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The relationship of irisin with metabolic syndrome components and insulin secretion and resistance in schoolchildren

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Abstract

Irisin, a novel myokine, is believed to be the crucial factor in converting white adipose tissue to beige adipose tissue. For this paper, we studied the relationship among irisin and components of metabolic syndrome (MetS), and insulin secretion and resistance in schoolchildren of Taiwan.

Subjects receiving routine annual health examination at elementary school were enrolled. Demographic data, anthropometry, MetS components, irisin, and insulin secretion and resistance were collected. Subjects were divided into normal, overweight, and obese groups for evaluation of irisin in obesity. Finally, the relationship between irisin and MetS was analyzed.

There were 376 children (179 boys and 197 girls), aged 10.3 ± 1.5 years, were enrolled. In boys, irisin levels were not associated with body mass index percentile, body fat, blood pressure, lipid profiles, insulin secretion or resistance. After adjusting for age, the irisin level in boys was negatively related to fasting plasma glucose (FPG) ($r = -0.21$, $P = .006$). In girls, after adjusting for age, the irisin levels were positively related only to FPG ($r = 1.49$, $P = .038$). In both genders, irisin levels were similar among normal, overweight, and obese groups, and between subjects with and without MetS.

The irisin levels were not associated with MetS in either boys or girls. In girls, circulating irisin levels have a nonsignificant declining trend in overweight and obese girls. However, irisin levels were negatively related to FPG in boys and positively related to FPG in girls. The contrary relationship between irisin and FPG in boys and girls needs further exploration.

Abbreviations: BAT = brown adipose tissue, BMI = body mass index, FPG = fasting plasma glucose, HOMA-β = homeostasis model assessment-β, HOMA-IR = homeostasis model assessment-insulin resistance, MetS = metabolic syndrome, TG = triglyceride, WAT = white adipose tissue.

Keywords: irisin, metabolic syndrome, schoolchildren

1. Introduction

In recent decades, obesity has become an epidemic worldwide, contributing to cardiovascular disease, type 2 diabetes, and metabolic syndrome (MetS). A complex of genetic factors, excessive energy intake, sedentary lifestyle, and accumulation of redundant massive adipose tissues leads to development of obesity. A growing number of researchers have studied the pathogenesis of obesity and obesity-related disease and tried to develop effective therapies. There are 2 different functions of adipose tissues, white (WAT) and brown adipose tissue (BAT), identified in animals and humans. Unlike WAT, BAT responds to non-shivering thermogenesis and burns energy equivalent to 4.1

Editor: Leena Mallik.

This work was supported by grants from the National Defense Medical Center, Tri-Service General Hospital [TSGH-C106-093, TSGH-C107-097], the Ministry of Science and Technology of Taiwan [MOST 105-2314-B-016-031-MY2], and Taipei Medical University [TMU105-AE1-B28].

The authors report no conflicts of interest.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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How to cite this article: Wu CZ, Chu NF, Chang LC, Cheng CW, Lin YF, Pei D, Fang TC, Chen JS. The relationship of irisin with metabolic syndrome components and insulin secretion and resistance in schoolchildren. Medicine 2021;100:5(e24061).

Received: 21 July 2020 / Received in final form: 31 October 2020 / Accepted: 5 December 2020

http://dx.doi.org/10.1097/MD.0000000000024061

Kg of WAT with 63 g of supraclavical BAT.[1,2] However, the mass of BAT is most abundant in infants and progressively decreases with age. Activating BAT has become a hot issue as an anti-obesity strategy.

Irisin, a novel myokine, is secreted from fibronectin type III domain containing protein 5 of skeletal muscle[3] and enriched in circulation after stimulation of exercise and cold exposure.[4] Irisin is believed to be a crucial factor in converting WAT to beige adipose tissue.[3] In an animal model, fibronectin type III domain containing protein 5 mRNA expression on skeletal muscle after exercise in obese rats was higher than that in lean rats.[5] In addition, serum irisin levels show greater increase in young rats than in old rats after exercise.[6] In clinical investigations, patients with type 2 and gestational diabetes mellitus have lower levels of irisin.[7] Similarly, irisin was significantly reduced in obese Chinese patients with MetS.[8] Furthermore, some studies found irisin increases cortical bone mass and improves neural differentiation.[9–11] Irisin also is associated with telomere length in adults and has potential anti-ageing effects.[12]

Childhood is an important period of maturation and development in physical activity, behavioral habits, and body composition.[13] The increasing prevalence of obesity and overweight in children worldwide has led to the onset of pediatric MetS and continues to adulthood.[14] However, MetS could be preventable if discovered and treated early.[15] Generally, exercise has been recommended as the ideal strategy to fight obesity and MetS, but the effect of exercise-related myokine on children is still unclear. In the present study, we explored the relationship between circulating irisin levels and components of metabolic syndrome, and insulin secretion and resistance in schoolchildren in Taiwan.

