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Exenatide treatment increases serum irisin levels in patients with obesity and newly diagnosed type 2 diabetes

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ABSTRACT

Objective: Irisin is a myokine secreted by skeletal muscle during exercise. Abnormal serum irisin levels are associated with obesity and type 2 diabetes (T2D). This study investigated the changes in serum irisin in the obese patients with newly diagnosed T2D following glucagon-like peptide-1 (GLP-1) receptor agonist (exenatide) treatment.

Methods: Fifty-four obese patients with T2D were treated with exenatide for 12 weeks. The control group included 54 age-, sex-, and body mass index (BMI)-matched subjects with normal glucose tolerance.

Results: Patients with T2D had lower irisin than the control group (38.06 [29.29–53.79] vs. 58.01 [43.07–87.79] ng/mL, $P < 0.01$]. Serum irisin was negatively associated with BMI ($r = -0.178$, $P < 0.05$), fasting blood glucose (FBG; $r = -0.170$, $P < 0.05$), and glycosylated hemoglobin (HbA1c; $r = -0.189$, $P < 0.01$) in patients with T2D. Exenatide treatment markedly increased serum irisin by 19.28 ng/mL (12.59–25.98) compared to baseline ($P < 0.01$). Increased irisin was significantly correlated with decreased FBG and HbA1c after exenatide treatment (FBG: $r = -0.35$; HbA1c: $r = -0.37$; both $P < 0.05$).

Conclusions: Exenatide treatment significantly increased irisin in patients with T2D. Post-treatment changes in irisin were correlated with decreases in FBG and HbA1c. The upregulation of irisin might be a novel mechanism for the beneficial effects of exenatide in type 2 diabetic patients.

1. Introduction

Irisin is a newly discovered myokine (Huh et al., 2014). It is secreted in response to exercise, which stimulates expression of the type I membrane protein fibronectin type III domain-containing protein 5 (FNDC5) in skeletal muscle, and then FNDC5 is cleaved and secreted into the circulation as irisin (Bostrom et al., 2012). Animal studies have shown that irisin regulates energy metabolism and mediates some of the beneficial effects of exercise (Huh et al., 2014). Abnormal serum irisin levels have also been associated with multiple metabolic diseases in human (Liu et al., 2013; Polyzos, Kountouras, Anastasilakis, Geladari, & Mantzoros, 2014; Yan et al., 2014). Several studies have demonstrated that patients with type 2 diabetes have decreased serum irisin (Choi et al., 2013; Xiang, Xiang, Yue, Zhang, & Zhao, 2014). Moreover, an animal study showed that metformin, a common hypoglycemic agent especially used in patients with obesity (Li, Yang, et al., 2015), increased FNDC5 expression of skeletal muscle cells and blood irisin levels in diabetic db/db mice (Li, Huang, et al., 2015). Furthermore, in women with polycystic ovary syndrome, metformin elevated circulating irisin levels (Li, Yang, et al., 2015).

Glucagon-like peptide-1 (GLP-1) receptor agonists are novel agents approved for treating type 2 diabetes (Liu, Wang, Jia, & Xu, 2015). In addition to reducing insulin resistance and glucagon production, these agents also enhance energy expenditure and reduce body weight, supporting their use in obese patients with type 2 diabetes (Liu et al., 2015). Several large-scale studies have demonstrated that a GLP-1 receptor agonist increases insulin sensitivity and causes more weight loss than does metformin (Liu et al., 2015; Sun et al., 2015). Similar to irisin, GLP-1 receptor agonists increase peroxisome proliferator-activated receptor α (PPARα) expression and AMP-activated protein kinase phosphorylation (Ding, Saxena, Lin, Gupta, & Anania, 2006; Lee et al., 2012). These similar effects of GLP-1 receptor agonists and irisin suggest a possible association between GLP-1 receptor agonists and irisin. However, to the best of our knowledge, there have been no studies into the relationship between irisin and GLP-1 receptor agonist treatment. As exenatide is a classical GLP-1 receptor agonist widely used in many countries, our study aimed to investigate the change in serum irisin levels in obese patients with newly diagnosed type 2 diabetes following exenatide treatment.

Disclosure: The authors declare that they have no conflicts of interest concerning this article.

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2. Methods

2.1. Study design and participants

Fifty-four obese patients with newly diagnosed with type 2 diabetes (T2D group) were consecutively enrolled from March 2013 to December 2013 at the Department of Endocrinology in Beijing Chao-yang Hospital Affiliated with Capital Medical University (Consultation, 2004). An oral glucose tolerance test (OGTT) was performed at screening. All patients had been diagnosed with type 2 diabetes within the previous 3 months according to the 2013 American Diabetes Association diagnostic criteria (American Diabetes, 2013). They had not received anti-diabetic drugs before enrollment, and they met the following inclusion criteria: 1) age 20–64 years old; 2) BMI ≥25 kg/m^2 (Consultation, 2004); and 3) glycosylated hemoglobin (HbA1c) ≥7%. Furthermore, we also enrolled 54 age-, sex-, and body mass index (BMI)-matched healthy subjects with normal glucose tolerance to evaluate whether the baseline irisin level of obese patients with newly diagnosed type 2 diabetes was different from obese subjects with normal glucose tolerance. The subjects in the control group underwent an OGTT to exclude potential diabetes. Exclusion criteria for both groups included: 1) pregnancy or possible pregnancy, 2) coronary artery disease, 3) thyroid disease, 4) liver or renal function impairment, 5) infectious disease, 6) systemic inflammatory disease, or 7) cancer. All subjects who were taking agents known to influence glucose or lipid metabolism were also excluded. The T2D group received 12 weeks of exenatide treatment (5 μg bid for the first 4 weeks and 10 μg bid for the next 8 weeks, subcutaneous injection). All patients were asked to maintain the same levels of exercise. This study was approved by the Ethics Committee of Beijing Chao-yang Hospital Affiliated with Capital Medical University, and all subjects received written information regarding this study and provided written informed consent.

