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The role of adipokines and ghrelin in interactions and clinical implications in childhood obesity

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Abstract:

BACKGROUND: Childhood obesity is a growing global health concern, especially prevalent in the Arabian Peninsula, and is known to contribute to metabolic syndrome and insulin resistance. This study aimed to investigate the interplay between adipokines (leptin and adiponectin), ghrelin, and insulin homeostasis in childhood obesity.

MATERIAL AND METHODS: A case–control study was conducted in Babylon involving 120 children/adolescents (7–17 years). The participants were divided into two groups: 60 obese and 60 healthy controls. Anthropometric and biochemical measures were examined, applying World Health Organization (WHO) growth standards to categorize weight status. Data on blood lipids, glucose, adipokines, and ghrelin were collected in Babylon (Merjan Medical City), ensuring accuracy and providing insights into pediatric obesity's metabolic and hormonal status.

RESULT: Clinical, anthropometric, and laboratory attributes of children were evaluated, with classification as normal-weight or obese based on BMI/Z-score and Waist Circumference. The obese group exhibited elevated triglycerides and insulin levels, as well as reduced adiponectin levels ($P \leq 0.001$). Leptin levels showed a positive correlation with BMI/Z-score ($r = 0.352$, $P = 0.006$). A diagnostic model demonstrated the significant diagnostic capacity of leptin (AUC > 99%) and its importance in predicting childhood obesity. Each unit increase in leptin elevated the probability of obesity by a factor of 1.197 (95% CI: 1.0507–1.3632, $P = 0.0068$).

CONCLUSION: The study revealed significant differences in clinical, biochemical, and biological markers of obesity between the research groups and the control group. Leptin emerged as a significant predictor of obesity, demonstrating high diagnostic accuracy. The complex interactions among these adipokines underscore the necessity for comprehensive obesity management strategies.

Keywords:

Adipokines, adiponectin, anthropometry, childhood obesity, insulin resistance, leptin

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Introduction

Childhood obesity is an escalating global public health issue, characterized by the excessive accumulation of body fat, which significantly raises the risk of morbidity and premature death. The development of obesity during childhood often persists into adulthood, resulting in chronic health complications and an elevated mortality risk. This pathological process is influenced by multiple factors, including imbalanced energy intake, increased consumption of energy-dense foods, and reduced physical activity.[1,2] Moreover, obesity is associated with the development of the metabolic syndrome, characterized by abdominal fat accumulation, hyperglycemia, hyperinsulinemia, dyslipidemia, and hypertension, all of which contribute to the onset of diabetes and cardiovascular diseases (CVD).[3]

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The global obesity epidemic has been escalating at an alarming rate, especially in the Arabian Peninsula. Over the past three decades, obesity has increased worldwide, affecting both high-income and low- to middle-income countries, the latter due to uncontrolled urbanization and a transition to westernized diets.[4-6] The global age-standardized prevalence of obesity in children has been rising considerably since the 1970s, with the mean body mass index (BMI) of children and adolescents plateauing in many high-income countries while accelerating in East, South, and Southeast Asia. Recent data show that the prevalence of childhood obesity in the Middle East is relatively high compared to other regions of the world, ranging from 15–25%. The World Health Organization (WHO) predicts that by 2025, the number of overweight or obese young children worldwide will reach 70 million, with estimates suggesting that 250 million children/adolescents aged 5–19 years will have obesity by 2030.[7,8]

Insulin resistance is a crucial factor in the development of childhood obesity, affecting the utilization (glycolysis) and regulation (gluconeogenesis) of blood glucose. Factors such as decreased pancreatic function or a reduction in insulin receptors contribute to the development of insulin resistance (IR). Childhood obesity has reached epidemic proportions, with obesity rates and related comorbidities rising at an alarming rate.[9] Although the precise mechanisms are still unclear, IR is commonly associated with obesity and high-calorie diets. IR occurs when cells requiring glucose for energy become resistant to the effects of insulin, impeding glucose entry and causing the pancreas to produce more insulin to maintain normal blood glucose levels. Over time, increasing IR can lead to hyperglycemia and type 2 diabetes, which are critical components of the metabolic syndrome.[10] Both adults and children can develop IR due to obesity, which is a contributing factor to the metabolic syndrome. While hyperinsulinemia is a consequence of IR, it can also exacerbate it by reducing insulin target cell sensitivity.[11,12]

