BMC Endocrine Disorders

RESEARCH

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The correlation between insulin-like growth factor 1 and left ventricular mass index in obese children

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Abstract

Objective Low levels of Insulin-like Growth Factor 1 (IGF-1) are known risk factors for cardiovascular diseases. Left Ventricular Mass Index (LVMI) serves as an early predictor of adverse cardiovascular events. Obese children have relatively low concentrations of IGF-1 in their blood. To date, there is no research on whether there is a correlation between IGF-1 levels and LVMI in obese children. This study aims to investigate the potential correlation between IGF-1 and LVMI in obese children at a single center.

Methods A total of 104 obese children were selected as the case group, while 61 healthy children undergoing physical examinations served as the normal control group. Anthropometric measurements, assessments of IGF-1, and cardiovascular metabolic factors were conducted. Echocardiographic examinations were also performed to calculate the LVMI.

Results Compared to the control group, the obese group had significantly higher LVMI and significantly lower standard deviation scores for Insulin-like Growth Factor 1 (IGF-1 SDS). After controlling for confounding factors including total cholesterol (TC), triglycerides (TG), and uric acid (UA), there was a significant linear negative correlation between IGF-1 SDS and LVMI, and a significant linear positive correlation between homeostasis model of assessment for insulin resistance (HOMA-IR) and LVMI. Each unit increase in IGF-1 SDS resulted in a 16.1% decrease in LVMI ($\beta = -0.161$; $p = 0.046$), and each unit increase in HOMA-IR resulted in a 24.1% increase in LVMI ($\beta = 0.241$; $p = 0.007$).

Conclusion IGF-1 and LVMI exhibit an independent negative correlation. Monitoring IGF-1 levels might provide valuable insights into the cardiovascular health of obese children, facilitating early identification and management of cardiovascular risk factors.

Clinical trial number Not applicable.

Keywords Obesity, Insulin-like growth factor, Left ventricular mass index

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Introduction

Obesity is a chronic disease caused by multiple etiologies has reached epidemic proportions globally, with over 1 billion affected individuals across all age groups [1]. In 2022, the global obesity rate for children and adolescents was approximately four times that of 1990, with 159 million affected worldwide [1]. Projections by the World Obesity Federation suggest that by 2025, the number of obese children and adolescents aged 5 to 19 could rise to 206 million, escalating to 254 million by 2030 [2]. Obesity stands as an independent risk factor for cardiovascular diseases, with even small increments in body mass index (BMI) elevating the risk of heart failure by 5% for overweight individuals and 7% for obese individuals [3]. Overweight during childhood increases the risk of persistent obesity and related cardiac metabolic events in adulthood [4]. Research has shown that children with obesity exhibit a notable decline in cardiac diastolic function compared to their healthy counterparts [5], indicating early damage to the cardiovascular system, specifically impaired left ventricular diastolic function [6].

The left ventricle, being the primary pumping chamber of the heart, plays a pivotal role in assessing cardiovascular health. Left Ventricular Mass (LVM) serves as a critical determinant of left ventricular function and a robust predictor of adverse cardiovascular outcomes such as heart failure, stroke, and coronary heart disease [7]. The Left Ventricular Mass Index (LVMI), derived from the ratio of LVM to body surface area, has been identified as an early indicator of cardiovascular events [8], with studies demonstrating that a lower LVMI in obese populations can mitigate the incidence and mortality of cardiovascular diseases [9].

Insulin-like Growth Factor 1 (IGF-1) is a polypeptide structurally similar to proinsulin in humans and is a key regulator of longitudinal growth after birth [10]. Previous studies have confirmed that IGF-1 levels are significantly lower in obese children compared to healthy children [11], and low levels of IGF-1 are independently associated with insulin resistance, the development of non-alcoholic fatty liver disease, low high-density lipoprotein cholesterol (HDL-C), hyperuricemia, metabolic syndrome, and other cardiovascular risk factors [11–14]. However, the correlation between IGF-1 and the early cardiovascular predictor LVMI in obese children remains unexplored. The study aims to investigate the potential relationship between IGF-1 and LVMI in obese children, with the goal of offering insights into diagnostic and therapeutic strategies for obesity-related cardiovascular complications.

