Rev. Fac. Med. Hum. 2024; 24(2):47-54.
DOI: 10.25176/RFMH.v24i2.6053
ORIGINAL PAPER

ISSN Versión Online: 2308-0531
Facultad de Medicina Humana URP
RFMH

HYPERTRIGLYCERIDEMIA ASSOCIATED WITH INSULIN RESISTANCE IN CHILDREN WITH OBESITY

HIPERTRIGLICERIDEMIA ASOCIADA A RESISTENCIA A LA INSULINA EN NIÑOS CON OBESIDAD

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ABSTRACT

Introduction: Hypertriglyceridemia has been linked to insulin resistance. **Objectives:** To evaluate the relationship and predictive capacity of hypertriglyceridemia for insulin resistance in obese children. **Methods:** A cross-sectional analytical study was conducted in obese children aged 6 to 14 years, treated at the Belén Hospital of Trujillo between 2014 and 2019. Fifty-eight randomly selected medical records were analyzed. Insulin resistance was measured using the Homeostasis Model Assessment (HOMA) index (≥3). Descriptive, correlational analyses, and Odds Ratio (OR) calculations were used, along with predictive indicators such as sensitivity and specificity. **Results:** Of the 58 children studied, 58.6% had elevated triglyceride levels and 74.1% showed insulin resistance. There was a significant correlation between triglyceride levels and the HOMA index (coef.: 0.543; p<0.001). Elevated triglyceride levels (OR=18.91; 95% CI: 3.67-97.36; p<0.001), fasting glucose (OR=46.20; 95% CI: 5.39-396.06; p=0.010), fasting insulin (OR=52.89; 95% CI: 6.11-457.55; p<0.001), and the presence of acanthosis nigricans (OR=36.17; 95% CI: 4.28-305.98; p<0.001) were significantly associated with insulin resistance. Hypertriglyceridemia showed a sensitivity of 74.4% and a specificity of 86.7% for predicting insulin resistance. **Conclusion:** Hypertriglyceridemia is significantly associated with insulin resistance in obese children and has an acceptable performance as a predictor. This factor may serve as an early marker and predictor to implement appropriate preventive measures in vulnerable populations.

Keywords: Hypertriglyceridemia; Insulin Resistance; Pediatric Obesity. (Source: MESH-NLM)

RESUMEN

Introducción: La hipertrigliceridemia se ha vinculado con la resistencia a la insulina. **Objetivos:** Evaluar la relación y capacidad predictiva de la hipertrigliceridemia para la resistencia a la insulina en niños obesos. **Métodos:** Se realizó un estudio transversal y analítico en niños de 6 a 14 años con obesidad, atendidos en el Hospital Belén de Trujillo entre 2014 y 2019. Se analizaron 58 historias clínicas elegidas aleatoriamente. La resistencia a la insulina se midió mediante el índice Homeostasis Model Assessment (HOMA) (≥3). Se usaron análisis descriptivos, correlacionales y cálculos de Odds Ratio (OR), además de indicadores de predicción como sensibilidad y especificidad. **Resultados:** De los 58 niños estudiados, el 58,6% presentaba niveles elevados de triglicéridos y el 74,1% mostró resistencia a la insulina. Hubo una correlación significativa entre los niveles de triglicéridos y el índice HOMA (coef.: 0,543; p<0,001). Los niveles elevados de triglicéridos (OR=18,91; IC 95%: 3,67-97,36; p<0,001), glicemia en ayunas (OR=46,20; IC 95%: 5,39-396,06; p=0,010), de insulina en ayunas (OR=52,89; IC 95%: 6,11-457,55; p<0,001) y la presencia de acantosis nigricans (OR=36,17; IC 95%: 4,28-305,98; p<0,001) se asociaron significativamente con la resistencia a la insulina. La hipertrigliceridemia mostró una sensibilidad del 74,4% y una especificidad del 86,7% para predecir la resistencia a la insulina. **Conclusión:** La hipertrigliceridemia está significativamente asociada con la resistencia a la insulina en niños obesos y tiene un rendimiento aceptable como predictor de la misma. Este factor puede servir como un marcador temprano y predictor para implementar medidas preventivas adecuadas en poblaciones vulnerables.

