Irisin is a biomarker for metabolic syndrome in prepubertal children

Young Suk Shim, Min Jae Kang, Seung Yang and Il Tae Hwang

Department of Pediatrics, Hallym University Medical Center, Hallym University College of Medicine, Seoul Korea

Abstract. The aim of the present study was to evaluate the association of irisin with obesity and metabolic syndrome (MetS) in Korean prepubertal children. A total of 96 children and adolescents aged 6 to 10 years (56 males) were included in this study. Subjects were divided into 3 groups: normal weight (n = 54), overweight (n = 16), and obese (n = 26). In the subgroup analyses, overweight/obese children were further divided based on their MetS status (with MetS vs. without MetS). Children with obesity tended to exhibit a lower mean irisin concentration compared to those with normal weight (p = 0.028). Using Pearson’s correlation coefficient to compare all the children in the study, there was a significant inverse correlation between irisin and body mass index (BMI) standard deviation scores (SDS) (r = –0.210, p = 0.041), waist circumference SDS (r = –0.203, p = 0.049), and glucose (r = –0.296, p = 0.004). In the subgroup analyses of overweight/obese children, irisin exhibited a significant inverse correlation with glucose (r = –0.507, p = 0.001) and triglycerides (r = –0.331, p = 0.033). Children with MetS exhibited lower irisin concentrations than those without MetS (14.70 ng/mL vs. 22.02 ng/mL, p = 0.001), and these associations were significant after adjusting for age, gender, and BMI SDS (14.51 ng/mL vs. 22.06 ng/mL, p = 0.002). The irisin level of 15.43 ng/mL was determined to be a possible cutoff to distinguish children with metabolic syndrome from overweight/obese children, with a sensitivity of 75% and a specificity of 94% (p < 0.001). Our results suggest that decreased irisin levels may be associated with MetS in prepubertal children and that irisin might be a biomarker for MetS in prepubertal children.

Key words: Irisin, Overweight, Obesity, Metabolic syndrome, Children

WITH an increasing population of overweight and obese children, metabolic complications associated with being overweight/obese, such as insulin resistance, hypertension and dyslipidemia, have become a major public health concern [1]. The incidence of childhood metabolic syndrome (MetS), which is closely related to insulin resistance, is defined as a clustering of abdominal obesity, hypertension, dyslipidemia and glucose intolerance and is increasing around the world, including in Korea [2]. The clustering of metabolic risk factors begins in childhood [3], and these multiple risk factors tend to persist from childhood into adulthood [4]. Childhood MetS is a risk factor for MetS, cardiovascular diseases and type 2 diabetes mellitus (T2DM) in adulthood [5]. It is therefore important to identify early MetS in children and adolescents.

Recently, adipokines (i.e., adipocyte-secreted proteins) and myokines (i.e., myocyte-secreted proteins) have been shown to be linked to obesity-associated metabolic and vascular diseases. Irisin is a new myokine that could decrease obesity and improve glucose metabolism [6]. Myokines are induced by exercise in rodents and humans, are related to browning in adipose tissue and are found to increase energy expenditure in mice without influencing movement and food intake, leading to a decrease in obesity and an improvement in glucose homeostasis [6]. Recent studies have reported that irisin is linked to T2DM [7] and MetS [8] in adults. However, there are only a few studies that have evaluated the relationship between irisin and MetS in pediatrics.

The current study aimed to evaluate the differences in the serum irisin concentration in overweight/obese compared to normal-weight prepubertal children. The current
study also sought to determine the relationship between irisin and various clinical parameters and to investigate the association between irisin and metabolic syndromes in overweight/obese prepubertal children using subgroup analyses.

**Materials and Methods**

**Subjects**

Ninety-six prepubertal Korean children (56 males and 40 females) aged 6.0–9.9 years old were included in the current study. All participants underwent a health examination at the Kangdong Sacred Heart Hospital between 2007 and 2013. Children with endocrine disorders, such as hypothyroidism, Cushing syndrome, T2DM or syndromic obesity, including Prader-Willi syndrome, were excluded. Subjects were divided into three groups according to body mass index (BMI): normal weight, overweight, and obese. The normal-weight group was defined as a BMI less than the 85th percentile of individuals of the same age and gender. Overweight was defined as a BMI from the 85th to 95th percentile, and obesity was defined as the ≥95th percentile for individuals of the same age and gender. Study protocols were approved by the Institutional Review Board of the Hallym University Kangdong Sacred Heart Hospital (IRB No. 2015-11-001-003). Informed consent was obtained from all subjects and their parents.

