

Peripheral Insulin Resistance Associated with Acanthosis Nigricans in Obese Children and Adolescents in Brazil

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ABSTRACT

Obesity in children and adolescents is a nutritional status disorder related to the increase in adipose tissue, with increased body weight and has become worrying with high rates in children in addition to the high prevalence of insulin resistance which, together with obesity, can contribute to the development of acanthosis nigricans. The objective of this study is to investigate the general epidemiology, common signs and symptoms in metabolic syndrome and correlate with acanthosis nigricans. The search for scientific articles was carried out in electronic databases such as Medline (PubMed) and SciELO from August to November 2023. The results found demonstrate that the highest incidence of excess weight in childhood is due to dietary patterns inadequate, in addition to increasingly sedentary behavior among children. Actions aimed at preventing this problem and raising awareness about childhood obesity and healthy lifestyle habits in schools, daycare centers and within the family are essential to reverse this situation.

Keywords: Acanthosis nigricans; Insulin resistance; Child obesity

INTRODUCTION

Acanthosis nigricans is a skin condition that manifests itself through thick, hyperpigmented brown plaques with a velvety texture, usually found in folds of the skin, which may indicate the presence of systemic health problems. It is a risk factor for developing type 2 diabetes often associated with hyperinsulinemia [1].

Furthermore, it is an important clinical marker to assess the presence of insulinemia, which is a skin sign related to the high risk of metabolic disorders such as hypertension, insulin resistance, diabetes and dyslipidemia. Such disorders play a key role in the link between obesity and these abnormalities [2].

A “gap” was observed in the literature and studies that identify the relationship between acanthosis nigricans and metabolic disorders in obese or overweight children and adolescents. A significant increase in the rate of childhood obesity was also observed and there was a need to delve deeper into this subject with such relevance for prevention and management.

Objectives

General: This work aims to evaluate the presence or absence of acanthosis nigricans in a group of children and adolescents with obesity and overweight and its association with metabolic changes.

Specifics: Study the general epidemiology of metabolic syndrome in children and adolescents identify the most common signs and symptoms of metabolic syndrome in children. Correlate acanthosis nigricans as an early sign of insulin resistance.

Theoretical foundation

Obesity is characterized by the excess accumulation of body fat, which results in negative impacts on individuals' health. Its origin is complex, involving an interaction of genetic, metabolic, nutritional, psychosocial and environmental factors, with lifestyle changes playing a role in its origin. The World Health

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Organization (WHO) recognizes obesity as one of the biggest public health epidemics in the world, and its prevalence is increasing in both developed and developing countries, increasingly affecting children and adolescents. The relevance of obesity lies in its association with several diseases, such as high blood pressure, dyslipidemia and type 2 diabetes, which make up the metabolic syndrome. In this context, insulin resistance and excessive insulin production (hyperinsulinemia) play an important role in the connection between obesity and these abnormalities. Additionally, there is evidence that the amount of body fat in adolescents is linked to the development of these conditions, including metabolic syndrome. Although the relationship between obesity and metabolic disorders is well established in adults, there is still no clear consensus on the diagnostic criteria for metabolic syndrome and the corresponding reference values in pediatrics. This justifies the need to expand our understanding of this relationship, especially in children and adolescents [3].

Childhood obesity, along with its metabolic complications, represents one of the main challenges of the 21st century. Approximately 110 million children worldwide are identified as being overweight or obese. Obesity is the main risk factor for the development of type 2 diabetes mellitus, which can appear as early as adolescence, and metabolic syndrome. Although there are more than 40 different criteria proposed for metabolic syndrome in children, the contribution of insulin resistance to its origin is well established [4].

Insulin Resistance (IR) is characterized by a reduction in the ability of target tissues to take up glucose in response to insulin, leading to an increase in insulin production by pancreatic β -cells, resulting in hyperinsulinism. It is important to note that IR precedes the development of type 2 diabetes mellitus by many years. Several factors may contribute to IR, including obesity, chronic inflammation, mitochondrial dysfunction, lipotoxicity, endoplasmic reticulum stress, oxidative stress, hepatic steatosis, and genetic factors. Some of the indicators associated with IR include children who were born with low weight for gestational age, early onset of puberty, presence of visceral obesity, accumulation of fat outside the usual place (such as in the liver, pericardium and within muscle cells), presence of acanthosis nigricans and polycystic ovary syndrome. Therefore, it is extremely important to recognize the presence of Insulin Resistance (IR) in obese children and adolescents who are at risk of developing type 2 diabetes mellitus, in order to implement preventive measures. Clinically, patients with IR often present obesity, especially with accumulation of visceral fat, high height and the presence of acanthosis nigricans [4].

