Journal of Diabetes and Its Complications 28 (2014) 208–213

Contents lists available at ScienceDirect

Journal of Diabetes and Its Complications

journal homepage: WWW.JDCJOURNAL.COM

Relationship between circulating irisin, renal function and body composition in type 2 diabetes☆,☆☆

Jian-Jun Liu [a], Sylvia Liu [a], Melvin D.S. Wong [a], Clara S.H. Tan [a], Subramaniam Tavintharan [b,c], Chee Fang Sum [b,c], Su Chi Lim [b,c,*]

[a] Clinical Research Unit, Khoo Teck Puat Hospital, Republic of Singapore
[b] Diabetes Centre, Khoo Teck Puat Hospital, Republic of Singapore
[c] Department of Medicine, Khoo Teck Puat Hospital, Republic of Singapore

ARTICLE INFO

Article history:
Received 15 August 2013
Received in revised form 25 September 2013
Accepted 26 September 2013
Available online 4 October 2013

Keywords:
Irisin
Type 2 diabetes
Diabetic nephropathy
Body composition
Chronic kidney disease

ABSTRACT

Aims: Chronic kidney disease (CKD) secondary to type 2 diabetes mellitus (T2DM) is associated with multifaceted energy dysmetabolism. We aim to study the relationship between renal function, body composition and irisin, the recently identified myokine which is involved in energy regulation, in T2DM.
Methods: Circulating irisin and body composition were measured in 365 T2DM subjects across a wide range of renal function.
Results: Circulating irisin was significantly decreased in T2DM with renal insufficiency (77.4 ± 13.7 ng/ml in T2DM with eGFR ≥ 60 ml/min/1.73 m^2 versus 72.5 ± 14.9 ng/ml in those with eGFR < 60 ml/min/1.73 m^2, $p = 0.001$) and the reduction in irisin was most pronounced in stage 5 CKD patients. In T2DM with preserved renal function, irisin was correlated with age ($r = -0.242$, $p = 0.001$) and pulse pressure ($r = -0.188$, $p = 0.002$). Among those with renal insufficiency, irisin was correlated with BMI ($r = 0.171$, $p = 0.022$), fat mass ($r = 0.191$, $p = 0.013$), percentage of fat mass ($r = 0.210$, $p = 0.007$) and eGFR ($r = 0.171$, $p = 0.020$). Multivariate linear regression models revealed that variations in circulating irisin were mainly attributable to eGFR and age in T2DM with and without renal impairment, respectively.
Conclusion: Our observations suggest that the level of circulating irisin may be associated with renal function in T2DM. The role of reduced irisin in energy dysmetabolism in diabetic patients with renal insufficiency deserves further investigation.

1. Introduction

Irisin was first discovered as a novel myokine released into circulation by cleavage and shedding of the membrane fraction of fibronectin type III domain containing 5 (FNDC5) in response to activation of peroxisome proliferator-activated receptor-γ coactivator-1α (PGC-1α). Irisin was found to induce browning of subcutaneous adipocytes and protect diet- and ageing-induced obesity and diabetes in mouse models (Bostrom et al., 2012). Whether these findings in animal models can be translated to humans has important clinical implications (Cunha, 2012; Kelly, 2012).

In our previous study, we found that circulating irisin was significantly lower in type 2 diabetes (T2DM) with a long diabetic duration compared with non-diabetic controls (Liu et al., 2013). Similar findings were reported in newly diagnosed T2DM (Choi et al., 2013). Although circulating irisin was found to be associated with some important clinical and biochemical parameters such as age, body mass index, total triglycerides and fasting plasma glucose in non-diabetic subjects, the relationship between plasma irisin and metabolic indicators among diabetic patients was largely unidentified (Choi et al., 2013; Liu et al., 2013; Timmons, Baar, Davidsen, & Atherton, 2012). The reason why the "expected" associations between circulating irisin and metabolic indicators in patients with type 2 diabetes could not be observed so far may be attributed to, 1) the multifaceted dysmetabolism in diabetes which may have confounded the associations and 2) the underpower of those prior small-sized studies.

