REVIEW ARTICLE

Major clinical and metabomic approaches to childhood obesity: a systematic review

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Abstract

Introduction: In the context of childhood obesity, of children under 5 years of age in Brazil, 7% are overweight and 3% meet the criteria for obesity. Globally, according to a report from the World Health Organization (WHO), it is estimated that the total number of overweight and obese children in the world could reach 75 million by the year 2025. Objective: It was to carry out a systematic review to present the main approaches to clinical and metabolomics of childhood obesity. **Methods:** The PRISMA Platform systematic review rules were followed. The research was carried out from February to April 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:** 110 articles were recruited for the initial evaluation. A total of 41 articles were evaluated and 19 were included in this systematic review. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 28 studies with a high risk of bias and 28 studies that did not meet GRADE. Most studies showed homogeneity in their results, with $X^2=58.7\%>50\%$. It was concluded that miRNAs are potential biomarkers for the development of pathologies, such as obesity. A heterogeneous group of these molecules was found to be associated with obesity in children. miR-15b-5p, miR-486-5p and hsa-miR-122-5p were considered good candidates for childhood obesity biomarkers. MiRNA-dependent mechanisms regulate up to 60% of all human genes. MiRNAs influence multiple pathways, including insulin signaling, immune-mediated inflammation, adipokine expression, adipogenesis, lipid metabolism, and regulation of food intake.

Keywords: Child obesity. Comorbidities. Meta-inflammation. MicroRNAs. Gene expression.

Introduction

In the scenario of chronic non-communicable diseases (NCDs), obesity stands out as a multifactorial disease affecting around 30% of the world's population. It is estimated that more than 60% of the world's population will be severely obese by 2030 [1]. Furthermore, according to data from the National Child Food and Nutrition Study (ENANI-2019), among children under 5 years of age in Brazil, 7% are overweight and 3% meet the criteria for obesity [2,3]. Globally, according to a report from the World Health Organization (WHO), it is estimated that the total number of overweight and obese children in the world could reach 75 million by 2025 [4].

In this context, it is essential to understand that childhood obesity is not an isolated pathology but is the manifestation of several pathological changes, which can culminate in dysfunctional physiological changes [5]. Among them, damage to the respiratory system can be highlighted, with a possible reduction in its performance. In this context, it is observed that the accumulation of body fat in childhood is associated with respiratory changes that include, among many changes, reduced lung expansibility, increased airway responsiveness, and reduced lung compliance [6]. Furthermore, an unbalanced diet, as well as obesity,

causes damage to the development and maintenance of the immune system, predisposing to illness and a worse prognosis of diseases [7].

As a potential aggravating factor, the emergence of the new coronavirus (SARS-CoV-2), which causes the disease COVID-19, has resulted in the worsening of obesity comorbidities [8]. It is necessary to understand the mechanisms by which obese patients are at greater risk of progressing to severe forms of the disease, even death. In this sense, immunity plays a decisive role in SARS-CoV-2 infection. The lack of regulation and the excessive immune response to the viral stimulus produce exacerbated pro-inflammatory cytokines (cytokine storm), reaching a state of hyperinflammation, with consequent damage to various tissues in the obese person [8].

In this context, molecules such as microRNAs (miRNAs) regulate gene expression by binding to a complementary mRNA sequence. MiRNA-dependent mechanisms regulate up to 60% of all human genes. MiRNAs influence multiple pathways, including insulin signaling, immune-mediated inflammation, adipokine expression, adipogenesis, lipid metabolism, and regulation of food intake. Disturbances in the expression of miRNAs affect gene expression and therefore cellular tissue function in the pathological process. Developing new ways to identify the progression from obesity to inflammation in the early stages will help understand the different mechanisms that regulate this process [9].