**Anthropometric Measurements**

Height was recorded to the nearest 0.1 cm using a Harpenden stadiometer. Weight was measured using an electronic scale that was accurate to the nearest 0.1 kg. Pubertal stage was determined by two experienced pediatric endocrinologists according to the method of Marshall and Tanner [9]. Prepubertal stage was defined as a testicular size <4 mL and no pubic hair for boys and as a lack of breast development and no pubic hair for girls. BMI was estimated as the weight in kg/square of the height in meters (kg/m$^2$). Because height, weight, BMI and waist circumference (WC) were not evenly distributed between various age groups of children, the standard deviation scores (SDS) of these measures were used and determined using the LMS method according to the 2007 Korean National Growth Charts [10]. Blood pressure (BP) was measured using a standard protocol. Briefly, all participants rested in a seated position for 10 minutes before measuring BP. Systolic BP (SBP, mmHg) and diastolic BP (DBP, mmHg) were measured twice on the right upper arm using a calibrated sphygmomanometer with an appropriate cuff size. Then, the mean of two measured values was used for analysis.

**Laboratory Measurements**

Blood samples were obtained from all subjects after ≥12 h of fasting in the morning. Collected specimens were stored at ~80°C after centrifugation. The samples were analyzed the same day. Serum irisin, insulin, glucose, total cholesterol (T-C), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) concentrations were measured.

Serum irisin levels were determined by an enzyme-linked immunosorbent assay (Phoenix Pharmaceuticals, Burlingame, CA). The intra-assay coefficients of variation (CV) was 4–8% and the inter-assay CV was 8–12%. Serum insulin concentration was determined using an immunoradiometric assay (BioSource, Nivelles, Belgium). A Hitachi-747 automatic analyzer (Hitachi, Tokyo, Japan) was used for estimating clinical parameters such as glucose, T-C, TG, HDL-C, and LDL-C. Bone age (BA) was determined according to the Greulich and Pyle method [11]. Differences between BA and chronological age were assessed as BA minus chronological age (BA–CA, years).

**Determination of insulin sensitivity index and MetS**

Insulin resistance was determined from the fasting glucose and insulin concentrations using the homeostasis model assessment for insulin resistance (HOMA-IR), which was determined by the following calculation [12]:

\[
\text{HOMA-IR} = \frac{\text{fasting insulin} (\mu\text{U/mL}) \times \text{fasting glucose} (\text{mmol/L})}{22.5}
\]

MetS was defined according to the modified National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) [13]. The diagnosis of MetS in this study constituted the presence of ≥3/5 of the following criteria: (i) abdominal obesity (i.e., WC ≥90th percentile for age and gender), (ii) SBP or DBP ≥90th percentile for age, gender, and height, or treatment with an anti-hypertensive medication, (iii) fasting glucose ≥110 mg/dL or previously diagnosed with T2DM, and (iv) HDL-C <40 mg/dL, or (v) TG ≥110 mg/dL.

**Statistical Analyses**

All analyses were performed using SPSS for Windows version 22 (IBM SPSS Inc., Chicago, IL, USA). The
Results

Clinical characteristics of children in the study (Table 1)
The clinical characteristics of the participants according to obesity are presented in Table 1. Fifty-four children were of a normal weight, 16 children were overweight, and 26 children were obese. Obese children tended to exhibit significantly higher means of age. 

The correlation of irisin with clinical parameters in all study populations or in subgroups of overweight/obese prepubertal children was determined by Pearson’s coefficient of correlation. In addition, the association of irisin and MetS with overweight/obese prepubertal children was evaluated using the Mann-Whitney U test because the continuous variables of overweight/obese prepubertal children with MetS were not normally distributed. Analysis of covariance (ANCOVA) was used to evaluate the adjusted associations between irisin and MetS after adjusting for possible confounding factors, such as age, gender, and BMI SDS, in overweight/obese prepubertal children. Receiver operating characteristic (ROC) curve analysis was conducted to assess the diagnostic performance of the studied parameters. Sensitivity (%) was plotted on the y-axis and specificity on the x-axis. The best cutoff value was determined using the Youden index (i.e., the point nearest to the left upper corner of the curve). Statistical significance was defined as \( p < 0.05 \).

