Research Article

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Irisin is inversely associated with intrahepatic triglyceride contents in obese adults

Hui-Jie Zhang[1,2,†], Xian-Feng Zhang[1,†], Zhi-Min Ma[3], Ling-Ling Pan[1], Zheng Chen[2], Hai-Wei Han[2], Cheng-Kun Han[2], Xiong-Jie Zhuang[2], Yan Lu[1], Xue-Jun Li[2], Shu-Yu Yang[2], Xiao-Ying Li[1,*]

[1]*Shanghai Clinical Center for Endocrine and Metabolic Diseases, Shanghai Key Laboratory of Endocrine Tumor, Shanghai Institute of Endocrinology and Metabolism, Rui-Jin Hospital, Shanghai Jiao Tong University School of Medicine, 197 Rui-Jin 2nd Road, Shanghai 200025, China;* [2]*Xiamen Diabetes Institute, Department of Endocrinology and Metabolism, The First Hospital of Xiamen, Xiamen University, 55 Zhenhai Road, Xiamen 361003, China;* [3]*Department of Endocrinology, The Second Affiliated Hospital of Soochow University, 1055 SanXiang Road, Suzhou City, Jiangsu Province 215004, China*

Background & Aims: Obesity is closely related to non-alcoholic fatty liver disease (NAFLD), which has become an important public health problem because of its high prevalence and association with metabolic syndromes. Irisin was recently identified as a novel peptide to improve obesity and glucose homeostasis, and considered to be therapeutic for human metabolic diseases. The aim of this study was to examine the association of serum irisin concentration and liver triglyceride contents in obese Chinese adults.

Methods: Serum irisin levels were measured and liver fat contents determined by ^{1}H MRS in 296 obese adults. Anthropometric parameters and blood biochemical indexes including liver enzymes, glucose, and lipid profiles were detected. The liver triglyceride contents of subjects were measured by ^{1}H MRS. The protein levels of irisin were determined by quantitative ELISA.

Results: We found that serum irisin levels were reduced in obese adults with NAFLD. By dividing the distribution of intrahepatic triglyceride (IHTG) contents into quartiles, serum irisin levels were reduced gradually with the increase of IHTG contents (p <0.01). Higher serum irisin levels were associated with preferable TG levels. Serum ALT and AST concentrations were inversely correlated with serum irisin levels. Multivariate linear regression analysis demonstrated that serum irisin levels were independently associated with liver fat (p <0.01). By logistic regression analysis, the odds ratio for higher IHTG contents was reduced by 12.4% per 1 SD increase in serum irisin concentrations after adjustment for multivariate metabolic factors [OR (95% CI); 0.876 (0.777–0.987)].

Conclusions: These results demonstrated that serum irisin concentrations were inversely associated with the triglyceride contents in the liver and liver enzymes in obese Chinese adults.
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Keywords: Non-alcoholic fatty liver disease; Intrahepatic triglyceride content; Irisin; Obesity.

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* Corresponding author. Address: Department of Endocrinology and Metabolism, Rui-Jin Hospital, Shanghai Jiao Tong University School of Medicine, 197 Rui-Jin 2nd Road, Shanghai 200025, China. Tel.: +86 21 64370045x610909; fax: +86 21 64373514.

E-mail address: lixy@sibs.ac.cn (X.-Y. Li).

† These authors equally contributed to this work.

Introduction

Non-alcoholic fatty liver disease (NAFLD) is recognized as an independent predictor of insulin resistance, metabolic syndrome, and cardiovascular diseases, affecting up to one third of the adult population in obese individuals in affluent nations [1,2]. Patients with NAFLD have an adverse proatherogenic lipid profile with elevated low density lipoprotein (LDL) levels, reduced high density lipoprotein (HDL) levels, increased systemic levels of proatherogenic cytokines, and altered cardiac metabolism [3].

