



ASPECTS OF INSULIN RESISTANCE IN CHILDREN WITH AUTISM

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ABSTRACT:

Purpose: To investigate aspects of insulin resistance in children with autism.

Material/Methods: In January 2024, the search was conducted using three bibliographic databases: PubMed, Scopus, Google Scholar, and Mendeley. The objective of the search was to find relevant sources on metabolic diseases Insulin resistance (IR) in Autism spectrum disorders (ASD) from 2016 to 2023. The search technique involved using the terms and keywords: “(IR OR Insulinopathie) AND (child OR toddler OR adolescent OR school age) AND (ASD OR Autism).” The two independent reviewers (RB and AT) systematically conducted the data extraction process.

Results: There is no conclusive evidence that prenatal insulin resistance is a risk factor for the onset of autism. Poor eating habits, lack of physical activity, presence of other medical conditions, and use of medications can contribute to increased obesity rates in children with ASD, leading to potential health issues like diabetes, insulin problems, and heart disease. Some experts highlight the metabolic risks, specifically insulin resistance, associated with prescribing antipsychotic drugs to children with autism. Risperidone causes a notable increase in weight and serum triglyceride levels, even when used briefly. Teenagers with autism spectrum disorder demonstrate increased HOMA-IR levels, possibly indicating decreased glucose utilization in certain areas of the brain.

Conclusion: Understanding how insulin resistance affects peripheral metabolism and the CNS could lead to extensive research to enhance the neuropsychological development of children with autism and have implications for public health.

Keywords: IR, Insulinopathie, ASD, child,

INTRODUCTION

ASD is a neurodevelopmental disease that harms central nervous system (CNS) function and the individual capability to process and respond to external stimuli, including impaired verbal and nonverbal communication, in addition to showing repetitive or stereotypical behaviors [1]. As the prevalence of ASD has increased worldwide dramatically in the past few decades [2], it is essential to understand what factors are contributing to the diet regarding ASD. ASD is likely to start before or after birth, affecting the immune system and brain development [3].

Among potential risk factors for ASD, maternal metabolic syndrome consists of several conditions with well-studied preventive and treatment approaches [4]. The metabolic syndrome includes a constellation of pathophysiological states, including obesity, insulin resistance, hypertension, and hypercholesterolemia, and predisposes individuals to develop numerous medical conditions, including diabetes mellitus (DM) [5]. Insulin resistance occurs when the activity of insulin is blunted in the liver, muscle, and adipose tissue and is linked to intra-abdominal fat [6].

It can be hypothesized that ASD and its related metabolic impairment are associated with maternal health status. It seems that prenatal metabolic syndrome may increase the risk of ASD prevalence [7].

Children with ASD are also at higher risk of developing overweight or obesity than typically developing (TD) children [8]. Individuals with ASD may face medical and health-related complications, including insulin resistance, which is prevalent in ASD [9].

Additionally, drugs can negatively impact the metabolic health of people with ASD. One example is risperidone, a commonly used medication for behavioral issues in individuals with ASD, which may lead to insulin resistance [10]. Based on the above, we set the goal of studying the manifestation of insulin resistance in children with autism.

MATERIALS AND METHODS:

In January 2024, the search was conducted using three bibliographic databases: PubMed, Scopus, Google Scholar, and Mendeley. The objective was to find relevant sources on metabolic diseases (IR) in ASD from 2016 to 2023.

The search technique involved using the terms and keywords: “(Insulin resistance OR Insulinopathie) AND (child OR toddler OR adolescent OR school age) AND (Autism spectrum disorders OR Autism).” The search results were obtained from the previous 8 years.

The two independent reviewers (RB and AT) systematically conducted the data extraction process. Every reviewer carefully analyzed the dataset to identify which articles satisfied the work’s objective. Disagreements and inconsistencies were addressed jointly and settled through agreement to uphold a fair selection process.

RESULTS:

The initial search in scientific databases identified 80 reports. After screening titles, 38 duplicate publications were excluded. Reading the abstracts removed 19 irrelevant articles. Finally, 23 publications in English were included in the review.

Conditions such as autism spectrum disorder and obsessive-compulsive disorder are often defined by a lack of flexibility in behavior. Studies have revealed the mechanisms of insulin involvement in behavior inflexibility, its impact on central nervous system outcomes, type 2 diabetes (T2D), and the brain circuits that support flexible behavior.

