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Relationship between serum irisin levels and urinary albumin excretion in patients with type 2 diabetes

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ABSTRACT

Aim: Irisin is first discovered as a potential mediator of obesity related energy homeostasis. Recent studies indicate that irisin is associated with endothelial dysfunction and atherosclerosis in patients with type 2 diabetes. Our objective was to examine the relationship between irisin and urinary albumin excretion in patients with type 2 diabetes.

Methods: 100 newly diagnosed patients with type 2 diabetes and 100 healthy subjects were selected. Serum irisin levels were measured by ELISA, and urine albumin was measured by radioimmunoassay. High resolution ultrasound was used to measure brachial artery diameter at rest, after reactive hyperemia (flow-mediated arterial dilation, FMD) and after sublingual glyceryltrinitrate.

Results: Patients with type 2 diabetes presented decreased irisin levels when compared to controls (14.12 ± 3.93 versus 28.98 ± 2.56 ng/ml, $P = 0.015$).Serum irisin levels in the microalbuminuric and macroalbuminuria subgroup were 9.89 ± 1.56 ng/ml and 5.67 ± 1.89 ng/ml, respectively, which were significantly lower than those in the normoalbuminuria (15.97 ± 3.12 ng/ml). In comparison to microalbuminuric subgroup, macroalbuminuria subgroup had lower levels of irisin. By dividing the distribution of serum irisin levels into quartiles, FMD was increased gradually with the increase of serum irisin levels ($P < 0.001$). Multiple stepwise linear regression analysis showed that FMD ($\beta = 0.75$, $P = 0.002$), 2-hBG ($\beta = -0.25$, $P = 0.038$) and UAE ($\beta = -0.87$, $P = 0.008$) were significantly associated with irisin. Pearson's correlation analyses showed a negative correlation between irisin and logUAE ($r = -0.57$) and between FMD and logUAE ($r = -0.47$), and positive correlations between irisin and FMD ($r = 0.51$).

Conclusions: Decreased plasma levels of irisin seem to be associated with UAE and FMD in patients with type 2 diabetes.

1. Introduction

Irisin is implicated as a novel hormone in the modulation of energy homeostasis. It has been proven as an effective cytokine that induced the browning of subcutaneous white adipocytes, which is through uncoupling protein 1 (UCP1)-mediated thermogenesis and energy expenditure (Boström et al., 2012). Serum irisin levels were acutely decreased in patients with type 2 diabetes compared with non-diabetic patients (Choi et al., 2013; Liu et al., 2013; Xiang, Xiang, Yue, Zhang, & Zhao, 2014). Recently, some studies have indicated that irisin also acts as an important regulatory molecule in the vasculature, and decreased serum irisin levels are associated with endothelial dysfunction in patients with type 2 diabetes (Xiang et al., 2014). (See Figs. 1– 3.)

Endothelial dysfunction is an early event in experimental studies of atherogenesis and likely plays a central role in the development of vascular disease (Celermajer et al., 1992). Flow-mediated dilation is a non-invasive method of the capacity of the endothelial function, when stimulated by reactive hyperemia, to cause smooth muscle cell relaxation and vasodilation (Celermajer et al., 1992). Impaired FMD has been shown to be an independent predictor of atherosclerosis and cardiovascular disease, as an initial step of pathophysiology (Gokce et al., 2002; Patti et al., 2005). Clinical studies have showed that the impairment of FMD exists in patients with type 2 diabetes (Guangda, Linshuang, Jie, Ling, & Huijuan, 2006; Xiang, Xu, Zhao, Yue, & Hou, 2006). In our study, the FMD technique has been chosen as a non-invasive measurement of endothelial function.

Urinary albumin excretion (UAE) has been strongly linked to cardiovascular disease in persons with or without diabetes mellitus (Lee, Saver, Chang, & Ovbiagele, 2010). Moreover microalbuminuria, a marker of endothelial dysfunction, might be associated with pathophysiologic processes leading to cardiovascular diseases in patients with type 2

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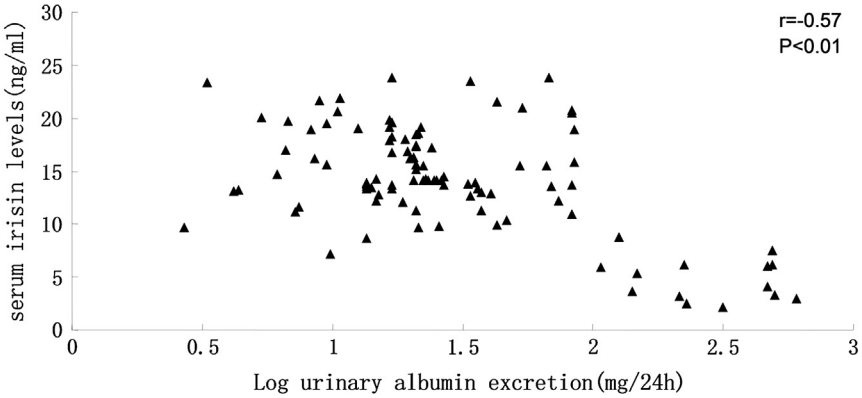

Fig. 1. Correlation between serum irisin levels and log urine albumin excretion in patients with type 2 diabetes.

diabetes (Abdelhafiz, Ahmed, & El Nahas, 2011; Turkmen et al., 2014). Reduced renal function and albuminuria predict cardiovascular events and mortality in patients with type 2 diabetes (Svensson et al., 2013).

