Association between plasma irisin and impaired glucose regulation among Chinese young men: a cross-sectional study

Lina Sun  
The First Hospital of Qinhuangdao  

Dongmei Fan  
The First Hospital of Qinhuangdao  

Yongfang Ma  
Chengde Medical College  

Xing Wang  
The First Hospital of Qinhuangdao  

Guohui Du  
The First Hospital of Qinhuangdao  

Weinan Zhang  
The First Hospital of Qinhuangdao  

Bowei Liu  
The First Hospital of Qinhuangdao  

Fuzai Yin (yinfuzai62@163.com)  
The First Hospital of Qinhuangdao  

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Abstract

Objective: To investigate the association between plasma irisin and impaired glucose regulation (IGR) among Chinese young men.

Materials and Methods: This cross-sectional study involved 86 Chinese male subjects, aged 18-45 years, who visited the First Hospital of Qinhuangdao (Hebei, China) in 2017 for annual health check-up. Anthropometric measurements, including height, weight and waist circumference (WC) were performed. All patients underwent an oral glucose tolerance test (OGTT) after 8 hours of fasting, and the levels of glucose, insulin, lipids and serum irisin were measured. Participants were categorized into: normal glucose tolerance (NGT) [fasting plasma glucose (FPG) 5.6 mmol/L, and 2-h plasma glucose (2hPG) 7.8 mmol/L after a 75-g OGTT]; IGR [impaired fasting glucose (IFG) (5.6mmol/l ≤ FPG 7.0 mmol/L, and 2hPG 7.8 mmol/L ) and impaired glucose tolerance (IGT) (FPG 5.6 mmol/L, and 7.8 mmol/l ≤ 2hPG 11.1 mmol/L)].

Results: Subjects in the IGR group had higher body mass index (BMI), WC, FPG, 2hPG and homeostasis model assessment of insulin resistance (HOMA-IR), and lower high-density lipoprotein cholesterol (HDL-C) than subjects in the NGT group (P < 0.05). The levels of serum irisin (4.43 ± 1.44 vs. 6.25 ± 1.46 µg/mL) were significantly lower in the IGR group (P<0.05). The prevalence of obesity (42.2% vs. 65.9%), abdominal obesity (66.7% vs. 85.4%), high levels of triglyceride (22.2% vs. 41.5%), low levels of HDL-C (8.9% vs. 41.5%) and low levels of irisin (26.7% vs. 75.6%) was significantly higher among cases in the IGR group (P<0.05). A multiple logistic regression showed that irisin (OR=0.110, P= 0.000) and HOMA-IR (OR=5.586, P = 0.011) were independent risk factors for predicting IGR.

Conclusions: Serum irisin levels were reduced in Chinese young men with IGR. Reduced irisin may increase the occurrence of IGR. It suggested that irisin may predict the occurrence of impaired glucose homeostasis and should be examined in future studies.

Introduction

Impaired glucose regulation (IGR), as the early stage of diabetes, which includes impaired fasting glucose (IFG) and impaired glucose tolerance (IGT), is a transition state from normal glucose metabolism to diabetes mellitus (DM)(1–3). Similar to DM, IGR is strongly associated with the future incidence of cardiovascular disease (CVD) (4); furthermore, people with early-onset DM (< 45 years old) have a much higher risk of CVD than people with usual-onset DM (≥ 45 years old) (5). The American Diabetes Association (ADA) expert panel suggests that around 70% of individuals with prediabetes will eventually develop diabetes with an annual conversion rate of 5–10%(6). Also, it is said that a similar proportion of subjects will revert back to normoglycemia annually if proper and timely interventions are taken. Multifactorial interventions are effective in reducing the risk of impaired glucose homeostasis through control of obesity, hypertension and dyslipidemia. All of these risk factors share common pathogenetic mechanisms as components of insulin resistance (IR) syndrome(7). Hence, the identification and management of IGR is of paramount importance to determine the future burden of diabetes.
Irisin is a myokine which encodes the transcription cofactor peroxisome proliferator-activated receptor-γ co-activator 1α (PGC1α) that is involved in many pathways related to energy metabolism(8). It is secreted after exercise possibly leading to the browning of white adipose tissue, thereby increasing energy expenditure and improving systemic metabolism(9). Circulating irisin was found to be significantly reduced in long-term and new onset type 2 diabetes mellitus (T2DM) patients compared with controls(10), which suggested the diabetic state is accompanied by lower circulating irisin(10,11). Recently a study reported plasma irisin levels in mid-pregnancy were negatively associated with fasting plasma glucose(FPG) levels and IFG at 6–8 weeks postpartum among Chinese women(12). However, other literature reported a null(13) or even positive correlation(14). Taken together, no studies paid attention to young men at early stage of glucose metabolism disorders. Therefore, we carried out a study to investigated the association between serum irisin and IGR among Chinese young men.