Ghrelin, a 28-amino-acid peptide hormone primarily secreted in the stomach, plays a significant role in regulating food intake, body weight, and glucose metabolism. The involvement of ghrelin in obesity is multifaceted, as it promotes adiposity, activates hypothalamic orexigenic neurons, and influences lipid metabolism.[13-15] Ghrelin, often referred to as the hunger hormone, stimulates appetite and facilitates energy storage in the form of fat through various mechanisms. These mechanisms include the activation of hypothalamic orexigenic neurons, stimulating fat storage-related expression, the enhancement of lipogenesis, and the promotion of triglyceride uptake in adipocytes, primarily in white adipose tissue (WAT). Additionally, ghrelin affects glucose homeostasis by reducing insulin sensitivity.[16]

Adipokines are bioactive molecules that adipose tissue secretes. Among the extensively studied adipokines, leptin and adiponectin stand out as they play crucial roles in energy homeostasis, body weight regulation, and metabolism. Leptin, sometimes referred to as the satiety hormone, serves as a signal to the brain, indicating sufficient energy stores in the body and aiding in appetite regulation.[17,18] When an individual has adequate energy stored in their fat cells, leptin is released to communicate to the brain to cease eating. This hormone is critical to maintaining energy balance and regulating body weight. On the other hand, adiponectin has diverse beneficial effects on metabolic processes. It enhances the body's insulin sensitivity, possesses anti-inflammatory properties, and participates in the breakdown of fatty acids. Adiponectin is often associated with protection against type 2 diabetes and CVD.[19] The present study aimed to investigate the interplay between adipokines (leptin and adiponectin), ghrelin, and insulin homeostasis in childhood obesity.

Materials and Methods

The study designs and setting

A case–control study was conducted on a cohort of 120 children/adolescents, aged 7 and 17 years, in the city of Babylon. This population was stratified into two equal groups, with 60 subjects identified as obese and the remaining 60 recognized as healthy controls. The research duration spanned over a period of six months, commencing on September 1, 2022, and concluding on April 1, 2023. The selection criteria for the participants were carefully defined, and the children invited to participate in the study were solely those falling within the specified age bracket. All potential participants were scrutinized for eligibility before inclusion in the study. An extensive assessment of the children's medical history, alongside self-reporting or parental reporting, facilitated the exclusion of individuals suffering from chronic or acute illnesses that could potentially alter the study variables.

The exclusion criteria were specifically set to rule out individuals with genetic disorders, secondary obesity, and concomitant diseases such as diabetes, cardiac, pulmonary, and neurological ailments. Children with acute infections or those presently under medical treatment were also considered ineligible to participate in the study. Rigorous attention was dedicated to preventing the inclusion of children suffering from acute infections.

Study participants and sampling

This study used a standardized anthropometric measurement protocol to assess children and adolescents

aged between 5 and 19 years. Participants were measured while lightly dressed and barefoot. The measurements taken included height, weight, and waist circumference (WC). Height was recorded with a portable stadiometer (Seca 213, Germany) to the nearest millimeter, and weight was noted to the nearest 0.1 kg using a compact digital weighing scale (Seca 877 Class III, Germany). The WC was measured in centimeters using an automatic retractable portable tape measure (Lytown, China). The height measurements were taken from the base of the feet to the top of the head while the participant stood straight without shoes. For WC, the midpoint between the lowest rib and the iliac crest was identified, and a measurement was taken at the end of a normal expiration, ensuring accuracy to the nearest 0.1 cm. Body mass index (BMI), expressed as weight in kilograms divided by height in meters squared (kg/m^2), was calculated from these parameters. The BMI z-score, which takes into account the participant's age and sex, was derived based on the WHO methodology. Participants were categorized as underweight, normal, overweight, or obese using WHO growth standards for BMI-for-age percentiles and sex-specific BMI-for-age z-scores. Additionally, the presence of waist obesity was determined using reference tables developed specifically for the pediatric population.[20]

The weight statuses were defined as follows: a z-score below -3 signified severe thinness; a z-score between -3 and -2 denoted thinness; a z-score between -2 and 1 indicated normal weight; a z-score greater than 1 and up to 2 signified overweight; and a z-score exceeding 2 indicated obesity. The methodical approach to these measurements, along with strict adherence to WHO guidelines and standards, assured accurate and comparable data across all participants, providing a strong basis for understanding the anthropometric characteristics of this pediatric group.[20,21]

Data collection and biochemical analysis

Blood samples were collected in the early morning between 7 and 9 AM, after an overnight fast of 8–12 hours. These samples were obtained from venipuncture of the antecubital vein using Vacutainer tubes and were immediately processed to maintain their integrity. The blood samples were treated and centrifuged at 1,500 rpm at 4°C for 10 min. This process allowed the separation of serum into aliquots, which were subsequently stored at -40°C in preparation for further analysis. Biochemical analyses of these samples included the measurement of total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), and fasting plasma glucose (FPG). These parameters were determined using colorimetric methods on a Fujifilm DRI-CHEM NX600, an automated chemistry analyzer.

