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REVIEW ARTICLE

Major metabolic and inflammatory considerations of childhood obesity through immunological predictors and microRNAs: a systematic review

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Abstract

Introduction: In the scenario of chronic non-communicable diseases, obesity stands out as a multifactorial disease affecting around 30% of the world's population. 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 considerations metabolic and inflammatory mechanisms of childhood obesity through immunological predictors and microRNAs. **Methods:** The PRISMA Platform systematic review rules were followed. The research was carried out from January to March 2025 in the Scopus, Embase, 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, immunemediated inflammation, adipokine expression, adipogenesis, lipid metabolism, and regulation of food intake.

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

Introduction

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

In this context, it is essential to understand that childhood obesity is not an isolated pathology, but rather the manifestation of several pathological changes, which can culminate in dysfunctional physiological alterations **[5]**. Among these, damage to the respiratory system, with possible reduction in its performance, is noteworthy. In this context, it is observed that the accumulation of body fat in childhood is associated with respiratory changes, including reduced lung expansion, increased airway responsiveness, and decreased lung compliance **[6]**.

Furthermore, an unbalanced diet, as well as obesity, impairs the development and maintenance of the immune system, predisposing to illness and worsening disease prognosis **[7]**.

As a potential aggravating factor, the emergence of the novel coronavirus (SARS-CoV-2), which causes COVID-19, has worsened obesity comorbidities **[8]**. It is necessary to understand the mechanisms by which obese patients are at greater risk of developing severe forms of the disease, even death. In this sense, immunity plays a decisive role in SARS-CoV-2 infection. Lack of regulation and an excessive immune response to viral stimuli exacerbate the production of pro-inflammatory cytokines (cytokine storm), leading to a state of hyperinflammation, with consequent damage to various tissues in obese individuals **[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 miRNA expression affect gene expression and, therefore, cellular tissue function in the pathological process. Developing new ways to identify the progression of obesity to inflammation in the early stages will help us understand the different mechanisms that regulate this process **[9]**.

Therefore, the occurrence of immune dysfunction, a greater predisposition to infection, and mortality from sepsis is a reality. Obesity has been correlated with high leukocyte and lymphocyte counts (except for NK, suppressor T, and cytotoxic T cells), with suppressed 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. Thus, the ratio of pro-inflammatory to anti-inflammatory cytokines becomes unbalanced **[11]**. Consequently, damage to the vascular system occurs, promoting endothelial dysfunction, characterized by decreased nitric oxide production and increased synthesis of reactive oxygen species, which establishes an inflammatory state and oxidative stress. Regarding innate immunity, in obese patients, the immune environment in adipose tissue changes **[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 of inflammatory genes and a downregulation of anti-inflammatory genes **[13]**. However, this change in innate immune system cells is not limited to adipose tissue. Authors have demonstrated that circulating mononuclear cells in obese individuals are also in a pro-inflammatory state, with increased intranuclear factor-κB (NF-κB) and, consequently, increased transcription of pro-inflammatory genes regulated by it **[14]**.

As a corollary, the innate immune response in obese patients is altered, resulting in an imbalance in the line of defense against infections, an increased inflammatory response, and abnormal activation of T lymphocytes. Furthermore, the primary increase in the inflammatory response in obese patients serves as a predictor of 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]**.

Given the above, this study conducted a systematic review to present the main metabolic and inflammatory aspects of childhood obesity through immunological predictors and microRNAs.

Methods

Study Design

This study followed the international systematic review model, following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) guidelines. Available at: http://www.prisma-statement.org/?AspxAutoDetectCookieSupport=1.
Accessed on: January 17, 2025. The AMSTAR-2 (Assessing the Methodological Quality of Systematic Reviews) methodological quality standards were also followed. Available at: https://amstar.ca/. Accessed on: January 17, 2025.

Search Strategy and Search Sources

The literature search process was conducted from January to March 2025 and was based on Scopus, Embase, PubMed, Science Direct, Scielo, and Google Scholar, covering scientific articles from various periods to the present day. The following MeSH terms were used: *Child obesity. Comorbidities. Meta-inflammation. MicroRNAs. Gene expression*, using the Boolean expression "and" between MeSH terms and "or" between historical findings.

Study Quality and Risk of Bias

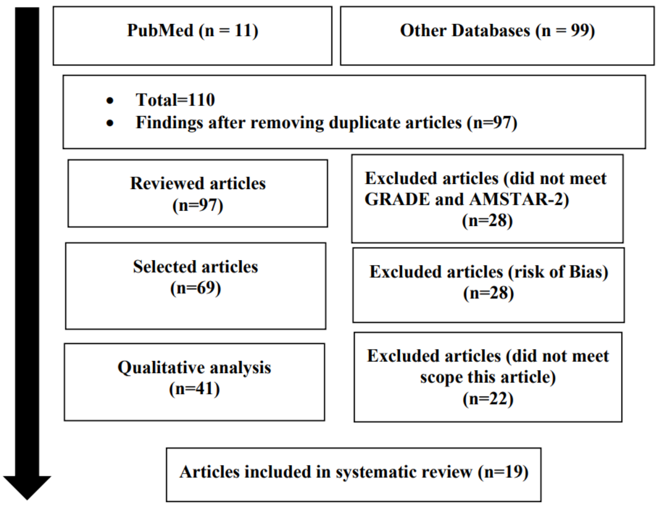
Quality was classified as high, moderate, low, or very low based on the risk of bias, clarity of comparisons, precision, and consistency of analyses. The most prominent factors were systematic reviews or meta-analyses of randomized controlled trials, followed by randomized clinical trials. Low-quality evidence was attributed to case reports, editorials, and brief communications, according to the GRADE instrument. Risk of bias was analyzed according to the Cochrane instrument by analyzing the funnel plot (sample size versus effect size) using Cohen's d test.

