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Efficacy Of Leptin And Adiponectin And Their Ratio As Prognostic Factor For Increased Insulin Resistance In Childhood Obesity

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ABSTRACT

Background: *Obesity is a chronic medical condition that is associated with a range of illnesses. Recently, there has been a suggestion that the leptin -to -adiponectin ratio (L/A) could serve as a novel indicator for predicting metabolic disorders and various other chronic illnesses. This study aimed to examine the predictive capacity of leptin and adiponectin hormones, specifically focusing on their ratio, in identifying insulin resistance among obese children. The primary objective of this study is to assess the efficacy of the leptin-to-adiponectin ratio as an early prognostic indicator.*
Materials and methods: *This are a case-control study involving 100 children/adolescents aged 8–16 years old. Anthropometric and biochemical measures were examined, applying World Health Organization (WHO) growth standards to categorize weight status. Blood samples were collected to evaluate glucose, insulin, leptin, and adiponectin levels. Insulin resistance (IR) (homeostasis model assessment of insulin resistance (HOMA-IR) was computed from fasting serum insulin and glucose.* ***Results:*** *Adiponectin, leptin, and the L/A ratio accurately predicted IR among adolescents. Leptin is a significant predictor of HOMA -IR, with a coefficient (β) of 0.273, a 95% confidence interval (CI) of 0.118 to 0.428, and a p-value of 0.0007. The L/A ratio is also a significant predictor, with a coefficient (β) of 0.052, a 95% CI of 0.036 to 0.067, and a p-value of less than 0.0001. The R-squared value of the model is 0.56, indicating that 56% of the variance in HOMA -IR, can be explained by this model.* ***Conclusions:*** *This study provides evidence for the efficacy of leptin and the L/A ratio as potential indicators of prognosis for heightened IR in children with obesity. The findings of this research could have significant implications for the prognosis and treatment of IR in this particular childhood population.*
Keywords: Children, Leptin, Adiponectin, Insulin Resistance, Leptin -To -Adiponectin Ratio, BMI/Z-Score.

Article Information

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INTRODUCTION

Obesity is a chronic disease characterized by abnormal or excessive body fat accumulation, leading to impaired health, increased mortality risks, and chronic health complications [(1)]. It has evolved into a global public health crisis, affecting individuals of various ages and socio-economic backgrounds. Childhood obesity is a particularly pressing concern in low-income countries and the Middle East. The World Health Organization (WHO) has reported a meteoric rise in the number of overweight or obese children, posing significant challenges to health systems and communities worldwide [(2,3)].

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Insulin resistance (IR) is a metabolic disorder that is linked to the increasing rates of childhood obesity. Adiposity in children, regardless of age, ethnicity, and gender, plays a crucial role in the development of IR [4]. Childhood obesity has reached epidemic proportions due to overconsumption of calories, raising concerns about long-term consequences related to IR and other metabolic disorders. IR is characterised by diminished responsiveness of the body's cells to insulin, a hormone essential for glucose uptake and utilisation. When cells that require glucose for energy production become resistant to insulin, the pancreas secretes more insulin to maintain normal blood glucose levels. However, the increasing demand for insulin may surpass its maximal capacity, leading to hyperglycemia and type 2 diabetes, a core element of the metabolic syndrome [5]. The pathophysiological underpinnings of IR encompass both systemic and cellular aspects in various tissues. High-calorie diets and obesity are significant contributors to the development of IR, with excess adipose tissue implicated in the development of IR in adults and critically in children [6,7].

Adipose tissue is considered an endocrine organ that produces various biologically active adipokines, including leptin and adiponectin [8]. These adipokines play crucial roles in regulating insulin sensitivity, glucose and lipid transport, cell differentiation, proliferation, immune cell recruitment, and endothelial function. through autocrine, paracrine, and endocrine actions. Additionally, they have significant control over appetite, fat storage, insulin sensitivity, and inflammation. Leptin, which is produced in relation to adiposity, has been linked to metabolic syndrome in obesity. On the other hand, adiponectin, an insulin-sensitizing hormone synthesized by adipocytes, exerts its effects on various tissues and shows an inverse correlation with adipose tissue mass [9,10]. Considering the opposite trends of leptin and adiponectin concerning body mass index (BMI), the leptin-to-adiponectin ratio (L/A) has been proposed as a more sensitive indicator of metabolic syndrome in children compared to individual serum levels of leptin or adiponectin [10,11]. Thus, our study aims to investigate the predictive potential of the hormones leptin and adiponectin, and more specifically, their ratio, in identifying increased insulin resistance (IR) in children with obesity. Moreover, the research will focus on determining the effectiveness of the L/A ratio as an early predictive tool for IR in obese children.