Simultaneously, hormonal analyses were performed to determine serum concentrations of insulin, ghrelin, leptin, and adiponectin. These concentrations were quantified using the enzyme-linked immunosorbent assay (ELISA) technique with commercially available kits supplied by Elabscience (catalogue no.: E-EL-H 2665, E-EL-H 1919, E-EL-H6017, and E-EL-H6122, respectively). The assays were performed using a Synergy 2 multi-mode reader (Biotek, Winooski, VT, USA). Moreover, indices of insulin resistance were calculated using fasting plasma insulin and glucose concentrations. The Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) and the Quantitative Insulin Sensitivity Check Index (QUICKI) were computed using the HOMA2 tool. This robust software was developed by the Diabetes Trials Unit at the University of Oxford.

Ethical consideration

The Clinical Research Ethics Committee approved the protocol, and this study adhered strictly to the institutional standards set by the College of Medicine at the University of Al-Qadisiyah. It was conducted in full compliance with scientific and ethical principles at Merjan Medical City and Imam Sadiq Hospital in Babylon Governorate. The parents or guardians of the potential subjects provided informed consent prior to their inclusion in the study.

Statistical analysis

The data collected were rigorously analyzed using MedCalc® (version 20.218) and GraphPad Prism® (version 9.5.1) software. The characteristics of both the exposed and control groups were examined. The analysis included detailed statistics, represented by means and standard deviations. The data were tested for normal distribution using the Kolmogorov–Smirnov test, and if not normally distributed, non-parametric tests were used. Various statistical tests, including Spearman's r, Pearson's correlation coefficient, Chi-square, independent-sample t-tests, and Mann–Whitney U tests, were utilized to draw inferences from the data. A *P* value equal to or below 0.05 was considered statistically significant. Independent-sample t-tests were used for normally distributed data, whereas Mann–Whitney U tests were used for non-normally distributed data. Correlations among continuous variables were evaluated using Spearman's r or Pearson's coefficients. Additionally, a Receiver Operating Characteristic (ROC) curve was used to assess the effectiveness of binary classifiers, providing a deeper understanding of the variable dynamics.

Results

Sample description

The clinical, anthropometric, and laboratory attributes of the children in this study are detailed in in Table 1.

Table 1: Comparative assessment of demographic and biochemical in obese and normal-weight child participants

Variable	Normal weight (*n*=60) Mean (SD or %)/(min.-max.)	Obese (*n*=60) Mean (SD or %)/(min.-max.)	*P*
Gender			
Male (*n*)	30 (50.0%)	30 (50.0%)	>0.9999
Female (*n*)	30 (50.0%)	30 (50.0%)	
Age (years)	11.77±3.12/(7-17)	12.75±3.11/(7-17)	0.085
Anthropometric variables			
Weight, kg	39.15±11.89/(21-78)	81.26±22.95/(33-132)	<0.001***
BMI, kg/m^2	18.06±2.17/(14.5-23)	33.50±4.75/(22.5-44.6)	<0.001***
BMI *Z* score	0.34±0.214/(0.1-0.92)	3.26±0.48/(2.25-4.6)	<0.001***
WC (cm)	65.1±6.33/(50-80)	95.13±13.51/(67-128)	<0.001***
Biochemical parameters			
TC (mg/dL)	124±8.81/(108-142)	164.7±25.06/(118-226)	<0.001***
HDL-C (mg/dL)	66.33±7.56/(42-81)	51.37±8.3/(28-66)	<0.001***
LDL-C (mg/dL)	43.27±10.44/(24.6-72.4)	91.81±25.84/(39.6-150)	<0.001***
TG (mg/dL)	70.95±5.65/(61-84)	104.9±31.7/(62-208)	<0.001***
VLDL (mg/dL)	14.36±1.78/(12.2-24.8)	20.97±6.34/(12.4-41.6)	<0.001***
Glucose Homeostasis Parameters			
FBS (mg/dL)	93.35±8.18/(79-112)	103.6±9.58/(80-122)	<0.001***
Insulin (μIU/mL)	5.58±1.97/(2.82-10.98)	9.87±4.29/(3.18-19.10)	<0.001***
HOMA-IR	0.741±0.25/(0.36-1.45)	1.32±0.56/(0.44-2.56)	<0.001***
QUICKI	1.5±0.52/(0.69-2.7)	0.93±0.47/(0.39-2.2)	<0.001***
Appetite hormone			
Ghrelin (ng/mL)	1.62±0.52/(0.6-2.52)	2.52±0.66/(1.21-3.76)	<0.001***
Leptin (pg/mL)	256.4±48.86/(141-325)	377.8±24.96/(309.1-421.9)	<0.001***
Adiponectin (ng/mL)	2.56±1.24/(0.61-5.28)	1.47±1.02/(0.22-3.95)	<0.001***