Table 1 Clinical characteristics of study population (\( n = 96 \))

<table>
<thead>
<tr>
<th></th>
<th>Normal-weight (( n = 54 ))</th>
<th>Overweight (( n = 16 ))</th>
<th>Obesity (( n = 26 ))</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male (%)</td>
<td>27 (50%)</td>
<td>10 (62.5%)</td>
<td>19 (73.1%)</td>
<td>0.189</td>
</tr>
<tr>
<td>Age (years)</td>
<td>7.85 ± 1.06</td>
<td>8.57 ± 1.33</td>
<td>8.04 ± 1.06</td>
<td>0.003</td>
</tr>
<tr>
<td>BA (years)</td>
<td>7.35 ± 1.65</td>
<td>8.28 ± 1.68</td>
<td>8.83 ± 2.11</td>
<td>0.006</td>
</tr>
<tr>
<td>BA–CA (years)</td>
<td>−0.52 ± 1.18</td>
<td>−0.29 ± 0.91</td>
<td>0.79 ± 1.48</td>
<td>0.002</td>
</tr>
<tr>
<td>Height SDS</td>
<td>0.13 ± 0.94</td>
<td>0.49 ± 1.31</td>
<td>1.09 ± 1.18</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Weight SDS</td>
<td>−0.16 ± 0.81</td>
<td>1.15 ± 1.13</td>
<td>2.00 ± 0.59</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI SDS</td>
<td>−0.41 ± 0.83</td>
<td>1.41 ± 0.20</td>
<td>2.14 ± 0.42</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>WC SDS</td>
<td>−0.36 ± 1.21</td>
<td>1.05 ± 0.94</td>
<td>1.82 ± 0.39</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>101.46 ± 7.47</td>
<td>103.06 ± 15.62</td>
<td>102.25 ± 9.78</td>
<td>0.906</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>61.80 ± 4.63</td>
<td>65.00 ± 8.16</td>
<td>65.54 ± 7.36</td>
<td>0.044</td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
<td>93.71 ± 9.76</td>
<td>103.63 ± 12.57</td>
<td>106.50 ± 13.68</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Insulin (μU/mL)</td>
<td>4.68 ± 2.33</td>
<td>8.57 ± 2.68</td>
<td>9.96 ± 4.97</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>1.08 ± 0.60</td>
<td>2.19 ± 0.70</td>
<td>2.66 ± 1.48</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>T-C (mg/dL)</td>
<td>168.59 ± 22.07</td>
<td>180.19 ± 32.28</td>
<td>164.58 ± 27.18</td>
<td>0.235</td>
</tr>
<tr>
<td>TG (mg/dL)</td>
<td>63.24 ± 25.42</td>
<td>89.19 ± 55.55</td>
<td>90.81 ± 43.05</td>
<td>0.005</td>
</tr>
<tr>
<td>HDL-C (mg/dL)</td>
<td>60.59 ± 13.60</td>
<td>55.06 ± 10.12</td>
<td>52.46 ± 10.06</td>
<td>0.019</td>
</tr>
<tr>
<td>LDL-C (mg/dL)</td>
<td>96.35 ± 18.50</td>
<td>113.00 ± 27.55</td>
<td>105.04 ± 22.89</td>
<td>0.039</td>
</tr>
<tr>
<td>Irisin (ng/mL)</td>
<td>24.61 ± 18.50</td>
<td>19.49 ± 4.42</td>
<td>21.33 ± 6.84</td>
<td>0.028</td>
</tr>
</tbody>
</table>

The data are presented as means ± standard deviations (SD).

Statistical significance was assessed using the Kruskal-Wallis test for continuous variables and chi-square test for categorical variables. BA, bone age; BA–CA, difference between BA and chronological age; SDS, standard deviation score; BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; HOMA-IR, homeostatic model assessment of insulin resistance; T-C, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.
Correlations between irisin levels and clinical parameters in prepubertal children (Table 2)

The correlation between irisin and clinical parameters in the subjects (n = 96) is shown in Table 2. Irisin exhibited a significant inverse correlation with weight SDS (r = −0.219, p = 0.033), BMI SDS (r = −0.210, p = 0.041), WC SDS (r = −0.203, p = 0.049), and glucose (r = −0.296, p = 0.004). The relationship between irisin and BMI SDS was significant after adjusting for age and gender (r = −0.221, p = 0.033).

