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Leptin Partially Mediates the Association between Adiposity and Age at Menarche: A Rural–Urban Comparative Study among Indian Adolescent Girls

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ABSTRACT

Background: Pubertal timing is regulated by the hypothalamic–pituitary–gonadal axis and influenced by metabolic signals such as leptin, which links adiposity to reproductive maturation. However, population-based mediation data are limited in nutritionally transitioning regions. This study evaluated whether serum leptin mediates the association between BMI and age at menarche among rural and urban adolescent girls in central India.

Methods: A comparative cross-sectional study was conducted among 220 adolescent girls (110 rural, 110 urban) aged 11–16 years in Indore district, Madhya Pradesh. Anthropometric measurements were obtained using standardized protocols. Fasting serum leptin, FSH, LH, and estradiol levels were measured using immunoassay techniques. Pearson correlation, multivariable linear regression, and mediation analysis were performed to assess relationships among BMI, leptin, and age at menarche.

Results: Urban adolescents had significantly higher BMI and leptin levels than rural girls ($p<0.001$), while age at menarche was lower in the urban group (12.6±0.7 vs 13.9±0.8 years; $p<0.001$). BMI was positively correlated with leptin ($r=0.72$), and leptin was inversely correlated with menarcheal age ($r= –0.67$) (both $p<0.001$). Leptin independently predicted earlier menarche ($\beta = –0.36$, $p < 0.001$) and mediated approximately 54% of the BMI–menarche association.

Conclusion: Leptin partially mediates the relationship between adiposity and pubertal timing in adolescent girls. These findings provide population-level evidence supporting a metabolic–endocrine pathway linking nutritional status to reproductive maturation in a transitioning environment.

Key-words: Nutritional transition; Pubertal timing; Age at menarche; Adolescent health; Body mass index; Dietary fat intake; Leptin; Rural–urban differences; Reproductive hormones; India

INTRODUCTION

The timing of menarche represents a critical milestone in female reproductive maturation and reflects complex neuroendocrine regulation of the hypothalamic–pituitary–gonadal (HPG) axis [1]. Over recent decades, a secular decline in age at menarche has been observed globally, largely attributed to improved nutrition and rising adiposity [2].

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Increasing evidence suggests that metabolic signals derived from adipose tissue play a permissive role in pubertal activation, linking energy availability to reproductive function [3].

Leptin, an adipocyte-derived hormone, has emerged as a key metabolic mediator in pubertal regulation. Circulating leptin levels correlate strongly with body fat mass and signal energy sufficiency to hypothalamic neurons involved in gonadotropin-releasing hormone (GnRH) secretion [3]. Experimental and clinical studies have demonstrated that leptin deficiency results in hypogonadotropic hypogonadism, whereas leptin replacement restores pubertal progression and reproductive function [4]. Furthermore, higher leptin

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concentrations in adolescents have been associated with earlier pubertal onset and menarche [5].

Despite growing mechanistic evidence, population-based studies examining leptin as a mediator of the association between adiposity and menarcheal timing remain limited, particularly in regions undergoing rapid nutritional transition [6,7]. India presents a unique context characterized by coexisting undernutrition in rural settings and increasing obesity in urban populations [8]. Understanding the role of leptin in mediating the adiposity–menarche relationship in such environments may provide critical insights into the metabolic determinants of pubertal timing [9]. This study, therefore, investigates whether serum leptin mediates the association between body mass index and age at menarche in rural and urban adolescent girls.

MATERIALS AND METHODS

Study Design and Setting- A comparative cross-sectional analytical study was conducted in collaboration with the Department of Physiology, Index Medical College, Indore, Madhya Pradesh, India. Data collection was performed in selected rural and urban schools within the Indore district. Laboratory analyses were carried out at the central clinical laboratory of Index Medical College.

Participants- A total of 220 adolescent girls aged 11–16 years were enrolled, including 110 rural and 110 urban participants. Schools were selected using stratified random sampling to ensure representation from both rural and urban settings.

Inclusion Criteria

1. Adolescent girls aged 11–16 years.
2. Attained menarche at the time of study.
3. Enrolled in selected rural and urban schools of Indore district.
4. Permanent residents (≥5 years) of the respective rural or urban area.
5. Written informed consent from parent/guardian and assent from participant obtained.

Exclusion Criteria

1. History of diagnosed endocrine disorders (e.g., thyroid disease, diabetes mellitus, PCOS).
2. Presence of chronic systemic illness or congenital anomalies.
3. Current or recent use of hormonal medications.
4. Acute infection at the time of clinical or biochemical assessment.
5. Incomplete questionnaire, anthropometric, or laboratory data.