Two recent studies suggested that circulating irisin might also be associated with renal function in humans. Wen et al. reported that plasma irisin was significantly lower in non-diabetic patients with stage 5 chronic kidney disease (CKD) compared with age- and sex-

☆ Grant Support: This work was supported by Alexandra Health enabling grant KPREF13EG03Z, Small Innovation Grant SIGII/08005, SIG/11029 and SIGII/11001.
☆☆ Statement of Conflict of Interest: The authors have no financial and personal relationships with other people or organizations that could inappropriately influence (bias) the current work.
* Corresponding author. Department of Medicine, Khoo Teck Puat Hospital, 90 Yishun Central, 768828 Republic of Singapore. Tel.: +65 6602 2353; fax: +65 66023772.

1056-8727/$ – see front matter © 2014 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.jdiacomp.2013.09.011

matched controls (Wen, Wang, Lin, & Hung, 2013). In our earlier study, we also observed that estimated glomerular filtration rate (eGFR) was the only clinical parameter which was significantly correlated with circulating irisin in T2DM patients (Liu et al., 2013). Notably, both studies were small in size. Larger clinical studies are awaited to validate these preliminary observations.

Recent studies also suggest that irisin is not only a myokine but also a novel adipokine, although the contribution of adipose tissue to the abundance of circulating irisin remains unknown (Moreno-Navarrete et al., 2013; Roca-Rivada et al., 2013). Data from Stengel et al. suggested that circulating irisin was positively correlated with BMI and fat mass (Stengel et al., 2013). However, another study showed that circulating irisin was negatively correlated with BMI and percentage of fat mass in male subjects (Moreno-Navarrete et al., 2013). These inconsistencies suggest that more clinical studies are needed to address this important question.

In this work, we aim to study 1) the association of circulating irisin with renal function in T2DM and 2) the relationship between circulating irisin and body composition in T2DM patients.

2. Subjects and methods

2.1. Subjects

T2DM subjects were recruited consecutively from the diabetes clinic in a single secondary hospital in Singapore. Diagnosis of T2DM was based on ADA (2006). A standardized questionnaire was used to record the medical history and medications in use. T2DM subjects with cancer, those with renal replacement therapy for late stage renal disease and subjects without mental capability for informed consent were excluded from the study. As the main purpose of the study was to elucidate the relationship between irisin and changes in renal function secondary to T2DM, subjects were also excluded when involvement of other causes of renal diseases was suspected: urinary tract infection, polycystic kidney disease, presence of overt hematuria, glomerulonephritis and a history of rapidly progressive renal failure.

The study complied with principles laid down by Declaration of Helsinki and it was approved by our institution's domain specific ethics review board. Written informed consent was obtained from all participants.

2.2. Laboratory measurement

HDL-cholesterol, LDL-cholesterol and total triglycerides were quantified by enzymatic method using Kodak Ektachem chemistry slides. An early morning spot urine sample was collected and urinary albumin was measured based on a solid phase competitive chemiluminescent enzymatic immunoassay with a lower detection limit of 2.5 μg/ml (Immulite, DPC, Gwynedd, UK). HbA1c was measured using immunoturbidimetric method (Cobas Integra 800 Chemistry Analyzer, Roche, Basel, Switzerland). Estimated glomerular filtration rate (eGFR) was calculated based on Modified Diet in Renal Disease (MDRD) formula (Stevens, Coresh, Greene, & Levey, 2006).

Quantification of plasma irisin was based on a competitive enzyme immunoassay and the assay kits were purchased from Phoenix Pharmaceuticals Inc (Burlingame, CA). Details on the ELISA assay have been described elsewhere (Huh et al., 2012). The intra-assay coefficients of variability (CVs) and inter-assay CVs reported by the manufacturer were 4%–6% and 8%–10%, respectively. The minimum detectable concentration was 7.0 ng/ml. Plasma samples were coded and the assays were performed in duplicate by one researcher to ensure technical consistency. The researcher who performed the ELISA assays did not know the identity of the subjects.

