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Serum irisin levels are associated with adverse cardiovascular outcomes in patients with acute myocardial infarction

I-Chang Hsieh, Ming-Yun Ho, Ming-Shien Wen, Chun-Chi Chen, Ming-Jer Hsieh, Chia-Pin Lin, Jih-Kai Yeh, Ming-Lung Tsai, Chia-Hung Yang, Victor Chien-Chia Wu, Kuo-Chun Hung, Chun-Chieh Wang, Chao-Yung Wang *

Department of Cardiology, Chang Gung Memorial Hospital, Chang Gung University College of Medicine, Taiwan

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ABSTRACT

Irisin, a recently identified myokine, regulates mitochondrial function and energy expenditure. The concentration of irisin is significantly altered after ST-elevation myocardial infarction (STEMI). We hypothesized that serum irisin concentration is associated with adverse cardiovascular outcomes after myocardial infarction. Serum irisin concentrations were measured using enzyme-linked immunosorbent assay (ELISA) in 399 patients 28 d after the onset of STEMI in a prospective single-center cohort study. We assessed the association between irisin concentrations and adverse cardiovascular events during a 3-year follow-up. The excess risks of cardiovascular mortality, stroke, heart failure, and revascularization were predominantly seen among those with the highest concentrations of irisin, with concentrations higher than 75th percentile of the overall distribution had a ~4-fold increase in risk (hazard ratio = 3.96, 95% confidence interval 1.55 to 10.11, $P < 0.01$). Our findings showed that serum concentrations of irisin are elevated in post-STEMI patients with increased risk for adverse cardiovascular events. Novel therapies targeting irisin may represent a new direction in the treatment of STEMI.

1. Introduction

Recent studies have identified a novel polypeptide, irisin, which exhibits increases in serum concentration with exercise. Irisin is the shed extracellular domain of a human fibronectin type III domain containing-5 (FNDC5) protein [1]. Irisin contains 112 amino acids and is secreted by skeletal muscles and adipose tissue [2]. Young male athletes have been shown to have significantly higher irisin levels than middle-aged obese women [3]. Patients with diabetes or chronic kidney diseases have lower serum irisin abundances [4]. In mice, the overexpression of irisin using adenovirus vector increases total body energy expenditure, reduces body weight, and improves glucose intolerance [5]. Elevated blood irisin levels induce the expression of neuroprotective genes in the mouse hippocampus [6]. Irisin also modulates mitochondrial gene expression and controls browning phenotype changes in adipocytes [7]. These previous data suggest that the exercise-related myokine, irisin, may have different physiological functions in many organs.

Changes in mitochondrial functions greatly influence the prognosis and cardiovascular events after myocardial infarction (MI) [8]. Mitochondrial homeostasis modulates the apoptosis, oxidative stress, and survival of cardiomyocytes after hypoxia [9]. Prior studies have suggested that recombinant irisin may act through mitochondrial regulation to inhibit cell proliferation and increase oxygen consumption in cardiomyoblasts [10]. Skeletal and myocardial irisin expressions in mice are increased after MI [11]. However, serum and saliva irisin abundances are decreased after MI in humans [12]. Given these known relationships between irisin concentration and MI, we hypothesized that irisin in patients with MI may affect the prognosis after ST-elevation myocardial infarction (STEMI). This study aimed to evaluate the irisin concentration in STEMI patients and to assess its direct effects on the myocardium.

2. Methods

2.1. Study cohort

A prospective Obesity and Clock for Elegant AgiNg – AMI (OCEAN–AMI) cohort study was performed. The study has been recruiting consecutive STEMI patients from July 9, 2011 in a single 3500-bed tertiary university hospital. Patients who received primary percutaneous coronary intervention (PCI) within 12 h of symptom onset and the infarct-related artery identified clearly were included. Patients who had a history of taking steroid medications, previous regular aerobic exercise (>2 times a week for >6 months), chronic kidney diseases with GFR <15 mL/min or on dialysis, BMI >35 kg/m^2, liver cirrhosis with Child class C, and neuromuscular diseases were excluded.