Therefore, the occurrence of immune dysfunction, greater predisposition to infection, and mortality from sepsis is a reality. Obesity was correlated with high leukocyte and lymphocyte counts (except NK, suppressor T, and cytotoxic T cells), with suppression of lymphocyte proliferation of T and B lymphocytes and with higher rates of oxidative activity and phagocytosis by monocytes and granulocytes, demonstrating the consequences of this pathology on the immune system [10]. In addition to these changes, it is known that obesity initially favors the development of inflammation in adipose tissue, through increased production of pro-inflammatory adipokines, such as IL-6 and TNF-α. In this way, the proportion between pro-inflammatory and anti-inflammatory cytokines becomes unbalanced [11]. Consequently, damage occurs to the vascular system, promoting endothelial dysfunction, characterized by a decrease in the production of nitric oxide and an increase in the synthesis of reactive oxygen species, which establishes an inflammatory state and oxidative stress. Regarding innate immunity, in obese patients, there is a modification of the immune environment in adipose tissue [12].

In this context, obesity induces a change in the macrophage profile, with an increase in the M1 (pro-inflammatory) phenotype. This effect corresponds to an upregulation in inflammatory genes, and a downregulation in anti-inflammatory genes [13]. However, it is not only in adipose tissue that this change occurs in cells of the innate immune system. Thus, authors demonstrated that circulating mononuclear cells in obese individuals are also in a pro-inflammatory state, with an increase in intranuclear factor κB (NF-κB) and, consequently, with an increase in the transcription of pro-inflammatory genes. inflammatory processes regulated by it [14]. As a corollary, the innate immune response in patients with obesity is altered, resulting in an imbalance in the line of defense against infections, an increase in the inflammatory response, and an abnormal activation of T lymphocytes. Furthermore, the primary increase in the inflammatory response in obese patients works as a predictor for the hyperinflammatory state observed in COVID-19. Therefore, this primary increase can be amplified by SARS-CoV-2 infection, increasing the production of cytokines such as TNF-α, IL-1, and IL-6 [8].

Therefore, the present study performed a systematic review to present the main clinical and metabolomic approaches to childhood obesity.

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. They were accessed on: 03/16/2024. The methodological quality standards of AMSTAR-2 (Assessing the methodological quality of systematic reviews) were also followed. Available at: https://amstar.ca/. it was accessed on: 03/16/2024.

Search Strategy and Search Sources

The literary search process was carried out from February to April 2024 and developed in the Scopus, PubMed, Science Direct, Scielo, and Google Scholar databases, covering scientific articles from various eras to the present. It used the descriptors from the DeCS platform (available at: https://decs.bvsalud.org/) with the MeSH Terms: "Childhood obesity. Comorbidities. Meta-inflammation. MicroRNAs. Gene expression", and using the Boolean "and" between the terms MeSH 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 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 and AMSTAR-2 instruments. 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

As a corollary of the literary search system, a total of 110 articles were found that were subjected to eligibility analysis and, subsequently, 19 of the 41 final studies were selected to compose the results of this systematic review. The studies listed were of medium to high quality (Figure 1), considering in the first instance 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 $X^2=58.7\%>50\%$. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 28 studies with a high risk of bias and 28 studies that did not meet GRADE and AMSTAR-2.

Figure 1. Flowchart showing the article selection process.
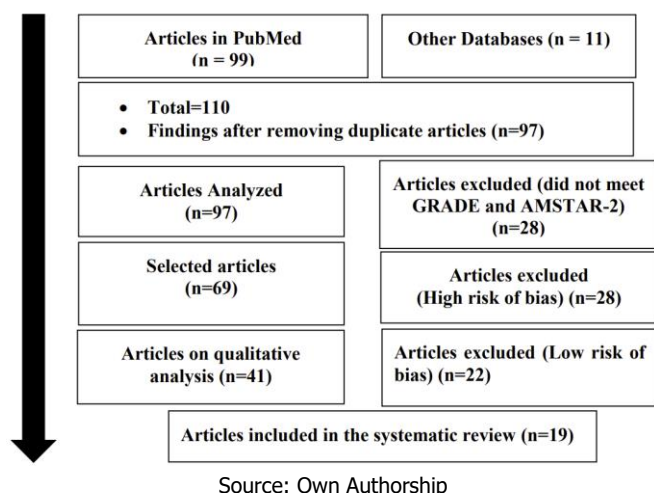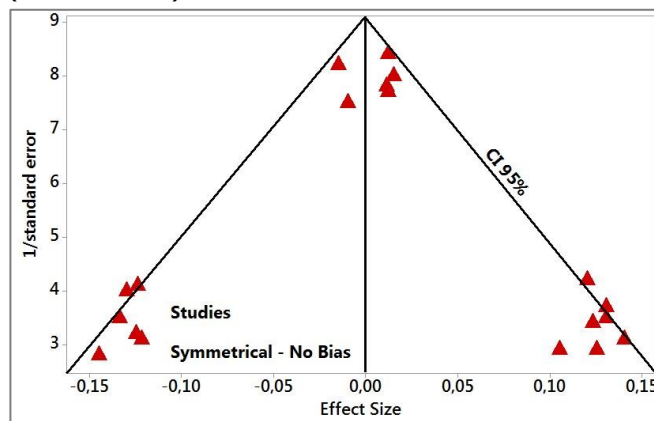