Physical exercise, as a crucial component of behavioral interventions, has been shown to be effective in improving NAFLD while combined with reduction of food intake. Recent clinical trials have shown that a 6.5% to 10% weight loss through lifestyle modification improved liver biochemistry and markers of liver injury including lobular inflammation and hepatocellular ballooning [4,5]. Some studies showed that even without any weight loss, moderate intense exercise appeared to improve insulin sensitivity, and reduce liver enzymes and hepatic steatosis [6–8]. However, the potential mechanism of exercise on improvement of hepatic steatosis and hepatic metabolic function in obese people with NAFLD has been controversial.

With the discovery that exercise provokes an increase in a number of cytokines from skeletal muscles, a possible link between skeletal muscle contractile activity and metabolic changes was established [9]. Muscle-derived interleukin (IL)-6 has been implicated in modulating hepatic steatosis and other pathophysiological changes leading to insulin resistance and non-alcoholic steatohepatitis (NASH) development [10,11]. It was also reported that exercise induced IL-6 could enhance insulin secretion by increasing glucagon like peptide-1 (GLP-1) from

intestinal L-cells and pancreatic alpha cells [12]. Recent studies showed that physical exercise induced intramuscular expression of the transcriptional co-activator PGC-1α and its downstream molecule, the membrane protein fibronectin type III domain containing 5 (FNDC5), which is proteolytically cleaved to form irisin [13]. The circulating irisin could induce the differentiation of stromal vascular cells isolated from mouse subcutaneous white fat into a brown adipocyte phenotype, a process known as white fat "browning" [14]. Irisin acts on white adipose cells to stimulate the expression of uncoupling protein 1(UCP1), which is characteristic of brown adipose tissues [15,16]. UCP1 funnels the energy generated from respiration into heat production. And then, this change is accompanied by an increase in total body energy expenditure, modest weight loss, and modest improvements in glucose intolerance.

Therefore, it would be interesting to explore the association of the circulating irisin levels with non-alcoholic fatty liver diseases. Irisin activated downstream signaling pathways involve the peroxisome proliferator activated receptors α (PPARα), which plays a crucial role in fatty acid β-oxydation in the liver [17–19]. In the present study, we investigated the protective role of irisin in NAFLD in obese adults.

Patients and methods

Study subjects

Obese subjects were screened with physical examination and type B ultrasonography for fatty liver in the Lianqian community, Xiamen, China from April to August 2011. A total of 1043 adult subjects with waist circumference of greater than 90 cm for males and 85 cm for females were included. Of those, 296 subjects received the measurement of intrahepatic triglyceride (IHTG) contents by Magnetic Resonance Spectroscopy (MRS) and abdominal fat areas by computed tomography (CT). 75-g oral glucose tolerance test and blood biochemical measurements were conducted. All participants completed a uniform questionnaire including physical activities, diets, and histories of present and past illnesses and medication. Subjects were excluded if they had biliary obstructive diseases, acute or chronic virus hepatitis, drug-induced liver diseases, total parenteral nutrition, autoimmune hepatitis, Wilson's disease, known hyperthyroidism or hypothyroidism, presence of cancer, and current treatment with systemic corticosteroids. The alcohol drinkers current or in the past 6 months, with alcohol consumption ⩾140 g/week for men or 70 g/week for women were also excluded from the study.

The study was approved by the Human Research Ethics Committee of the Xiamen First Hospital. The written informed consent was obtained from each subject.

Anthropometric and biochemical measurements

Anthropometric measurements include body weight, height, waist circumference, blood pressure (BP), body mass index (BMI), and body fat. Body mass index (BMI) was calculated as the weight in kilograms divided by the square of the height in meters. Waist circumference was measured at the midpoint between the inferior costal margin and the superior border of the iliac crest on the midaxillary line. Body fats were quantified with the HOLOGIC whole body DXA systems (Hologic Inc., Bedford, MA).