MATERIALS AND METHODS

Subjects

A case-control study was conducted on a cohort of 100 children/adolescents, aged between 8 to 16 years, in the city of Babylon. This population was stratified into two groups, with 51 subjects identified as obese and the remaining 49 as healthy controls. The research involved carefully selected participants, ensuring only children within the designated age range were included. A thorough evaluation of medical history and self-report allowed for the identification and exclusion of individuals with chronic or acute illnesses. Exclusion criteria excluded individuals with genetic disorders, secondary obesity, and concurrent diseases like diabetes, cardiac conditions, pulmonary ailments, and neurological disorders. Children with acute infections or undergoing medical treatment were excluded, with significant effort made to ensure their exclusion. This study strictly adhered to institutional guidelines established by the College of Medicine at the University of Al-Qadisiyah, and the protocol was sanctioned by the Clinical Research Ethics. It

was conducted in full compliance with scientific and ethical principles at Merjan Medical City in Babylon. Prior to the inclusion of the potential subjects in the study, informed consent was obtained from their parents or guardians.

Anthropometric measurements

The present study employed a standardised anthropometric measurement protocol in order to evaluate a cohort of individuals between the ages of 5 and 19, encompassing children and adolescents. Participants were dressed in minimal clothing and did not wear footwear during the data collection process, which included the collection of height, weight, and waist circumference (WC) measurements. The measurements for weight and height were collected from children who were barefoot and wearing only lightweight clothing. Participants' height was meticulously measured to the nearest millimetre using a portable stadiometer, while their weight was recorded to the nearest 0.1 kg with the use of a standard electronic digital scale. Body Mass Index (BMI) was calculated by dividing weight in kilograms by the square of height in metres (kg/m^2). The BMI/Z-score was determined using the World Health Organization (WHO)'s established methodology, taking into account the participant's age and sex. Participants were categorised into either 'normal' or 'obese' groups based on the World Health Organization's standards for BMI-for-age percentiles and sex-specific BMI-for-age z-scores [(12)].

The weight statuses were categorised as follows: severe thinness was defined as a z-score less than -3; thinness was classified as a z-score between -3 and -2; normal weight was indicated by a z-score between -2 and 1; overweight was denoted by a z-score between greater than 1 and 2; and obesity was labelled as a z-score greater than 2. A systematic approach and adherence to WHO guidelines ensured accurate and comparable data across all participants, providing a solid foundation for understanding the anthropometric characteristics of this paediatric cohort [(13)].

Biochemical measurements

The biochemical measurements of a cohort of children were conducted with meticulous attention to detail, adhering to scientifically validated protocols. A venous blood sample was obtained following an overnight fasting period. Furthermore, each child and their respective family were requested to diligently fill out a standardized questionnaire pertaining to their personal and familial medical background. Blood samples were treated and centrifuged at 1,500 g for 10 minutes, separating serum into aliquots and stored at -40°C for analysis. The aforementioned parameters were ascertained utilising colorimetric techniques on a Fujifilm DRI-CHEM NX600, an automated apparatus employed for chemical analysis. Concurrently, a series of hormonal analyses were conducted in order to ascertain the serum levels of insulin, leptin, and adiponectin. The concentrations were determined utilising the enzyme-linked immunosorbent assay (ELISA) methodology, employing commercially available kits provided by Elabscience (catalogue numbers: E-EL-H 2665, E-EL-H6017, and E-EL-H6122, correspondingly). Furthermore, alongside these fundamental measurements, indices pertaining to insulin resistance were computed by utilising fasting plasma insulin and glucose concentrations. The Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) and Quantitative Insulin Sensitivity Check Index (QUICKI) were determined through the utilisation of specific

formulas. HOMA-IR, as described by [14], involves the multiplication of fasting glucose levels by fasting insulin levels, followed by division by a certain factor. The QUICKI equation is a widely employed method for estimating insulin sensitivity in individuals, as evidenced by its utilisation in studies conducted by [15,16].