2. Methods

2.1. Subjects

We enrolled subjects, aged 6 to 12 years, who were receiving their routine annual health exam at elementary schools in Taipei. Subjects having the history of major medical diseases, including stage II hypertension (blood pressure ≧140/90 mm Hg),[16] diabetes mellitus, heart disease, liver cirrhosis, renal failure, and other significant medical or surgical issues, were excluded. Subjects taking medications affecting insulin resistance or secretion within 1 month were also excluded. In addition, subjects who refused to participate or had missing or incomplete data were excluded. The aims and potential risks of the study were explained to the subjects and their parents before obtaining their informed consent to participate. The protocol for the research project has been approved by a suitably constituted ethics committee of the institution (National Defense Medical Center Approval No: TYGH102021) within which the work was undertaken and that it conforms to the provisions of the Declaration of Helsinki.

2.2. Anthropometry and laboratory measurements

All participants received complete physical examinations including pubertal status (the development of penis/testes and pubic hair for boys and breast growth and pubic hair for girls) by trained nurses. Most anthropometry and laboratory measurements were part of a routine health exam. Body height was recorded to the nearest 0.1 cm while subjects were barefoot and wearing light indoor clothing. Body weight was recorded to the nearest 0.1 kg using a segmental body composition analyzer (Tanita Corp., Tokyo, Japan). Body mass index (BMI) was calculated as body weight (kg) divided by the square of body height (m). Body fat was assessed by bioelectrical impedance analysis. Systolic and diastolic blood pressure were measured on the right arm after participants rested for 10 minutes in a sitting position, using an appropriately sized cuff of a HEM-740C automatic digital blood pressure monitor (Omron Corp., Tokyo, Japan) by the nursing staff.

Around 10 mL of venous blood samples was collected from an antecubital vein using venous containers after fasting for 10 to 12 hours overnight. Plasma and serum were separated by centrifugation within 1 hour, then stored at –80°C until measurement. Triglyceride were measured with randox reagent on a Hitachi 7150 autoanalyzer (Hitachi, Tokyo, Japan). High density lipoprotein-cholesterol and low density lipoprotein-cholesterol were measured enzymatically with Daiichi reagent on an Olympus AU600 autoanalyzer (Olympus, Tokyo, Japan). Fasting plasma glucose (FPG) was measured using the YSI 203 glucose oxidase analyzer (Yellow Spring Instrument, Yellow Spring, Ohio). Insulin was measured using the Coat-A-Count solid-phase radioimmunoassay kit (Diagnostic Products, Los Angeles, CA). High-sensitive C-reactive protein was measured using IMMULITE 2000 immunoassay system (Siemens, Los Angeles, CA). Irisin levels were measured by Irisin, Recombinant (Human, Rat, Mouse, Canine) ELISA kit (EK-067-29, Phoenix Pharmaceutical, Inc.). The intra- and inter-assay variations were <10% and <15%, respectively. Homeostasis model assessment-insulin resistance (HOMA-IR) and -β (HOMA-β) were measured to assess insulin resistance and insulin secretion, respectively.[17] The formula of HOMA-IR and HOMA-β is shown as below:

$$\text{HOMA} - \text{IR} = (\text{fasting insulin} \times \text{fasting glucose})/22.5$$

$$\text{HOMA}-\beta = (20 \times \text{fasting insulin})/(\text{fasting glucose} - 3.5)$$

2.3. Statistical analysis

PASW statistics version 18.0 package for Windows (IBM analytics) was used for data analysis. Subjects were divided into normal, overweight, and obese groups by the BMI percentile as defined by the Ministry of Health and Welfare standard in Taiwan (normal: 0%–90%, overweight: 90.1%–95%, obese: >95%). Furthermore, development of MetS in boys and girls was assessed. The criteria of MetS in children were based on the definition of the International Diabetes Federation.[18] The continuous variables were expressed as mean ± SD. The correlation between the irisin and components of MetS in different genders were evaluated with Pearson correlation. One-way ANOVA with Bonferroni post hoc test was applied to compare the difference among normal, overweight, and obese groups in boys and girls. Independent Student *t* test was applied to assess irisin levels between children with MetS and without MetS. All statistical data were expressed as 2-sided, and *P* values less than .05 were considered to be statistically significant.