**Materials And Methods**

**Study design**

We performed a cross-sectional study in Chinese young men aged from 18 to 45. The inclusion criteria included the following: 1) subjects were clinically stable with no previous medical history of diabetes, hypertension, dyslipidemia, coronary artery diseases, or cerebral stroke, 2) subjects without clinical evidence of endocrinopathy, and 3) subjects were not taking medications known to affect glucose and lipid metabolism, such as statins and glucocorticoids. The exclusion criteria included the following: 1) subjects with hepatic or renal dysfunction (> 1.5-fold elevation of alanine aminotransferase, aspartate aminotransferase, or serum creatinine > 115µmol/L), and 2) subjects with acute and chronic inflammation. This study was approved by the ethics committee of the First Hospital of Qinhuangdao. All subjects provided written informed consent before study initiation.

**Cases and controls**

We enrolled 86 healthy Chinese young men who had gone to the First Hospital of Qinhuangdao for health examinations during 2017. Obesity was defined as body mass index (BMI) ≥ 28kg/m², and abdominal obesity was defined as waist circumference (WC) ≥ 90 cm in males(3). Based on the American Diabetes Association criteria, glucose tolerance condition was defined as following(3): 1) normal glucose tolerance (NGT) [FPG 5.6 mmol/L and 2-h plasma glucose (2hPG) 7.8 mmol/L after a 75-g OGTT]; 2) IFG (5.6mmol/l ≤ FPG 7.0 mmol/L, and 2hPG 7.8 mmol/L after a 75-g OGTT ); 3) IGT (FPG 5.6 mmol/L and 7.8 mmol/l ≤ 2hPG 11.1 mmol/L after a 75-g OGTT). IGR was defined as the combined prevalence of IFG and IGT. High levels of triglyceride(H-TG) were defined as TG ≥ 1.7 mmol/L, and low levels of high-density lipoprotein cholesterol (L-HDL-C) were defined as HDL-C 0.9mmol/L in males according to diagnostic criteria for metabolic syndrome(15). Low levels of irisin (L-irisin) was defined as below the mean of irisin.

**Anthropometric measurements**

Anthropometric measurements, including height, weight and WC, were obtained while the subjects were in light clothing and not wearing shoes. BMI was calculated by dividing weight (kg) by height squared (m²)
WC was measured after a normal exhalation at the level midway between the lowest rib margin and the iliac crest. Patients were asked to stand with their arms raised up and their abdomen uncovered, according to the international standardized technique (16). Each measurement was taken 2 times and the average was obtained.

**Laboratory examinations**

All subjects underwent OGTT with 75 g of oral anhydrous glucose at 8:00 AM after 8 hours of fasting. 75 g anhydrous glucose was dissolved in 250 mL water. Peripheral venous blood samples were taken at 0 and 120 minutes after glucose loading. Plasma glucose concentration was measured using the glucose oxidase method and serum lipids were measured using enzymatic procedures with an autoanalyzer (Hitachi, Tokyo, Japan). Serum irisin levels were determined using a commercially available human ELISA kit (Bio Vision, Milpitas, CA 95035 USA). The sensitivity of the assay was 0.2 µg/ml. The ELISA kits of insulin were purchased from USCNLIFE company, USA. Insulin and serum irisin were measured using an enzyme linked immunosorbent assay (ELISA) with a model 680 microplate reader (BIO-RAD, USA). The following equation for homeostasis model assessment of insulin resistance (HOMA-IR) was used: fasting insulin level (µU/mL) x fasting glucose level (mmol/L)/22.5(17).