$$\text{HOMA} - \text{IR} = \frac{\text{fasting glucose } \left(\frac{\text{mg}}{\text{dL}}\right) \times \text{fasting insulin } \left(\frac{\mu\text{U}}{\text{mL}}\right)}{405}$$

$$\text{QUICKI} = 1 / [\text{Log FPG } (\text{mg/dL}) + \text{Log FPI } (\mu\text{U/mL})]$$

Statistical analysis

The study used GraphPad Prism® software to analyze the data, examining the characteristics of both obese and control groups. The data was normalized using the Kolmogorov-Smirnov test, and non-parametric tests were used for non-normal data. Statistical tests included Spearman's r, Pearson's correlation coefficient, chi-square, independent-sample t-tests, and Mann-Whitney U tests. A p-value of less than 0.05 indicated statistical significance. Independent-sample t-tests were used for normal data, while Mann-Whitney U tests were used for non-normal data. Correlations among continuous variables were evaluated using Spearman's r or Pearson's coefficients. Linear regression was used to provide a more comprehensive understanding of the variable's dynamics.

RESULTS

Sample Description

The clinical, anthropometric, and laboratory characteristics of the children involved in this study have been compiled and are presented in (**Table 1)**. The participants were categorised into two groups based on specific measurements such as Body Mass Index Standard Deviation Score (BMI/SDS Z-score) and Waist Circumference (WC). The study categorized participants into normal weight and obese groups based on weight classification. Normal weight participants had a mean age of 12 years, while obese individuals had a slightly higher average age of 12.9 years. However, the difference in average ages was not statistically significant, with a p-value of 0.11, exceeding the 0.05 threshold. However, Significant disparities were observed in multiple variables when analyzed using the independent-sample t-test or the Mann-Whitney U-test. The study demonstrated that the group classified as obese exhibited significantly elevated levels of insulin, HOMA-IR, and leptin compared to the group classified as normal-weight ($p \leq 0.001$). Conversely, the obese group exhibited notably lower levels of adiponectin and QUICKI ($p \leq 0.001$). The reported mean the L/A ratio for the obese group was 26.71 (SD = 12.70), significantly higher than that in the normal-weight group, which was 11.86 (SD = 6.64). The p-value ($p \leq 0.001$) highlights a statistically significant difference between the L/A ratio in the two groups.

Furthermore, the investigation into the relationship between adipokines and L/A ratio revealed significant associations in both individuals of normal weight and those who are obese, as documented in (**Table 2**). Specifically, Leptin exhibited a positive correlation with both BMI/Z-score [r = 0.332 ($p \leq 0.001$)] and insulin [r = 0.353 ($p \leq 0.001$)] levels. This positive trend was also observed with HOMA IR [r = 0.317 ($p \leq 0.001$)]. The L/A ratio exhibited a significant positive correlation with BMI/Z-score (r = 0.336, $p \leq 0.001$) levels as well as with HOMA IR (r = 0.286, $p \leq 0.001$). In contrast, a significant negative correlation was found between adiponectin levels and BMI/Z-score (r = -0.272, $p \leq 0.001$).

Table 1: Comparative assessment of demographic and biochemical in obese and normal-weight child participants (Anthropometric and metabolic parameters).