Correlation between irisin and clinical parameters in overweight/obese prepubertal children (Table 3)

Subgroup analyses were conducted among overweight/obese prepubertal children (n = 42). The correlation between irisin and clinical parameters is presented in Table 3. Although irisin exhibited a significant positive correlation with SBP (r = 0.314, p = 0.048) and DBP (r = 0.331, p = 0.037), irisin exhibited a significant inverse correlation with glucose (r = −0.507, p = 0.001) and TG (r = −0.431, p = 0.033). The relationship between irisin and BMI SDS was not significant in the subgroup of overweight/obese children (r = −0.038, p = 0.811).

Clinical characteristic of the study population according to MetS in overweight/obese prepubertal children (Table 4)

In the subgroup analyses, overweight/obese prepubertal children were divided into two groups according to the presence of MetS (n = 42). The overweight/obese prepubertal children with MetS exhibited significantly
higher means of glucose (118.25 mg/dL vs. 102.38 mg/dL, \( p = 0.001 \)) and TG (113.00 mg/dL vs. 84.82 mg/dL, \( p = 0.029 \)) compared to those without MetS. The irisin concentration was significantly lower in overweight/obese prepubertal children with MetS than overweight/obese prepubertal children without MetS (14.70 ng/mL vs. 22.02 ng/mL, \( p = 0.001 \)).

**Table 4** Clinical characteristics of the study population according to the presence of metabolic syndrome in overweight/obese children aged 6–10 years (\( n = 42 \))

<table>
<thead>
<tr>
<th></th>
<th>No MetS (( n = 34 ))</th>
<th>MetS (( n = 8 ))</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male (%)</td>
<td>22 (65%)</td>
<td>7 (88%)</td>
<td>0.208</td>
</tr>
<tr>
<td>Age (years)</td>
<td>8.17 ± 1.03</td>
<td>8.54 ± 1.75</td>
<td>0.694</td>
</tr>
<tr>
<td>Height SDS</td>
<td>0.93 ± 1.33</td>
<td>0.54 ± 0.80</td>
<td>0.275</td>
</tr>
<tr>
<td>Weight SDS</td>
<td>1.65 ± 0.99</td>
<td>1.78 ± 0.62</td>
<td>0.987</td>
</tr>
<tr>
<td>BMI SDS</td>
<td>1.83 ± 0.50</td>
<td>2.03 ± 0.49</td>
<td>0.261</td>
</tr>
<tr>
<td>WC SDS</td>
<td>1.50 ± 0.82</td>
<td>1.64 ± 0.29</td>
<td>0.888</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>104.00 ± 12.94</td>
<td>96.88 ± 7.04</td>
<td>0.153</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>66.03 ± 8.07</td>
<td>62.50 ± 4.63</td>
<td>0.278</td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
<td>102.38 ± 12.39</td>
<td>118.25 ± 7.89</td>
<td>0.001</td>
</tr>
<tr>
<td>Insulin (μU/mL)</td>
<td>9.21 ± 4.24</td>
<td>10.38 ± 4.51</td>
<td>0.582</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>2.34 ± 1.19</td>
<td>3.06 ± 1.46</td>
<td>0.157</td>
</tr>
<tr>
<td>T-C (mg/dL)</td>
<td>170.18 ± 29.02</td>
<td>172.00 ± 35.25</td>
<td>0.671</td>
</tr>
<tr>
<td>TG (mg/dL)</td>
<td>84.82 ± 48.91</td>
<td>113.00 ± 34.98</td>
<td>0.029</td>
</tr>
<tr>
<td>HDL-C (mg/dL)</td>
<td>54.23 ± 10.04</td>
<td>49.75 ± 9.79</td>
<td>0.368</td>
</tr>
<tr>
<td>LDL-C (mg/dL)</td>
<td>106.26 ± 22.14</td>
<td>115.75 ± 33.71</td>
<td>0.289</td>
</tr>
<tr>
<td>Irisin (ng/mL)</td>
<td>22.02 ± 5.56</td>
<td>14.70 ± 4.29</td>
<td>0.001</td>
</tr>
</tbody>
</table>

The data are presented as the means ± standard deviations (SD). Statistical significance was assessed using the Mann-Whitney U test for continuous variables and chi-square test for categorical variables.