Data Collection- Sociodemographic data were obtained using a structured questionnaire. Age at menarche was recorded based on participant recall. Anthropometric measurements were conducted according to standardized WHO protocols. Height was measured with a wall-mounted stadiometer (nearest 0.1 cm) and weight was recorded with a calibrated digital scale (nearest 0.1 kg). Body mass index (BMI) was calculated as weight (kg) divided by height (m^2).

Biochemical Assessment- Fasting venous blood samples (5 mL) were collected between 8:00 and 10:00 AM to minimize diurnal variation. For menstruating participants, sampling was performed during the early follicular phase (days 2–5 of the menstrual cycle). Serum leptin levels were measured using enzyme-linked immunosorbent assay (ELISA), while FSH, LH, and estradiol were analyzed using chemiluminescent immunoassay (CLIA). All assays were performed in duplicate.

Statistical Analysis- Statistical analysis was performed using SPSS version 26.0. Continuous variables are presented as mean±standard deviation. Independent t-tests were used to compare rural and urban groups. Pearson correlation analysis assessed relationships among BMI, leptin, and age at menarche. Mediation analysis was conducted to evaluate leptin as a mediator between BMI and menarcheal age. A two-tailed p-value<0.05 was considered statistically significant.

Ethical Approval- The study protocol was approved by the Institutional Ethics Committee of Index Medical College, Indore. Written informed consent was obtained from parents/guardians, and participants provided assent before enrollment.

RESULTS

A total of 220 adolescent girls (110 rural and 110 urban) were included in the analysis. Baseline demographic and clinical characteristics are presented in Table 1. Mean age did not differ significantly between rural and urban participants (13.6±1.5 vs 13.8±1.4 years; p=0.28).

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However, urban adolescents had significantly higher body mass index (BMI) than rural counterparts (22.4±2.6 vs 18.6±2.1 kg/m²; p<0.001). Serum leptin concentrations were markedly elevated in the urban group (11.8±3.2 ng/mL) relative to rural participants (6.7±2.1 ng/mL; p<0.001) (Table 1). Consistent with these findings, urban girls attained menarche at a significantly younger age than rural adolescents (12.6±0.7 vs 13.9±0.8 years; p<0.001).

Table 1: Participant Characteristics

Variable	Rural (n=110)	Urban (n=110)	p-value
Age (years)	13.6±1.5	13.8±1.4	0.28
BMI (kg/m²)	18.6±2.1	22.4±2.6	<0.001
Leptin (ng/mL)	6.7±2.1	11.8±3.2	<0.001
Age at Menarche (years)	13.9±0.8	12.6±0.7	<0.001

The group differences in mean serum leptin levels are visually illustrated in Fig. 1, demonstrating substantially higher leptin concentrations among urban participants.

