Contents available at ScienceDirect

Diabetes Research and Clinical Practice

journal homepage: www.elsevier.com/locate/diabres

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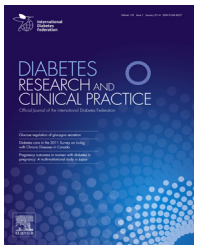

Serum irisin concentrations were increased after transient continuous subcutaneous insulin infusion in type 2 diabetes mellitus patients

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ARTICLE INFO

Article history:
Received 13 August 2015
Received in revised form
17 January 2016
Accepted 22 January 2016
Available online 2 February 2016

Keywords:
Irisin
CSII
T2DM
Lipid profiles
HbA1c

ABSTRACT

Irisin, identified as a novel myokine, plays an important role in improving metabolic disorders, including type 2 diabetes mellitus (T2DM). In this interventional study, we investigated the alteration of serum irisin levels in T2DM subjects after transient continuous subcutaneous insulin infusion (CSII) treatment.

1. Introduction

Skeletal muscle secretes a variety of cytokines (myokines), impacting on metabolic processes of related organs and tissues [1,2]. The newly identified peptidic myokine "irisin" is the proteolytic product of fibronectin type III domain containing 5 (FNDC5) [3]. Irisin can promote browning of white adipocytes [3,4], which enhances energy expenditure and weight loss, and improves glucose–lipid homeostasis [5]. It is reported that T2DM patients have lower circulating irisin concentrations compared with healthy controls [6–9].

Intensive insulin therapy optimized by CSII can quickly relieve hyperglycemia and effectively recover the β-cell function in T2DM patients [10,11]. CSII can also improve lipid profiles [12–14]. In this study, we aimed to evaluate the change in serum irisin levels in T2DM patients after transient CSII treatment.

2. Materials and methods

Twenty T2DM patients and 13 healthy controls (all from a Chinese Han population) participated in this study. The study was completed in 2 months and none dropped out. Those with severe organic diseases, including cardiac insufficiency, chronic renal dysfunction, digestive disorders, malignant cancers, and other types of diabetes mellitus or with acute

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http://dx.doi.org/10.1016/j.diabres.2016.01.030
0168-8227/

diabetic complications were excluded. The study was conducted in accordance with the Declaration of Helsinki and the protocol was approved by the Ethics Committee of Shanghai Tenth People's Hospital. Each participant signed a written informed consent.

There was 1 premenopausal woman and 1 male smoker among the T2DM patients. We advised all the subjects to keep their usual exercise levels during the study and the T2DM patients underwent a regulated diet regimen supplied by the hospital. Most T2DM subjects received oral medications before the study, and 4 of them also used insulin treatment. Those who were on metformin (8 subjects, 1.0–2.0 g/day) and on acarbose (12 subjects, 150 mg/day) continued with their initial treatment regimen. Apart from metformin and acarbose, all the other anti-diabetic drugs were stopped. Prior to the study, none received lipid lowering treatments, but, once started, 3 T2DM patients received a statin (20 mg/day). No other lipid lowering medications were used in the T2DM group. Additionally, healthy controls did not receive any lipid lowering or anti-diabetic medication.

The 20 T2DM patients were treated with CSII for 1 week using MiniMed 712E insulin pump (Medtronic MiniMed, Northridge, CA, USA). The daily regular human insulin (Humulin R, Lilly France S.A.S., Fegersheim, France) doses were adjusted accordingly based on capillary blood glucose. After an 8–10 h overnight fasting time, venous blood samples were obtained on the first and last day of the study. Serum was collected by centrifugation and stored frozen at −80 °C. Triglycerides (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-c), high-density lipoprotein cholesterol (HDL-c), fasting blood glucose (FBG), 2 h postprandial blood glucose (2hPBG), glycated albumin (GA), and glycated hemoglobin A1c (HbA1c) were measured by colorimetric enzymatic assay systems (Roche MODULAR P-800, Switzerland). Serum irisin was measured with a commercial ELISA kit (Phoenix Pharmaceuticals, Belmont, CA, USA) following the manufacturer's instructions. Statistical analyses were conducted using the PASW Statistics 20 software (IBM Corporation, Armonk, New York, USA). P values <0.05 were considered to be statistically significant.