All blood samples were obtained after 12 h of fasting. Plasma glucose, liver enzyme levels, and serum lipid profiles, including triglyceride (TG), total cholesterol (TC), and high-density lipoprotein cholesterol (HDL-C) were determined on a Hitachi 7450 analyzer (Hitachi, Tokyo, Japan). Low-density lipoprotein cholesterol (LDL-C) was calculated using the Friedewald's formula. Fasting plasma glucose concentration (FPG) and 2-h plasma glucose concentration (2hPG) were measured by the hexokinase method. Serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were measured by standard enzymatic methods. Serum gamma-glutamyltransferase (GGT) was measured by the Szasz-Persijn method. Serum fasting insulin concentrations were measured by electrochemiluminescence immunoassay (Roche Elecsys Insulin Test, Roche Diagnostics, Mannheim, Germany). HOMA–insulin resistance (HOMA-IR) was calculated by fasting serum insulin (FIns, mU/ml) × fasting blood glucose (FBG, mmol/L)/22.5.

Measurement of intrahepatic triglyceride contents and abdominal fat areas

Magnetic resonance spectroscopy (^{1}H MRS) images of the liver were performed using a 3.0-T Avanto MR system (Siemens AG, Erlangen, Germany) by an experienced radiologist. A sagittal, coronal, and axial cube of a 2 cm^3 volume in the right lobe of the liver was acquired. Quantification of the spectra (water and methylene resonances) was performed as described previously [20,21]. Areas of resonances from protons of water and methylene groups in fatty acid chains were obtained with time-domain non-linear fitting routine using a commercial software (Syngo spectroscopy VB15, Siemens AG). IHTG contents were calculated by dividing the integral of the methylene groups in fatty acid chains of the hepatic triglycerides by the sum of methylene groups and water.

Abdominal subcutaneous fat area and intra-abdominal fat area were measured by computed tomographic scans (GE Medical Systems, Milwaukee, WI, USA) at the level of the fourth lumbar vertebra as described previously [22,23]. Tissue compartments were measured by planimetry with a trackball-controlled cursor. The area of adipose tissues in each compartment was quantified by manufacturer-supplied software that sums the area of pixels in the digital image with CT values from −250 to −50 Hounsfield Units (HUs), which correspond to adipose tissues [22].

Serum irisin measurement

Serum irisin concentrations were measured by using the enzyme-linked immunosorbent assay (ELISA) kits (Aviscera Biosciences, Santa Clara, CA). The assay was proven to be highly sensitive to human irisin [24]. The sensitivity of the assay was 0.2 ng/ml and the linear range of the standard was 5–500 ng/ml. The intra- and inter assay variations were both less than 10%.

Statistical analysis

Statistical analyses were performed with SAS, version 9.2. Data are presented as means ± standard deviation (S.D) or means ± standard error (SEM) or median (interquartile range). Data that were not normally distributed were logarithmically transformed before analysis. Unpaired Student's *t*-test (or Mann Whitney *U*-test) and Chi-square test were used for testing differences for numerical and nominal variables. The χ^2-test was used to compare categorical variables between groups. The correlation of irisin level with metabolic parameters was analyzed by Pearson correlation and multivariate linear regression analysis. The subjects were classified into four quartiles according to IHTG contents or irisin levels, respectively. The different groups were compared using an ANOVA test. The definition of the upper normal limit of IHTG contents was set at the 75th upper percentile of the IHTG contents distribution in subjects. Multiple logistic regression analysis was used to assess the odds ratio (OR) for the presence of higher IHTG content according to different irisin levels. Two-sided values of $p < 0.05$ were considered significant.

Results

Clinical characteristics of subjects

A total of 296 obese adults (age ⩾40 years) receiving measurement of IHTG contents by ^{1}H MRS were evaluated in the present study. Clinical characteristics for all subjects are shown in Table 1. The mean age of the subjects was 54 ± 7 years. All subjects were divided into four quartiles according to IHTG contents (%) (5.7 ± 2.0, 11.0 ± 1.6, 18.0 ± 2.8, and 31.7 ± 7.5, respectively). By dividing the distribution of IHTG contents into quartiles, there were no differences in age, gender, physical activity, TC, LDL, fasting plasma glucose, and postprandial plasma glucose between the four groups. Compared to subjects in the lowest quartile of IHTG contents, those in the highest had significantly higher BMI, waist circumference, TG, systolic blood pressure (SBP), diastolic blood pressure (DBP), and fasting serum insulin (*p* for trend

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