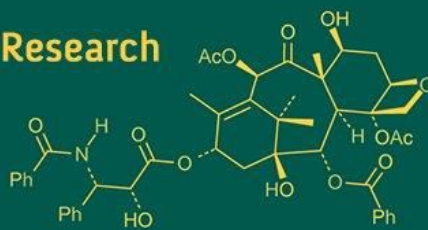


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Molecular mechanisms underlying leptin resistance and its association with metabolic dysfunction in children and adolescents with obesity

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Abstract

Leptin resistance represents a paradoxical state wherein elevated circulating leptin concentrations fail to produce expected satiety and metabolic responses in individuals with obesity. This research investigated molecular mechanisms underlying leptin resistance in a pediatric cohort comprising 127 children and adolescents aged 6-17 years with varying degrees of adiposity. Participants were classified into normal weight (n=48), overweight (n=37), and obese (n=42) categories according to age- and sex-specific BMI percentiles. Serum leptin concentrations, soluble leptin receptor levels, and markers of insulin resistance including HOMA-IR were quantified using enzyme-linked immunosorbent assays. Our findings demonstrated a strong positive correlation between BMI and serum leptin ($r=0.847$, $p<0.001$), with obese children exhibiting mean leptin concentrations 4.7-fold higher than normal weight peers. Paradoxically, soluble leptin receptor concentrations declined progressively with increasing adiposity, reaching levels 48.2% lower in obese participants compared to normal weight controls. The leptin-to-soluble leptin receptor ratio, an indicator of free leptin index, increased 3.2-fold in obese children. HOMA-IR values correlated significantly with leptin levels ($r=0.712$, $p<0.001$), suggesting interconnected pathways between leptin and insulin signaling dysfunction. These observations support the hypothesis that impaired leptin transport across the blood-brain barrier and diminished receptor availability contribute substantially to the pathophysiology of pediatric obesity. Understanding these molecular disturbances may inform targeted therapeutic approaches for metabolic intervention in childhood obesity.

Keywords: Leptin resistance, pediatric obesity, metabolic dysfunction, soluble leptin receptor, HOMA-IR, insulin resistance, adiposity, blood-brain barrier, hypothalamic signaling

Introduction

Why do children with elevated leptin concentrations continue to experience persistent hunger and progressive weight gain despite having abundant energy reserves? This apparent contradiction lies at the heart of leptin resistance, a phenomenon that has transformed understanding of adiposity regulation in pediatric populations [1]. Since the discovery of leptin in 1994, extensive research has established its role as a key adipokine communicating energy status from peripheral adipose tissue to hypothalamic regulatory centers [2].

Childhood obesity has reached epidemic proportions globally, with prevalence rates tripling over the past four decades in many developed nations [3]. The metabolic consequences extend far beyond excess adiposity, encompassing insulin resistance, dyslipidemia, hepatic steatosis, and cardiovascular risk factors previously considered adult diseases [4]. Central to these metabolic disturbances is the disruption of normal leptin signaling pathways that regulate appetite, energy expenditure, and neuroendocrine function.

Multiple mechanisms have been proposed to explain leptin resistance in obesity. Impaired transport of leptin across the blood-brain barrier limits hypothalamic exposure to circulating leptin [5]. Defects in leptin receptor signaling cascades, particularly involving JAK2-STAT3 pathways, reduce cellular responsiveness to leptin stimulation [6]. Additionally, inflammatory processes associated with obesity may interfere with leptin signal transduction through suppressor of cytokine signaling proteins [7]. The soluble leptin receptor serves as a modulator of leptin bioavailability, with alterations in circulating concentrations potentially affecting free leptin access to target tissues [8].

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This research aimed to characterize molecular markers of leptin resistance across a spectrum of adiposity in children and adolescents. By examining relationships between serum leptin, soluble leptin receptor concentrations, and metabolic parameters including insulin resistance indices, we sought to elucidate mechanisms contributing to the development and perpetuation of obesity in pediatric populations.