**Statistical analysis**

Data are expressed as mean ± standard deviation (SD) or medians with interquartile ranges (IQR). When data was not normally distributed, they were ln transformed for analysis. Comparisons were conducted between groups using the t-test. The χ2 test was used to test for differences in proportions. Multivariate logistic regression analyses were constructed to identify the prognostic markers of IGR. Analyses were performed with the computer software SPSS 23.0 (IBM, NY, USA). Statistical significance was established at P < 0.05.

**Results**

The age, TG and insulin were similar in the two groups (P > 0.05). Table 1 showed clinical and laboratory characteristics in the study subjects. Subjects in the IGR group had higher BMI, WC, FPG, 2h PG and HOMA-IR, and lower HDL-C than subjects in the NGT group (P < 0.05). The levels of serum irisin (4.43 ± 1.44 vs. 6.25 ± 1.46 µg/mL) were significantly lower in the IGR group (P < 0.05).
### Table 1
Clinical and laboratory characteristics of the subjects in different groups.

<table>
<thead>
<tr>
<th>group</th>
<th>AGE</th>
<th>BMI</th>
<th>WC</th>
<th>TG</th>
<th>HDL-C</th>
<th>FBG</th>
<th>2hPG</th>
<th>In INS</th>
<th>In HOMA-IR</th>
<th>IRISIN</th>
</tr>
</thead>
<tbody>
<tr>
<td>NGT</td>
<td>37.07±</td>
<td>26.80±</td>
<td>93.44±</td>
<td>1.90±</td>
<td>1.31±</td>
<td>5.18±</td>
<td>5.83±</td>
<td>2.39</td>
<td>0.93±</td>
<td>6.25±</td>
</tr>
<tr>
<td>n = 45</td>
<td>6.8</td>
<td>3.48</td>
<td>9.14</td>
<td>2.94</td>
<td>0.24</td>
<td>0.24</td>
<td>0.92</td>
<td>± 0.35</td>
<td>± 0.37</td>
<td>± 1.46</td>
</tr>
<tr>
<td>IGR</td>
<td>37.80±</td>
<td>29.14±</td>
<td>97.71±</td>
<td>2.22±</td>
<td>1.11±</td>
<td>5.77±</td>
<td>7.74±</td>
<td>2.53</td>
<td>1.17±</td>
<td>4.43±</td>
</tr>
<tr>
<td>n = 41</td>
<td>4.8</td>
<td>2.66</td>
<td>± 8.41</td>
<td>± 1.74</td>
<td>0.27</td>
<td>0.46</td>
<td>1.95</td>
<td>± 0.40</td>
<td>± 0.39</td>
<td>± 1.44</td>
</tr>
<tr>
<td></td>
<td>-0.585</td>
<td>-3.517</td>
<td>-2.244</td>
<td>-0.606</td>
<td>3.715</td>
<td>-7.266</td>
<td>-5.743</td>
<td>-1.668</td>
<td>-2.924</td>
<td>5.804</td>
</tr>
<tr>
<td></td>
<td>0.560</td>
<td>0.001</td>
<td>0.027</td>
<td>0.546</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
<td>0.099</td>
<td>0.004</td>
<td>0.000</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± standard deviation (SD) or medians with interquartile ranges (IQR). When data was not normally distributed, it was ln transformed for analysis. Abbreviations: BMI, body mass index; WC, waist circumference; TG, triglycerides; HDL-C, high density lipoprotein cholesterol; FBG, fasting plasma glucose; 2hPG, postprandial plasma glucose; INS, fasting insulin; HOMA-IR, homeostasis model assessment of insulin resistance; SD, standard deviation; IQR, indicates interquartile range.