Palabras clave: Hipertrigliceridemia; Resistencia a la Insulina; Obesidad Infantil. (Fuente: DeCS-BIREME)

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Cite as: Cacha Villacorta RP, Salcedo Espejo E, Saavedra-Camacho JL, Iglesias-Osores S. Hypertriglyceridemia associated with insulin resistance in children with obesity. Rev Fac Med Hum. 2024;24(2):47-54. doi 10.25176/RFMH.v24i2.6053

Journal home page: http://revistas.urp.edu.pe/index.php/RFMH

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INTRODUCTION

The prevalence of overweight and obesity in children and adolescents aged 5 to 19 years has increased from 4% in 1975 to over 18% in 2016, affecting both girls and boys. These issues, once confined to high-income countries, are now rapidly expanding in low- and middle-income countries. In Africa, the number of children under 5 years old who are overweight has increased by about 50% since 2000[1]. Over the past four decades, the number of children and adolescents with obesity has increased tenfold worldwide. A WHO study predicts that by 2022, there will be more children and adolescents with obesity than those with severe underweight[2].

International studies have documented high frequencies of insulin resistance in patients with dyslipidemia: Calderín et al.[3] found 75% in Cuba, and Barja et al.[4] found 32% dyslipidemia, primarily hypertriglyceridemia, in children with insulin resistance in Chile. In Lima, Pajuelo et al.[5] reported that 28.1% of obese adolescent girls had insulin resistance, with a strong association with hypertriglyceridemia. In the same city, the prevalence of overweight and obesity is 31.6% and 7.2%, respectively, and childhood obesity is associated with an 80% probability of persisting into adulthood[6].

Obesity is related to the metabolic syndrome (MS), which includes hyperinsulinemia, hypertension (HTN), dyslipidemia, and type 2 diabetes mellitus (T2DM). This syndrome, initially described in adults, is also observed in the pediatric population due to nutritional and social changes resulting from globalization, which negatively affect eating habits and physical activity. Indicators of insulin resistance include obesity, physical inactivity, body adiposity, age, and hyperinsulinemia, with abdominal obesity posing the highest risk. Obesity promotes the development of dyslipidemias, which interfere with insulin action and constitute a primary factor in insulin resistance, stimulating triglyceride synthesis and lipolysis, generating hypertriglyceridemia[7].

Previous reports have linked hypertriglyceridemia with insulin resistance in various studies[8,9]. However, this study is novel not only for focusing on a pediatric population in Trujillo but also because it provides local data that may be crucial for designing more effective prevention and treatment strategies. The socioeconomic conditions, eating habits, and access to healthcare services in Trujillo may differ significantly from other contexts. Therefore, the general objective of this study is to determine if hypertriglyceridemia is associated with insulin resistance in obese children, and the specific objective is to evaluate the predictive capacity of hypertriglyceridemia for insulin resistance.

METHODS

Study design and area

A cross-sectional, analytical, and retrospective design was adopted. The study focused on children aged 6 to 14 years diagnosed with obesity, attended at the Hospital Belén de Trujillo during the period 2014 to 2019. The hospital is located in the urban environment of Trujillo, a city with a diverse socioeconomic composition. This context is relevant for researching chronic conditions in vulnerable pediatric populations.

Population and sample

The target population included all children diagnosed with obesity at the Hospital Belén de Trujillo during the specified years. Inclusion criteria encompassed children with clinical histories of obesity and fasting triglycerides, glucose, and insulin levels, with complete and legible information for the study. Exclusion criteria included clinical histories of children with secondary obesity due to endocrinological diseases, genetic syndromes, hypothalamic lesions, Down syndrome, and cerebral palsy.

The sampling unit was the clinical history of each pediatric patient who met the inclusion and exclusion criteria, attended by the hospital's Pediatric outpatient clinic during the mentioned period. Simple random sampling was used, and the sample size was calculated considering a population of 130 children, with an expected proportion of 43.4%[10], an expected OR of 7[11], a 95% confidence level, and a maximum sample error of 5%. The calculation resulted in a sample of 52 children, to which 10% was added expecting a similar exclusion rate.

Variables and instruments

The dependent variable was insulin resistance, measured by the HOMA index (Homeostasis Model Assessment) [12], with values equal to or greater than three indicating resistance. The HOMA index is a tool used to assess pancreatic function and insulin sensitivity. It is calculated using fasting insulin and fasting glucose levels with the formula: HOMA = (fasting glucose [mg/dL] × fasting insulin [µU/mL]) / 405. This index has been validated in previous studies and is widely accepted in the scientific community as a reliable method for estimating insulin resistance [13]. Independent variables included hypertriglyceridemia [14], defined as elevated triglyceride levels in the blood, with specific values according to age.

