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# Elevated serum irisin levels in boys with central precocious puberty independent of BMI

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## Abstract

**Introduction:** Central precocious puberty (CPP) is a prevalent endocrine disorder. Research has indicated that pubertal development is linked to nutritional metabolism. Irisin, a novel myokine/adipokine, has been identified as a potential predictor of CPP in girls. This study aims to examine the relationship between serum irisin levels and CPP in boys.

**Material and methods:** An enzyme-linked immunosorbent assay (ELISA) was used to measure serum irisin levels in 32 boys diagnosed with CPP and 33 prepubertal age-matched boys as normal controls (NC). To assess the impact of body mass index (BMI) on irisin levels, both the CPP and NC groups were divided into overweight/obese and normal-weight subgroups. Spearman correlation analysis was employed to assess the connection between irisin and clinical and biochemical parameters. Additionally, a receiver operating characteristic curve was utilised to determine the optimal threshold value for irisin.

**Results:** In the normal-weight subgroups, boys with CPP exhibited elevated irisin levels compared to controls, but not in the overweight/obese subgroups. The optimal cut-off value for irisin levels to predict CPP in the normal-weight groups was 93.09 ng/mL, yielding a sensitivity of 47.6% and a specificity of 100%. Furthermore, a positive correlation was noted between irisin levels and bone age (BA), bone age advancement (BA-CA), and BMI.

**Conclusions:** Serum irisin levels correlate with BMI and pubertal development. Given its limited sensitivity, irisin level can only be utilised as a supplementary rather than a standalone diagnostic indicator for CPP. (*Endokrynol Pol* 2024; 75 (2): 216–221)

**Key words:** *irisin; central precocious puberty; BMI; boys*

## Introduction

Central precocious puberty (CPP) is a condition that is more frequently observed in girls, with a female-to-male ratio ranging from 10–37:1 [1–3]. The incidence and prevalence of CPP have shown a significant increase in recent years, with the annual rate in boys rising by 83.3-fold [4, 5]. Childhood obesity has been identified as a significant contributor to this trend for both genders [6–8]. While the relationship between obesity-related metabolic signals, such as adipokines (leptin and ghrelin) and hormones (insulin), and CPP has been previously explored [9], the mechanisms and mediators linking the observed metabolic changes to pubertal onset remain incompletely understood, particularly with respect to boys. Further research is needed to better understand the complex interplay between obesity and puberty in boys.

Irisin is a recently discovered myokine/adipokine that is encoded by the *FNDC5* gene, and it has been implicated in the regulation of fat and energy metabolism [10, 11].

While primarily secreted from muscle and adipose tissue, irisin is also expressed in organs related to the hypothalamic-pituitary-gonadal (HPG) axis, including the hypothalamus, pituitary gland, pineal gland, testes, ovaries, and uterus [12–17]. Moreover, *Fndc5* transcripts display an increase during distinct postnatal developmental stages in the mouse brain [18], and significant upregulation of *FNDC5* mRNA expression is observed in the hypothalamus from the juvenile to pubertal stages in both sexes of marmoset monkeys [16]. Furthermore, irisin has been shown to stimulate the expression and release of gonadotrophin-releasing hormone (GnRH), gonadotropins, as well as sex hormones, indicating a potential role in the onset of puberty [16, 17, 19–22].

The current paediatric study reports increased irisin levels in 5 obese subjects entering puberty [23]. Furthermore, our prior investigations demonstrated significantly elevated serum irisin levels in girls with CPP compared to healthy prepubertal girls, consistent with an earlier study [24, 25]. However, there is a lack of research on circulating irisin levels in boys

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with CPP. Hence, the current study seeks to examine the alterations in serum irisin levels in boys with CPP and controls to elucidate the potential role of irisin in CPP diagnosis.

## Material and methods

### Ethics

The experiments conducted in this study were approved by the Scientific Ethics Committee of the First Affiliated Hospital of Guangxi Medical University (2023-E309-01) in compliance with the Declaration of Helsinki. Informed consent was obtained from all families involved in this study.