SD: Standard deviation; BMI: Body mass index; min: Minimum; max: Maximum; BMI *Z* score: Body mass index standard deviation score; WC: Waist circumference; LDL-C: Low-density lipoprotein-cholesterol; HDL-C: High density lipoprotein-cholesterol; VLDL: Very low-density lipoprotein; TC: Total cholesterol; TG: Triglycerides; FBS: Fasting blood sugar; HOMA-IR: Homoeostasis model assessment for insulin resistance; QUICKI: Quantitative insulin sensitivity check index. Used Independent-sample *t*-tests (parametric variables) and Mann–Whitney *U*-tests (non-parametric variables). The Chi-square test was used for categorical variables. Statistical significance was denoted by *P<0.05, **P<0.01, and ***P<0.001

Participants were classified into two sets, normal-weight and obese, according to metrics like Body Mass Index Standard Deviation Score (BMI/Z-score) and Waist Circumference (WC). The mean age across groups was 11.77 ± 3.12 years for normal-weight children and 12.75 ± 3.11 years for obese children, with no significant age differences within these groups ($P > 0.085$). However, other variables exhibited marked differences when analyzed using the independent sample *t*-test or Mann–Whitney U test. A subsequent, more in-depth analysis highlighted pronounced variances in nearly all variables, where the obese group had higher triglycerides and insulin levels and lower high density lipoprotein cholesterol (HDL-c) and adiponectin levels than the normal weight group ($P < 0.001$). Notably, discovered that leptin levels were considerably lower in normal-weight children ($P < 0.001$), and similar patterns were observed with ghrelin levels, highlighting the significant biochemical variations between the two groups ($P < 0.001$). These findings are graphically illustrated in Figure 1.

Moreover, examined the correlation between adipokines and ghrelin and found meaningful associations in both the normal weight and obese groups, as shown in Table 2. Leptin showed a positive correlation with both BMI/Z-score [r = 0.352, P = 0.006**] and insulin levels [r = 0.320, P = 0.013*], and the same trend was observed with HOMA IR levels [r = 0.314, P = 0.015*] and cholesterol levels [r = 0.262, P = 0.043*]. Similarly, ghrelin showed a positive correlation with insulin levels [r = 0.322, P = 0.012*] levels and HOMA IR [r = 0.319, P = 0.013*]. Contrastingly, a negative correlation was observed with adiponectin and BMI/Z-score [r = -0.311, P = 0.016*]. Similar negative correlations were observed between leptin and QUICKI [r = -0.315, P = 0.014*] and between ghrelin and QUICKI [r = -0.342, P = 0.007*].

Obesity diagnostic accuracy and discriminant capacity of the study variables

The findings from this study, as detailed in Tables 3 and 4, underscore the discriminating capacity of various diagnostic variables in diagnosing childhood obesity. Foremost among these variables is leptin, which demonstrated a remarkable discernment ability for obesity status, as signified by an Area Under the Curve (AUC) value exceeding 99% in Figure 2. Subsequently, the biomarker ghrelin also exhibited

