Original Article

# The Role of Leptin and Insulin Resistance in the Onset of Precocious Puberty among Obese Pediatric Patients



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## ABSTRACT

**Objective:** To determine the relationship between insulin resistance, leptin, and CPP in obese children and to clarify their diagnostic role.

**Study Design:** Cross-sectional study

**Place and Duration of Study:** This study was conducted at the Pediatric Endocrinology Outpatient Clinic Iraq from 15th May 2025 to 14th October 2025.

**Methods:** 90 children ages 5–10 years were enrolled. They were divided into three groups of healthy (Group A), obese without puberty (Group B), and obese with central precocious puberty (Group C). Each group consisted of 30 children. Pubertal signs, fasting insulin, homeostatic model assessment for insulin resistance, leptin, and hormonal profile were assessed. Central precocious puberty predictors were determined using logistic regression and receiver operating characteristic curves.

**Results:** The degree of leptin actually escalated: 3.22, 1.8, with the groups (A), 12.4, 4.7 (B), 18.9, 6.3 (C). The same was true of homeostatic model assessment for insulin resistance: (1.5 + 0 7), (4.4 + 1.8), and (5.9±2.3) respectively. luteinizing hormone was very high in group C. Homeostatic model assessment for insulin resistance (r=0.78) and body mass index Z-score (r=0.82) were significantly related to leptin. Leptin 14.2 ng/mL or greater predicted central precocious puberty was definite sensitivity (90 %) and specificity (87%).

**Conclusion:** The evidence confirms the bi-functional location of leptin in the metabolic/reproductive endocrine system, which solidly attaches this molecule to insulin resistance and the emergence of central precocious puberty. Leptin and homeostatic model assessment for insulin resistance as independent predictors were validated using multivariate analysis.


**Key Words:** Leptin, Insulin resistance, Precocious puberty, Body mass index

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## INTRODUCTION

Childhood obesity is rising worldwide and is closely linked to accelerated pubertal development, especially central precocious puberty (CPP) in girls.[1] In obese children, persistently high leptin can produce a leptin-resistant paradox: normal metabolic responses are blunted, yet premature pubertal signals are still switched on. This has turned the interplay between adiposity, hormonal signaling, and reproductive maturation into an important clinical question.[2] The process is multifactorial but is driven mainly by leptin and insulin resistance.

Leptin stimulates the hypothalamic-pituitary-gonadal (HPG) axis through kisspeptin and nitric oxide pathways, while insulin resistance and hyperinsulinemia disturb both metabolic and reproductive signalling.[3] Because raised leptin in obese children often coexists with leptin resistance, it is still unclear whether leptin and insulin resistance are only markers or true independent predictors of CPP.[4] Epidemiological data report wide shifts in the timing of puberty across populations, giving this problem a paradoxical, multi-faceted impact on both short-term child health and long-term adult outcomes.[5,6] The relationship between obesity and precocious puberty is therefore bidirectional and depends on hormone networks that regulate energy balance, growth, and reproduction. Excess adiposity disturbs many of these pathways, most notably through insulin resistance,

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hyperinsulinemia, and the inflammatory state that accompanies obesity and diabetes.[7,8]

Obese children with precocious puberty also carry higher risks of metabolic syndrome, type 2 diabetes, cardiovascular disease, and psychological problems that persist into adult life.[9,10] Leptin seems to be the key metabolic gateway that links obesity to pubertal onset. Its leptin-rich state disrupts normal metabolic control and lets pubertal pathways be triggered early[11], and leptin levels are further influenced by the oxidant–antioxidant balance, which is altered in obesity, insulin resistance, and diabetes.[12,13]

Therefore, this study examined leptin and insulin resistance as major mediators of obesity-related CPP and assessed their diagnostic capacity, aiming to clarify their role in the neuroendocrine control of puberty and to support earlier detection and treatment of vulnerable children.

# METHODS

This was a cross-sectional study was conducted at Pediatric Endocrinology Outpatient Clinic Iraq from 15th May 2025 to 14th October 2025 vide letter No. UoM.Dent. 25/1083 dated 11th May 2025. The sample comprised 90 children aged 5-10 years recruited from community settings and clinic attendees. They were divided into three groups and each group comprised 30 children according to body mass index percentiles and pubertal status:

Group A: Healthy-weight control subjects, BMI 5th to 85th percentile, prepubertal.

Group B: Obese without puberty, BMI ≥95th percentile.

Group C: Obese with central precocious puberty (CPP), BMI ≥95th percentile, before age 8 in girls or 9 in boys.