Cortese and colleagues’ research in 2022 [11] indicates that there is insufficient strong evidence to support claims of a notable link between ASD and diabetes. Another author, Sullivan Ā al., [12], shows that the accumulation of evidence points to the importance of insulin, not just in metabolic roles.

Insulin and IGF1 receptors are prominent in the brain, and alterations in white and grey matter volume and functional connectivity are linked to T2D. Brain insulin or insulin from outside the brain impacts neurophysiological functions, with links between T2D and different cognitive, neurological, and neurodegenerative conditions, such as ASD. Initial findings by Mukhtarova K et al. [13] indicate an intricate connection between autism spectrum disorder and genetic mutations linked to vulnerability in maintaining glucose and insulin balance.

In the last few years, there has been a rise in the occurrence of ASD linked to high intake of energy (specifically fructose) and a rise in metabolic syndrome, marked by insulin resistance, obesity, hyperlipidemia, and systemic inflammation.

The fetus’s brain development is influenced by the pregnant woman’s metabolic condition. The child’s cognitive and behavioral development can be significantly impacted by changes in the metabolic state of the parents, as the child’s brain is highly sensitive to these changes. Offspring of diabetic, obese, and insulin resistant mothers are more likely to develop ASD [14].

Children of obese mothers tend to have high blood pressure, left ventricular thickening, macrosomia, increased abdominal adipose tissue, increased aortic root diameter, hyperlipidemia with reduced high-density lipoprotein levels, insulin resistance, and increased inflammatory markers [15]. Myers-Morrison K [16] reviewed the lit-

erature and the adverse outcomes for children born to obese mothers. Newborns of obese women had increased body fat at birth, increasing the risk of childhood obesity. The authors believe that increased maternal insulin resistance before pregnancy and concomitant hyperinsulinemia, inflammation, and oxidative stress contribute to early placental and fetal dysfunction [17].

Epidemiological studies have found an increased risk of intellectual deficits, attention deficit hyperactivity disorder (ADHD), ASD, cerebral palsy (CP), and epilepsy in children born to overweight or obese women during pregnancy [18]. According to a study by Flores-Dorantes M et al., [19] high levels of free fatty acids contribute to IR and hyperglycemia and lead to impaired cognitive processes.

Obese mothers generate elevated levels of inflammatory mediators that have the ability to pass through the blood-placental barrier, impacting the growth of the fetus. Exposure during pregnancy can lead to neurodevelopmental disorders like schizophrenia, attention deficit hyperactivity disorder, and autism spectrum disorder. No single mechanism seems to be behind all negative perinatal outcomes of maternal obesity, but higher maternal insulin resistance and resulting issues like hyperinsulinemia, inflammation, and oxidative stress may play a role in early placental and fetal problems [20].

Factors such as eating habits, lack of physical activity, existing health conditions, and the use of medication in children with ASD could contribute to increased rates of obesity. Children with ASD are frequently more prone to being overweight or obese when compared to typically developing (TD) children. Childhood obesity has adverse health consequences such as IR, diabetes, heart, and some malignancies, as well as a negative impact on children’s physical and emotional development, socialization, and academic performance [8, 21].

Children with ASD often display food selectivity. The core of this changed eating behavior stems from sensory challenges like oral sensitivity, resulting in a restricted range of foods and reluctance towards specific textures and flavors.

Although children with ASD may consume a limited variety of foods, they prefer sugary foods and beverages that lead to weight gain [22]. People with ASD repeatedly eat and drink sugary beverages to deal with different emotions like anxiety, stress, and happiness. Children of parents consuming high amounts of simple sugars are also likely to adopt this unhealthy diet [14].

The growing consumption of affordable foods containing high levels of glucose, fructose, and/or saturated fat, along with sedentary habits, are significant factors in the increase of obesity and the likelihood of developing insulin resistance. A high amount of fructose in food impacts metabolism by promoting the synthesis of triacylglycerols and certain amino acids like leucine, isoleucine, and valine, leading to an increase in obesity. A connection has been made between higher intake of fructose and ASD. Disturbances in energy metabolism and behavioral regulation can occur due to the direct impact

of fructose on neuronal signaling pathways. It is hypothesized to affect neural network activity in brain regions involved in functions (executive control) that are often impaired in ASD [14]. Gluten- and casein-free diets given to children with ASD might decrease the consumption of certain micronutrients, and low levels of vitamins A, D, B-complex, calcium, and zinc are linked to higher fat storage [22].