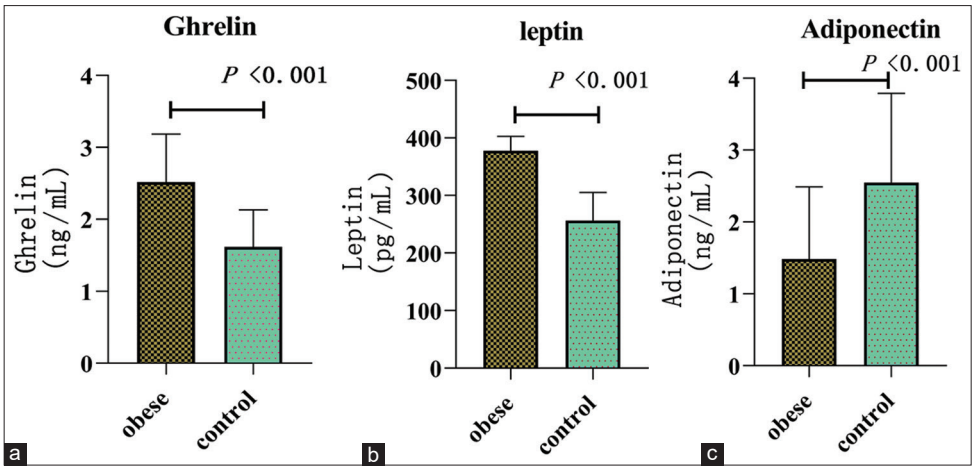

Figure 1: Bar charts (a-c) illustrating ghrelin, leptin, and adiponectin distribution in obese and normal-weight children's Statistical differences are evident between the normal and obese groups

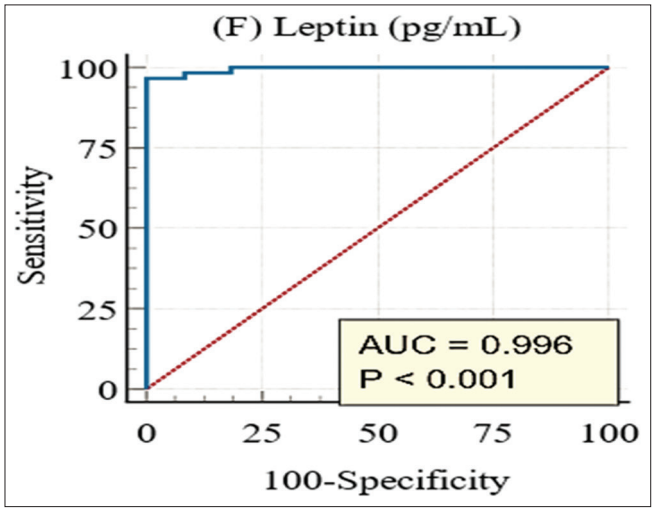

Figure 2: Receiver Operating Characteristic (ROC) curve, the association of leptin with diagnosing obesity

significant diagnostic potential, reflected by an AUC of 85%. Furthermore, the parameters linked to glucose homeostasis, specifically insulin, HOMA IR, and the QUICKI, yielded a promising diagnostic capacity, registering an AUC above 80%. The final diagnostic variable examined, adiponectin, showed a moderate discriminative potential with an AUC of 76%.

Drawing from these observations, a diagnostic model for obesity in children was formulated. The model emphasizes the statistically significant variables while eliminating any variables that might introduce high collinearity *a priori*. This diagnostic model highlighted leptin as a critical predictive factor in diagnosing childhood obesity, a conclusion supported by a ($P = 0.0068$). The model reveals that with each unit increase in leptin levels, the probability of a child being classified as obese increases by a factor of 1.197 (95% Confidence Interval: 1.0507 to 1.3632). Therefore, leptin not only demonstrates a significant diagnostic capability but also appears to have a vital role in the development of childhood obesity, as suggested by its positive correlation with obesity status.

Discussion

Childhood obesity, an alarming and escalating public health challenge, is associated with intricate changes in adipokine levels. The current research evaluates fasting serum levels of leptin, adiponectin, and ghrelin in a wide range of pediatric populations, both with and without obesity. Additionally, the interrelationships among these adipokines, IR, and other markers of metabolic disorders are examined. The identification of obesity-related morbidities necessitates the use of clinical and molecular biomarkers, with particular emphasis on adipokines such as leptin, adiponectin, and ghrelin due to their significant roles in the metabolic consequences of obesity. By comprehending these adipokine levels alongside other clinical markers, a comprehensive metabolic profile can be established, facilitating the development of preventive measures.[22] There are variations in the metabolic phenotypes of obesity, which include atherogenic lipid profiles and IR. Numerous studies investigate the connections between obesity, biochemical markers, and proposed mechanisms of action. This understanding is crucial since not all obese individuals develop the same metabolic complications, and there are variations in the severity and onset of these conditions. Recognizing this heterogeneity can lead to more targeted and effective interventions.[23]

Obesity has a significant impact on lipid metabolism, resulting in increased synthesis and distribution of cholesterol, triglycerides, LDL-C, and VLDL, while inhibiting HDL-C activity. As a complex condition influenced by genetic, behavioral, and environmental