2.2. Clinical and biochemical measurements

Patients were followed up every 4 weeks, fasting blood samples were taken, and side effects were recorded at each visit. During the 12 weeks of exenatide administration, we did not observe hypoglycemia in any patients, but three patients dropped out of the study because of moderate to severe nausea and vomiting.

Anthropometric tests and laboratory assays were performed at baseline and after 12 weeks of exenatide administration. Height and weight were measured to the nearest 0.1 cm and 0.1 kg, respectively, by the same trained researchers. Blood samples were collected in the morning after an overnight fast and stored at −80 °C. Total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglycerides (TG) were measured by means of colorimetric enzymatic assays, using an autoanalyzer (Hitachi 7170). Fasting blood glucose (FBG) and fasting insulin (FINS) were measured at the central chemistry laboratory of Beijing Chao-yang Hospital Affiliated with Capital Medical University. At the same time, serum irisin levels were measured in duplicate using ELISA kits (Aviscera Biosciences, Santa Clara, CA). The sensitivity of the assay was 0.2 ng/mL, and the linear range of the standard was 5–500 ng/mL. BMI was calculated as the weight in kilograms divided by the height in meters squared. We calculated the homeostasis model assessment of insulin resistance (HOMA-IR) and homeostasis model assessment of β-cell function (HOMA-β) according to the following formulas: HOMA-IR = FINS (μIU/mL) × FBG (mmol/L)/22.5; HOMA-β = 20 × FINS (μIU/mL)/FBG (mmol/L) − 3.5 (Matthews et al., 1985).

2.3. Statistical analysis

Continuous data with normal distributions were expressed as means ± standard deviations. Because of skewed distribution, the values of TG, fasting insulin (FINS), irisin, HOMA-IR, and HOMA-β were reported as medians and the upper limit of the lowest quartile and the lower limit of the highest quartile. The skewed distributed data were fitted to a normal distribution after log transformation. The differences between groups were analyzed using the independent sample t-test. The differences in proportions were analyzed using the chi-square test. We used Pearson and Spearman analysis to assess the correlation between serum irisin levels and metabolic parameters at baseline. Changes in parameters from baseline were evaluated using the paired t-test. Bivariate correlation analyses were also used to identify relationships between changes in the variables. Statistical analyses were conducted using SPSS statistical software, version 17.0 (SPSS Inc., Chicago, IL, USA). All tests were two-tailed, and statistical significance was inferred when $P < 0.05$.

3. Results

3.1. Baseline patient characteristics

Baseline characteristics of the T2D and control groups are summarized in Table 1. Age, sex, and BMI were similar between groups, whereas increased TG, FBG, HbA1c, and HOMA-IR levels and decreased HOMA-β and HDL-C levels were observed in the T2D group compared to the control group (all $P < 0.01$). TC, LDL-C, and FINS levels were not different between the two groups. Importantly, serum irisin levels were significantly lower in the T2D group than those in the control group (38.06 [29.29–53.79] vs. 58.01 (43.07–87.79) ng/mL, $P < 0.01$).

3.2. Correlation between irisin and metabolic parameters

In addition, there was no correlation between serum irisin levels and metabolic parameters in both groups. Serum irisin levels were significantly and negatively associated with BMI, FBG, and HbA1c levels (BMI: $r = -0.178$, $P < 0.05$; FBG: $r = -0.170$, $P < 0.05$; HbA1c: $r = -0.189$, $P < 0.01$) in the T2D group. After adjusting for BMI and TG, a negative association remained between irisin and HbA1c levels in the T2D group ($r = -0.201$, $P < 0.01$). No significant correlations between serum irisin level and metabolic parameters were observed in the control group.

3.3. Influence of exenatide on metabolic parameters in patients with obesity and newly diagnosed with type 2 diabetes

Our study did not accurately measure the specific food intake, but 84.3% patients (43/51) reported that their food intake decreased by at least one third. Changes in metabolic parameters after exenatide treatment in the T2D group were summarized in Table 1. BMI values significantly decreased from baseline after 12 weeks of exenatide treatment ($P < 0.01$). Moreover, exenatide treatment significantly decreased FBG and HbA1c levels compared with baseline (both $P < 0.01$). However, FINS levels did not significantly change. Compared with baseline, exenatide treatment significantly decreased TG and TC levels (both $P < 0.01$), but it did not affect LDL-C or HDL-C levels. Decreased HOMA-IR values and increased HOMA-β values were also observed after exenatide treatment (both $P < 0.01$). Serum irisin levels also significantly increased after exenatide treatment ($P < 0.01$, Fig. 1).

3.4. Correlations between the increase in irisin and changes in metabolic parameters after exenatide treatment

The increase in irisin levels was not significantly related to the changes in BMI, TC, LDL-C, HDL-C, TG, FINS, HOMA-IR, or HOMA-β levels. Interestingly, the increase in irisin levels after exenatide