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ORIGINAL PAPER

IGF-1 Levels are Dependent on Age, but Not Weight Status in Children

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ABSTRACT

Introduction: *The intersecting pathways involved in linear growth, glucose, and lipid metabolism may play a key part in the imbalances leading to the dysmetabolic changes observed in obese children, and later adults. The growth-hormone/insulin growth factor 1 (GH/IGF-1) axis is a prime example in this regard and IGF-1 levels have been shown to correlate with insulin resistance.*

Objectives: *The aim of this study is to examine whether there is a relationship between circulating IGF levels and weight status in children as an independent relationship, regardless of insulin sensitivity.*

Materials and method: *We retrospectively collected data from patients aged 5–12 years referred to the Pediatric Clinical Hospital Sibiu between January 2010 and May 2023, for which IGF-1 levels were documented. We excluded patients with pathologies or medication which could have influenced weight status, glucose and lipid metabolism, or growth hormone secretion, and those with short stature or a growth velocity of under 5 cm a year. Anthropometric measurements were retrieved and BMI Z-score was calculated.*

Results: *Our study included 66 patients (32 females and 34 males) with a mean age of 100,09 months (SD: 24,754 months). Initial bivariate analysis showed a significant negative correlation between BMI Z-score and IGF-1 values. However, adjusting for age indicated that there was in fact no significant relationship between these two parameters. Insulin-like growth factor 1 levels did however vary significantly with patient age.*

Conclusions: *Levels of IGF-1 showed an age-dependent variation which should be accounted for in data analysis. Our study found no correlation between weight status and IGF-1 levels when adjusting for age-dependent variation. Further studies may shed light on the possible role of IGF-1 in discerning between obese children with or without increased insulin resistance.*

Keywords: childhood obesity, insulin resistance, insulin growth factor 1.

INTRODUCTION

There is a growing body of evidence pointing towards the ill effects of obesity as a cardiovascular risk factor, with consistent results indicating that excess weight developing during childhood tends to carry on towards adult age (1, 2). As such, the increasing prevalence of overweight and obesity in children is indicative of a potential increase in the cardiovascular burden associated with this status in the years to come (3, 4). Significant efforts have been made to define the precise profile of metabolic changes behind the increase in cardio-

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vascular risk attributable to obesity (5). One of the research directions in this regard aims to explore the relationship between growth and development, and alterations in insulin sensitivity (6). The latter is a major pathway toward the development of type 2 diabetes and subsequent cardiovascular affliction in obese patients and can be of particular interest when exposure to excess adiposity starts in childhood (7-9).

The intersecting pathways involved in linear growth, glucose, and lipid metabolism may play a key part in the imbalances leading to the dysmetabolic changes observed in obese children and later adults. The growth hormone/insulin-like growth factor 1 (GH/IGF-1) axis is a prime example in this regard. Insulin-like growth factor 1 is a small peptide involved in GH-mediated somatic growth and GH-independent anabolic regulation in a variety of tissues. It is synthesized in the liver as well as in certain peripheral tissues under the influence of GH and, in the case of peripheral secretion, various local regulatory factors. Insulin-like growth factor 1 is then secreted in the circulation by the liver, and to some extent, by the peripheral tissues which synthesize it. In the latter instance, IGF-1 plays mostly autocrine and paracrine regulatory roles. Circulating IGF-1 travels bound to characteristic transport proteins and interacts mainly with its specific, broadly distributed receptor, triggering systemic growth (10). In addition to this pathway, IGF-1 also exerts growth-inducing effects within peripheral tissues where it is synthesized, in a paracrine/autocrine manner. The association between these two mechanisms enables IGF-1 to mediate tissue growth both on a systemic scale, as well as locally, where necessary (for example in wound healing). In addition, IGF-1 plays a role in lipid and glucose metabolism too (11).

In obese prepubertal boys, IGF-1 levels have been shown to correlate with insulin resistance (12). The aim of this study is to examine whether or not there is a relationship between circulating IGF levels and weight status in children as an independent relationship, regardless of insulin sensitivity.

MATERIALS AND METHOD

Study design and setting

We performed a retrospective study, collecting data from patients who had been referred to the Pediatric Clinical Hospital Sibiu, Romania, between January 2010 and May 2023. We included patients aged 5–12 years who had documented IGF-1 levels and excluded those with pathologies or medication which could have influenced the weight status, glucose and lipid metabolism, or growth hormone secretion, such as (but not limited to): patients with malignant diseases or other chronic consumptive states, as well as type 1 or 2 diabetes. Patients with short stature, defined as having a height of under 2 standard deviations for their age and sex or which had a growth velocity of under 5 cm a year were excluded. Our inclusion/exclusion protocol was mostly similar to (12), to which we added female participants, however.

Data collection

Data collection was performed retrospectively from the medical files of patients deemed eligible for the study. Body weight measurement during hospitalization utilized an electronic weight scale and height had been measured with a margin of error of 0.5 cm for each patient. The body mass index (BMI) was calculated as $BMI = BW/H^2$ (13). Subsequently, BMI Z-scores were calculated by using the 2007 WHO growth references for children from 5 to 19 years. The LMS method was implemented in this regard, according to the instructions provided for z-score computation and the expanded tables for constructing national health cards available online on the WHO official website (14). Overweight and obesity were defined according to WHO criteria as a measured BMI exceeding the WHO Growth Reference median BMI-for-age with one standard deviation for overweight or two standard deviations for obesity (15).

Circulating IGF-1 levels were measured by use of a chemiluminescence assay from blood samples that had been collected after a 12-hour overnight fast, similar to (12).