Materials and methods

Subjects

The study followed the ethical standards for human medical research stated in the Declaration of Helsinki and was approved by the Ethics Committee of The Second Hospital of Shandong University. All participants and their parents agreed to participate in the study and signed informed consent forms.

Inclusion Criteria of the obese group: Children aged 6–14 who visited the Pediatrics Department of the Second Hospital of Shandong University from July 2021 to November 2022 with a BMI exceeding the 95th percentile for their race, age, and gender [15]. Exclusion Criteria: Children with severe liver or kidney diseases, tumors, diabetes, or other major illnesses; children with combined genetic metabolic disorders or other syndromes; children on special medications (1. Medications affecting insulin sensitivity: Metformin, thiazolidinediones [e.g., rosiglitazone, pioglitazone]0.2. Medications affecting growth: Growth hormone, glucocorticoids[if used long-term]. 3. Medications affecting cardiac function: Beta-blockers, ACE inhibitors, or ARBs. 4. Other medications affecting metabolism: Antipsychotics [e.g., olanzapine, risperidone], antiepileptic drugs [e.g., sodium valproate]); children with a history of passive drinking or smoking; children who had myocardial diseases, anemia, or other conditions that could impair cardiac function; children with short stature, precocious puberty, abnormal thyroid or adrenal axis hormone levels, or other endocrine syndromes affecting blood IGF-1 levels.

A total of 104 obese children (86 males, 18 females, average age 10.52 ± 2.03 years) who meeting the aforementioned criteria were included in the study. Healthy children undergoing physical examinations at the pediatrics department during the same period served as the normal control group, with a total of 61 children (46 males, 15 females, average age 9.79 ± 2.36 years) included.

Methods

Anthropometry examination

During the measurement process, the child wore light clothing, no hat, no shoes, and stood against the measuring ruler with their back, occiput, buttocks, and heels close to the column. Measurements of weight and height were taken in the morning using the same set of equipment. When reading the measurements, the eyes were level with the scale. Height was accurate to 0.1 cm and weight to 0.01 kg. All measurements were conducted by the same doctor To avoid confounding factors such as gender and age, the Body mass index standard deviation score (BMI SDS) and height standard deviation score (Ht SDS) were calculated [15, 16].

Determine developmental staging based on Tanner criteria [17]. The standard for boys before puberty is: no

pubic hair and testicular volume ≤ 4 ml; The standard for girls before puberty is no pubic hair and no breast development. These assessments were conducted by the same pediatric endocrinologist during physical examinations.

Laboratory examination

All participants fasted for at least 8 h, following which venous blood samples were collected the next day for testing. IGF-1 and other metabolic parameters were measured. Fasting blood glucose (FBG), fasting insulin, alanine aminotransferase (ALT), uric acid (UA), total cholesterol (TC), low density lipoprotein-cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C,) and triglycerides (TG) were examined by an Olympus AU5400 automated biochemistry analyzer (Olympus Corporation, Tokyo, Japan). Serum IGF-1 was tested using Siemens' IMMULITE 2000 XPi fully automatic immunoassay analyzer and matching reagent kits. Fasting insulin was determined using Roche's fully automatic biochemistry Cobas8000 c702 analyzer and matching reagent kits. The Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) was calculated as fasting insulin (uIU/ml) × fasting blood glucose (mmol/l) / 22.5 [18]. To standardize IGF-1 levels across different ages and genders, IGF-1 was converted into. IGF-1 standard deviation score (IGF-1 SDS) [19]. 110 obese children underwent an evaluation of their metabolic health status. Among them, 38 obese children with fasting blood glucose levels greater than 5.6 mmol/L underwent the oral glucose tolerance test (OGTT) to exclude type 2 diabetes, and 6 children diagnosed with type 2 diabetes were excluded from the primary analysis.