The HOMA-IR model is frequently used in research to evaluate peripheral insulin resistance. Melania Manco and her team [23] point out that several metabolic abnormalities, such as low-grade inflammation, elevated oxidative damage, reduced carnitine levels, high lactate levels, and increased levels of branched-chain amino acids (which can be harmful to the central nervous system in excess), are linked to ASD. The scientists suggest that these irregularities could be linked to decreased glucose metabolism in the central nervous system due to insulin resistance. Researchers found that the HOMA-IR test not only evaluated peripheral insulin resistance in children with ASD, such as in muscle but also assessed insulin resistance in the brain. The hypothesis was verified by the authors that young individuals with ASD had higher HOMA-IR levels compared to those without ASD, irrespective of their BMI and medication usage. In a multivariable linear regression model, individuals with ASD had HOMA-IR levels 0.31 units higher than controls, even after accounting for factors that affect HOMA-IR. In patients with ASD, HOMA-IR may reflect reduced glucose metabolism in some areas of the brain, as observed in healthy individuals and patients affected by other neurological diseases [24].

Excessive energy intake and reduced physical activity predispose to obesity and type 2 diabetes [14]. Physical activity is crucial for preventing obesity in children with ASD despite challenges like social, behavioral, and motor deficits that may limit their movement. More opportunities to use computers and phones lead to inactive habits that require minimal energy. Extended periods of inactivity can lead to adverse health effects, including increased body weight, heart-related issues, and type 2 diabetes [25].

The quality and duration of sleep can contribute to the risk of obesity. Sleep issues in obese children can appear as obstructive sleep apnea. Evidence suggests that there is a negative relationship between sleep quality and BMI with the risk of being overweight or obese. Lack of sleep can impact the hormones responsible for regulating hunger (ghrelin and leptin) and how the body processes glucose, leading to an increase in weight. A correlation was discovered between high levels of leptin and low levels of ghrelin in relation to overall sleep duration. Children with ASD are more prone to insomnia, obstructive sleep apnea, and circadian rhythm disorders, which can lead to specific metabolic issues like insulin resistance and hypertension if they experience poor sleep quality

and inadequate sleep duration [21]. In addition to obesity, behavioral factors and psychotropic medications may contribute to the risk of type 2 diabetes in individuals with autism [26].

Some writers emphasize the metabolic adverse effects, including the onset of insulin resistance, when prescribing antipsychotic medications to children with autism. Depression and ADHD can occur together in individuals with autism spectrum disorder. Pharmaceutical medications such as selective serotonin reuptake inhibitors, antipsychotics, and stimulants are commonly used in treating behavioral symptoms in children with ASD, with a percentage between 27-64% (median 41.9%). Research showed that 1 out of every 6 children with ASD are given antipsychotic medications to address coexisting behavioral symptoms such as hyperactivity, irritability, and aggression, but the short-term use of risperidone leads to significant weight gain and higher levels of serum triglycerides [25].

The study by Scahill L et al. [27] provides new information on the metabolic effects of risperidone in children with ASD. They observed group effects on insulin, leptin, and adiponectin. These findings offer an understanding of the possible metabolic impacts of risperidone, yet interpreting them in specific children may pose challenges. Antipsychotic drugs are essential in the field of child and adolescent psychiatry, playing a crucial role in managing psychotic disorders like schizophrenia, bipolar disorder, and psychotic depression, as well as in treating behavioral issues associated with autism spectrum disorder, tic disorders, and pediatric aggression. While they are successful, these medications come with a significant chance of negative outcomes, typically involving issues such as increased weight and heart-related problems. Central obesity, insulin resistance, dyslipidemia, and systemic inflammation are all linked to cardiometabolic abnormalities [28].

CONCLUSION:

Increasing evidence suggests that insulin is crucial for both metabolism and the regulation of neurophysiological processes. Understanding the effects of insulin resistance on peripheral metabolism and at the CNS level can lead to significant opportunities for improving the cognitive development of children with autism, as well as implications for public health. Our research should be viewed as a bold effort to delve into the literature on autism as a “metabolic” disorder, suggesting that IR could point to more severe metabolic issues in specific individuals.

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