Intervening variables were fasting glucose (normal values below 100 mg/dL); total cholesterol (normal value less than 200 mg/dL); acanthosis nigricans, a skin condition that can be a marker of hyperinsulinemia; basal fasting insulin (normal values below 15 UI); body mass index (BMI) to identify obesity according to the World Health Organization (WHO), considering obesity if it is greater than two standard deviations (SD) and morbid obesity if greater than 3 SD; and demographic variables such as sex and age of the children, divided into two age groups. All these variables were extracted from the patients' clinical histories.

Procedures

After obtaining approval from the Research Committee of the Faculty of Human Medicine at the Universidad Privada Antenor Orrego and the Multidisciplinary Research Laboratory (LABINM), and authorization from the director of the Hospital Belén de Trujillo. Following this, the register of clinical histories corresponding to the population was requested, and the clinical histories were randomly selected, evaluated, and data were recorded. Relevant information was recorded in data collection forms and coded for statistical analysis.

Statistical analysis

Descriptive statistics were used to describe the data, including absolute and relative frequencies, as well as measures of central tendency and dispersion. The association between variables was evaluated using Pearson's Chi-square test and Fisher's exact test when necessary. Pearson correlation analysis was conducted to assess the relationship between triglyceride level and HOMA-IR value. Crude and adjusted Odds Ratio (OR) analysis was applied to identify factors associated with insulin resistance, considering variables such as fasting glucose, fasting insulin level, and the presence of acanthosis nigricans. Finally, the HOMA test's capacity to predict hypertriglyceridemia was determined by evaluating its sensitivity, specificity, positive and negative predictive value, and positive and negative likelihood ratios. All analyses were performed using IBM SPSS version 26.

Ethical aspects

The study adhered to rigorous ethical standards, respecting the privacy and confidentiality of patients and following the norms of the Declaration of Helsinki, the Universal Declaration on Bioethics and Human Rights, and the Code of Ethics and Deontology of the Medical College of Peru. Emphasis was placed on the importance of publishing the results honestly and transparently, avoiding malpractices such as falsification or plagiarism. After obtaining approval from the Research Committee of the Faculty of Human Medicine at the Universidad Privada Antenor Orrego and the Multidisciplinary Research Laboratory (LABINM), authorization was also received from the director of the Hospital Belén de Trujillo.

RESULTS

Among the 58 study participants, 37.9% were aged six to nine years, and 62.1% were aged ten to 14 years. Of the total, 43.1% were girls, and 56.9% were boys. Regarding triglyceride levels, 41.4% had normal values, and 58.6% had elevated levels. Additionally, 74.1% of the participants showed insulin resistance, measured by the HOMA index, while 25.9% did not. Normal fasting glucose levels were observed in 41.4% of the children, and 58.6% had elevated levels. Regarding cholesterol, 24.1% had normal levels, and 75.9% had elevated levels. Furthermore, 39.7% showed normal fasting insulin levels, and 60.3% had elevated levels. All participants exhibited obesity, and 55.2% had acanthosis nigricans (Table 1).

Table 1. General, clinical, and laboratory characteristics of obese children at Hospital Belén de Trujillo during the period 2014 – 2019.

Age	Frequency	Percentage (%)
6 to 9 years	22	37.9
10 to 14 years	36	62.1
Sex		
Female	25	43.1
Male	33	56.9
Triglyceride Levels		
Normal	24	41.4
Elevated	34	58.6
HOMA Value		
≤3	15	25.9
>3	43	74.1
Fasting Glucose Levels		
<100 mg/dL	24	41.4
≥100 mg/dL	34	58.6
Cholesterol Levels		
<200 mg/dL	14	24.1
≥200 mg/dL	44	75.9
Fasting Insulin Levels		
< 15 UI	23	39.7
≥ 15 UI	35	60.3
Obesity Levels		
Obesity	58	100.0
Morbid Obesity	0	0.0
Acantosis nigricans		
Absent	26	44.8
Present	32	55.2

HOMA: Homeostasis Model Assessment. BMI: Body Mass Index. SD

In Table 2, it can be observed that 38.2% of children aged 6 to 9 years had elevated triglyceride levels, while in the 10 to 14 years group, this figure was 61.8%. Similarly, most children with elevated HOMA values (>3) had elevated triglyceride levels (94.1%).

In contrast, 54.2% of children with normal triglyceride levels had normal HOMA values (≤3). There was a significant correlation between HOMA and triglyceride levels according to Pearson's correlation test (coef.: 0.543; p-value <0.001).

Table 2. Distribution of triglyceride and HOMA levels in obese children at Hospital Belén de Trujillo during the period 2014 – 2019.