Table 1 Characteristics of clinical and laboratory data in the study population

Variable	obese group (Mean ± SD)	control group (Mean ± SD)	*p*
	(*n* = 104)	(*n* = 61)	
age	10.52 ± 2.04	9.79 ± 2.36	0.073
male/female	86/18	46/15	0.491▲
BA	11.88 ± 2.49	9.35 ± 2.03	< 0.001*
IGF-1 SDS	-0.92 ± 1.57	0.40 ± 1.11	< 0.001*
BMI SDS	1.99 ± 0.67	0.05 ± 0.83	< 0.001*
Ht SDS	0.99 ± 1.3	0.15 ± 0.97	< 0.001*
HOMA-IR	6.25 ± 4.29	1.70 ± 0.39	< 0.001*
TC (mmol/L)	4.58 ± 0.90	3.91 ± 0.59	< 0.001*
HDL-C (mmol/L)	1.24 ± 0.26	1.57 ± 0.26	< 0.001*
LDL-C (mmol/L	2.72 ± 0.76	1.91 ± 0.45	< 0.001*
UA(μmol/L)	382.88 ± 100.99	293.57 ± 55.26	< 0.001*
ALT(U/L)	62.63 ± 40.35	16.87 ± 7.49	< 0.001*
LVMI(g/m$^{2.7}$)	63.37 ± 12.62	54.15 ± 13.87	< 0.001*
TG (mmol/L)	1.51 ± 1.23	0.80 ± 0.28	< 0.001*

▲Chi-square test or Mann-Whitney U test * p<0.05

Cardiac echocardiography measurement

Cardiac echocardiography measurements were conducted by the Department of Ultrasound Diagnosis using the GE Vivid E9 color Doppler ultrasound diagnostic instrument with an M5S ultrasound probe (frequency 1.7–3.3 MHz). All image acquisition and data recording were performed by the same ultrasound doctor, with measurements taken for left ventricular end-diastolic dimension (LVEDD), left ventricular posterior wall thickness (LVPWT), and interventricular septal thickness (IVST). Images were captured over at least three consecutive cardiac cycles, with measurements taken three times for each examined child and averaged. LVMI was indexed to body surface area (BSA). LVMI was calculated as $0.80 \times (1.04 \times ((\text{LVEDD} + \text{IVST} + \text{LVPWT})\text{^}3 - \text{LVEDD}\text{^}3)) + 0.60 / \text{BSA}$ [20, 21].

Statistical methods

Data analysis was performed using SPSS 26.0 statistical software. Continuous variables with a normal distribution were expressed as mean ± standard deviation ($\bar{x} \pm s$), while non-normally distributed continuous variables were expressed as median (interquartile range) [M(Q)]. Categorical variables were indicated by the number of cases (n), with comparisons between categorical variables made using the chi-square test. Group comparisons were conducted using either independent samples t-test or Mann-Whitney U test based on the distribution of the sample. Pearson or Spearman correlation analysis was used to assess the relationship between metabolic indicators and LVMI. Multiple linear regression analysis, adjusted for confounding factors, was employed to examine the correlation between IGF-1 SDS and LVMI. To address collinearity, HOMA-IR was used as a representation for FBG and insulin in the multiple linear regression analysis. Results were considered statistically significant at $p < 0.05$.

Results

Clinical and laboratory characteristics of the study subjects

Table 1 displays the detailed clinical and laboratory characteristics of the study participants. The average age of the healthy children in the control group was 9.79 ± 2.36 years, while the average age of the obese group was 10.52 ± 2.04 years. In the control group, out of 61 children, 46 (75.4%) were male, with 33 prepubertal children, accounting for 54.1%. In the obese group, out of 104 children, 86 (82.7%) were male, including 62 prepubertal children, accounting for 59.6%. There were no significant statistical differences in sexual development stage, gender, or age between the two groups ($p > 0.05$). There were statistical differences in the measured indicators (Ht SDS, BMI SDS, LVMI, IGF-1 SDS, HDL-C, LDL-C, HOMA-IR, UA, TC, TG, ALT) between the two groups

($p < 0.05$). The obese group exhibited significantly higher BMI SDS, HOMA-IR, UA, TC, TG, ALT ($p < 0.001$), and significantly lower HDL-C ($p < 0.001$), indicating abnormalities in liver enzymes and glucose and lipid metabolism in obese children. While the obese group exhibited significantly higher Ht SDS compared to the control group ($p < 0.001$), the bone age (BA) in the obese group was also significantly advanced when compared to the control group ($p < 0.001$). Furthermore, the IGF-1 anomaly was noted in the obese group, with IGF-1 SDS significantly lower than in the control group ($p < 0.001$) (Fig. 1), and LVMI significantly higher than in the control group ($p < 0.001$) (Fig. 2).