### Study participants

The research was conducted at the First Affiliated Hospital of Guangxi Medical University (Nanning, China) from October 2020 to October 2023. The CPP group included 32 boys diagnosed with idiopathic CPP, while the normal control (NC) group consisted of 33 age-matched prepubertal healthy boys attending routine check-ups during the same period. To evaluate the influence of body mass index (BMI) on irisin levels, both the CPP and NC groups were categorised into overweight/obese and normal-weight subgroups. Criteria for inclusion of idiopathic CPP comprised a testicular volume  $\geq 4$  mL, baseline luteinising hormone (LH)  $\geq 0.3$  IU/L (ICMA), and/or peak level of luteinising hormone (PLH) after GnRH stimulation  $> 5$  IU/L in boys under 9 years old. Subjects with neoplasms, central organic brain disease, organic or endocrine disorders, syndromic diseases, and those receiving pharmacotherapy were excluded from the study [26]. The criteria for overweight/obesity classification were based on a body mass index (BMI) above the 85<sup>th</sup> percentile, while normal-weight boys were defined as those with a BMI between the 3<sup>rd</sup> and 85<sup>th</sup> percentiles [27]. In addition, the exclusion criteria encompassed subjects with obesity resulting from Cushing's syndrome, chronic corticosteroid use, and monogenic obesity syndromes.

### Anthropometric and laboratory measurements

Professional personnel conducted anthropometric measurements by following standardised protocols. Tanner stages were estimated by palpating the testicular volume with a Prader' orchidometer. All boys with CPP underwent pituitary magnetic resonance imaging and bone age assessment. All blood samples were collected in the morning from participants who had undergone an overnight fast. Serum levels of LH, follicle stimulating hormone (FSH), and testosterone (T) were quantified using immunochemiluminometric assays (Mindray, CL-2000i, Shenzhen, China). The GnRH stimulation test was conducted utilising triptorelin (Ferring GmbH) at a dosage of 2.5  $\mu\text{g}/\text{kg}$  (up to 100  $\mu\text{g}$ ), in accordance with established protocols. LH and FSH were assessed for their baseline serum levels prior to the injection, followed by measurements at 30, 60, 90, and 120 minutes post-injection. Serum irisin levels were quantified using a Human Irisin Elisa Kit (CUSABIO, Wuhan, China) with a detection limit of 0.78 ng/mL and intra- and inter-assay coefficients of variation less than 8% and 10%, respectively.

### Statistical analysis

Statistical analysis was conducted using SPSS software (version 23.0, IBM, Armonk, NY, USA). Normality of the data was assessed using the Shapiro-Wilk test, with values greater than 0.05 considered normally distributed. Normally distributed continuous variables were presented as means and standard deviations (SDs), while non-normally distributed variables were expressed as medians and interquartile ranges. Student's t-tests and one-way ANOVA were used to compare normally distributed continuous variables, and the SNK test was employed for between-group comparisons.

Mann-Whitney and Kruskal-Wallis nonparametric tests were utilised for non-normally distributed variables, with post hoc analyses conducted using the Bonferroni correction method. Spearman's correlation was employed to assess the relationship between irisin and other biochemical indicators. P-values  $< 0.05$  were considered statistically significant.

## Results

### Subject characteristics and serum irisin levels in boys

This study encompassed 11 overweight/obese patients with CPP, 21 normal-weight patients with CPP, 11 overweight/obese controls in the NC group, and 22 normal-weight controls in the NC group (mean age:  $10.39 \pm 1.07$  vs.  $10.15 \pm 0.97$  vs.  $9.90 \pm 1.31$  vs.  $9.46 \pm 1.22$  years, respectively;  $p = 0.107$ ). As expected, the CPP group had higher serum basic LH as well as serum FSH, testosterone levels, and testicular volume than the NC group. The NC normal-weight group had the lowest bone age (BA) and bone age advancement (BA-CA) (Tab. 1).

In both the CPP and NC groups, the overweight/obese subgroup exhibited elevated serum irisin levels compared to the normal-weight subgroup. A notable disparity in serum irisin levels was noted between the normal-weight subgroups of the CPP and NC groups, while no significant distinction was observed in the overweight/obese subgroups (Tab. 1, Fig. 1).