Resistance to insulin action is described as a primary and early change in the development of the disease. It is characterized by a reduction in insulin's ability to stimulate the use of glucose by the body's tissues. In its initial phases, this resistance is compensated by an increase in insulin secretion. However, as this process persists for long periods, a detrimental effect on glucose regulation occurs, known as glucotoxicity. This means that the increase in insulin resistance is accompanied by a decrease in the function of beta cells in the pancreas, due to the sharp rise in blood glucose levels [5].

Type 2 diabetes mellitus in children and adolescents resembles what is seen in adults, especially with regard to insulin resistance and changes in the beta cells of the pancreas. The age group with the highest incidence of this condition is generally between 12 and 14 years of age [5]. Children with type 2 diabetes often have no symptoms for long periods. On average, around half of them are referred to specialized clinics due to the detection of glycosuria (glucose in the urine) or hyperglycemia (high blood glucose levels) in routine examinations. Approximately 30% of patients may eventually develop symptoms such as increased urinary frequency (polyuria), increased thirst (polydipsia), slight weight loss and the appearance of acanthosis nigricans (a hyperpigmentation of the skin with thickening in areas such as the neck, armpits and region). Inguinal pain which is a characteristic sign of insulin resistance. Some children may present with ketonuria (presence of ketone bodies in the urine) and/or ketoacidosis, which manifests itself with symptoms such as nausea, vomiting and dehydration [5].

Acanthosis nigricans is a symmetrical dermatosis characterized by brown, hyperkeratotic, hyperpigmented plaques with a velvety appearance and located in skin folds. Acanthosis nigricans is sometimes a cutaneous manifestation of various systemic diseases, being a risk factor associated with hyperinsulinemia and the development of type 2 diabetes mellitus. Acanthosis nigricans is associated with insulin resistance, and is therefore considered a "clinical surrogate" for the determination of hyperinsulinemia in the laboratory [6].

From a clinical point of view, the area most commonly affected by acanthosis nigricans in children is the neck (93%-99%), followed by the axillary area (73%). However, this dermatosis can also affect the eyelids, lips, vulva, mucous surfaces and the back of the hands, groin, knees and elbows. Although acanthosis nigricans is asymptomatic, itching may be present on some occasions. The dark color of the lesions is due to hyperkeratosis rather than an increase in melanin pigmentation as previously suggested [2].

There is evidence that hyperinsulinemia also facilitates the indirect development of acanthosis nigricans. This hypothesis suggests that increased levels of circulating insulin have the ability to bind to IGF-1 receptors, leading to epidermal proliferation in patients with acanthosis nigricans. Studies have demonstrated an association between hyperinsulinemia and acanthosis nigricans; however, these findings differ with regard to the other components of metabolic syndrome, such as obesity, hypertension, high triglyceride levels, low HDL and high LDL levels, and glucose intolerance [2].

The presence of metabolic syndrome in adults in the United States generates a risk of heart disease equivalent to that found with smoking and a 3.5 fold increase in the risk of developing diabetes mellitus. However, studies on children and adolescents are scarce. Therefore, evaluating the relationship between acanthosis nigricans, insulin resistance and the components of metabolic syndrome is crucial for the management of clinical cases [2-7,8]. Thus, the objective of the present study is to determine the association between acanthosis nigricans, insulin resistance and components of the metabolic syndrome in overweight children and adolescents.

LITERATURE REVIEW

Protocol and registration

The review article protocol will be registered on the PROSPERO platform (International prospective register of systematically reviews). The protocol can be accessed at: https://www.crd.york.ac.uk/prospero/record_email.php

Eligibility criteria

The selection of articles was based on the correspondence of topics with the objectives of this study, excluding those that, even appearing in the search results, did not address the relationship between metabolic syndrome and acanthosis nigricans in overweight children and adolescents. Inclusion criteria comprised overweight children or adolescents defined by a Body Mass Index (BMI) greater than 25 or BMI above the 85th percentile for age.