If the patient consented, blood samples were obtained immediately after PCI and at 8 h, 16 h, 3 d, 7 d, and 28 d. The study protocol was approved by the Chang Gung Memorial Hospital Institutional Review Board, and all participants provided written informed consent. The study complied with the Declaration of Helsinki. 72 patients agreed to the blood test at 8 h, 16 h, 3 d, 7 d, and 28 d, among which 5 patients reached the primary

* Corresponding author at: 5 Fu-Hsing Street, Taoyuan 333, Taiwan.
E-mail address: cwang@ocean.ag (C.-Y. Wang).

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end point of death. Therefore, only 67 patients were analyzed for the acute changes of irisin level after STEMI. To analyze the serum irisin levels and the major adverse cardiovascular events, the total number of patients included was 399.

2.2. Serum samples and ELISA.

For all serum samples tested 28 d after STEMI, blood was drawn after 8 h of fasting. For the serum samples tested immediately during primary PCI, blood was drawn from the femoral or radial sheaths. Serum was prepared by centrifugation for 10 min (4 °C, 3500g) and stored at −80 °C until analyzed. Circulating levels of irisin were determined by competitive ELISA (AdipoGen, Liestal, Switzerland) [13,14]. The intra-assay coefficient of variation was 7.1% and the inter-assay coefficient of variation was 8.8%. For the irisin assay, we assessed three different assay kits on sample dilution, assay range, sensitivity, and irisin levels corresponding to the physical activity history in subjects. The Adipogen assay was selected because of its established correlations to the physical activity history in study subjects and because of its high sensitivity (0.001 μg/mL).

2.3. End Points and follow-up

The primary endpoint was a composite of death due to cardiovascular causes, recurrence of MI, recurrence of angina, stroke, new or worsening heart failure, and unscheduled revascularization. The secondary endpoint was all-cause mortality. Scheduled PCI or coronary artery bypass grafting as a consequence of the index infarction was not registered as an adverse cardiovascular event. The endpoints were recorded either by outpatient clinic visits or by telephone contact.

2.4. Statistical analysis

Our preliminary analysis suggested that relationships between irisin and adverse cardiovascular risk might be limited to those with high irisin levels in a nonlinear model. We divided irisin levels into quartiles that defined four patient groups. All associations of irisin and primary end points were calculated with a multivariate Cox regression model that included age, gender, body mass index, smoking, hypertension, diabetes mellitus, and dyslipidemia. The adjusted hazard ratios were calculated for patients in each of the quartiles relative to patients in the lowest quartile. Event-free survival analysis was based on Kaplan-Meier estimates and log-rank tests. To calculate the statistical power to test the hazard ratio of adverse cardiovascular event rates by quartiles of irisin level, the event rates of patients in the 1st and 4th quartile, the superiority margin of 0.2, and type I error (α) of 5% were used. The group sample size of 100 with type I error rate of 5% provide 93% power.

3. Results

We enrolled 399 patients with STEMI. The baseline characteristics of the study participants are shown in Table 1. In a subset of 72 patients, baseline blood was collected immediately after PCIs. Five patients reached the primary end point of death. Blood samples at 8 h, 16 h, 3 d, 16 d, 7 d, and 28 d were obtained from 67 patients to profile the serial serum irisin changes after STEMI. The clinical characteristics of these 72 patients are shown in the Supplementary Table.

3.1. Serum irisin profiles during the first month in patients with STEMI

Fig. 1 illustrates the time course of serum irisin changes after STEMI. Baseline irisin concentrations were 0.47 ± 0.23 μg/mL at the time when patients received primary coronary intervention. Serum irisin concentrations peaked at 8 h (0.59 ± 0.17 μg/mL, $P < 0.01$; 8 h versus 0 h) and the nadir occurred at 3 d (0.31 ± 0.10 μg/mL, $P < 0.0001$; 3 d versus 0 h) after STEMI. There was no significant difference in irisin concentrations at 7 d and 28 d after STEMI when compared to the baseline concentration (Fig. 1). These results were compatible to the previous reports in that serum and saliva irisin concentrations decreased after MI [12].