Variable	Normal-weight (n = 49) Mean (SD or %)	Obese (n = 51) Mean (SD or %)	*P*
Male (n)	25 (51.02%)	26 (50.98%)	>0.9999
Female (n)	24 (48.98%)	25 (49.02%)	
Age (years)	12.00 (2.6)	12.90 (2.88)	0.11
Weight, kg	40.18 (10.82)	82.54 (22.95)	<0.001
BMI/Z-score	0.36 (0.22)	3.34 (0.46)	<0.001
WC (cm)	65.73 (5.36)	96 (13.66)	<0.001
FBS (mg/dL)	94.41 (8.32)	104.2 (9.24)	<0.001
Insulin (µIU/mL)	5.64 (1.96)	10.26 (4.35)	<0.001
HOMA-IR	1.31 (0.44)	2.65 (1.16)	<0.001
QUICKI	0.39 (0.022)	0.33 (0.025)	<0.001
Leptin (ng/mL)	25.94 (4.91)	38.01 (2.44)	<0.001
Adiponectin (µg/mL)	2.69 (1.19)	1.76 (0.88)	<0.001
leptin-to-adiponectin ratio	11.86 (6.64)	26.71 (12.70)	<0.001

SD: standard deviation; WC: waist circumference; FBS: fasting blood sugar; HOMA-IR: homoeostasis model assessment for insulin resistance; BMI/Z-score: body mass index standard deviation score; 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.

Table 2: The correlation between levels of leptin, Adiponectin, and L/A ratio and various clinical and metabolic indicators in both obese children and healthy controls.

Variable	Leptin		Adiponectin		L/A ratio	
	Obese *r* (*P-value*)	Control *r* (*P-value*)	Obese *r* (*P-value*)	Control *r* (*P-value*)	Obese r (P-value)	Control r (P-value)
Weight, kg	0.152 *	0.109	0.087	0.119	-0.09	-0.05
BMI/Z-score	0.332 **	0.09	-0.272 **	0.07	0.336 **	0.115
WC (cm)	0.191 **	0.124	0.205	0.15	0.08	-0.039
FBS (mg/dL)	0.264 **	0.114	-0.076	-0.065	0.02	0.092
Insulin (µIU/mL)	0.353 **	0.089	-0.232 **	0.008	0.116	-0.039
HOMA-IR	0.317 **	0.097	-0.198 **	0.002	0.286 **	0.013
QUICKI	-0.304 **	-0.074	0.244 **	0.06	-0.121	0.012

Leptin (ng/mL)			**-0.115**	**-0.034**	**0.470 *****	**0.051**
Adiponectin (µg/mL)	**-0.115**	**-0.034**			**-0.808 *****	**-0.774 *****
L/A ratio	**0.470 ****	**0.051**	**-0.808 *****	**-0.774 *****		

The Pearson or Spearman correlation test was employed to investigate the relationship. r = correlation coefficient. *Significance correlation at <0.05; **significance correlation at 0.01. WC: waist circumference; BMI/Z-score: body mass index standard deviation score; FBS: fasting blood sugar; HOMA-IR: homoeostasis model assessment for insulin resistance; QUICKI: quantitative insulin sensitivity check index; L/A ratio: leptin\adiponectin ratio.