Case and control studies, cohort studies, screening studies and observational studies that aimed to investigate children and adolescents were considered eligible. Furthermore, the Jadad score was used to evaluate the methodological quality of each research.

Information sources

SciELO, MEDLINE, EMBASE databases will be used in the period 2023 to 2024. In addition, clinical trial registries, including Clinicaltrials.gov, will be searched. Articles to be included must be in Portuguese, English and Spanish.

The research was organized following the PICO structure, which is an acronym for target Population, Intervention, Comparison and "Outcomes" (PICO). Given the purpose of this research, the acronyms "outcomes" and intervention were not incorporated, as they were not relevant or applicable to the study objectives. The target population to be analyzed in this project is overweight children or adolescents defined by a Body Mass Index (BMI) greater than 25 or BMI above the 85th percentile for their age, whether or not they present peripheral insulin resistance with the presence of acanthosis nigricans. The comparison is made with the development or not of peripheral insulin resistance in overweight children and whether there is an associated clinical manifestation of acanthosis nigricans.

Search

To facilitate the replication of the search strategy, the research carried out in the databases is exemplified, with results obtained between the years 2013 and 2023.

Search: Acanthosis nigricans, insulin resistance related to acanthosis nigricans, obesity and acanthosis nigricans in children and adolescents.

Filters: Experimental studies, case report and narrative review

Data collection process

An active search and review of all texts will be carried out by two reviewers. In cases of lack of agreement, the conflict will be resolved by discussion and consensus. In the event of disagreement over the inclusion of a citation, the article will be independently assessed and reviewed by another reviewer. If disagreement persists, a third evaluator (advisor) will judge whether or not the article should be included.

RESULTS AND DISCUSSION

Studies compatible with the eligibility criteria will be independently reviewed by two authors, who will extract relevant outcome data, including study design (Table 1).

Variables	Overview
Kind of study	Retrospective observational study
Independent variable	Obese children and pre-teens
Dependent variable	Insulin resistance with manifestation of acanthosis nigricans
Local	Brazil
Data collect	PUBMED, DATASUS, SciELO, MEDLINE, EMBASE databases
Data analysis	It will be divided into 10 steps: Data extraction Data standardization Descriptive synthesis Qualitative analysis Quantitative analysis (meta-analysis) Assessment of heterogeneity Subgroup and sensitivity analysis Interpretation of results Presentation of results: Following PRISMA guidelines (Preferred Reporting Items for Systematic Reviews and Meta- Analyses). Conclusions and recommendations

Table1: Characteristics and analysis procedure of entire study.

Contextualization of the study (2023 to 2024): The study will be carried out in the years 2023 to 2024, analyzing a database from the years 2013 to 2023, to understand the impact of childhood obesity on the development of metabolic syndromes in the last 10 years.

Participant characteristics: overweight children or adolescents defined by a Body Mass Index (BMI) greater than 25 or BMI above the 85th percentile for age.

Outcomes: In the present study, we sought to compare the impact of the influence of diet and physical exercise during the treatment of obese children with peripheral insulin resistance and associated acanthosis nigricans, regardless of their socioeconomic status.

Risk of bias in each study

The risk of bias will be assessed by 2 authors independently, using the New-Castle-Ottawa criteria, with specific risk of bias items:

- Selection bias
- Comparison bias
- Outcome detection bias

Information on the risk of bias that was not contained in the included article will be requested from the study authors.

CONCLUSION

In conclusion, the study underscores the pressing issue of childhood obesity and its association with metabolic complications, emphasizing the significance of addressing inadequate dietary patterns and sedentary behaviors. To combat this growing concern, proactive measures within educational institutions and families are important to promote awareness and instill healthy lifestyle habits among children. The exclusion steps and the studies those were included in the systematic review. In a table containing the details of each included study, characteristics of the studied population, the intervention, the

control group, outcomes and other basic results will be presented.

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