3. Results

3.1. Relationship among irisin levels and components of MetS, insulin resistance and secretion

There were 376 children (179 boys and 197 girls) enrolled in the study. The general characteristics, components of MetS,

Table 1

General characteristics, metabolic syndrome components, insulin resistance, and secretion in boys and girls.

	Boys	Girls
N	179	197
Age (yr)	10.4 ± 1.5	10.2 ± 1.5
Irisin (mg/dL)	501.8 ± 490.1	479.7 ± 407.3
Body fat (%)*	23.8 ± 5.4	22.0 ± 4.2
BMI percentile (%)*	73.3 ± 27.2	63.8 ± 28.9
Waist circumference (cm)	68.5 ± 10.2	64.2 ± 9.1
Fasting plasma glucose (mmol/L)*	5.07 ± 0.37	4.97 ± 0.39
Systolic blood pressure (mm Hg)	117.0 ± 10.5	117.4 ± 10.3
Diastolic blood pressure (mm Hg)	72.3 ± 8.2	73.8 ± 9.5
Total cholesterol (mmol/L)	4.37 ± 0.78	4.31 ± 0.71
Triglyceride (mmol/L)	0.76 ± 0.43	0.86 ± 0.69
High density lipoprotein (mmol/L)	1.35 ± 0.33	1.35 ± 0.32
Low density lipoprotein (mmol/L)	2.53 ± 0.62	2.44 ± 0.62
HOMA-IR	3.83 ± 4.91	4.07 ± 4.56
HOMA-β	209.7 ± 191.7	240.8 ± 239.3

Data shows as mean ± SD.
* $P < .05$ compared with 2 genders.

Table 2

The correlation coefficient between irisin and metabolic syndrome components, insulin resistance, and secretion after adjusting of age in boys and girls.

	Boys	Girls
Body fat	–0.040	–0.095
BMI percentile	0.081	–0.016
Waist circumference	0.068	–0.012
Fasting plasma glucose*	–0.205	0.150
Systolic blood pressure	0.071	–0.020
Diastolic blood pressure	0.013	–0.048
Total cholesterol	0.008	–0.018
Triglyceride	0.028	–0.049
High density lipoprotein	–0.029	–0.022
Low density lipoprotein	0.059	0.015
HOMA-IR	–0.079	–0.020
HOMA-β	–0.024	–0.042

BMI = body mass index, HOMA-β = homeostasis model assessment-β, HOMA-IR = homeostasis model assessment-insulin resistance.
* $P < .05$.

HOMA-IR and -β are shown in Table 1. Comparing MetS components, insulin resistance, and secretion between boys and girls, boys had more body fat, BMI percentiles, and higher FPG than girls. However, the circulating irisin levels between boys and girls showed no significant difference. As the mass of BAT declined with age, we analyzed the correlation of irisin and MetS components, insulin resistance, and secretion after adjusting the confounding factor of age. The correlation coefficient among irisin levels after adjusting for age and components of MetS, insulin resistance and secretion is shown in Table 2. We found that irisin levels in boys were negative related to FPG, but positively related to FPG in girls. Irisin levels showed no significant association with other MetS components, insulin secretion, and resistance. The majority of children were at puberal stage I. Only a few girls (n = 7) were at pubertal stage II. The irisin levels in girls at pubertal stage between I and II showed no significant difference. After adjustment for pubertal stage, all results were similar.

3.2. Irisin levels in normal, overweight, and obese children

The irisin levels in normal, overweight and obese children of different genders are depicted in Figure 1. The irisin levels in obese boys is nonsignificantly higher than those in normal and overweight boys. In girls, the circulating irisin seemed to decline in overweight and obese girls, but not significantly.