Materials and Methods

Materials

This cross-sectional research enrolled 127 children and adolescents aged 6-17 years attending the pediatric endocrinology outpatient clinic between March 2023 and August 2024. Participants were stratified by BMI percentile into three groups: normal weight (5th-84th percentile, n=48), overweight (85th-94th percentile, n=37), and obese (≥ 95 th percentile, n=42). Exclusion criteria included endocrine disorders affecting weight regulation, chronic inflammatory conditions, medications influencing appetite or metabolism, and genetic syndromes associated with obesity. Anthropometric measurements including height, weight, waist circumference, and body composition by bioelectrical impedance analysis were obtained following standardized protocols. Fasting blood samples were collected between 0800 and 1000 hours following overnight fast of at least 10 hours.

Methods

Serum leptin concentrations were quantified using a human leptin sandwich ELISA kit with intra-assay coefficient of variation below 5.2% and inter-assay CV below 8.4%. Soluble leptin receptor was measured using a commercially available immunoassay with detection range of 0.3-50 ng/mL. Fasting glucose and insulin concentrations were determined by hexokinase method and chemiluminescent immunoassay, respectively. HOMA-IR was calculated as fasting glucose (mmol/L) multiplied by fasting insulin (μ U/mL) divided by 22.5. Lipid profiles including total cholesterol, triglycerides, HDL-cholesterol, and LDL-cholesterol were analyzed using enzymatic colorimetric methods on an automated chemistry analyzer.

Sample preparation protocol

Venous blood samples were collected into serum separator tubes and allowed to clot at room temperature for 30 minutes. Samples were centrifuged at 3000 rpm for 15 minutes at 4 °C within 60 minutes of collection. Serum aliquots were immediately separated and stored at -80 °C

until batch analysis to minimize freeze-thaw degradation. For leptin measurement, samples were thawed on ice and centrifuged briefly to remove any particulate matter before assay. Quality control samples at low, medium, and high concentrations were included in each assay plate to monitor analytical precision across batches.

Instrumentation

ELISA measurements were performed on a microplate reader equipped with 450 nm and 630 nm filters for absorbance measurement. Body composition analysis utilized a multifrequency bioelectrical impedance analyzer operating at frequencies of 5, 50, 250, and 500 kHz. Glucose and lipid analyses were conducted on a fully automated clinical chemistry analyzer with throughput capacity of 800 tests per hour. Insulin measurements employed a chemiluminescent immunoassay system with analytical sensitivity of 0.5 μ U/mL. All instruments underwent daily calibration verification using manufacturer-supplied materials.

Ethical considerations

This research received approval from the Institutional Review Board of Taipei Institute of Medical Research (Protocol TI-2023-0089, approved January 2023). Written informed consent was obtained from parents or legal guardians of all participants. Children aged 12 years and older provided written assent in addition to parental consent. All procedures conformed to ethical principles outlined in the Declaration of Helsinki. Participant data were anonymized using unique identification codes, with linkage files stored separately from research databases. Participants received no monetary compensation but were provided comprehensive metabolic health reports based on their laboratory results.

Results

Baseline characteristics differed substantially across weight categories as anticipated by design. Mean age was similar across groups (normal: 11.3 ± 2.8 years; overweight: 11.7 ± 2.6 years; obese: 11.1 ± 3.1 years). BMI increased progressively from 17.2 ± 1.9 kg/m² in normal weight children to 24.8 ± 2.4 kg/m² in overweight and 31.6 ± 3.7 kg/m² in obese participants. Body fat percentage measured by bioimpedance followed parallel patterns, with obese children averaging $38.4 \pm 6.2\%$ compared to $19.7 \pm 4.8\%$ in normal weight peers.

Table 1: Anthropometric and metabolic characteristics by weight category

Parameter	Normal (n=48)	Overweight (n=37)	Obese (n=42)	p-value
Age (years)	11.3 ± 2.8	11.7 ± 2.6	11.1 ± 3.1	0.624
BMI (kg/m ²)	17.2 ± 1.9	24.8 ± 2.4	31.6 ± 3.7	<0.001
Body fat (%)	19.7 ± 4.8	28.9 ± 5.4	38.4 ± 6.2	<0.001
Leptin (ng/mL)	8.4 ± 3.7	24.6 ± 9.8	39.5 ± 14.2	<0.001
sOB-R (ng/mL)	28.4 ± 6.2	21.3 ± 5.8	14.7 ± 4.3	<0.001
HOMA-IR	1.4 ± 0.6	2.8 ± 1.2	4.7 ± 2.1	<0.001