Correlation analysis of LVMI and other indicators

Table 2 presents the results of the two-variable correlation analysis. IGF-1 SDS (r = -0.211, $p < 0.05$) and HDL-C (r = -0.168, $p < 0.05$) exhibited significant negative correlations with LVMI levels. Conversely, BMI SDS ($r = 0.25$, $p < 0.001$), HOMA-IR ($r = 0.27$, $p < 0.001$), LDL-C ($r = 0.172$, $p < 0.05$), and ALT ($r = 0.155$, $p < 0.05$) showed significant positive correlations with LVMI levels. No significant correlations were found between TC, TG, UA, and LVMI ($p > 0.05$).

Linear correlation analysis of IGF-1 SDS and LVMI in obese children

In the multiple linear regression analysis, after controlling for confounding factors including TC, TG, and UA, a significant linear negative correlation between IGF-1 SDS and LVMI was observed (Fig. 3), along with a significant linear positive correlation between HOMA-IR and LVMI. Specifically, for every 1 unit increase in IGF-1 SDS, LVMI decreased by 16.1% (β = -0.161; $p < 0.05$), while for every 1 unit increase in HOMA-IR, LVMI increased by 24.1% (β = 0.241; $p < 0.05$) (Table 3).

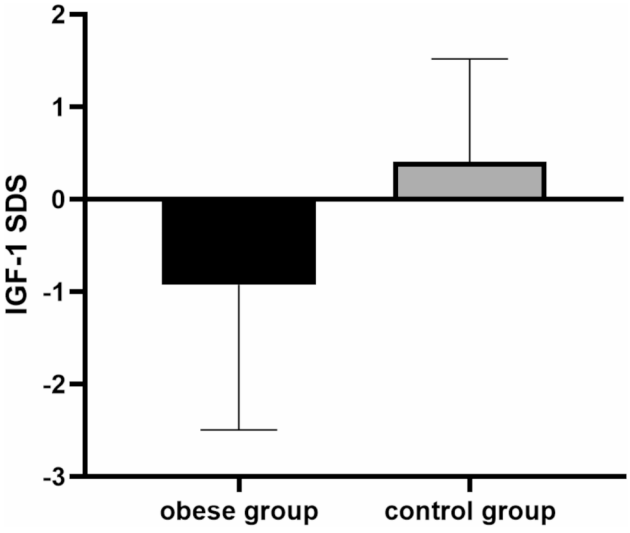

Fig. 1 Comparison of IGF-1 SDS in the study population

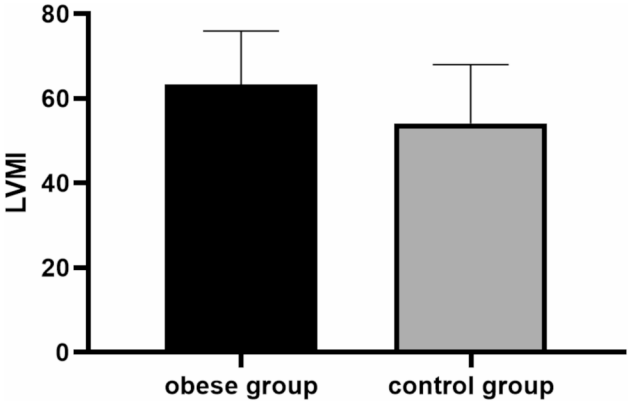

Fig. 2 Comparison of LVMI in the study population

Table 2 Correlation analysis of LVMI and laboratory-related indicators

Variable	*r*	*p*
BMI SDS	0.25	< 0.001*
IGF-1 SDS	-0.211	0.007*
HOMA-IR	0.27	< 0.001*
TC (mmol/L)	0.147	0.060
HDL-C (mmol/L)	-0.168	0.031*
LDL-C (mmol/L)	0.172	0.027*
TG (mmol/L)	0.069	0.376
UA(μmol/L)	0.145	0.062
ALT(U/L)	0.155	0.047*