2.3. Assessment of body composition

Body composition was determined by multifrequency bioelectrical impedance analysis (InbodyS20, Biospace Co., CA, USA). The validity and accuracy of bioimpedance analysis (BIA) have been compared with dual-energy X-ray absorptiometry (DEXA) earlier (Anderson, Erceg, & Schroeder, 2012; Volgyi et al., 2008). BIA also performed well for assessment of fat and muscle composition in patients with chronic kidney diseases (Macdonald et al., 2006; Zoccali, Torino, Tripepi, & Mallamaci, 2012).

2.4. Statistics

Normally distributed continuous data were expressed as mean ± SD. Urinary albumin-to-creatinine ratio (ACR) was presented as median (interquartile) and log-transformed before data analysis. Categorical data were expressed as percentage.

Subjects were divided into tertiles based on plasma irisin levels. Differences in variables across three tertile groups were analyzed by ANOVA (for continuous variables) or Pearson χ^2 test (categorical variables). Differences in irisin levels in different CKD stages were analyzed by ANCOVA and log-transformed urinary ACR was entered as a covariate. Differences between two groups were further analyzed with post hoc Bonferroni correction.

Bivariate Pearson correlation analysis was employed to study the relationship between circulating irisin and clinical parameters, biochemical variables and body composition. As percentage of fat mass and percentage of nonfat lean mass were highly correlated in diabetic subjects with renal insufficiency, partial correlation was used to study the relationship between percentage of nonfat lean mass and irisin after controlling for percentage of fat mass. Multivariate linear regression models were used to study which variables were independently associated with circulating irisin. In our model, age and gender were entered as main confounders. All the other parameters with p value less than 0.1 in bivariate analysis with irisin were entered as covariates. A 2-tailed $p < 0.05$ was considered as statistically significant.

3. Results

As shown in Table 1, T2DM subjects with irisin levels in the lowest tertile were relatively older and were more likely to have a lower eGFR. Also, subjects with a lower irisin were more likely to have a higher pulse pressure even though their systolic blood pressure did not show significant difference. In addition, subjects with higher plasma irisin levels were more likely to have higher body mass index (BMI), higher fat mass and higher percentage of fat mass.

Circulating irisin was significantly decreased in T2DM with renal insufficiency (77.4 ± 13.7 ng/ml in T2DM with eGFR ≥ 60 ml/min/1.73 m^2 versus 72.5 ± 14.9 ng/ml in T2DM with eGFR < 60 ml/min/1.73 m^2, $p = 0.001$). Further analysis by ANCOVA showed that reduction in circulating irisin was most pronounced in stage 5 CKD (irisin levels in CKD stage 1 to 5 were 77.1 ± 14.2, 77.8 ± 13.2, 74.2 ± 14.5, 76.8 ± 15.3 and 67.1 ± 14.0 ng/ml, respectively, $p = 0.0001$ for trend by ANCOVA after adjustment for urinary ACR; $p < 0.0001$ between CKD stage 5 and stage 1 and 2; $p = 0.028$ between stage 5 and 3 and $p = 0.020$ between stage 5 and 4 after Bonferroni correction).

Bivariate correlation analysis revealed that circulating irisin was negatively correlated with age ($r = -0.200$, $p < 0.0001$) and pulse pressure ($r = -0.167$, $p = 0.0010$) and positively correlated with BMI ($r = 0.148$, $p = 0.005$), fat mass ($r = 0.162$, $p = 0.003$), percentage of fat mass ($r = 0.137$, $p = 0.012$) and eGFR ($r = 0.194$, $p < 0.001$). We did not observe a significant correlation between irisin and nonfat lean mass and percentage of nonfat lean mass in bivariate analysis (Table 2).