Therefore, in this study, we examined serum irisin levels in patients with type 2 diabetes, and the relationship among irisin, UAE and FMD in patients with type 2 diabetes was investigated. We hypothesized that UAE and FMD were associated with lower levels of serum irisin. The aim of this study was to evaluate the effect of irisin on UAE and FMD in patients with type 2 diabetes.

2. Material and methods

2.1. Subjects

From Jan 2013 to May 2014, 100 newly diagnosed patients with type 2 diabetes referred to our hospital were selected. Some patients are from rural regions with little access to medical care, and these people probably have had diabetes for quite some time. During the same period, 100 healthy subjects were selected as controls. Each subject was asked details of family history of cardiovascular diseases. Obese (BMI > 30 kg/m^2) subjects, smokers, malignant neoplasms or liver diseases, renal failure (serum creatinine ≥176 μmol/L), oedema, or endocrinological disease other than diabetes mellitus were also excluded from the study. In addition, no patient was taking any drugs, such as thyroxine, oestrogen supplements, diuretics, antihypertensive drugs or β-blockers or lipid-lowering drugs. This study has been reviewed by the appropriate ethics committee and has therefore been performed in accordance with the ethical standards laid down in an appropriate version of the 1964 Declaration of Helsinki. All persons gave their informed consent prior to their inclusion in the study. The study protocol was in agreement with the guidelines of the ethics committee at our hospital.

2.2. Diagnostic criteria

The diagnosis of type 2 diabetes fulfilled the American Diabetes Association criteria (American Diabetes Association, 2012). Hypertension was defined as a systolic blood pressure ≥140 mmHg or a diastolic blood pressure ≥90 mmHg. Persistent albuminuria at level 30–299 mg/24 h is the presence of early diabetic nephropathy. Overt nephropathy or macroalbuminuria (persistent albuminuria at level ≥300 mg/24 h) may be present in newly diagnosed patients with type 2 diabetes (American Diabetes Association, 2012). Those patients, with clinical or laboratory evidence of other kidney or renal tract disease, have been excluded from our study.. Retinopathy was considered to be present if at least one retinal hemorrhages and/or microaneurysms, hard exudates, new vessels, fibrous proliferations, and macular edema in either eye was observed by fundus examination. Patients should be screened for diabetic neuropathy using tests as pinprick sensation, vibration perception, 10 g monofilament pressure sensation at the distal plantar aspect of both great toes and metatarsal joints, and assessment of ankle reflex (American Diabetes Association, 2012). Cardiovascular events were based on the history of stroke, coronary artery disease or transient ischemic attack. Patients with coronary heart disease are documented by at least one of the following: previous myocardial infarction, previous percutaneous coronary intervention (PCI) or coronary-artery bypass grafting (CABG), or multivessel coronary artery disease.

2.3. Methods

2.3.1. Laboratory methods

The parameters were performed as described previously (Wang & Xiang, 2014). Venous blood samples were drawn after a 12- to 14-h overnight fast. The serum irisin levels were measured in EDTA-plasma

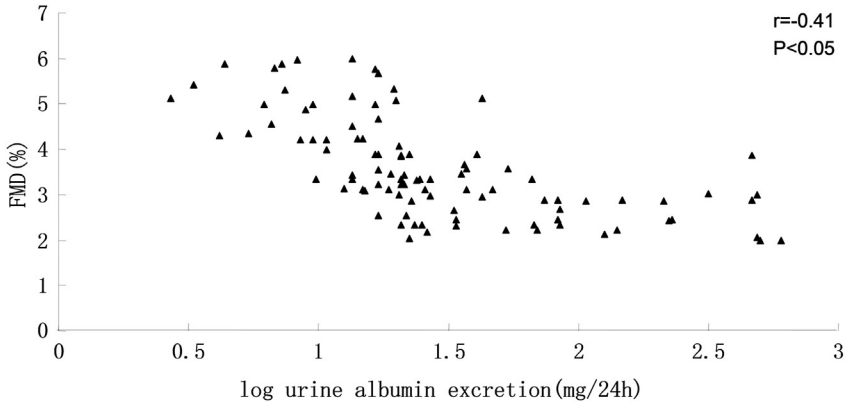

Fig. 2. Correlation between FMD and log urine albumin excretion in patients with type 2 diabetes.

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