 39 studies).



Source: Own authorship.

Main Clinical Outcomes – Nutrotherapy in Obesity

In the context of nutritional therapy in patients with obesity, manipulation of the intestinal microbiota through diet has been postulated as a promising therapeutic target. In this sense, the secretion of extracellular vesicles derived from the intestinal microbiota is gaining special attention, standing out as a key factors that could mediate intestinal microbiota-host communication. Exosomes, such as exosomes, derived from gut microbiota and probiotic bacteria allow encapsulation of a wide range of bioactive molecules (such as/or including proteins and nucleic acids) that can travel short and long distances to modulate important biological functions with global impact. on the health of the host. EVs derived from specific bacteria induce differential physiological responses. There is a need to understand the potential role of gut microbiota and probiotic-derived EVs in the initiation, progression, and management of obesity and diabetes, through the modulation of inflammation, metabolism, and intestinal permeability **[28]**.

Furthermore, patients with obesity are at greater risk of community-acquired and nosocomial infections. Obesity may be associated with an increased incidence of ventilator-associated pneumonia (VAP). A study carried out by authors Nseir et al. (2021) **[29]** analyzed the impact of early enteral nutrition versus parenteral nutrition on mortality in patients requiring mechanical ventilation and catecholamines (NUTRIREA2), an open, randomized, and controlled trial, carried out in 44 French ICUs. Adults receiving invasive mechanical ventilation and vasopressor support for shock and parenteral

nutrition or enteral nutrition were included. Obesity was defined as BMI ≥ 30 kg/m^2 on admission to the ICU. The diagnosis of VAP was judged by an independent, blinded committee based on all available clinical, radiological, and microbiological data. A total of 699 (30%) of the 2,325 patients included were obese. A total of 224 first episodes of VAP were diagnosed (60 and 164 in the obese and non-obese groups, respectively). The incidence of VAP on day 28 was 8.6% versus 10.1% in both groups (hazard ratio, 0.85; 95% CI 0.63-1.14; P = 0.26). After adjustment for sex, McCabe score, age, antiulcer treatment, and sequential assessment of organ failure at randomization, the incidence of VAP remained nonsignificant among obese and non-obese patients (hazard ratio, 0.893; 95% CI, 0. 66-1.2; p= 0.46). Although no significant differences were found in the duration of mechanical ventilation and length of ICU stay, 90-day mortality was significantly lower in obese patients than in non-obese patients (272 of 692 [39.3%] patients vs 718 of 1,605 [44.7%]; p=0.02). In a subgroup of patients (n=123) with available pepsin and alpha-amylase measurements, no significant difference was found in the rate of copious microaspiration of gastric contents or oropharyngeal secretions between obese and non-obese patients.

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) **[27]**. In 2023, it was identified that microRNA (miR-143) also promotes brown adipose tissue thermogenesis and inhibits white adipose tissue adipogenesis **[28]**.

In this context, microRNAs 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 regulating various metabolic processes **[29]**.

Furthermore, studies accumulate evidence that circulating miRNAs are associated with obesity **[30,31]**. Some miRNAs have been implicated in the control of body weight gain, glucose homeostasis, insulin resistance, and lipid metabolism **[32-35]**. miR-21-5p, miR-103ª and miR-221-3p were found downregulated in blood samples from individuals with obesity in a meta-analysis study **[36]**. 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 **[37,38]**.

Also, 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. Although 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 **[39]**.

Conclusion

It was concluded that exosomes and miRNAs, through enteral/parenteral nutritional therapy, are involved in the control of weight gain, glucose homeostasis, and lipid metabolism. Some clinical studies have shown that enteral nutritional therapy is effective and safe before bariatric surgery, with ketogenic enteral nutrition leading to better clinical outcomes than hypocaloric enteral nutritional protocols in glycemic and lipid profiles to satisfy better regulation of exosomes. and microRNAs, mainly from the intestinal microbiota, for the control of inflammatory and metabolic processes.

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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.

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