* $p<0.05$

Discussion

Left ventricular hypertrophy (LVH) serves as an independent predictor of cardiovascular disease incidence and mortality [22], with the Left Ventricular Mass Index (LVMI) playing a crucial role in determining left ventricular function and serving as an early predictor of adverse cardiovascular events [23]. The presence of excess weight is a significant factor contributing to LVH development in children and adolescents [24], with hemodynamic and metabolic factors potentially leading to an increase in LVMI [25]. Obesity and its associated complications, including abnormal lipid profiles, hypertension, and Type 2 Diabetes, can result in increased left ventricular mass (LVM), subsequently leading to ventricular remodeling and impaired cardiac function as an adaptation to chronic inflammation [26]. Sarmiento-Cobos et al. [27] have demonstrated that weight loss surgery can induce positive changes in the left ventricle's geometric structure, thereby promoting left ventricular remodeling. Rapid weight loss has been shown to reduce LVMI, consequently enhancing left ventricular contractility, overall cardiac dynamics, and function. This study revealed a significant elevation in LVMI among obese

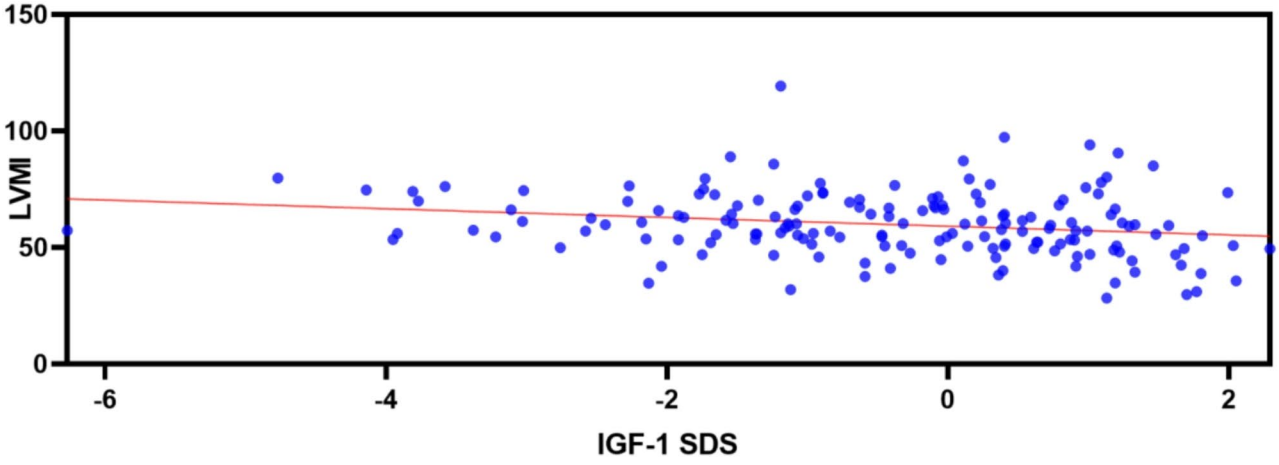

Fig. 3 Linear correlation analysis between IGF-1 SDS and LVMI

Table 3 Linear correlation analysis of relevant indicators with LVMI

Variable	β 95% CI	*p*
IGF-1 SDS	-0.161 (-2.838,-0.029)	0.046*
HOMA-IR	0.241 (0.229,1.401)	0.007*

* $p<0.05$

children compared to their healthy counterparts, indicating impaired cardiac function in obese children, consistent with previous research [28]. It is recommended that close attention be paid to the cardiac function of obese children during childhood, with LVMI serving as a vital indicator for monitoring purposes.

In this study, the obese group exhibited an earlier maturation of BA compared to the control group, with Ht SDS also significantly higher than in the control group, suggesting that obesity poses a risk factor for advanced BA development [23]. Dandan Ke et al. [29]. also found that obesity can lead to advanced bone age and accelerated height growth in the early stages, although the acceleration of bone age tends to decelerate in late adolescence, The results of our study, in line with previous research, suggest a potential link between obesity and advanced bone age development.