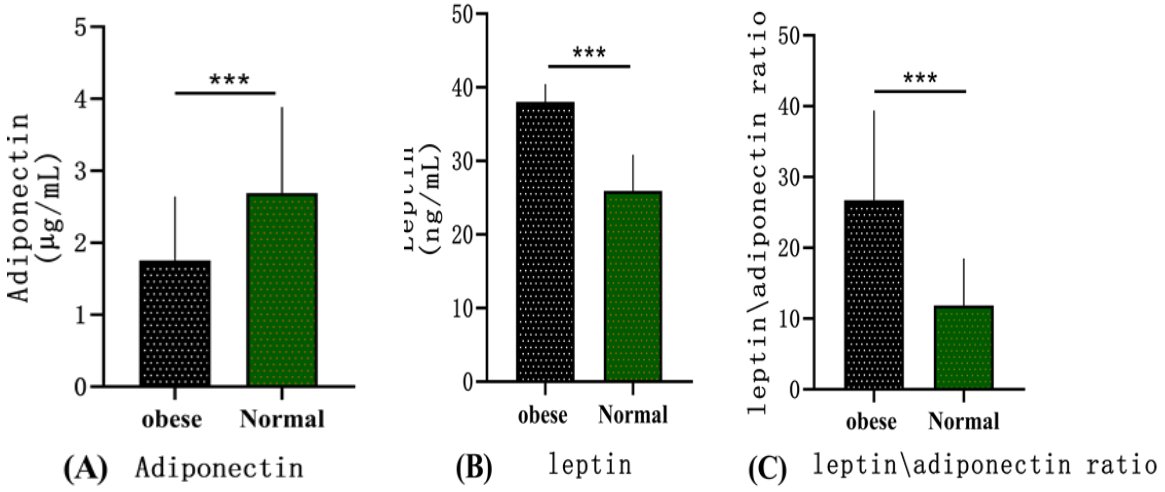

Figure (1): Bar charts show (A) adiponectin, (B) leptin, and (C) leptin-to-adiponectin ratio distributions in obese and normal weight children, showing statistical disparities between groups.

Multiple linear regression analysis examines leptin, adiponectin, and their ratios on HOMA IR.

The multiple linear regression model is utilised to elucidate the association between a set of independent variables (**Table 3**), namely leptin, adiponectin, and L/A ratio, and the dependent variable HOMA -IR. The research conducted revealed a significant association between leptin and HOMA -IR at a significance level of 0.05, with a coefficient (B) of 0.273. The L/A ratio is a significant predictor of HOMA -IR, as indicated by a coefficient (B) of 0.052. In contrast, the impact of adiponectin on HOMA -IR is not statistically significant at the 0.05 level, as indicated by a coefficient (B) of 0.026. The coefficient of determination, denoted by R-squared, is equal to 0.56, suggesting that 56% of the variance in HOMA IR can be accounted for by the predictor variables, namely leptin, adiponectin, and the leptin-adiponectin ratio.

Table 3: Multiple Linear Regression Analysis for the Prediction of HOMA IR from Leptin, Adiponectin, and Leptin/Adiponectin Ratio.

Variables	B (coef)	SE	t- value	*P*. Value	95% CI
adiponectin	**0.026**	**0.015**	**1.77**	**0.08**	**-0.0033 to 0.056**
leptin	**0.273**	**0.078**	**3.51**	**0.0007**	**0.118 to 0.428**
L/A ratio	**0.052**	**0.008**	**6.73**	**0.0001**	**0.036 to 0.067**

HOMA IR as dependent variable R^2 = 0.56; B (coef): Regression Coefficient; SE: Standard Error; CI: Confidence Interval; L/A ratio: leptin-to-adiponectin ratio.

DISCUSSION

Childhood obesity is an escalating global public health concern closely linked to significant changes in adipokine levels, particularly leptin and adiponectin. These changes could potentially serve as crucial biological indicators for assessing the risk of IR, a condition often seen as a precursor to metabolic disorders such as Type 2 diabetes. Recent research efforts have examined fasting serum levels of leptin, adiponectin, and their associated ratio in a wide range of pediatric populations, encompassing both obese and non-obese children [17,18].

An association exists between obesity and compromised glucose metabolism. Elevated FBS, insulin, and the HOMA-IR are indicators of this. In line with this, the obesity groups QUICK evaluations are decreasing. This relationship has been the focus of numerous researchers worldwide [19,20]. Studies conducted globally consistently underscore the prevalence of increased IR in obese children, resembling the findings of this particular study [20,21]. In contrast, our study reveals a significant decrease in QUICKI, an indicator of insulin sensitivity, within the population of obese children. These findings align with previous research [22,23] and indirectly suggest a reduction in insulin sensitivity due to heightened IR [24].

Numerous studies have provided evidence indicating that obese children exhibit heightened levels of leptin and reduced adiponectin, levels, which can be attributed to the enlargement of adipose tissue [25,26]. The increase in leptin production is prompted by an increase in adipose tissue, demonstrating the significant involvement of leptin in fat metabolism. However, despite the abundant presence of leptin, there exists a deficiency in the brain's reaction, commonly referred to as leptin resistance, which can maintain the inclination to engage in food consumption. The observed dynamics of leptin are consistent with findings from studies conducted in different geographical regions, such as China [27] and Spain [28], as well as among diverse populations [29,30]. The drop in adiponectin levels is believed to be a result of the inflammatory milieu linked to obesity, which impedes adiponectin synthesis, decreases insulin sensitivity, and augments the risk of metabolic complications [31,32].