Results and Discussion

Summary of Findings

As a result of the literature search, a total of 110 articles were found and submitted to eligibility analysis. Subsequently, 19 of the 41 final studies were selected to comprise the results of this systematic review. The selected studies were of medium to high quality (Figure 1), considering the level of scientific evidence of studies in meta-analysis, consensus, randomized clinical trials, prospective, and observational studies. Biases did not compromise the scientific basis of the studies. According to the GRADE instrument, most studies presented homogeneity in their results, with X2 = 58.7% > 50%. Using the Cochrane risk of bias tool, the overall assessment resulted in 28 studies with a high risk of bias and 28 studies that did not meet the GRADE and AMSTAR-2 criteria.

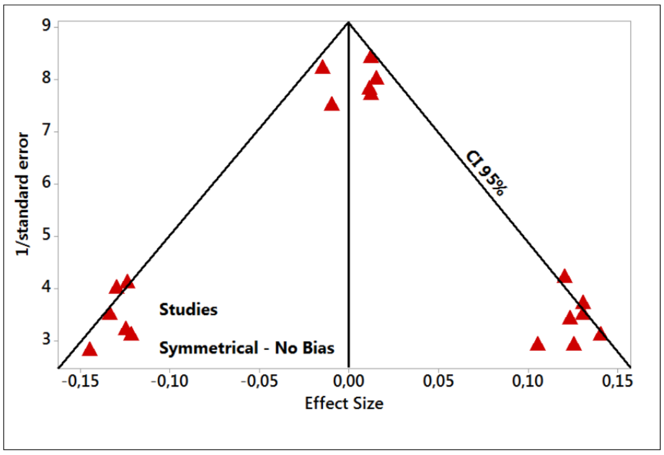
Figure 1. Flowchart showing the article selection process.



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 Cohen's d test. Precision (sample size) was determined indirectly by the inverse of the standard error (1/Standard Error). This graph exhibited symmetrical behavior, suggesting no significant risk of bias, either among studies with small sample sizes (lower precision), shown at the bottom of the graph, or among studies with large sample sizes, shown at the top.

Figure 2. The symmetrical funnel plot suggests no risk of bias among the small sample size studies shown at the bottom of the graph. High-confidence and highly recommended 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, an association between miRNA expression and childhood obesity was observed. 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 reviewed studies 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 analyzed the association between miRNA expression and 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 of normal weight. 40.64% (278) of the children were boys. The classification of obesity was inconsistent across studies, with various 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-486-17h. 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 have been considered good candidates for obesity biomarkers **[18]**.

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 avenue for diagnostic innovation. Thus, a study reported new findings on associations between circulating miRNAs, PLIN1 gene regulation, and susceptibility to childhood obesity. In a sample of 135 unrelated individuals, 35 children with obesity (aged 3-13 years) and 100 healthy controls (aged 4-16 years), we examined the expression levels of four candidate miRNAs (hsa-miR-4777-3p, hsa-miR-642b-3p, hsamiR-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% of the 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%. Consistent with the biological polarity of the observed association, for example, hsa-miR-642b-3p was upregulated, while PLIN1 expression decreased in obese participants compared to healthy controls **[19]**.

Thus, obesity, determined by the accumulation of adipose tissue in the human body, is considered a chronic disease with a multifactorial etiology **[2,3]**. In the pediatric population, the identification and diagnosis of this condition involve the correlation of various data points that must be stratified according to each individual's sex and age group. To obtain more accurate data, it is recommended to use methods complementary to the physical examination that assess, in summary, weight, height, abdominal circumference, and skinfold thickness **[5]**.

In terms of population assessment and classification, the BMI, calculated based on a 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 children, severe obesity is also classified as exceeding the 99.9th percentile and the Z+3 score **[1]**.

It is important to emphasize that weight, like BMI, does not reflect an individual's body composition and, therefore, should not be used as an isolated method. 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]**. To complement BMI, skinfold thickness, bioelectrical impedance analysis (BIA), as well as more complex methods such as hydrostatic weight and computed tomography (CT) can be useful in differentiating body fat from other non-fat components such as muscle tissue, bone mass, and total body water **[5]**.

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

The association between obesity and inflammatory disease is highlighted. There are three possibilities: the first reflects the production and release from organs other than adipose tissue, primarily 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 an immediate source of some, or many, of these inflammatory markers **[10,11]**.

Cytokines have been attributed their role as sensors of energy balance. Among all the adipokines associated with 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 that low concentrations of the anti-inflammatory adipokine (adiponectin) are associated with the occurrence of various types of cancer, and high concentrations are associated with tumor growth inhibition **[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), 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 significant impact on various bodily functions. These include food intake and energy balance control, the immune system, insulin sensitivity, angiogenesis, blood pressure, lipid metabolism, and body homeostasis, all of which are strongly correlated with cardiovascular disease **[13]**. Adipokines with anti-inflammatory action include IL-1 receptor antagonist (IL-1ra), transforming growth factor-β (TGF-β), those produced by Th2 cells (IL-4, IL-5, and IL-10), and adiponectin. An imbalance between pro- and anti-inflammatory cytokines can induce inflammatory or hypersensitivity responses. Furthermore, high plasma adiponectin concentrations are associated with a reduced risk of myocardial infarction in men. Adipokine is inversely proportional to C-reactive protein (CRP) concentrations. It has the ability to negatively regulate CRP gene expression in adipocytes **[8,20]**.

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.

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The authors declare no conflict of interest.

Similarity Check

It was applied by Ithenticate@.

Application of Artificial Intelligence (AI)

Not applicable.

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It was performed.

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