3.3. Irisin levels in children with and without MetS

There were 12 boys (6.7%) and 6 girls (3.05%) who fit the definition of MetS. The change of irisin in boys and girls with or without MetS is shown in Figure 2. However, there was no significant difference in irisin levels in children with and without MetS in both genders.

4. Discussion

The present study showed different presentation of metabolic syndrome components between 2 different sexes in children. Circulating irisin levels in boys and girls showed contrary relation to FPG. Irisin levels in girls showed nonsignificantly declining trend in obesity. However, there was no significant difference between children with and without MetS.

After irisin, a novel myokine, was reported, there were several studies investigating the relationship between irisin and metabolic syndrome in adults. Park and his colleagues found irisin was higher in adults with MetS and negatively associated to adiponectin. In addition, irisin was positively associated to

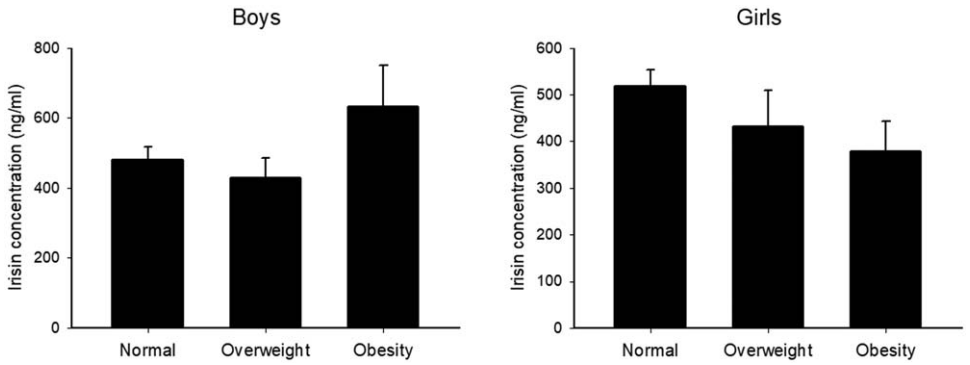

Figure 1. Irisin levels in normal, overweight, and obese groups of boys and girls. In obese boys, irisin levels showed mild nonsignificantly higher than those in other 2 groups. In overweight and obese girls, irisin levels showed mild nonsignificant declining trends.

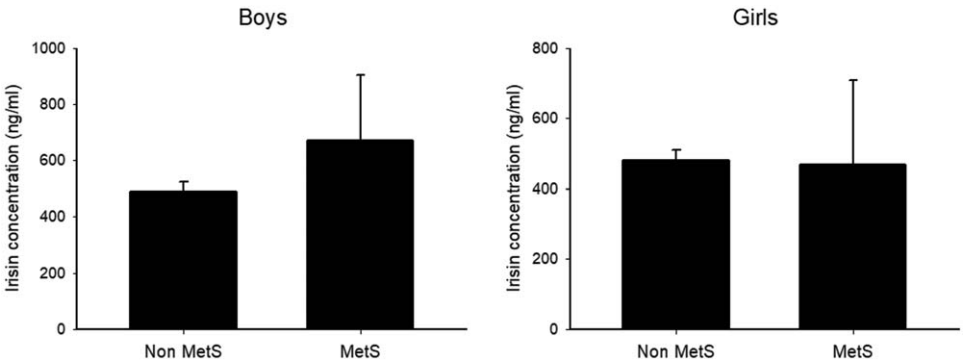

Figure 2. Comparison of irisin levels between subjects without and with metabolic syndrome in boys and girls. There was on significant difference between subjects without and with metabolic syndrome neither in boys nor in girls.

BMI, systolic blood pressure, diastolic blood pressure, FPG, Triglyceride, and HOMA-IR.[19] Contrarily, Yan et al explored 1,115 Chinese obese adults, mean aged of 52 years, and found that irisin levels were reduced in subjects with MetS.[8] In a meta-analysis, circulating irisin showed positively associated with insulin resistance in non-diabetic adults.[20] Till now, there is no consistent conclusion on the relationship between irisin and MetS. It is reasonably speculated that there are several factors affecting irisin levels, such as body compositions in different races, and exercise types.[21] In our study, we did not find significant difference of irisin in young boys and girls with or without MetS. Besides of the different amount of muscle mass, puberty is another important factor affecting difference of irisin levels between adults and children. As the surge of growth and sex hormones during puberty, insulin resistance increased with pubertal stage.[22] Thereafter, insulin resistance in adults is more prominent than that in children. Accordingly, the difference of irisin in adults with and without MetS showed more obvious.