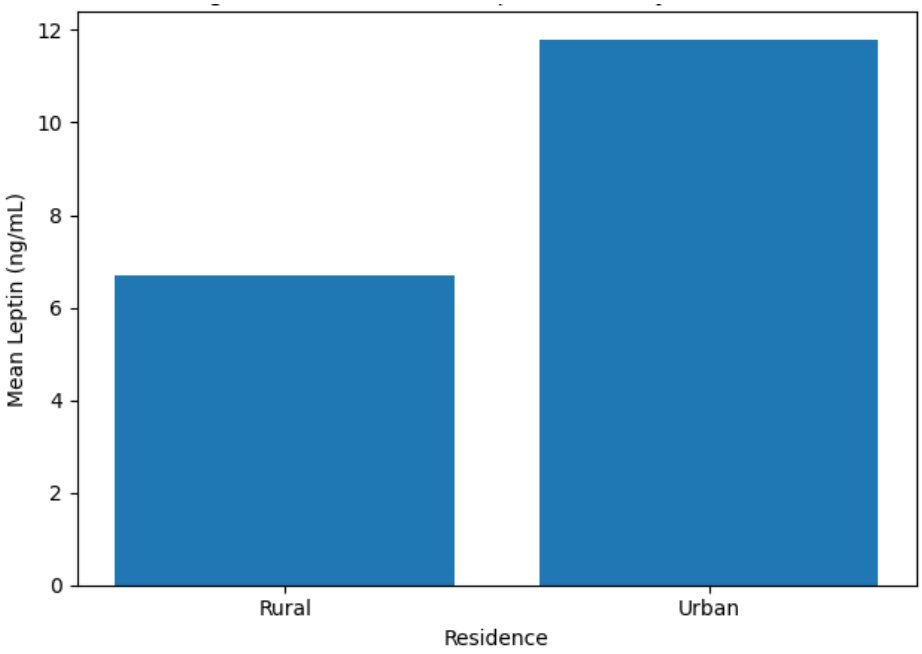

Fig. 1: Mean Serum Leptin Levels by Residence

Pearson correlation analysis revealed significant associations among BMI, leptin, estradiol, and age at menarche. BMI demonstrated a strong positive correlation with serum leptin levels (r=0.72, p<0.001). Leptin levels were inversely correlated with age at menarche (r = –0.67, p < 0.001), indicating that higher leptin concentrations were associated with earlier pubertal onset. BMI also showed a significant inverse correlation with menarcheal age (r = –0.61, p < 0.001). Additionally, leptin levels were positively associated with estradiol concentrations (r=0.64, p<0.001) (Table 2).

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Table 2: Correlation Analysis

Correlation	r-value	p-value
BMI vs Leptin	0.72	<0.001
Leptin vs Age at Menarche	-0.67	<0.001
BMI vs Age at Menarche	-0.61	<0.001
Leptin vs Estradiol	0.64	<0.001

The inverse relationship between BMI and age at menarche is depicted in Fig. 2, which demonstrates a negative linear association between increasing BMI and earlier menarcheal age.

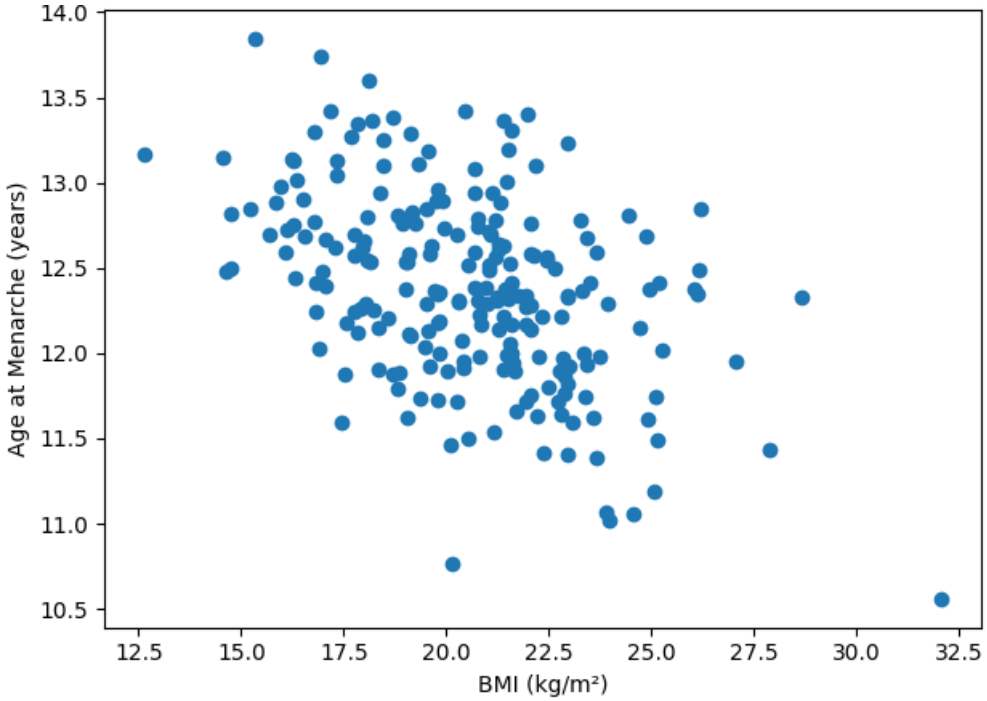

Fig. 2: Association between BMI and Age at Menarche

In multivariable linear regression adjusting for residence, hemoglobin concentration, and socioeconomic status, both BMI (β = –0.28, p<0.001) and leptin (β = –0.36, p<0.001) independently predicted age at menarche. The overall regression model was statistically significant (p<0.001) and explained 61% of the variance in menarcheal age (adjusted R^2=0.59).

Mediation analysis demonstrated that leptin partially mediated the association between BMI and age at menarche. Inclusion of leptin in the regression model attenuated the direct effect of BMI on menarcheal age (β reduced from –0.61 to –0.28). The indirect effect through leptin was statistically significant (Sobel Z=5.74, p<0.001), indicating partial mediation.