G Power software was used to calculate the minimum required sample size of 30 participants (n=90 in total) according to medium effect size (Cohen d = 0.5), 80% power and alpha = 0.05.

Comprehensive clinical assessment followed standardized protocols conducted by qualified pediatric endocrinologists. Anthropometry used a Harpenden Stadiometer for height and a SECA electronic scale for weight, with BMI calculated.

After a 12-hour fast, 15–20 mL blood samples were processed within 2 hours and serum was stored at -80°C. Serum leptin (ELISA), fasting insulin (CMIA), and glucose (hexokinase) were measured to calculate HOMA-IR (resistance > 2.5). LC-MS/MS tested reproductive hormones (LH, FSH, estradiol, testosterone). Thyroid (TSH, FT4) and growth axis parameters (IGF-1, IGFBP-3) were also analyzed.

The data was analyzed through SPSS-28. Group comparisons used ANOVA or the Kruskal-Wallis test with suitable post-tests, and Pearson or Spearman coefficients assessed correlations among leptin, insulin resistance parameters, and pubertal markers. Independent predictors of precocious puberty were identified by multivariate logistic regression of biologically plausible and univariate associations ($p<0.20$). ROC curve analysis and the Hosmer-Lemeshow goodness-of-fit test evaluated model performance.

# RESULTS

The three groups were comparable in age and sex, whereas weight and BMI were significantly higher in both obese groups (B and C) than in controls (Table 1). Children of Group C presented a significant increase in LH, FSH, LH/FSH ratio, estradiol (girls) and testosterone (boys) than the rest of the groups. Group C had significantly higher IGF-1 and IGFBP-3 levels than Groups A and B, indicating increased growth factor activity at puberty onset. Group C had highly elevated serum leptin, fasting insulin, and HOMA-IR, indicating severe metabolic dysregulation. Fasting glucose was higher in Groups B and C than in controls, but the smaller effect size points to early, subclinical glycemic changes (Table 2).

Insulin resistance (IR) was highly prevalent in obese children, particularly those with CPP (Group C). Across all HOMA-IR cutoffs, IR was significantly more frequent in Groups B and C than in Group A, with Group C showing the highest odds up to 72-fold above controls (Table 3). Leptin correlated strongly with HOMA-IR, BMI Z-score, LH, and bone age advancement, with the strongest associations seen across the overall cohort (Table 4).

Table 5 illustrates the multivariate logistic regression identified leptin (OR=1.28 per ng/mL), HOMA-IR (OR=1.42 per unit), and advanced bone age (OR=2.94 per year) as significant independent predictors of precocious puberty in obese children. Conversely, BMI Z-score and IGF-1 were non-significant. The robust model demonstrated excellent predictive power (AUC=0.89, Nagelkerke $R^2 = 0.73$).

**Table No. 1: Baseline demographics and anthropometric measurements**

| Variable | Group A (Controls) [n=30] | Group B (Obese, No Puberty) [n=30] | Group C (Obese + CPP) [n=30] |
|---|---|---|---|
| Age (years) | 7.2±1.4(A) | 7.5±1.3* | 7.8±1.2 (A) |
| Sex (Female/Male) | 16/14 (A) | 17/13* | 18/12 (A) |
| Height (cm) | 122.4±8.9 (A) | 125.8±9.2* (A) | 128.6±8.7 (B) |
| Weight (kg) | 23.1±4.2 (A) | 38.7±7.8** (B) | 41.2±8.9** |
| Body mass index (kg/m²) | 15.3±1.8 (A) | 24.2±3.1 (B) | 24.8±3.4** |