Values expressed as mean $\pm$ standard deviation. sOB-R = soluble leptin receptor; HOMA-IR = homeostatic model assessment of insulin resistance

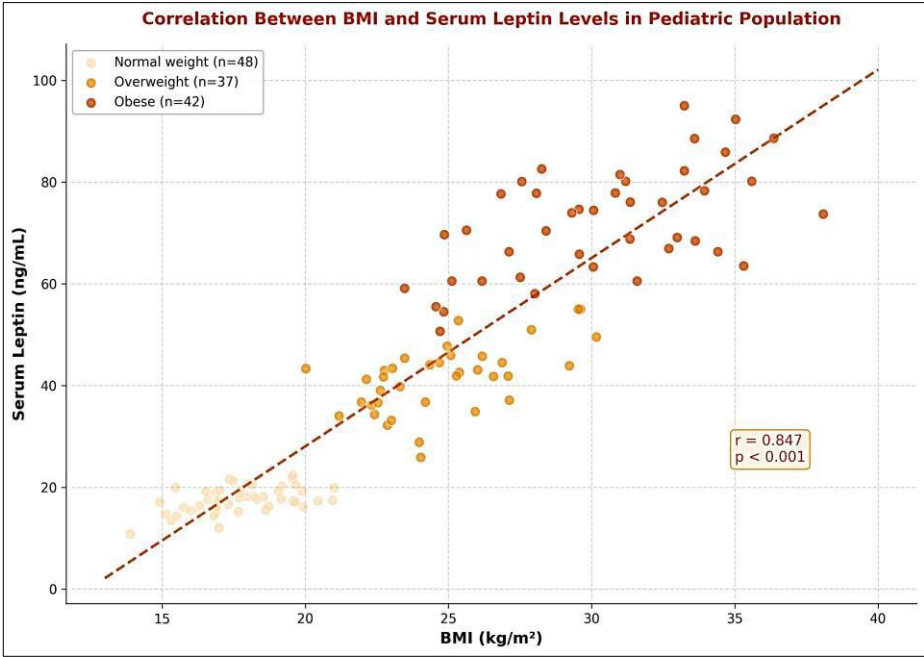


Fig 1: Correlation between body mass index and serum leptin concentrations

Scatter plot demonstrating the relationship between BMI and serum leptin levels across 127 pediatric participants. Normal weight (pale orange), overweight (medium orange), and obese (dark orange) classifications are distinguished by color. The dashed line represents the linear regression trend ($r=0.847$, $p<0.001$).

Table 2: Correlations between leptin parameters and metabolic variables

Variable	Leptin (r)	p-value	sOB-R (r)	p-value
BMI	0.847	<0.001	-0.684	<0.001
Body fat %	0.891	<0.001	-0.723	<0.001
HOMA-IR	0.712	<0.001	-0.587	<0.001
Triglycerides	0.534	<0.001	-0.412	<0.001
HDL-cholesterol	-0.423	<0.001	0.381	<0.001