Table 2: The correlation between levels of ghrelin, leptin, and adiponectin and various clinical and metabolic indicators in both obese children and healthy controls

Variable	Ghrelin		Adiponectin		Leptin	
	Obese	Control	Obese	Control	Obese	Control
BMI *Z* score						
r	0.049	-0.148	-0.311	0.014	0.352	0.218
P	0.711	0.258	0.016*	0.915	0.006**	0.086
WC (cm)						
r	0.114	0.134	-0.107	-0.036	0.109	0.385
P	0.384	0.304	0.417	0.784	0.407	0.002
TC (mg/dL)						
r	0.031	-0.013	-0.158	-0.267	0.262	0.044
P	0.815	0.920	0.228	0.039	0.043*	0.733
TG (mg/dL)						
r	-0.166	0.266	-0.122	-0.127	0.176	0.219
P	0.204	0.039*	0.355	0.333	0.178	0.092
HDL-C (mg/dL)						
r	0.089	-0.139	0.088	0.122	-0.032	-0.307
P	0.499	0.297	0.503	0.354	0.807	0.017*
LDL-C (mg/dL)						
r	0.076	0.084	-0.183	-0.341	0.238	0.251
P	0.563	0.521	0.161	0.008	0.067	0.05*
VLDL (mg/dL)						
r	-0.166	0.021	-0.122	-0.106	0.176	0.049
P	0.204	0.871	0.355	0.418	0.178	0.709
FBS (mg/dL)						
r	-0.022	0.196	-0.069	0.076	-0.162	0.183
P	0.870	0.132	0.699	0.560	0.216	0.160
Insulin (μIU/mL)						
r	0.322	-0.010	0.239	-0.029	0.320	0.066
P	0.012*	0.934	0.066	0.826	0.013*	0.612
HOMA-IR						
r	0.319	-0.029	0.230	-0.075	0.314	0.105
P	0.013*	0.824	0.077	0.568	0.015*	0.424
QUICKI						
r	-0.342	0.054	-0.228	0.084	-0.315	-0.165
P	0.007*	0.689	0.079	0.519	0.014*	0.208
Ghrelin (ng/mL)						
r			0.016	-0.127	0.189	0.069
P			0.903	0.332	0.148	0.579
Adiponectin (ng/mL)						
r	0.016	-0.127			-0.014	-0.118
P	0.903	0.332			0.917	0.368
Leptin (pg/mL)						
r	0.189	-0.136	-0.014	-0.118		
P	0.148	0.297	0.917	0.368		

The Pearson or Spearman correlation test was employed to investigate the relationship. *r*=Correlation coefficient. *Significance correlation at *P*<0.05; **Significance correlation at 0.01. BMI *Z* score: Body mass index standard deviation score; WC: Waist circumference; LDL-C: Low-density lipoprotein-cholesterol; HDL-C: High-density lipoprotein-cholesterol; VLDL: Very low-density lipoprotein; TC: Total cholesterol; TG: Triglycerides; FBS: Fasting blood sugar; HOMA-IR: Homoeostasis model assessment for insulin resistance; QUICKI: Quantitative insulin sensitivity check index

factors, obesity triggers metabolic shifts that profoundly affect lipid metabolism.[22] The surplus adipose tissue in obese individuals actively produces hormones and cytokines, which disrupt lipid metabolism and potentially exacerbate the synthesis and distribution of cholesterol, triglycerides, LDL-C, and VLDL, while impairing the production and functionality of HDL-C. This obesity-induced dyslipidemia in children has been documented in numerous studies worldwide, including in Slovenia, Portugal, Iran, Argentina, Egypt, Brazil, Turkey, Italy, and India.[22,24,25] The observations from the current study further corroborate these findings.

Additionally, elevated fasting blood sugar (FBS), insulin, and HOMA-IR levels as well as decreased QUICKI scores in the obesity group are indicators of impaired glucose

Table 3: Determining the Capacity to Discriminate and the Accuracy in Diagnosing Obesity Based on the Study Variables

Variables	Cut-off value	Sens**%	Spec%	PPV**	NPV	Accuracy	AUC%	*P* (AUC=0.05)
Insulin (μIU/mL)	>9.6	51.7	98.4	96.7	67.4	50	80	0.001**
HOMA-IR	>1.15	56.7	95	91.9	68.7	51.7	80.7	0.001**
QUICKI	≤0.81	53.4	98.3	97	67.8	51.7	80.7	0.001**
Ghrelin (ng/mL)	>2.37	61.7	98.3	97.4	72	60	85	0.001**
Adiponectin (ng/mL)	≤1.36	58.3	86.7	81.4	67.5	45	76.2	0.001**
Leptin (pg/mL)	>325.4	96.7	100	100	96.5	96.7	99.6	0.001**