### ROC analysis

According to ROC curve analysis, the area under the curve (AUC) for serum irisin levels in distinguishing normal-weight boys with or without CPP was 0.740 (95% CI: 0.588–0.892;  $p = 0.007$ ). An irisin level of 93.09 ng/mL was identified as the optimal threshold, yielding a sensitivity of 47.6% and a specificity of 100% (Fig. 2).

### Correlation analysis

Table 2 was utilised to examine the associations between serum irisin levels and other parameters. Positive correlations were observed between irisin levels and BA, BA-CA, and BMI. No association was observed between irisin levels and chronological age (CA), testicular volume, basic LH, FSH, testosterone, and IGF1.

## Discussion

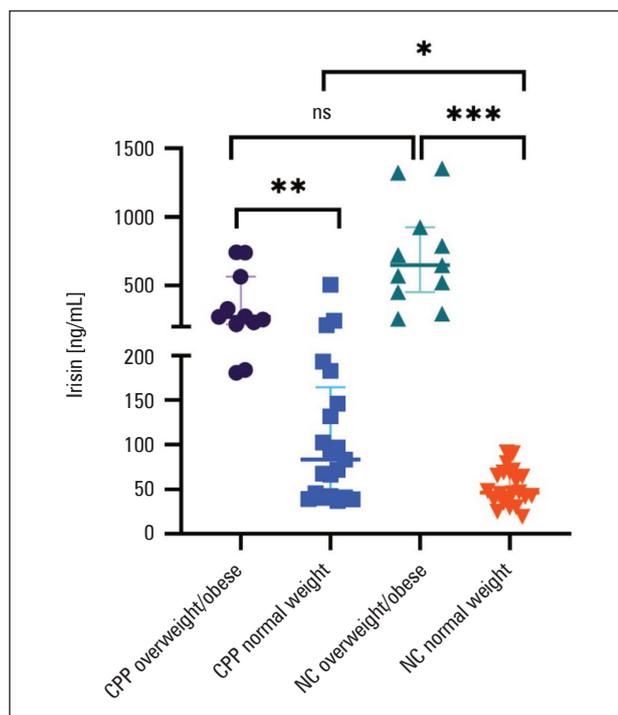
This study represents the inaugural inquiry into the association between irisin and CPP in male subjects. Within the normal weight subcategories, boys affected by CPP exhibited elevated irisin concentrations compared to their counterparts. Additionally, irisin was positively associated with BMI, with higher levels in children with