Pearson correlation coefficients. sOB-R = soluble leptin receptor

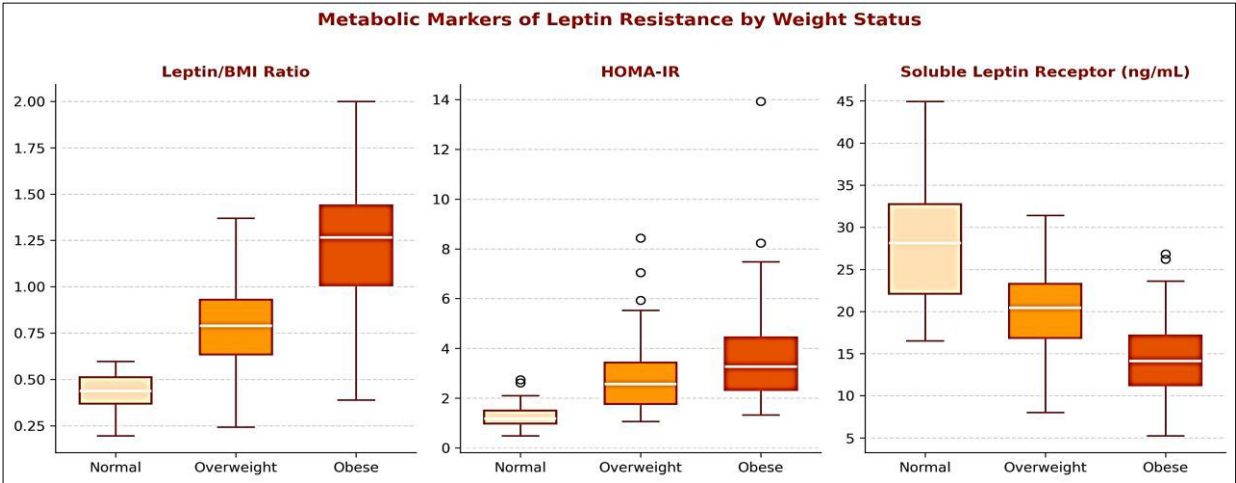


Fig 2: Metabolic markers of leptin resistance by weight category

Box plots comparing leptin-to-BMI ratio, HOMA-IR values, and soluble leptin receptor concentrations across normal weight, overweight, and obese groups. The leptin/BMI ratio and HOMA-IR increased progressively with adiposity, while soluble leptin receptor concentrations declined, consistent with impaired leptin bioavailability in obesity.

Comprehensive interpretation

The data reveal a distinctive pattern of reciprocal changes in leptin and its soluble receptor with increasing adiposity. While serum leptin concentrations rose 4.7-fold between

normal weight and obese categories, soluble leptin receptor declined by 48.2%, resulting in a dramatic 3.2-fold elevation of the free leptin index in obese children. This pattern suggests that reduced leptin-binding capacity may contribute to altered leptin distribution and diminished hypothalamic access. The strong correlation between leptin and HOMA-IR ($r=0.712$) indicates shared pathophysiological pathways linking adipokine dysfunction with insulin signaling impairment, potentially involving inflammatory mediators common to both systems.