Source: Own Authorship

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=19 studies).

Source: Own Authorship

Main Clinical and Metabolomic Approaches to Childhood Obesity

After the article selection and interpretation process, it was observed that there is an association between the expression of miRNAs and childhood obesity. Some authors have postulated a group of miRNAs as biomarkers to identify the risk of early obesity. miR-15b-5p, miR-486-5p, and hsa-miR-122-5p were considered good candidates for obesity biomarkers [15-17].

The studies reviewed suggested that modified microRNAs may be involved in regulating pathways related to the development of pathologies, and they may predict the presence of obesity during childhood. MicroRNAs (miRNAs) are factors that regulate gene expression by binding to a complementary mRNA sequence [9].

A systematic review study analyzed the association between the expression of miRNAs with overweight and obesity in children. A total of seven studies (684 children) were included. A total of 361 children were obese/overweight and 323 were normal weight. 40.64% (278) of the children were boys. The classification of obesity was inconsistent between studies with different classifications used. A total of 65 miRNAs were reported to be associated with obesity and overweight; at least two studies reported miR-122, miR-122-5p, miR-15b, miR15b-5p, miR191-5p, miR-222, miR-222-3p, miR 486, miR-486-3p, and miR-486- 5pm. Pathway analysis of the repeat miRNAs showed that they were involved in the

regulation of metabolic and signaling pathways, including fatty acid metabolism. Therefore, miRNAs are potential biomarkers for the development of pathologies, such as obesity. A heterogeneous group of these molecules was found to be associated with obesity in children. miR-15b-5p, miR-486-5p, and hsa-miR-122-5p were considered good candidates for obesity biomarkers [18].

Furthermore, the lipid gene perilipin 1 (PLIN1) is involved in the regulation of lipolysis and therefore represents a viable candidate mechanism for genetic research into obesity in children. Furthermore, the regulation of gene expression by circulating microRNAs (miRNAs) offers a new research site for innovation in diagnostics. Thus, a study reported new findings on associations between circulating miRNAs, regulation of the PLIN1 gene, and susceptibility to childhood obesity. In a sample of 135 unrelated individuals, 35 children with obesity (aged 3 to 13 years) and 100 healthy controls (aged 4 to 16 years), we examined the expression levels of four candidate miRNAs (hsa-miR-4777-3p, hsa -miR-642b-3p, hsa-miR-3671-1 and hsa-miR-551b-2) targeting PLIN1 as measured by real-time polymerase chain reaction in whole blood samples. The full genetic model, including the four candidate miRNAs and the PLIN1 gene, was found to explain a statistically significant 12.7% variance in childhood obesity risk (p = 0.0034). The four miRNAs together explained 10.1% of the risk (p = 0.008). The percentage of variation in childhood obesity risk explained by hsa-miR-642b-3p and age was 19%. In line with the biological polarity of the observed association, for example, hsa-miR-642b-3p was upregulated, while PLIN1 expression was decreased in obese participants compared to healthy controls [19].