	Triglyceride Level		HOMA Value	
	Normal n (%)	Elevated n (%)	≤3 n (%)	>3 n (%)
Age				
6 – 9 years	9 (37.5)	13 (38.2)	4 (26.7)	18 (41.9)
10 – 14 years	15 (62.5)	21 (61.8)	11 (73.3)	25 (58.1)
HOMA Value				
≤3	13 (54.2)	2 (5.9)	-	-
>3	11 (45.8)	32 (94.1)	-	-
Total	24 (100.0)	34 (100.0)	15 (100.0)	43 (100.0)

HOMA: Homeostasis Model Assessment.

In Table 3, it can be observed that several factors are significantly associated with an elevated HOMA index in obese children. Elevated triglycerides (OR=18.91; 95% CI: 3.67-97.36; p<0.001), asting glucose ≥ 100 mg/dL (OR=46.20; 95% CI: 5.39-396.06; p=0.010), fasting insulin level ≥ 15 Ul (OR=52.89; 95% CI: 6.11-457.55; p<0.001), and the presence of acanthosis nigricans (OR=36.17; 95% CI: 4.28-305.98; p<0.001) show a significant association with an elevated HOMA index.

Table 3. Factors associated with elevated HOMA index in obese children at Hospital Belén de Trujillo during the period 2014 – 2019.

Factor	OR	Elevated HOMA (>3) 95% CI		p
		Lower Limit	Upper Limit	
Age (6 – 9 years vs. 10 – 14 years)	1.98	0.54	7.23	0.300
Sex (Female vs. Male)	0.82	0.25	2.68	0.750
Triglycerides (Elevated vs. Normal)	18.91	3.67	97.36	<0.001
Fasting Glucose (≥ 100 mg/dL vs. < 100 mg/dL)	46.20	5.39	396.06	0.010
Cholesterol Level (≥ 200 mg/dL vs. < 200 mg/dL)	2.92	0.81	10.57	0.100
Fasting Insulin Level (≥ 15 Ul vs. < 15 Ul)	52.89	6.11	457.55	<0.001
Acantosis nigricans (Present vs. Absent)	36.17	4.28	305.98	<0.001

HOMA: Homeostasis Model Assessment. Ic95%: 95% Confidence Interval

The capacity of hypertriglyceridemia to predict HOMA was demonstrated with a sensitivity of 74.4%, specificity of 86.7%, positive predictive value (PPV) of 94.1%, negative predictive value (NPV) of 54.2%, positive likelihood ratio of 5.6, and negative likelihood ratio of 0.3.

DISCUSSION

After examining the results, it was evident that children with hypertriglyceridemia showed a strong association with insulin resistance compared to those with low triglyceride levels. This finding aligns with previous studies that have also evaluated this association, finding similar results.

For example, a study conducted in Cuba showed a significant association in obese adolescents (r = 0.23; p = 0.03)[15].

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Similarly, in Ecuador, this significant association was found ($X^2 = 5.56$; $p = 0.02$) (7), and congruent findings were observed in studies conducted in China [16] and Taiwan [17]. Additionally, a national study reported that elevated triglyceride levels were associated with insulin resistance in obese adolescents (OR = 10.9; 95% CI = 5.4 – 26.6; $p < 0.001$)[5].

These results can be explained by the loss of insulin's suppressive effects on lipolysis, mediated by the reduction of cAMP levels and inhibition of protein kinase A (PKA) activity, which attenuates the phosphorylation of hormone-sensitive lipase (HSL) and perilipin[18]. This increases free fatty acids in adipocytes, boosting their flow to the liver and stimulating VLDL secretion (very low-density lipoprotein), resulting in hypertriglyceridemia. Triglycerides in VLDL are transferred to HDL (high-density lipoprotein) and LDL (low-density lipoprotein) through the action of cholesterol ester transfer protein (CETP), generating HDL and LDL particles enriched with triglycerides [19].

Regarding the frequency of children with hypertriglyceridemia, it was found that more than half of the participants had this disorder. This figure is close to that reported in studies in Cuba (64.4%) [15] and the Dominican Republic (66.7%)[20], but differs from studies in Chile (9.4%)[4], Ecuador (37.4%) [7], and Mexico (43.4%) [10]. These differences may be attributed to variations in overweight, obesity, physical inactivity, and high-carbohydrate diets in each country. In Peru, these factors can elevate triglyceride levels, while in developed countries, triglyceride levels double from early to middle adulthood due to weight gain and adiposity, increasing hepatic triglyceride synthesis and VLDL secretion [21]. Elevated triglyceride levels are associated with the accumulation of large VLDL1 particles (50-80 nm, 70% triglycerides) and a moderate elevation of smaller VLDL2 particles (30-50 nm, 30% triglycerides) [21]. Regarding insulin resistance, a prevalence of 74.1% was found in this study, consistent with a study in Cuba where 75% was found[15]. However, it differs from studies in the Dominican Republic (100%) [20], Cuba (37.8%) [15], and Ecuador (51.6%)[7].