MetS, metabolic syndrome; SDS, standard deviation score; BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; HOMA-IR, homeostatic model assessment of insulin resistance; T-C, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

**Discussion**

In the present study, irisin levels were significantly lower in prepubertal children that were overweight and obese compared to those of a normal weight. Irisin levels also exhibited a significant inverse correlation with obesity as determined by BMI SDS of normal-weight and overweight/obese prepubertal children. However, this relationship was not significant in the subgroup analyses of overweight/obese prepubertal children. Irisin concentrations were significantly lower in overweight/obese prepubertal children with MetS compared to those without MetS (14.51 ng/mL vs. 22.06 ng/mL, \( p = 0.002 \)) after adjusting for the previously described variables.

**ROC curve analyses between irisin and MetS in overweight/obese prepubertal children (Fig. 2)**

A cutoff value for irisin was performed using ROC curve analyses to distinguish overweight/obese prepubertal children with MetS from overweight/obese prepubertal children without MetS. Fig. 2 shows the results of the ROC curve analyses. The optimal irisin concentration that was used as the cutoff value was 15.43 ng/mL, with a sensitivity of 75%, a specificity of 94%, and an area under the curve (AUC) of 0.87 (0.71–1.00) \( (p < 0.001) \).
out MetS, and this association was significant after adjusting for age, gender and BMI SDS. The possible cutoff value for differentiating children with MetS from overweight/obese prepubertal children was approximately 15 ng/mL using ROC curve analyses.

Increasing evidence indicates that skeletal muscles have a secretory function. Myokines, which are released from a variety of cytokines from skeletal muscles during or immediately after physical activity, mediate the beneficial effects that exercise has on metabolism. A newly discovered myokine, called irisin, was proposed to be associated with the beneficial effects that result from exercising. Irisin is a signaling protein that is released into the blood from skeletal muscles after proteolysis of the membrane protein fibronectin type III domain containing 5 (FNDC5) [6]. FNDC5, which is encoded by the FNDC5 gene, has two fibronectin domains and one hydrophobic domain that is likely to be membrane-inserted, C-terminally cleaved, and subsequently secreted into the blood stream [14]. Irisin is related to the activity of subcutaneous white adipose tissue and stimulates uncoupling protein 1 (UCP1) expression in vitro and in vivo, as well as induces brown adipocytes in white adipose tissue depots in a process known as white fat browning [6]. Irisin increases total energy expenditure in rodents, and the expression of irisin in mice that were fed a high-fat diet resulted in a significant improvement in glucose tolerance and a reduction in fasting insulin levels [6]. Irisin also induced an increase in thermogenesis, which is related to insulin sensitivity, body weight, and glucose metabolism in mice [15]. The relationship between irisin and glucose homeostasis was reported to be associated with increased fatty acid oxidation and utilization of glucose via the adenosine monophosphate-activated protein kinase (AMPK) signaling pathway in a diabetic mouse model [16]. These studies suggested that decreased irisin levels are associated with the development of insulin resistance and its related diseases, such as T2DM and MetS. Our results indicate that decreased irisin levels are significantly associated with MetS and corroborate these previous studies.

Atherosclerosis begins as early as childhood, and its development is related to cardiovascular risk factors, including MetS [17]. Children with MetS have been associated with early atherosclerotic lesions, including the exhibition of early anatomically verifiable lesions [18]. Early identification of MetS is important in children that are overweight and obese, as these children are considered to be at high risk for the disease. To date, various serologic markers have been suggested for identifying the children with MetS among overweight/obese children. There is a possibility that irisin may be a surrogate marker for MetS. Most studies in adults showed that levels of irisin were linked to the incidence of T2DM [7], insulin resistance [19, 20], and dyslipidemia [21], which are components of MetS. However, there were discrepancies reporting the relationship between irisin and metabolic diseases. In pediatric fields, there are only a few studies that have investigated the association between irisin and metabolic diseases. Reinehr et al. [22] reported that irisin was significantly associated with pubertal stage, HDL-C, and insulin resistance but not to any other parameter of metabolic syndrome. In our study, irisin levels were significantly lower in prepubertal children with MetS compared to those without MetS, and this relationship was significant after controlling for possible confounders. The AUC for the association between irisin and MetS ranged from 0.71 to 1.00 in the ROC curve analyses. Our results support the conclusion that irisin is linked to MetS, which was observed in adults. Based on our studies and future studies, it is expected that irisin may be used as a serological marker for MetS in children.
Irisin and metabolic syndrome