Several studies have investigated an increased leptin/adiponectin (L/A) ratio in children affected by obesity. This increase can primarily be attributed to the expansion of adipose tissue, indicating the crucial role of the L/A ratio in adipose tissue metabolism [11,33,34]. While various investigations have explored the L/A ratio in relation to obesity risk in children, the results remain inconclusive, predominantly due to the small population sizes within these studies. In [35] it was concluded that the L/A ratio was not an effective predictor of insulin sensitivity compared to the combined effect of leptin and adiponectin levels. Contrarily, others studies [34,36,37] have reported that the L/A ratio is a significant predictor of IR. These conflicting findings highlight the need for larger, more comprehensive studies to ascertain the true role of the L/A ratio in pediatric obesity and IR. The present investigation demonstrates a significant association between BMI/Z-score, IR, insulin sensitivity, and biomarkers such as leptin, adiponectin, and the L/A ratio in individuals diagnosed with obesity. There exists a positive correlation between the L/A ratio and both BMI/Z-score and IR[38].

The findings derived from the multiple linear regression analysis conducted in this study indicate potential associations between leptin levels, adiponectin levels, and the L/A ratio with HOMA IR. The results of the study revealed a noteworthy positive association between leptin and HOMA IR, suggesting that elevations in leptin levels are

accompanied by concurrent increases in HOMA IR values. This finding is consistent with prior studies that reported a similar trend in obese adults and children [23,39]. Hyperleptinemia in the context of obesity may reflect a state of leptin resistance, which could be the triggering factor for the subsequent IR.

The significant higher associations between the L/A ratio and HOMA IR is also noteworthy. The L/A ratio, an emerging indicator of metabolic health, was found to be more strongly associated with IR than either leptin or adiponectin alone. This observation suggests that the balance between leptin and adiponectin, rather than the absolute concentration of either hormone, could better reflect the state of insulin sensitivity or resistance. The robust R-squared value of the regression model provides evidence of the model's effectiveness in explaining the variability in HOMA IR, thereby reinforcing the role of leptin and the L/A ratio in the etiology of IR. However, the model does not fully account for the observed variance in HOMA IR, implying the existence of other unidentified factors that may influence IR. The results of this study provide further evidence in line with previous studies [40] indicating that levels of leptin and the L/A ratio may serve as potential biomarkers for IR in children with obesity.

Limitations

The research has some limitations that should be considered. First, it suggests that there are other factors not included in this model that could influence IR, such as dietary and lifestyle factors, genetics, and other biochemical markers. Secondly, this analysis solely focused on examining the correlations between insulin resistance (IR) and adiposity indexes. However, it is important to acknowledge the potential influence of nutrition and physical activity on insulin sensitivity. Additionally, Leptin and adiponectin levels were measured at a single point in time, which may not reflect their chronic levels or fluctuations over time. While it is a commonly used and validated measure for IR, it is not the most precise method. More accurate measures like the hyperinsulinemic-euglycemic clamp could provide more accurate assessments of IR.

Future directions

Future research should investigate unknown factors affecting HOMA-IR, validate leptin and the L/A ratio as biomarkers, and resolve the discrepancy between adiponectin and insulin resistance. This could involve a nuanced examination of adiponectin role, considering confounding variables and different population subsets. Further validation of these biomarkers would provide more clarity. Additionally, there is a growing scholarly focus on examining the complex interplay between the homeostatic regulation of adipokines in children and adolescents who have obesity and the related medical conditions. The next research should focus on discovering children susceptible to severe complications associated with obesity and clarifying the links between adipokines and glucose metabolism.

CONCLUSION

This study provides evidence for the efficacy of leptin and the L/A ratio as potential indicators of prognosis for heightened IR in children with obesity. The findings of this research could have significant implications for the prognosis and treatment of IR in this particular childhood population.

List of abbreviations

HOMA-IR: homoeostasis model assessment for insulin resistance; BMI/Z-score: body mass index standard deviation score; QUICKI: quantitative insulin sensitivity check index; L/A ratio: leptin-to-adiponectin ratio; WHO: World Health Organization; IR: Insulin resistance; FBS: fasting blood sugar.

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