For obese individuals, surplus adipose tissue could directly release inflammatory cytokines and atherosclerotic molecules, prompting the liver to increase endogenous fatty acid production and lipid absorption. This process leads to elevated production of very low-density lipoprotein particles, alongside reductions in high-density lipoprotein cholesterol and low-density lipoprotein particles [30]. Accumulation of lipids in the pancreas affects its response to heightened blood sugar levels, diminishing insulin secretion and fostering insulin resistance (IR), thereby amplifying the risk of heart disease [31]. Iacobellis et al. have revealed that impaired insulin sensitivity is linked to an increase in left ventricular mass in individuals with simple obesity [32]. This finding is consistent with the results of this study, which observed a significant decrease in HOMA-IR among obese children, with HOMA-IR being independently positively correlated with LVMI.

This study is the first to investigate the association between IGF-1 SDS and LVMI in a Chinese population of obese children. Although bivariate correlation analysis revealed a weak negative correlation between IGF-1 SDS and LVMI (r = -0.211, $p<0.05$), multivariate linear regression further confirmed an independent negative correlation between IGF-1 SDS and LVMI after adjusting for age, sex, BMI, and multiple metabolic indicators (β = -0.161, 95% CI: -2.838 to -0.029, $p=0.046$). These findings suggest that for every 1-unit increase in IGF-1 SDS, LVMI may decrease by 16.1%. The negative correlation between IGF-1 SDS and LVMI remained statistically significant after controlling for confounding factors, indicating that IGF-1 may play an independent role in left ventricular remodeling in obese children. However, it is important to note that while the results of this study support a statistical association between IGF-1 SDS and LVMI, we do not propose that IGF-1 SDS should be considered a definitive determinant of LVMI. Instead, IGF-1 SDS should be regarded as a potential biomarker, with its dynamic changes potentially linked to variations in LVMI. Nevertheless, it is not the sole or decisive factor in explaining LVMI variability.

Previous research has provided diverse perspectives on the relationship between IGF-1 and LVMI. Gómez-Guzmán E et al. [33]. observed that both IGF-1 and LVMI levels were low in patients with growth hormone deficiency (GHD), and after one year of growth hormone treatment, an increase in IGF-1 levels was accompanied by an improvement in LVMI. This finding highlights the close correlation between IGF-1 and LVMI in the context of GHD. However, not all studies have reached consistent

conclusions. For instance, Eichner et al. [34]. found no significant association between IGF-I and LVMI in their study of the adult population in Pomerania. These discrepancies may be attributed to the heterogeneity of the study populations, differences in age groups, and the diversity of demographic characteristics. Specifically, age may influence the cardiac effects of IGF-1, as children's myocardium might be more sensitive to metabolic changes. Additionally, coexisting metabolic abnormalities (such as the strong association between HOMA-IR and LVMI revealed in this study) may obscure or modify the effects of IGF-1.

At the mechanistic level, the potential link between IGF-1 and LVMI may involve multiple pathways, including: (1) Interaction with the insulin signaling pathway: Low levels of IGF-1 may exacerbate insulin resistance [35], which has been identified as one of the factors promoting myocardial hypertrophy; (2) Weakening of myocardial protective functions: IGF-1 enhances the sensitivity of myofilaments to Ca2+, strengthens myocardial contractility, and inhibits myocardial cell apoptosis induced by ischemia-reperfusion, thereby exerting a protective effect on myocardial cells. A reduction in IGF-1 levels may attenuate this myocardial protective effect [36]; (3) Involvement in inflammation regulation: The negative correlation between IGF-1 and high-sensitivity C-reactive protein (hs-CRP) in obese children [37] suggests that IGF-1 may indirectly influence cardiac structure through anti-inflammatory pathways [38]. Although this study provides new insights into the relationship between IGF-1 and LVMI, caution is warranted when interpreting these findings. These potential mechanisms require further validation in future longitudinal intervention studies, especially considering the limitations of cross-sectional data, which cannot exclude the possibility of reverse causality. Therefore, IGF-1 could serve as a potential biomarker for obesity-related myocardial remodeling, warranting more in-depth research in conjunction with other relevant indicators.