3. Results

Twenty T2DM patients (11 males and 9 females, with age 48.4 ± 14.5 years and disease duration 8.1 ± 6.2 years) and 13 healthy controls (5 males and 8 females, with age 41.5 ± 10.6 years) were enrolled in the study. Clinical biochemical parameters are shown in Table 1.

Healthy controls had lower body mass index (BMI), FBG, 2hPBG, GA, and HbA1c levels than pre-treatment T2DM patients ($P < 0.05$ or $P < 0.001$, adjusted for age and BMI). Independent t-test analysis suggested that pre-treatment T2DM subjects had lower irisin concentrations compared with healthy controls (15.4 ± 6.6 ng/mL vs. 20.4 ± 6.8 ng/mL, $P = 0.048$, Fig. 1). However, after adjustment for age and BMI, it was not statistically significant ($P = 0.076$).

The 20 T2DM patients with CSII treatment achieved relatively good glycemic control within 2–4 days, FBG and 2hPBG decreased from 9.9 ± 3.3 mmol/L to 7.5 ± 2.4 mmol/L, $P = 0.004$, and from 20.3 ± 4.2 mmol/L to 10.3 ± 4.1 mmol/L, $P < 0.001$, respectively. There was also a statistically significant reduction in GA and HbA1c (both $P < 0.001$). Decreases in TG, TC, and LDL-c levels ($P < 0.01$ or $P < 0.001$) were observed. Furthermore, irisin levels were significantly elevated (from 15.4 ± 6.6 ng/mL to 20.4 ± 8.0 ng/mL, $P = 0.020$, Fig. 1) in the T2DM subjects.

4. Discussion

In this study, we found that serum irisin was significantly increased accompanied by improved glycemic control and lipid profiles in T2DM subjects after transient CSII treatment.

Previous studies have suggested the favorable role of CSII on lipid metabolism besides excellent glucose management for its physiological-like insulin secretory functions [10–14]. Following CSII treatment for 1 week, FBG, 2hPBG, and GA of the T2DM patients were significantly reduced. Furthermore, although a slight decrease in HbA1c was noted (samples were only 1 week apart), it was statistically significant ($P < 0.001$).

Table 1 – Clinical characteristics of healthy controls and T2DM subjects before and after CSII treatment.

	Control	Pre-treatment T2DM	Post-treatmentT2DM	P value*	P value**
Gender (Male:Female)	5:8	11:9		0.353	–
Age (year)	41.5 ± 10.6	48.4 ± 14.5		0.147	–
BMI (kg/m^2)	23.1 ± 2.4	25.9 ± 4.0	25.6 ± 5.2	0.042	0.054
TG (mmol/L)	0.9(0.6–1.2)	1.4(1.1–2.5)	1.0(0.9–1.6)	0.260	0.007
TC (mmol/L)	5.3(4.7–6.0)	4.8(4.3–5.8)	4.1(3.8–4.5)	0.578	<0.001
LDL-c (mmol/L)	2.6(2.5–3.5)	3.0(2.4–3.7)	2.3(2.1–2.8)	0.549	0.002
HDL-c (mmol/L)	1.3 ± 0.3	1.2 ± 0.3	1.2 ± 0.3	0.882	0.775
FBG (mmol/L)	5.2 ± 0.6	9.9 ± 3.3	7.5 ± 2.4	<0.001	0.004
2hPBG (mmol/L)	6.1 ± 0.5	20.3 ± 4.2	10.3 ± 4.1	<0.001	<0.001
GA (%)	13.5 ± 3.2	33.1 ± 11.9	28.4 ± 10.0	<0.001	<0.001
HbA1c (%)	5.5 ± 0.4	10.9 ± 2.1	10.3 ± 1.9	<0.001	<0.001
HbA1c (mmol/mol)	37 ± 5	95 ± 23	90 ± 21	<0.001	<0.001
Irisin (ng/mL)	20.4 ± 6.8	15.4 ± 6.6	20.4 ± 8.0	0.076	0.020

Data are expressed as mean ± standard deviation, or median (interquartile ranges).
* P value, comparison between healthy controls and pre-treatment T2DM subjects.
** P value, comparison between pre-treatment and post-treatment T2DM subjects.