Sens: Sensitivity; Spec: Specificity; PPV: Positive predictive value; NPV: Negative predictive value; AUC: Area under curve; HOMA-IR: Homeostatic model assessment of insulin resistance; QUICKI: Quantitative insulin sensitivity check index; ***Significance at $P \leq 0.001$

Table 4: Childhood obesity and its association with Ghrelin, Adiponectin, and Leptin: Insights from a Logistic Regression Analysis

Variables	*B* (coef)	SE	Odds ratio	95% CI for odds ratio	*P*
Ghrelin	0.708	1.223	2.029	0.1847 to 22.3065	0.5627
Adiponectin	-0.788	0.787	0.455	0.0972 to 2.1274	0.3168
Leptin	0.180	0.067	1.197	1.0507 to 1.3632	0.0068**

B (coef): Regression coefficient; SE: Standard Error; CI: Confidence Interval

metabolism, which is associated with obesity. Numerous researchers have emphasized these associations.[24,26,27] The prevalence of heightened IR in obese children is consistently highlighted in global studies, which supports the observations of this study. In contrast, this study reveals a significant decrease in QUICKI, a measure of insulin sensitivity, among obese children. These findings align with the research conducted by Kelsey *et al*.[28] and indirectly suggest a decrease in insulin sensitivity due to the increased IR reported by Abdelhamed *et al*.[29]

Multiple studies demonstrate elevated leptin levels in obese children, which can be attributed to the expansion of adipose tissue.[30-32] This increase in leptin synthesis is driven by the expansion of adipose tissue, highlighting the significant role of leptin in fat metabolism. However, despite the abundance of leptin, an inadequate brain response, known as leptin resistance, can perpetuate the drive to consume food.[33,34] These dynamics of leptin align with research conducted in various regions, including China and Spain, as well as among diverse populations.[35-38]

However, conflicting with certain studies by Wali *et al*., Tsiroukidou *et al*., and Tahir *et al*. that demonstrate a compensatory decrease in ghrelin when adipose tissue increases, this study reveals increased ghrelin levels in obese children.[15-38,39] This discrepancy suggests that the potential negative feedback mechanism to regulate energy consumption may not be present, as the lower concentration of ghrelin observed in obese children challenges the expected pattern.[40] Instead, these findings align with the studies that show a significant elevation in ghrelin levels among the obese groups. This heightened level of ghrelin could be a response aimed at securing additional energy through increased consumption, indicating that obesity impairs the regulatory mechanisms governing energy management.[41,42]

In contrast, adiponectin levels are notably decreased in obese children, likely due to obesity-induced inflammation.[43,44] This decrease is likely a consequence of the inflammatory environment associated with obesity, which hinders adiponectin production, reduces insulin sensitivity, and increases the likelihood of metabolic complications. The study suggests that being overweight or obese during adolescence can influence the relationship between adiponectin and metabolic syndrome (Met S).[45] The current investigation reveals significant correlations between obesity measures such as BMI/Z-score, IR, insulin sensitivity, and biomarkers, including leptin, ghrelin, and adiponectin, among those diagnosed with obesity. Leptin shows a positive correlation with BMI/Z-score and insulin IR parameters, likely due to its role in energy regulation and the phenomenon of leptin resistance in obesity.[46-48] Ghrelin, also positively correlated with IR, may be upregulated in response to IR as a compensatory mechanism to secure additional energy, although it could potentially lead to reduced insulin sensitivity.[42] On the other hand, adiponectin exhibits a negative correlation with BMI/Z-score, indicating its role in maintaining metabolic health and suggesting a decrease with increasing BMI. This finding is supported by previous studies,[22,46,47,49,50] which further establish adiponectin's insulin sensitivity-enhancing and anti-inflammatory properties. Other factors, such as ethnicity and contemporary lifestyle, may also influence adiponectin levels.[51]