*=Non significant, **b=p<0.05 versus Group A, **=p<0.05 versus Group B

**Table No. 2: Metabolic hormones and growth factors and leptin concentrations and insulin resistance parameters**

| Variable | Group A | Group B | Group C |
|---|---|---|---|
| **Reproductive Hormones** | | | |
| LH (IU/L) | 0.18±0.12 | 0.21±0.15 | 2.34±1.87 |
| FSH (IU/L) | 1.42±0.89 | 1.58±0.94 | 4.67±2.13 |
| LH/FSH Ratio | 0.13±0.08 | 0.14±0.09 | 0.52±0.31 |
| Estradiol (pg/mL) - Girls | 8.2±3.1 | 9.4±3.8 | 28.7±12.4 |
| Testosterone (ng/dL) - Boys | 12.4±4.2 | 14.1±5.3 | 89.3±34.7 |
| **Metabolic hormones and growth factors** | | | |
| IGF-1 (ng/mL) | 142.3±28.7 | 168.9 ± 34.2 | 198.4 ± 41.6 |
| IGFBP-3 (μg/mL) | 2.8±0.6 | 3.2 ± 0.7 | 3.9 ± 0.9 |
| IGF-1/IGFBP-3 Ratio | 51.2±8.9 | 53.1 ± 9.4 | 51.8 ± 8.7 |
| TSH (mIU/L) | 2.1±0.8 | 2.3 ± 0.9 | 2.2 ± 0.7 |
| Free T4 (ng/dL) | 1.2±0.2 | 1.1 ± 0.2 | 1.2 ± 0.2 |
| **Leptin concentrations and insulin resistance parameters** | | | |
| Serum Leptin (ng/mL) | 3.2±1.8 | 12.4±4.7[a] | 18.9±6.3[a,b] |
| Fasting Glucose (mg/dL) | 89.4±6.7 | 94.2±8.9[a] | 97.8±9.4[a] |
| Fasting Insulin (μU/mL) | 6.8±2.9 | 18.7±7.2[a] | 24.3±8.9[a,b] |
| HOMA-IR | 1.5±0.7 | 4.4±1.8[a] | 5.9±2.3[a,b] |

**Table No. 3: Insulin resistance prevalence by group**

| HOMA-IR Cutoff | Group A (%) | Group B (%) | Group C (%) | $\chi^2$ p-value | OR (95% CI) B vs A | OR (95% CI) C vs A |
|---|---|---|---|---|---|---|
| ≥2.5 | 4 (13.3%) | 24 (80.0%) | 28 (93.3%) | <0.001 | 25.0 (6.8-92.1) | 72.0 (8.7-595.2) |
| ≥3.0 | 2 (6.7%) | 19 (63.3%) | 26 (86.7%) | <0.001 | 22.8 (4.8-108.3) | 72.0 (13.8-375.8) |
| ≥4.0 | 1 (3.3%) | 12 (40.0%) | 21 (70.0%) | <0.001 | 19.0 (2.3-157.4) | 70.0 (8.4-583.2) |

**Table No. 4: Correlations between leptin, insulin resistance and pubertal parameters**

| Variable Pair | Overall (n=90) | Group A (n=30) | Group B (n=30) | Group C (n=30) |
|---|---|---|---|---|
| Leptin vs HOMA-IR | r = 0.78*** | r = 0.42* | r = 0.61*** | r = 0.54** |
| Leptin vs BMI Z-score | r = 0.82*** | r = 0.38* | r = 0.59*** | r = 0.47** |
| Leptin vs LH | r = 0.69*** | r = 0.21 | r = 0.34 | r = 0.58*** |
| Leptin vs Bone Age Advancement | r = 0.64*** | r = 0.18 | r = 0.41* | r = 0.52** |
| HOMA-IR vs LH | r = 0.58*** | r = 0.19 | r = 0.28 | r = 0.49** |
| HOMA-IR vs Bone age advancement | r = 0.51*** | r = 0.15 | r = 0.33 | r = 0.44* |
| BMI Z-score vs LH | r = 0.71*** | r = 0.23 | r = 0.31 | r = 0.41* |

*p<0.05, **p<0.01, ***p<0.001

**Table No. 5: Logistic regression - predictors of precocious puberty in obese children (Groups B+C)**

| Variable | Univariate OR (95% CI) | Multivariate OR (95% CI) |
|---|---|---|
| Leptin (per ng/mL) | 1.34 (1.18-1.52) | 1.28 (1.09-1.51) |
| HOMA-IR (per unit) | 1.67 (1.28-2.18) | 1.42 (1.05-1.92) |
| BMI Z-score (per unit) | 2.14 (0.89-5.15) | 1.78 (0.68-4.67) |
| Bone Age Advancement (per year) | 3.89 (2.12-7.14) | 2.94 (1.45-5.96) |
| IGF-1 (per 10 ng/mL) | 1.23 (1.08-1.40) | 1.15 (0.98-1.35) |
| Sex (Female vs Male) | 1.85 (0.67-5.12) | - |

Area Under ROC Curve: 0.89 (95% CI: 0.81-0.97); Hosmer-Lemeshow $\chi^2$: 6.34, p = 0.609 (good fit); Nagelkerke $R^2$: 0.73.