Table 2 showed the comparison of the risk factors of IGR between the two groups. The prevalence of obesity (42.2% vs. 65.9%), abdominal obesity (66.7% vs. 85.4%), H-TG (22.2% vs. 41.5%), L-HDL-C (8.9% vs. 41.5%) and L-irisin (26.7% vs. 75.6%) was significantly higher among cases in the IGR group ($P < 0.05$).

### Table 2
Prevalence of the risk factors in different groups[n(%)].

<table>
<thead>
<tr>
<th>group</th>
<th>Obesity(BMI)</th>
<th>AO(WC)</th>
<th>H-TG</th>
<th>L-HDL-C</th>
<th>L-Irisin</th>
</tr>
</thead>
<tbody>
<tr>
<td>NGT</td>
<td>19 (42.2%)</td>
<td>30 (66.7%)</td>
<td>10 (22.2%)</td>
<td>4 (8.9%)</td>
<td>12 (26.7%)</td>
</tr>
<tr>
<td>(n = 45)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IGR</td>
<td>27 (65.9%)</td>
<td>35 (85.4%)</td>
<td>17 (41.5%)</td>
<td>17 (41.5%)</td>
<td>31 (75.6%)</td>
</tr>
<tr>
<td>(n = 41)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$P$</td>
<td>0.024</td>
<td>0.038</td>
<td>0.046</td>
<td>0.000</td>
<td>0.000</td>
</tr>
</tbody>
</table>

AO, abdominal obesity; WC, waist circumference; H-TG, high levels of triglyceride; L-HDL-C, low levels of high-density lipoprotein cholesterol; L-Irisin, low levels of irisin.

When IGR was considered as the dependent variable in a multiple logistic regression analysis with age, BMI, WC, HDL-C, HOMA-IR and irisin as independent variables, irisin ($\beta = -2.209$, OR = 0.110, $P = 0.000$) and HOMA-IR ($\beta = 1.768$, OR = 5.586, $P = 0.011$) were independent risk factors for predicting IGR (Table 3).
Table 3
Multiple logistic regression analysis for IGR (Stepwise Method).

<table>
<thead>
<tr>
<th></th>
<th>B</th>
<th>P</th>
<th>OR</th>
<th>95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Irisin</td>
<td>-2.209</td>
<td>0.000</td>
<td>0.110</td>
<td>0.039</td>
</tr>
<tr>
<td>ln HOMA-IR</td>
<td>1.768</td>
<td>0.011</td>
<td>5.586</td>
<td>1.506</td>
</tr>
<tr>
<td>constant</td>
<td>-0.862</td>
<td>0.256</td>
<td>0.422</td>
<td></td>
</tr>
</tbody>
</table>

Multiple logistic regression analysis, IGR was considered as the dependent variables in a multiple logistic regression analysis with age, BMI, WC, HDL-C, HOMA-IR and irisin as independent variables. Abbreviations: IGR, impaired glucose regulation; BMI, body mass index; WC, waist circumference; HDL-C, high density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance.

Discussion

In the present study, we found that the serum irisin level was reduced in Han young males with IGR. Although we ruled out the factor of metabolic abnormalities, serum irisin still plays an important role in impaired glucose regulation. Multiple logistic regression analysis showed that serum irisin and HOMA-IR were significant independent predictors for IGR. Our findings suggest that reduced serum irisin levels may increase the occurrence of glucose disorders and may predict the occurrence of diabetes in Chinese young men.