Statistical analysis

Data analysis and visualization were performed using Microsoft Excel® and IBM® SPSS® Statistics software. Comparison between continuous normally distributed variables was conducted by utilizing the student t-test and correlations were investigated using the Pearson correlation coefficient. Partial correlation was employed in order to isolate the relationship between two variables of interest, accounting for the potential influence of other variables. Results were considered statisti-

cally significant for an alpha level under 0.05. Normal distribution was investigated by visual inspection of box-plots and Q-Q-plots and tested by using the Shapiro-Wilk test as well as skewness and kurtosis analysis.

RESULTS

We included 66 patients (32 females and 34 males) with a mean age of 100,09 months (SD: 24,754 months). Age was normally distributed within the group as well as when stratified by gender. There was no significant difference in age between male and female participants. The BMI Z-score (mean: 0.9441; SD: 0.9425) and circulating IGF levels (mean: 173,5424; SD: 82,7548) similarly exhibited a normal distribution as a whole and within each gender group with no statistical differences discernible between genders.

Bivariate analysis

Initial bivariate analysis showed moderate significant correlations between IGF-1 and age (Pearson correlation coefficient=0,58; p <0,01) as well as BMI Z-score (Pearson correlation coefficient=-0,587, p<0,01). Scatter plots showing the strength of these correlations are represented in Figures 1 and 2.

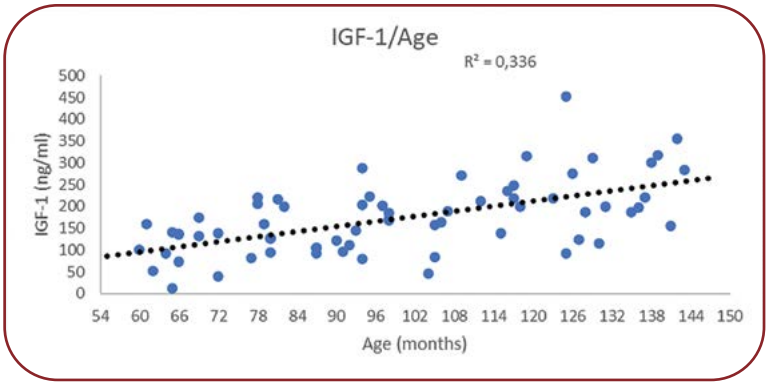

FIGURE 1. Relationship between IGF-1 and age

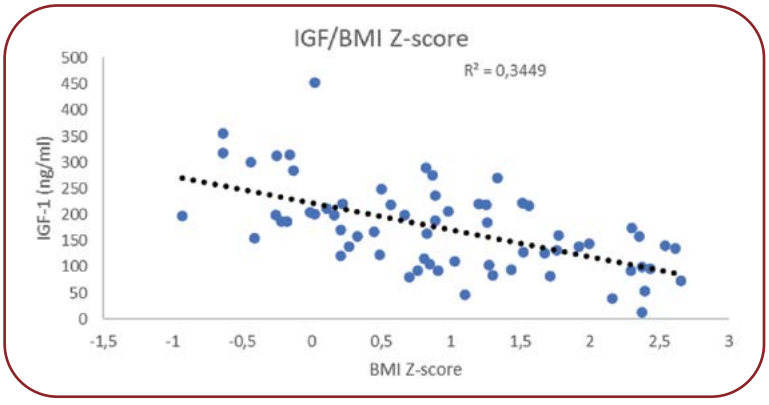

FIGURE 2. Relationship between IGF-1 and BMI Z-score

Partial correlation

When controlling for age, the relationship between BMI Z-score and IGF levels lost its statistical significance (partial correlation coefficient=-0,226; p=0,071).

DISCUSSION

Although initial bivariate analysis showed a significant negative correlation between BMI Z-score and IGF-1 values, adjusting for age showed there was no relationship between these two parameters. Our results are in agreement with previous findings which described the GH/IGF-1 axis profile of obese children as consisting of suppressed GH values despite normal IGF-1 levels (16). Obesity is known to correlate with increased insulin resistance in children (17) and can prompt the initiation of treatment with biguanides, for example in an attempt to increase insulin sensitivity (18). The exact moment when the mechanisms leading to this increase in insulin resistance varies from one individual to another. Several trials have made use of the HOMA-IR values in order to guide the decision of initiating treatment to increase insulin sensitivity in children (19-21). In the context of previous publications raising the issue of a dependency between insulin resistance and IGF-1 levels in obese children (12), it might be possible that IGF-1 levels could help discern between obese patients with or without insulin resistance and further aid in guiding treatment or estimating the prognosis with regard to this aspect.

The relationship between IGF-1 levels and age is well documented in the literature (22). Our results are consistent with findings that have been previously described in this regard. Accounting for age differences when utilizing IGF-1 values is paramount for correct data interpretation.

CONCLUSION

Insulin-like growth factor 1 levels show an age-dependent variation which should be accounted for in data analysis. Our study found no correlation between weight status and IGF-1 levels when adjusting for age-dependent variation. Further studies may shed light on the possible role of

IGF-1 in discerning between obese children with or without increased insulin resistance. ❑

Ethics approval and consent to participate: The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Committee (registration number 6731/05.10.2021). Participants in this study gave their consent for data use in anonymized form, for purposes including, but not limited to, medical education and research, in accordance with personal data processing protocols implemented in the Pediatric Clinical Hospital Sibiu as part of patient admission, in both hospital and outpatient settings.

Conflicts of interest: none declared.

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