**Table 1. Clinical and biochemical characteristics of the study groups**

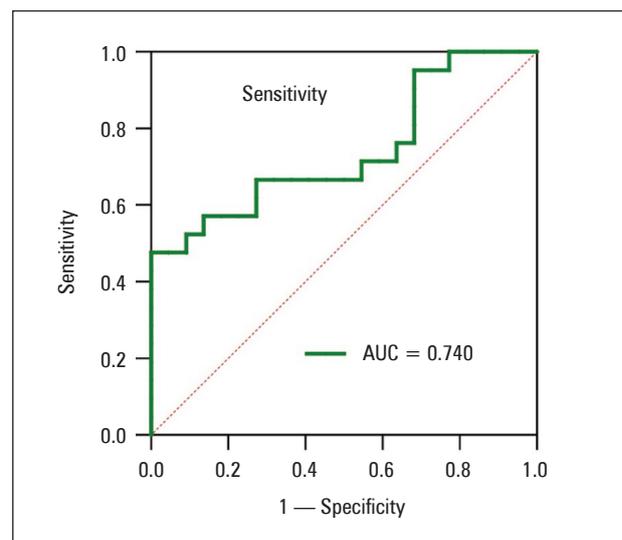
Variables	CPP		NC		p-value
	Overweight/obese (n = 11)	Normal weight (n = 21)	Overweight/obese (n = 11)	Normal weight (n = 22)	
CA (years)	10.39 ± 1.07 <sup>a</sup>	10.15 ± 0.97 <sup>a</sup>	9.90 ± 1.31 <sup>a</sup>	9.46 ± 1.22 <sup>a</sup>	0.107
BA (years)	13.00 [11.00, 13.50] <sup>a</sup>	11.88 [10.25, 12.88] <sup>a</sup>	10.00 [8.38, 12.50] <sup>a</sup>	8.00 [7.00, 9.00] <sup>b</sup>	< 0.001
BA-CA (years)	1.87 ± 1.51 <sup>a</sup>	1.15 ± 1.67 <sup>a</sup>	0.38 ± 1.48 <sup>a</sup>	-1.50 ± 1.18 <sup>b</sup>	< 0.001
Testicular volume [mL]	15.0 [5.50, 17.50] <sup>a</sup>	13.50 [6.25, 15.00] <sup>a</sup>	3.00 [2.50, 3.00] <sup>b</sup>	2.00 [2.00, 3.00] <sup>b</sup>	< 0.001
Testosterone [ng/mL]	1.74 [0.10, 2.51] <sup>a</sup>	1.89 [0.43, 6.18] <sup>a</sup>	0.06 [0.04, 0.19] <sup>b</sup>	0.04 [0.01, 0.07] <sup>b</sup>	< 0.001
B-LH [mIU/mL]	1.98 [1.31, 3.21] <sup>a</sup>	2.54 [1.50, 3.67] <sup>a</sup>	0.19 [0.10, 0.33] <sup>b</sup>	0.19 [0.11, 0.32] <sup>b</sup>	< 0.001
B-FSH [mIU/mL]	3.32 [2.20, 4.10] <sup>a</sup>	2.92 [2.33, 5.42] <sup>a</sup>	1.73 [0.86, 2.99] <sup>b</sup>	1.72 [1.06, 2.80] <sup>b</sup>	0.001
p-LH [mIU/mL]	27.94 [23.42, 54.46] <sup>a</sup>	27.86 [17.42, 34.24] <sup>a</sup>	—	—	0.505
p-FSH [mIU/mL]	7.00 [5.35, 18.36] <sup>a</sup>	7.07 [4.57, 13.17] <sup>a</sup>	—	—	0.721
p-LH/p-FSH	3.90 ± 1.09 <sup>a</sup>	3.85 ± 2.32 <sup>a</sup>	—	—	0.968
IGF-1 [ng/mL]	334.00 [165.00, 369.20] <sup>ab</sup>	295.40 [216.30, 389.10] <sup>a</sup>	153.00 [126.00, 206.00] <sup>bc</sup>	115.00 [91.30, 162.20] <sup>c</sup>	< 0.001
Irisin [ng/mL]	270.83 [218.14, 565.24] <sup>a</sup>	83.42 [41.55, 164.52] <sup>b</sup>	649.57 [451.62, 924.84] <sup>a</sup>	46.17 [36.61, 69.21] <sup>c</sup>	< 0.001

B — base; BA — bone age; BA-CA — bone age advancement; CA — chronological age; CPP — central precocious puberty; FSH — follicle stimulating hormone; IGF-1 — insulin-like growth factor-1; LH — luteinising hormone; NC — normal control; P — peak. Different superscripts lowercase letters significant differences ( $p < 0.05$ ), and the same superscripts lowercase letters no significant differences ( $p \geq 0.05$ )

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**Figure 1. Comparative analysis of serum irisin levels among varied groups.** CPP — central precocious puberty; NC — normal control. \* $p < 0.05$ ; \*\* $p < 0.01$ ; \*\*\* $p < 0.001$ ;  $^{ns}p > 0.05$



**Figure 2. The area under the curve (AUC) for identifying the normal-weight boys with or without central precocious puberty (CPP) was 0.740 [95% confidence interval (CI): 0.588–0.892;  $p = 0.007$ ]. An irisin level of 93.09 ng/mL was found to be the most appropriate, with a sensitivity of 47.6% and specificity of 100%**

obesity. These findings suggest a potential association of irisin with BMI and pubertal development.