Study strengths and limitations

The academic novelty of this study lies in its groundbreaking confirmation of the correlation between reduced LVMI and IGF-1 in obese children. This finding offers a fresh perspective for delving into the research on obesity-related cardiac function impairment. However, the study also has certain limitations. Firstly, while our results reached statistical significance, future studies with larger cohorts are warranted to validate these findings. And the gender imbalance in the obese group (82.7% males) raises questions about the generalizability of results to female populations, given potential sex-specific differences in obesity-related cardiovascular adaptations. Secondly, as a cross-sectional survey, it cannot establish the exact causal relationship between IGF-1 and LVMI without further longitudinal studies. Although the correlation between IGF-1 SDS and LVMI is statistically significant, its strength is weak. While this suggests a potential link between lower IGF-1 levels and increased left ventricular mass in obese children, the clinical significance remains unclear. Therefore, further in-depth research is needed to elucidate the molecular mechanisms underlying the relationship between serum IGF-1 levels and LVMI, to clarify their intrinsic biological connection. Thirdly, this study was conducted as a single-center study in China, and the generalizability of its results may be influenced by regional and ethnic differences. To gain a more comprehensive understanding of the universality and specificity of this phenomenon, multicenter studies should be conducted in different regions and ethnic groups to validate and expand upon the conclusions of this study. Finally, while this study adjusted for several confounders, including lipid profile and insulin resistance, we were unable to account for other potentially important factors such as physical activity, dietary habits, and socioeconomic status due to the lack of systematic data collection. Future research should aim to incorporate these factors to provide a more comprehensive understanding of the relationship between IGF-1 and LVMI.

Conclusion

In conclusion, this study demonstrates that obese children exhibit significantly reduced IGF-1 SDS and increased LVMI compared to the normal control group. Multiple linear regression analysis reveals an independent negative correlation between IGF-1 SDS and LVMI, irrespective of other cardiovascular risk factors. These results underscore the potential clinical importance of evaluating IGF-1 levels in this population for proactive cardiovascular care. Further research is needed to investigate whether elevating IGF-1 levels can mitigate cardiovascular damage induced by obesity and whether IGF-1 or recombinant human growth hormone (rhGH) could be utilized as a novel preventive and therapeutic strategy for obese children.

Abbreviations

ALT	Alanine aminotransferase
BA	Bone Age
BMI	SDS Body mass index standard deviation score
BSA	Body Surface Area
FBG	Fasting blood glucose
GH	Growth hormone
GHD	Growth Hormone Deficiency
HDL-C	High-density lipoprotein cholesterol
HOMA-IR	Homeostasis model assessment of insulin resistance
hs-CRP	High-sensitivity C-reactive protein
Ht	SDS Height standard deviation scores
IGF-1	Insulin-like growth factor 1
IGF-1	SDS Insulin-like growth factor 1standard deviation scores
IR	Insulin resistance

LAD	Left atrial dimension
LDL-C	Low density lipoprotein-cholesterol
LVEDD	Left ventricular end-diastolic dimension
LVM	Left ventricular mass
LVMI	Left ventricular mass index
LVPWT	Left ventricular posterior wall thickness
NAFLD	Non-alcoholic fatty liver disease
OB	Obesity
OGTT	Oral Glucose Tolerance Test
rhGH	Recombinant human growth hormone
TC	Total cholesterol
TG	Triglycerides
UA	Uric acid

Acknowledgements
The authors are grateful to all participant and their parents for participating in this study.

Author contributions
WXN, CL and SL contributed to the study concept and design. WXN, ZRW and SL contributed to the data acquisition. WXN performed the statistical analysis. WXN and SL drafted the manuscript. All authors contributed to the analysis and interpretation of the data and critically revised the manuscript. All authors have approved the final version of the manuscript.

Funding
The authors did not receive support from any organization for the submitted work.

Data availability
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The study protocol was approved by the Ethics Committee of The Second Hospital of Shandong University (approval number KYLL-2019-(KJ)P-0207, March 1, 2020). All the patients and their parents written informed consent. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Received: 27 September 2024 / Accepted: 1 April 2025
Published online: 16 April 2025

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