**Table No. 6: ROC Analysis for predicting precocious puberty**

| Predictor | AUC (95% CI) | Optimal Cutoff | Sensitivity (%) | Specificity (%) |
|---|---|---|---|---|
| Leptin (ng/mL) | 0.94 (0.88-1.00) | 14.2 | 90.0 | 86.7 |
| HOMA-IR | 0.78 (0.66-0.90) | 4.8 | 73.3 | 76.7 |
| Combined Model | 0.96 (0.92-1.00) | - | 93.3 | 90.0 |

**Table NO> 7: Primary parameter clinical diagnostic levels**

| Parameter | Clinical Cutoff | Sensitivity (%) | Specificity (%) | Clinical Utility |
|---|---|---|---|---|
| Leptin | 14.2 ng/mL | 90 | 87 | Excellent screening tool |
| HOMA-IR | 4.8 | 73 | 77 | Good metabolic marker |
| LH | 1.2 IU/L | 87 | 93 | Excellent pubertal marker |
| Combined Model | Probability > 0.7 | 93 | 90 | Superior diagnostic accuracy |

Serum leptin (AUC=0.94) and HOMA-IR (AUC=0.78) diagnose precocious puberty in obese children. Combining them improves accuracy (AUC=0.96, 93.3% sensitivity, 90.0% specificity), enhancing clinical potential (Table 6).

Leptin, HOMA-IR, and LH each showed clinical usefulness for diagnosing precocious puberty in obese children, and their combined model optimized accuracy (93% sensitivity, 90% specificity) for early clinical application (Table 7).

# DISCUSSION

The current research showed that the values of leptin and HOMA-IR showed progressive rises in the obese children with and without central precocious puberty (CPP). These results are aligned with the already existing evidence indicating that leptin is a metabolic signal and permissive factor of pubertal activation. In agreement with our Group C findings, Badr et al[14] have noted the paradoxical effect of the resistance of leptin on obesity that increased leptin does not regulate appetite but promotes the activation of the hypothalamic–pituitary-gonadal (HPG) axis. On the same note, the reference level of leptin in healthy children as reported by Gajewska et al[15] were very similar to our control group, which confirms our methodology.

We also found that there were significant correlations between leptin and BMI Z-score, which is in accord with previous findings that leptin is a robust surrogate of adiposity.[16] The sex-related differences, where the girls had higher leptin concentrations, are in agreement with the literature in endocrinology studies in paediatrics.[17] Notably, our insulin resistance prevalence (93.3% among obese children with CPP) is in keeping with the international prevalence of 70-90% in obese pediatric cohorts.[18] Therefore, our results validate as well as expand the international literature by presenting data on an Iraqi pediatric sample.

Both leptin and insulin resistance and pubertal markers were strongly linked to the hypothesis that these factors are not mere side effects of obesity, but may also mediate early HPG axis activation. The positive correlations between leptin and LH and bone age advancement reinforce its dual role in metabolic and reproductive pathways. The pathophysiology of leptin and HOMA-IR is intertwined as their relationship was synergistic and represents a vicious cycle between adiposity, hormonal regulation, and maturation.[19]

Diagnostic analysis showed that leptin =14.2 ng/mL displayed a high discriminatory validity to CPP (AUC = 0.94), and a leptin model combined with HOMA-IR showed even better validity (AUC = 0.96). These findings indicate that leptin and insulin resistance can be considered practical biomarkers in early screening particularly in groups where clinical evaluation becomes difficult due to excess adiposity. Also, the CPP child metabolic syndrome clustering (60 percent) underscores that early puberty obesity is not a solitary endocrine occurrence, but a component of a more generalized metabolic risk factor.[20]

The present was conducted on leptin, insulin resistance and precocious puberty in obese children. This minimized bias because of the use of a clearly defined control group and inclusion/exclusion criteria. The standardized Tanner staging, bone age assessment, and radiological verification were used to clinical assessment which guaranteed diagnostic accuracy. Validated assays have been used to conduct laboratory analyses and more sophisticated statistical methods like multivariate logistic regression and ROC curve analysis have been used to enhance the strength of our findings. The use of both sexes permitted the investigation of gender peculiarities of correlations, which enriched the result set.[21]

# CONCLUSION

Leptin and insulin resistance are confirmed as the independent predictors of central precocious puberty among the obese children. A leptin cut-off threshold at least 14.2 ng/mL and HOMA-IR of at least 4.8 were highly diagnostic, and both together provided better predictive validity. These results indicate that metabolic dysfunction is critically important in the premature pubertal activation and justify the incorporation of leptin and insulin resistance index into routine pediatric endocrine evaluation.

**Author's Contribution:**

| | |
|---|---|
| Concept & Design or acquisition of analysis or interpretation of data: | Ghada Abd Arhman Taqa, Abeer Mansour Abdel Rasool |
| Drafting or Revising Critically: | Ghada Abd Arhman Taqa, Zeyad Khalaf Maded |
| Final Approval of version: | All the above authors |
| Agreement to accountable for all aspects of work: | All the above authors |

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