The study identified the significant potential of serum leptin as a diagnostic marker for childhood obesity, demonstrating high sensitivity, specificity, and accuracy. These findings align with the research conducted by Redondo *et al*.[52] Furthermore, Cheng *et al*.[53] emphasized the risk of metabolic syndrome and abdominal obesity in individuals with high leptin levels, despite having a normal BMI. Also, Solorzano *et al*.[36] and Akcan *et al*.[54] supported the role of leptin in obesity diagnosis, indicated

adiponectin as a potential marker.[55] The study also recognized an imbalance in leptin-adiponectin levels as an early indicator of obesity development. A wide range of research supports the role of leptin and adiponectin in obesity diagnosis.[56-58] Practical applications, such as using serum leptin as an adiposity marker in adolescent boys with type 1 diabetes, were also suggested. These findings underscore the complex relationship between these biomarkers and obesity in children, highlighting the necessity for a comprehensive approach to obesity diagnosis and prediction.[52]

This research study aimed to uncover the underlying mechanisms involved in childhood obesity, focusing on the role of leptin, an adipocyte-derived hormone that signals the brain to reduce food intake and increase energy expenditure as fat mass increases. The findings from the logistic regression model demonstrated leptin as a significant predictor of childhood obesity, indicating a crucial link between this hormone and body weight regulation. These findings are consistent with a wealth of research confirming the association between leptin and obesity.[36,54,59] Importantly, these studies provided evidence that leptin could serve as a clinical indicator of adiposity and, therefore, a biomarker for obesity. They also revealed that leptin levels are not only associated with obesity, but also with IR and metabolic impairment,[60] providing further insights into the relationship between leptin and obesity.

Moreover, the interaction between leptin and other adipokines, particularly adiponectin, was found to be of potential interest.[61] However, it is crucial to approach the practical implementation of these findings with caution due to the varying conditions and objectives of different studies. The role of adiponectin in obesity remains uncertain and may be overshadowed by the dynamic relationship between leptin and adiponectin. The leptin-to-adiponectin ratio emerges as a potentially more informative indicator of obesity risk, although further research, especially in pediatric populations, is necessary. The findings of this study hold clinical significance and emphasize the importance of gaining a deeper understanding of adipokines in relation to obesity.[31,62]

Limitations and recommendation

Limitations

- The research robustly utilized both domestic and international studies to validate its results and presented a comprehensive understanding of the roles of various biomarkers in childhood obesity.
- The significant correlations between obesity measures, insulin resistance, insulin sensitivity, and biomarkers were clearly identified.
- The study provides valuable insights into the complex interplay between obesity and adipokines, namely leptin, ghrelin, and adiponectin, and their implications for lipid and glucose metabolism.
- The potential of serum leptin as a diagnostic marker for childhood obesity was demonstrated with high sensitivity, specificity, and accuracy.

Recommendation

- Given the complex interaction between genetic, lifestyle, and environmental factors, the study might not have completely addressed all potential confounding variables.
- The study predominantly relies on BMI for obesity diagnosis, which may not capture the complexity and heterogeneity of obesity adequately.
- While the study provides insight into the roles of leptin, ghrelin, and adiponectin, the interplay between these and other potential adipokines remains complex and underexplored.
- Despite a large number of research references, the generalizability of the study's findings might be limited due to potential geographical, ethnic, and cultural differences.

Future directions

Future research should investigate the multifaceted aspects of pediatric obesity by exploring genetic variations, hormonal interactions, and environmental factors. Studies should aim to develop personalized treatments by understanding genetic influences on metabolism and the dysregulation of adipokines, particularly leptin and adiponectin. Further research is needed to comprehend the influence of diet and physical activity on hormonal dynamics and lipid profiles in children. It is also crucial to identify early markers for metabolic disorders in obese children, and the long-term health implications of these disorders warrant a better understanding. Expanding obesity diagnostic parameters beyond BMI and conducting comprehensive studies that account for confounding factors will provide deeper insights. Additionally, research across diverse geographical, ethnic, and cultural backgrounds will enhance the generalizability of findings. These comprehensive investigations can guide the development of personalized, effective strategies for obesity management and prevention.

Conclusion

The study highlights the crucial roles that leptin, ghrelin, and adiponectin play in the pathophysiology of childhood obesity. Disruptions in hormonal regulation due to obesity are indicated by elevated levels of leptin and ghrelin, and reduced levels of adiponectin. Leptin is especially noteworthy, emerging as a significant predictor

of childhood obesity. This reflects its fundamental role in energy regulation and the occurrence of leptin resistance often seen in obesity cases. Additionally, these adipokines have potential as diagnostic markers for childhood obesity. Leptin, in particular, exhibits high sensitivity, specificity, and accuracy. Finally, understanding the complex interactions among these adipokines is essential in managing obesity. This underlines the need for a comprehensive approach to diagnosing and managing obesity.

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Conflicts of interest

There are no conflicts of interest.

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