Irisin is elevated in obese children and is positively correlated with BMI in our study, which is in line with previous research [28–32]. These higher irisin levels in obese children may indicate a compensatory mechanism to increase subcutaneous brown adipose tissue

**Table 2.** Parameters associated with irisin levels

Variables	n	R-value	p-value
CA [years]	65	0.028	0.825
BA [years]	62	0.362	0.004**
BA-CA [years]	62	0.410	0.001**
BMI [kg/m <sup>2</sup> ]	65	0.834	< 0.001***
Testicular volume [mL]	65	0.184	0.143
Testosterone [ng/mL]	65	0.094	0.458
B-LH [mIU/mL]	65	0.052	0.679
B-FSH [mIU/mL]	65	0.026	0.835
IGF-1 [ng/mL]	60	0.119	0.365

B — base; BA — bone age; BA-CA — bone age advancement; CA — chronological age; FSH — follicle stimulating hormone; IGF-1 — insulin-like growth factor-1; LH — luteinising hormone; P — peak. The correlation coefficient was calculated with Spearman correlation analysis. \*\*p < 0.01; \*\*\*p < 0.001

and energy expenditure, and improve obesity-related insulin resistance [33]. Circulating irisin may serve as a marker of overall body adiposity in children. When assessing irisin concentrations, it is essential to carefully evaluate adiposity indices.

Irisin may play a role in the initiation of puberty. Two prior studies on serum irisin levels in girls with CPP indicated a significant elevation compared to healthy prepubertal girls [24, 25], but did not include obese individuals or boys. To date, only one study has investigated irisin levels in boys, finding no difference after the onset of puberty or during progressing pubertal maturation; however, the comparison between pubertal and prepubertal irisin levels was not conducted [34].

We observed a significant increase in irisin levels concurrent with the onset of puberty in normal-weight boys, providing further evidence supporting the proposed involvement of irisin in pubertal initiation. However, we did not detect elevated serum irisin levels in obese children with central precocious puberty compared to obese prepubertal children. In individuals with obesity or overweight, the increase in irisin levels associated with fat mass might mitigate puberty-related differences. Furthermore, we found that overweight/obese normal controls also exhibited higher BA, BA-CA, and IGF-1 levels, which are believed to be associated with puberty [25, 35]. Therefore, we propose that serum irisin levels could be utilised for the diagnosis of central precocious puberty in individuals of normal body weight. In our study, the ROC operating characteristic curve for identifying normal-weight boys with or without central precocious puberty was 0.740. The optimal cut-off value for irisin concentration was 93.09 ng/mL, with a sensitivity of 47.6% and a specificity of 100%. Due to low sensitivity, serum irisin levels could only serve as a supplementary indicator rather than a standalone diagnostic marker for central precocious puberty.

The mechanism underlying irisin's involvement in puberty remains unclear. It has been proposed that irisin may act as a metabolic trigger, influencing the activation of the HPG axis that governs puberty onset by conveying information about the body's metabolic state and energy reserves [36]. Additionally, irisin has been shown to stimulate the expression and release of GnRH, gonadotropins, and sex hormones [16, 17, 19–22]. This stimulator effect, which appears to operate in a dose-dependent manner, led to increased dominance of the excitatory system in the hypothalamic GnRH pulse generator [21]. Nevertheless, the specific neural targets of central irisin signalling remain unknown.

The present study is subject to several limitations, comprising a small sample size and a cross-sectional design, which restrict the statistical analysis power and generalisability of the findings. Moreover, it does not account for other confounding factors such as body composition. While we established a cut-off value for irisin levels, the sample size was limited; thus, we recommend confirming this discovery through larger-scale studies for greater accuracy.

## Conclusion

In summary, to the best of our knowledge, the present study is the first to comparatively investigate irisin levels in CPP and healthy prepubertal boys. Serum irisin levels correlate with BMI and pubertal development. Given its limited sensitivity, irisin levels can only be utilised as a supplementary rather than a standalone diagnostic indicator for CPP.

## Data availability statement

All data generated or analysed during this study are included in this article. Further inquiries can be directed to the corresponding author.

### Ethics statement

The experiments conducted in this study were approved by the Scientific Ethics Committee of the First Affiliated Hospital of Guangxi Medical University (2023-E309-01) in compliance with the Declaration of Helsinki. Informed consent was obtained from all families involved in this study.

### Author contributions

D.L. designed the study, supervised experimentation, and modified the manuscript. D.Z. completed the experimental part of this study and drafted the manuscript. Y.C., T.X., W.Q., and Q.M. performed the specimen collection. All the authors approved the final version of the manuscript.

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### Conflict of interest

The authors affirm that they have no financial or other potential conflicts of interest.

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