There is no clear consensus in the literature as to the relationship between irisin and BMI. In our study, irisin concentrations were more likely to be lower in overweight and obese children compared to normal-weight children, and irisin exhibited a significant inverse correlation with BMI SDS in all the children in this study. Studies have reported that irisin is related to BMI; however, irisin was not significantly correlated with BMI in other studies [23, 24]. The circulating irisin levels have been shown to be negatively correlated with BMI [25-27], whereas some reports suggested that irisin concentrations were positively associated with BMI [20, 28]. Moreover, although a few studies have demonstrated that there is no direct relationship between irisin and BMI, their results support the hypothesis of a positive correlation between irisin and BMI. In a recent study, irisin concentrations were not correlated with BMI in overweight/obese women, but irisin levels decreased after weight loss [29]. In another study, there was a significant positive correlation between irisin levels and BMI, but this relationship was not significant after possible confounders were adjusted [30]. This particular study also showed that circulating irisin levels decreased after surgically induced weight loss and decreases in body mass. Similar to the link between irisin and BMI, there are inconsistent findings regarding the association of irisin with cardiometabolic risk factors. A recent study showed that increased irisin is associated with a higher risk of metabolic syndrome and cardiovascular disease in humans [19]. This study suggested that increased secretion by muscle tissue and/or a compensatory increase in irisin may play a role in regulating energy expenditure and glucose metabolism in obese and/or glucose intolerant individuals; this compensatory role for irisin was found in insulin and leptin resistance associated with obesity and metabolic abnormalities. However, prepubertal children may not have enough compensatory mechanisms and may have other pathologies because they exhibit relatively low muscle mass compared to adolescents or adults. Increases in BMI during childhood are generally attributed to the lean rather than the fat component of BMI until the end of puberty [32]. Moreno-

Navarrete et al. [25] showed that muscle \textit{FNDC5} gene expression was positively associated with BMI, but \textit{FNDC5} gene expression in human adipose tissue was inversely associated with obesity. These authors also suggested that the stimulation of browning on adipocytes may enhance irisin production. Higher fat mass and decreased browning of white adipose tissue, which play a role in MetS, may be associated with the negative correlation between irisin levels and both BMI and MetS. In addition, it has been shown that Asian children and adolescents exhibit a higher fat percentage at the same BMIs compared to their white counterparts [33]. Our results are in line with previous studies suggesting a negative link between irisin and both obesity and MetS. Nevertheless, it could be valuable to assess the exact relationship between irisin and obesity, MetS, and T2DM, all of which should be evaluated in future studies.

The present study has some limitations. First, our results were based on cross-sectional data, and the causality between irisin and MetS could not be determined. Second, we did not measure \textit{FNDC5} gene expression from muscle tissue or the levels of the other circulating myokines or adipokines that may be simultaneously secreted from muscle and adipose tissue. Third, the study population of children with MetS was small. Nevertheless, the results of the current study showed a sufficient statistical significance in the AUC, sensitivity and specificity of ROC curve analyses. Finally, we could not show a significant association between irisin and either insulin or HOMA-IR in any of the participants or in the subgroup of overweight/obese children (a marginal relationship between irisin and HOMA-IR among overweight/obese children), although we demonstrated a significant relationship between irisin and glucose. The main effect of irisin on glucose metabolism was related to increased glucose uptake and expenditure in adipose tissue and muscle tissue, and these effects may play a role in decreased insulin resistance. However, the direct effect of irisin on insulin is not fully understood. Some reports suggested that irisin is not correlated with \(\beta\)-cell function (HOMA-\(\beta\)), fasting C-peptide, or fasting insulin levels [34]. Nevertheless, it is notable that irisin was significantly associated with MetS, although irisin was not correlated with insulin and HOMA-IR in our study.

In conclusion, the concentrations of irisin were significantly lower in children that were overweight or obese compared to children of a normal weight. Iribin levels exhibited a significant inverse correlation with BMI SDS in normal-weight and overweight/obese prepubertal chil-
dren. However, this relationship was not significant when study groups were defined as overweight/obese prepubertal children. In the subgroup analyses of overweight/obese prepubertal children, the irisin concentration was significantly lower in overweight/obese children with MetS compared to those without MetS, and this association was significant after adjusting for age, gender, and BMI SDS. The possible cutoff value for differentiating children with MetS from overweight/obese prepubertal children without MetS was approximately 15 ng/mL. Our results suggest that decreased irisin levels may be associated with MetS in prepubertal children and that irisin may be a biomarker for MetS in this population.

Acknowledgement

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Disclosure

No conflict of interest to disclose and industry relationship.

References