In this context, obesity, determined by the accumulation of fatty tissue in the human body, is considered a chronic disease with multifactorial etiology [2,3]. In the pediatric population, the identification and diagnosis of this pathology involves the correlation between various data that must be stratified according to the sex and age group of each individual. To obtain more accurate data, it is recommended to use complementary methods to the physical examination that evaluates, in short, weight, height, abdominal circumference, and skin folds [5].

In terms of population assessment and classification, the body mass index (BMI), calculated based on the child's weight and height, is globally accepted. According to WHO data, the diagnosis is established when values exceed the 99.9th percentile in children aged 0 to 5 years and above the 97th percentile in those aged 5 to 20 years. In these, there is also the classification of severe obesity when they exceed the 99.9th percentile and the Z+3 Score [1].

It is important to emphasize that weight, as well as BMI, do not reflect an individual's body composition and, therefore, should not be used as isolated methods. This is because children and adolescents can manifest pathophysiological changes due to the accumulation of body fat, even if they are of normal weight [2]. For complementary assessment to BMI, skinfolds, bioelectrical impedance, as well as more complex methods such as hydrostatic weight and computed tomography (CT) can be useful to differentiate the amount of body fat from other fat-free components such as tissue muscle, bone mass and the amount of total body water [5].

In this aspect, the circulating level of cytokines and acute phase proteins associated with inflammation is elevated in patients with obesity. Thus, adipocytes secrete several cytokines and acute-phase proteins that increase the production and circulation of factors related to inflammation. The inflammatory process may be due to resistance to insulin action and other disorders associated with obesity, such as hyperlipidemia and metabolic syndrome [10].

The association between obesity and inflammatory disease stands out. There are three possibilities, the first reflects production and release from organs other than adipose, mainly the liver (and immune cells). The second explanation is that white adipose tissue secretes factors that stimulate the production of inflammatory markers by the liver and other organs. The third possibility is that adipocytes themselves are a ready source of some, or several, of these inflammatory markers [10,11].

In addition, effects such as sensors of energy balance have been attributed to cytokines. Among all the adipokines related to inflammatory processes, interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), leptin, and adiponectin stand out.5 In this context, some studies have shown low concentrations of the anti-inflammatory adipokine (adiponectin) associated with the occurrence of several types of cancer, and high concentrations inhibit the growth of tumors [8-12]. Adiponectin and leptin are the most abundant adipokines synthesized by adipose tissue, although there are others such as TNF-α, IL-6, IL-1, CC-chemokine ligand 2 (CCL2), a visceral adipose-tissue-derived serine protease inhibitor (vaspin) and retinol-binding protein 4 (RBP4) [8].

Finally, excess adipose tissue increases the production of several adipokines that have a major impact on various bodily functions. In this case, the control of food intake and energy balance, immune system, insulin sensitivity, angiogenesis, blood pressure, lipid metabolism, and body homeostasis stand out, as

situations strongly correlated with cardiovascular disease [13]. The most notable adipokines with anti-inflammatory action are the IL1 receptor antagonist (IL-1ra), transforming growth factor-β (TGF-β), those produced by Th2 cells (IL-4, IL-5, and IL-10), and adiponectin. The imbalance between pro- and anti-inflammatory cytokines can induce inflammatory or hypersensitivity responses. Furthermore, high plasma concentrations of adiponectin are associated with a reduced risk of myocardial infarction in men. Adiponectin is inversely proportional to the concentration of C-reactive protein (CRP). It can negatively regulate CRP gene expression in adipocytes [8].

Conclusion

It was concluded that miRNAs are potential biomarkers for the development of pathologies, such as obesity. A heterogeneous group of these molecules was found to be associated with obesity in children. miR-15b-5p, miR-486-5p, and hsa-miR-122-5p were considered good candidates for childhood obesity biomarkers. MiRNA-dependent mechanisms regulate up to 60% of all human genes. MiRNAs influence multiple pathways, including insulin signaling, immune-mediated inflammation, adipokine expression, adipogenesis, lipid metabolism, and regulation of food intake.

CRediT

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Ethical Approval

Not applicable.

Informed Consent

Not applicable.

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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