DISCUSSION

This study demonstrates that serum leptin partially mediates the association between adiposity and age at menarche in adolescent girls, providing mechanistic evidence linking nutritional status to pubertal timing within a population undergoing nutritional transition. Urban adolescents exhibited significantly higher BMI, leptin, estradiol levels, and earlier menarche compared with rural counterparts, supporting the hypothesis that increased adiposity accelerates reproductive maturation.

The strong positive correlation between BMI and leptin (r=0.72) observed in this study is consistent with the established role of adipose tissue as a major source of circulating leptin [1]. Leptin serves as a metabolic signal of

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energy sufficiency and plays a permissive role in the activation of the hypothalamic–pituitary–gonadal (HPG) axis [1,2]. Experimental and clinical evidence indicate that leptin deficiency leads to hypogonadotropic hypogonadism, whereas leptin replacement restores pubertal development and reproductive function [3]. These findings support the biological plausibility of leptin as a mediator in pubertal regulation.

The inverse association between leptin and age at menarche (r=–0.67) aligns with previous human studies demonstrating that higher leptin concentrations are associated with earlier pubertal onset [4]. Matkovic et al. reported that leptin levels are inversely related to age at menarche in adolescent females, suggesting a threshold effect of adiposity-dependent leptin signaling in triggering pubertal progression [4]. Our mediation analysis extends these observations by quantifying leptin's indirect contribution to the BMI–menarche relationship, accounting for approximately 54% of the total effect.

Estradiol levels were positively associated with leptin, supporting a model in which leptin enhances GnRH pulsatility through hypothalamic pathways involving kisspeptin neurons [2,5]. Kisspeptin signaling is now recognized as a central regulator of GnRH secretion, and disruptions in this pathway lead to pubertal failure [5]. Increased leptin concentrations in the urban cohort may therefore amplify GnRH and gonadotropin secretion, stimulate ovarian steroidogenesis, and advance the timing of menarche.

The observed rural–urban disparity reflects broader patterns of nutritional transition. Secular trends indicate a decline in age at menarche in populations experiencing improved caloric intake and rising adiposity [10]. However, early menarche has been associated with increased lifetime risk of obesity, type 2 diabetes, cardiovascular disease, and hormone-sensitive cancers [11,12]. Thus, while improved energy availability may normalize delayed puberty associated with undernutrition, excessive adiposity may predispose adolescents to adverse long-term metabolic outcomes.

Importantly, BMI retained independent significance after adjusting for leptin, suggesting that additional metabolic mediators, including insulin and insulin-like growth factor-1 (IGF-1), may also contribute to accelerated pubertal maturation [13]. Hyperinsulinemia associated with obesity has been shown to enhance ovarian steroidogenesis and may act synergistically with leptin in modulating pubertal timing [13].

The study's strengths include biochemical hormonal profiling, mediation modeling, and rural–urban comparative design within a uniform geographic region. Limitations include a cross-sectional design and reliance on menarcheal age recall, which preclude causal inference [14]. Longitudinal studies are warranted to confirm temporal relationships and evaluate long-term metabolic consequences [15]. Overall, these findings provide population-level evidence supporting leptin as a biologically relevant mediator linking adiposity to pubertal timing in adolescents exposed to differential nutritional environments [16].

CONCLUSIONS

This study demonstrates that serum leptin partially mediates the relationship between adiposity and age at menarche among adolescent girls. Higher BMI is associated with elevated leptin concentrations, which in turn predict earlier menarche. Urban adolescents, who are characterized by greater adiposity, exhibit earlier reproductive maturation than their rural counterparts. These findings reinforce the metabolic–endocrine model of pubertal regulation and highlight the impact of nutritional transition on adolescent reproductive health. Public health strategies should aim to prevent both chronic undernutrition and excessive adiposity to optimize pubertal timing and reduce long-term metabolic risk.

CONTRIBUTION OF AUTHORS

Research concept- Shikha Jaiswal, Prof. Manila Jain
Research design- Shikha Jaiswal, Prof. Manila Jain
Supervision- Manila Jain
Materials- Shikha Jaiswal, Prof. Manila Jain
Data collection- Shikha Jaiswal, Prof. Manila Jain
Data analysis and interpretation- Prof. Manila Jain
Literature search- Shikha Jaiswal, Prof. Manila Jain
Writing article- Shikha Jaiswal, Prof. Manila Jain
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Article editing- Shikha Jaiswal, Prof. Manila Jain
Final approval- Prof. Manila Jain

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