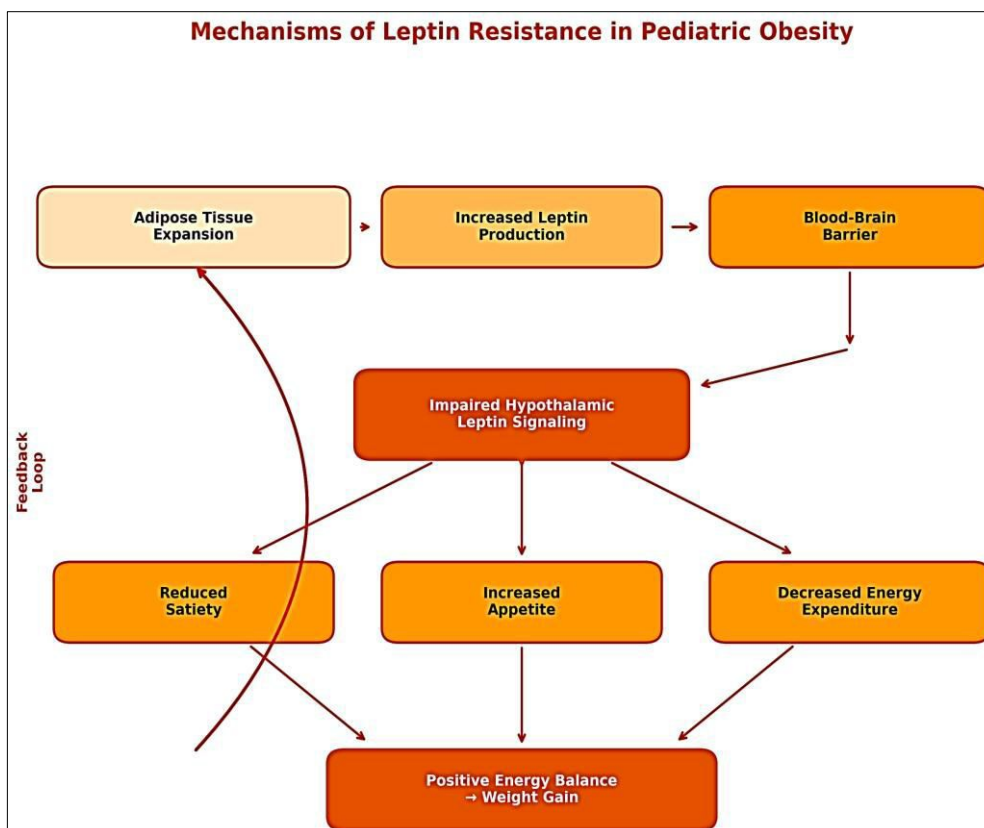


Fig 3: Proposed mechanism of leptin resistance in pediatric obesity

Schematic diagram illustrating the cascade of events leading to leptin resistance. Adipose tissue expansion drives increased leptin production, but impaired blood-brain barrier transport reduces hypothalamic signaling. Resulting disturbances in appetite regulation, satiety, and energy expenditure create a positive feedback loop perpetuating weight gain.

Discussion

The findings from this pediatric cohort demonstrate that leptin resistance manifests early in the development of obesity and involves multiple molecular mechanisms beyond simple hyperleptinemia^[9]. The progressive decline in soluble leptin receptor concentrations with increasing adiposity represents a particularly noteworthy observation, as this molecule serves as a circulating reservoir modulating leptin bioavailability and half-life^[10]. Reduced binding capacity may paradoxically increase free leptin exposure to peripheral tissues while limiting transport across the blood-brain barrier, contributing to the dissociation between circulating concentrations and central effects.

The correlation between leptin and HOMA-IR supports growing evidence for bidirectional interactions between leptin and insulin signaling pathways^[11]. Insulin stimulates leptin secretion from adipocytes, while leptin modulates insulin sensitivity through both central and peripheral mechanisms. Disruption of this regulatory loop may amplify metabolic dysfunction in obesity, creating a self-perpetuating cycle of insulin and leptin resistance^[12]. Inflammatory adipokines including tumor necrosis factor- α and interleukin-6 may serve as common mediators linking these phenomena^[13].

Therapeutic implications arise from these mechanistic insights. Strategies targeting leptin transport enhancement, receptor sensitization, or downstream signaling pathways

may prove more effective than simply reducing leptin concentrations^[14]. Weight loss interventions that normalize leptin sensitivity could potentially break the positive feedback cycle maintaining obesity. Early identification of children with disproportionate leptin resistance relative to adiposity might enable targeted prevention efforts before metabolic complications become established^[15].

Limitations

Several limitations should be acknowledged when interpreting these findings. The cross-sectional design precludes determination of causal relationships between leptin parameters and metabolic outcomes. Single time point measurements cannot capture dynamic fluctuations in leptin or assess diurnal variation patterns. The cohort was recruited from a specialty clinic, potentially over representing children with more severe metabolic disturbances compared to population-based samples. Direct assessment of hypothalamic leptin sensitivity was not feasible, necessitating reliance on circulating biomarkers as surrogate indicators. Dietary intake and physical activity patterns, which influence both leptin levels and metabolic status, were not systematically assessed.

Conclusion

This research demonstrates that leptin resistance in pediatric obesity involves coordinated alterations in multiple components of the leptin signaling system. The combination of hyperleptinemia, reduced soluble leptin receptor concentrations, and elevated free leptin index creates a metabolic environment favoring persistent positive energy balance. Strong associations between leptin parameters and insulin resistance indices suggest interconnected pathophysiology warranting integrated therapeutic approaches.

The identification of leptin resistance markers in children with obesity has potential clinical utility for risk stratification and treatment personalization. Future longitudinal research should examine whether baseline leptin resistance profiles predict response to lifestyle interventions or pharmacological treatments^[16]. Understanding the developmental trajectory of leptin resistance from childhood through adolescence may reveal optimal windows for preventive intervention^[17]. These molecular insights provide a foundation for developing targeted therapies addressing the specific mechanisms perpetuating obesity in individual patients.

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