In recent 5 years, there were some small studies of investigating the role of irisin in children. Reinehr and his colleagues enrolled 40 obese and 20 normal-weight children and explored the association of serum irisin and MetS components.[23] They found irisin levels are highest in obese children with impaired fasting glucose and associated with high density lipoprotein-cholesterol and HOMA-IR. However, there is no association to age, gender, BMI, or other MetS components. Another study, enrolled 40 children, found circulating irisin levels were lower in underweight children and positively related BMI percentile.[24] Nigro, et al investigated 27 obese and 13 control children and found irisin was significantly higher in obese than in control children.[25] Nevertheless, these studies enrolled relative small group of children and did not compared with different genders, which showed different distribution of skeletal muscle, adiposity, and other body compositions.[26] In our study, we found irisin levels were not significant different between normal, overweight and obese in boys and girls. However, we found irisin levels in obese boys were mildly higher than those in normal and overweight boys. Contrarily, obese girls had the lowest irisin levels, followed by overweight girls although no significant difference among these groups. According to our results, irisin levels had different responses to obese in 2 different genders.

In animal study, irisin contributes to regulate glucose metabolism by inhibiting hepatic gluconeogenesis and increasing glycogen synthesis via the PI3K/Akt pathway.[27] In adults, several studies also found circulating irisin is independently associated with FPG. In a Saudi's children study, Al-Daghri et al investigated 153 children and found FPG is negatively related to and a significant predictor of circulating irisin in children.[28] In addition, HOMA-IR in girls, not in boys, is negatively associated to irisin level. Thereafter, there were few studies compared the role of irisin with 2 different genders in children. In our study, we found the contrary associations between irisin and FPG in boys and girls, respectively. Other studies also showed different associations in 2 different genders. In a Japanese clinical investigation, they enrolled 66 obese adults and found irisin is positively related to FPG in men, not in women.[29] Skeletal muscles and adipose tissues are 2 major tissues of regulating glucose metabolism in human. Majority of irisin molecules are secreted from these 2 important tissues. In addition, the body compositions, including of skeletal muscle mass and adipose tissues, of boys and girls show different proportion and position.[30] It is reasonably presumed that the different metabolic relationship, especially FPG, of irisin in boys and girls. Moreover, we speculate that sex and growth hormones in difference races may also contribute sexual contrary relationship between circulating irisin and FPG. The changes of sex hormones show diverse in different ethnic groups,[26,31] which influence the muscle mass and adiposity. On the other hand, 1 study explored 36 girls with Turner syndrome after treating growth hormone.[32] They found serum irisin levels are negatively associated with FPG after treatment of growth hormone. In animal model, circulating irisin, body weight and adiposity significantly increased in female rats receiving ovariectomy, but not in male rats receiving orchiectomy.[33] Accordingly, sex and growth hormones may play important roles of regulating circulating irisin levels in boys and girls.

However, there are some limitations in our study. First, circulating irisin is affected by several other factors, such as degrees and kinds of daily physical exercise and inflammation. We did not have the questionnaires or information about these children' exercise or daily activities. Nevertheless, blood sampling was performed in fasting status in the early morning. Our children did not receive any physical training class at that time. Second, some studies in adults showed irisin levels are influenced by temperature and changed with seasons.[34] Our subjects received the exams in the same season and similar temperature. The variability of irisin levels in different time declined. Third, a large bundle of studies showed the tight associations between irisin and lean muscular mass. We did not have the data of lean body mass in these children. However, the

aim of the present study explored the irisin and MetS components in children. We may propose the related research in the future. Although our present study had the above limitations, our contribution is still not neglected.

5. Conclusion

In conclusion, circulating irisin levels is not significant difference between children without and with MetS in boys and girls. There was 1 nonsignificant declining trend of irisin level in normal, overweight, and obese girls. Irisin is contrary association with FPG in different genders.

Acknowledgment

All authors acknowledge the help of Professor Mary Goodwin, native American, in English Department, National Taiwan Normal University, in manuscript English editing.

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