Insulin resistance in obese children shares factors with hypertriglyceridemia, hindering cellular response to insulin and forcing the pancreas to produce more insulin. Insulin resistance is due to defects in glucose uptake and oxidation, decreased glycogen synthesis, and reduced capacity to suppress lipid oxidation, primarily affecting skeletal muscle, adipocytes, and liver tissue[22]. The difference with studies from Ecuador and Cuba may be due to the low frequency of high fasting glucose in children and adolescents, which could have influenced the association result with insulin resistance.

In the analysis of other factors associated with insulin resistance, fasting hyperglycemia, hyperinsulinemia, and the presence of acanthosis nigricans were identified. These findings are consistent with a study in Taiwan where fasting glucose was significantly associated with insulin resistance [17]; however, they differ from studies in Ecuador and Cuba where no significant relationship was found[7,15]. Additionally, they differ from a national study where total cholesterol was significantly associated with insulin resistance[5]. Other studies have identified factors such as LDL [5], systolic blood pressure, BMI, waist circumference, and HDL as associated with insulin resistance [17].

Acanthosis nigricans has been related to insulin resistance and type 2 diabetes, affecting the liver, adipose tissue, and skeletal muscle. One study found that adolescents with acanthosis nigricans had higher insulin and HOMA-IR levels compared to those without this condition. Another study showed that the severity of acanthosis nigricans exacerbates insulin resistance. Although the pathogenesis is not fully known, hyperinsulinemia inhibits the synthesis of IGFBP-1 and increases that of IGF-1, which can trigger the proliferation of fibroblasts and keratinocytes. Prolonged insulin administration can attenuate the insulin response, suggesting that hyperinsulinemia could be a cause of insulin resistance [23-25].

Regarding hyperinsulinemia, it has been causally related to the onset of diabetes in the early stages of insulin resistance and in T2DM, negatively affecting insulin-sensitive tissues such as the liver, adipose tissue,

and skeletal muscle. In humans, prolonged insulin administration can attenuate the insulin response, independent of hyperglycemia. Therefore, this suggests a potential role of hyperinsulinemia as a cause of insulin resistance [26].

This study presents several limitations that should be considered when interpreting the results. First, the cross-sectional and retrospective design does not allow for establishing causal relationships between hypertriglyceridemia and insulin resistance. Additionally, the sample is limited to 58 children from a single institution, which may not be representative of the general population and limits the generalizability of the findings. Data collection was based on clinical records, which may have incomplete or inaccurate information. Moreover, other possible confounding variables such as physical activity level, diet, and family history, which may influence insulin resistance, were not included. Finally, insulin resistance measurement was conducted only using the HOMA index, without including other evaluation methods that could provide a more comprehensive view of the phenomenon studied.

CONCLUSIONS

This study concludes that hypertriglyceridemia is significantly associated with insulin resistance in obese children treated at the Hospital Belén de Trujillo. The findings demonstrated a strong correlation between the two factors, suggesting that hypertriglyceridemia could be an early indicator of insulin resistance. This should be further studied in future research. Additionally, hypertriglyceridemia was identified as an acceptable predictor of insulin resistance, highlighting its potential utility in implementing appropriate preventive measures. Other associated factors identified included elevated fasting glucose and insulin levels and the presence of acanthosis nigricans. These results underscore the importance of hypertriglyceridemia as a potential marker for implementing suitable preventive measures in this vulnerable population. Therefore, this study contributes to understanding the role of hypertriglyceridemia in insulin resistance and highlights the need for early intervention strategies to prevent metabolic complications in obese children.

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Authorship contribution: RPCV participated in the conceptualization, data curation, investigation, and drafting of the original manuscript. ESE contributed to the conceptualization, formal analysis, methodology, supervision, and writing - review and editing. JLSC was involved in methodology, formal analysis, visualization, and writing - review and editing. SIO participated in project administration, validation, resource provision, and writing - review and editing. All authors approved the final version to be published.

Funding: Self-funded.

Conflict of interest: The authors declare no conflict of interest.

Received: November 15, 2023.
Approved: April 01, 2024.

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