Many clinical studies have reported lower levels of irisin in patients with T2DM than in controls (17–19). For instance, Ali EY et al, reported irisin was lower in T2DM patients with macrovascular complications as compared to controls (17). Similarly, another study showed a negative association between irisin and FBG in subjects with new-onset T2DM (20). Further, our previous studies also observed a decreased level of circulating irisin in metabolically healthy, obese adults (21). Meanwhile, in animal studies, irisin can positively affect glucose homeostasis, lipid profile and other metabolic parameters related to obesity (22,23). Several underlying mechanisms linking irisin to glucose homeostasis and other metabolic parameters, were suggested as follows. First, it was reported that irisin regulated glucose utilization and improved fatty acid oxidation via adenosine monophosphate-activated protein kinase signaling pathway activation (22). What's more, irisin functioned as a muscle-derived energy-expenditure signal that induced browning of white adipocytes. At molecular level, irisin upregulated the expression of mitochondrial uncoupling protein-1 and other brown adipose tissue-associated genes by activation of the p38 mitogen-activated protein kinase and extracellular signal-regulated kinase signaling pathway(24).

However, there is some contradictory evidence that described a positive association between irisin and glucose levels, whole-body mass and fat mass in different subpopulations. Patients with anorexia nervosa had significantly lower levels of irisin than normal-weight people or individuals with obesity (25). Serum irisin is also positively associated with fasting insulin and blood glucose levels in individuals who are obesity but not T2DM, and in women with polycystic ovary syndrome (26,27). There is one possible explanation for the association between irisin and fat mass, which is the development of irisin resistance.
It’s speculated that in order to achieve metabolic balance, the irisin increased secretion in obesity is aimed to maximize energy usage and glucose homeostasis.

In our study, we also evaluated other metabolic parameters. The subjects in the IGR group were found to have significantly higher BMI, WC and HOMA-IR, and lower HDL-C. Although IGR, obesity and dyslipidemia are all risk factors for T2DM and CVD, the combination of these risk factors has been consistently associated with a more adverse risk profile than neither of the isolated categories(28). In a meta-analysis of randomized, subjects with IGR in control group structured changes in lifestyle reduced incident cases of T2DM by almost 50%, as long as a weight loss of at least 5% was achieved(29).

There were some limitations in our study. First, it only included young men of the Han ethnicity in our study and the low number of subjects included on each group that can decrease the power of the statistical analysis performed. So similar studies in a larger population are needed to evaluate the generalizability. Second, a causal relationship is not possible to infer due to the cross-sectional nature of the study design. Future research should focus on the effect of irisin on insulin secretion and signal pathway, and on any possible interactions between the two pathways that might affect glucose homeostasis.

In conclusion, the present study demonstrates that serum irisin levels were reduced in Chinese young men with IGR. In addition, reduced irisin may increase the occurrence of IGR. It suggested that irisin may predict the occurrence of impaired glucose homeostasis and should be examined in future studies.

Abbreviations

IGR: impaired glucose regulation; IFG: impaired fasting glucose; IGT: impaired glucose tolerance; DM: diabetes mellitus; T2DM: type 2 diabetes mellitus; CVD: cardiovascular disease; IR: insulin resistance; PGC1α: peroxisome proliferator-activated receptor-γ co-activator 1α; FPG: fasting plasma glucose; 2hPG: 2-h plasma glucose ; OGTT: oral glucose tolerance test; BMI: body mass index; WC: waist circumference; NGT: normal glucose tolerance; TG: triglyceride; HDL-C: high-density lipoprotein cholesterol; HOMA-IR: homeostasis model assessment of insulin resistance.

Declarations

Ethics approval and consent to participate

The experimental protocol was established, according to the ethical guidelines of the Helsinki Declaration and was approved by the Human Ethics Committee of the First Hospital of Qinhuangdao. All subjects provided written informed consent before study initiation.

Consent for publication

Not applicable.
Data availability statement

All data included in this study are available upon request by contact with the corresponding author through email.

Competing interests

The authors report no conflict of interest.

Funding

Not applicable.

Author Contributions statement

Lina Sun collected and interpreted the data, performed the data analyses, and wrote the manuscript. Yongfang Ma Xing Wang and Dongmei Fan performed the data analyses. Guohui Du and Weinan Zhang collected the data. Bowei Liu and Fuzai Yin designed the study, reviewed the manuscript. All authors agreed to be accountable for all aspects of the work.

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References