3.2. Elevated serum irisin and major adverse cardiovascular events

We measured circulation irisin levels among post-MI patients enrolled in the Obesity and Clock for Elegant AgiNg – AMI (OCEAN– AMI) cohort who were prospectively monitored for incident adverse cardiovascular events. The baseline clinical characteristics of the cohort population are presented in Table 1. In this cohort, 8.5% of patients were ≥75 years old, 3.3% had prior history of MI, 3.8% had prior history of revascularization, and 16.3% presented with cardiogenic shock. At study entry, 28.1% of patients had diabetes mellitus and 55.1% were current smokers.

Table 1
Baseline clinical characteristics.

Characteristics	Total ($n = 399$)
Age, y, mean ± SD (range)	58 ± 11 (35–92)
Gender (female), n (%)	172 (43.1%)
Weight, kg, mean ± SD	71.1 ± 11.2
Height cm, mean ± SD	165.1 ± 7.1
Body mass index, kg/m^2, mean ± SD	26.1 ± 3.3
Dyslipidemia, n, (%)	187 (46.9%)
Systemic hypertension, n, (%)	183 (45.9%)
Diabetes mellitus, n, (%)	112 (28.1%)
Current smoker, n, (%)	220 (55.1%)
Systolic blood pressure, mm Hg, mean ± SD	121.2 ± 20.2
Prior myocardial infarction, n (%)	13 (3.3%)
Prior PCI, n (%)	15 (3.8%)
Prior coronary artery bypass graft, n (%)	0 (0%)
Killip class on admission, n, (%)	
1	268 (67.2%)
2	33 (8.3%)
3	33 (8.3%)
4	65 (16.3%)
Infarct-related artery, n, (%)	
LAD	239 (59.9%)
RCA	118 (29.6%)
LCx	40 (10%)
LM	2 (0.5%)
Therapy after discharge, n (%)	
Aspirin	374 (93.7%)
Statin	317 (79.4%)
β-Blocker	356 (89.2%)
ACE inhibitor or ARB	277 (69.4%)
Biochemical analysis at admission	
BUN, mg/dL, mean ± SD	16.5 ± 7.2
Creatinine, mg/dL, mean ± SD	1.0 ± 0.4
Total cholesterol, mg/dL, mean ± SD	181.2 ± 44.7
Triglyceride, mg/dL, mean ± SD	144.4 ± 81.2
LDL, mg/dL, mean ± SD	115.6 ± 39.3
HDL, mg/dL, mean ± SD	39.1 ± 9.9
Uric acid, mg/dL, mean ± SD	6.3 ± 1.7
Fasting glucose, mg/dL, mean ± SD	116.0 ± 40.0
Peak troponin I, μg/L, mean ± SD	14.7 ± 34.4
LV ejection fraction, n (%)	53.8 ± 11.8
Plasma irisin, μg/mL, mean ± SD	0.5 ± 0.2

Overall, irisin concentrations among the study participants followed a skewed distribution, with a median value of 0.48 μg/mL and an

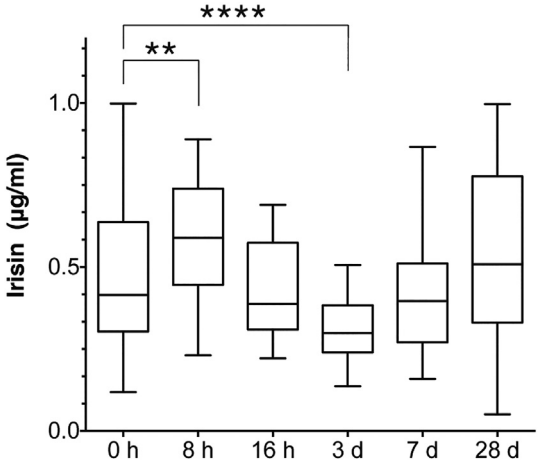

Fig. 1. Alteration of serum levels of irisin in patients with acute myocardial infarction. Box plots (median, interquartile ranges) of serum irisin levels. Serum samples from patients with ST-elevation myocardial infarction (STEMI) were examined at 0 h (at the time of primary percutaneous coronary intervention), 8 h, 16 h, 3 d, 7 d, and 28 d after myocardial infarction ($n = 72$). One-way analysis of variance with Greisser-Greenhouse correction and Holm-Sidak's multiple comparisons were used to calculate the changes in irisin levels. $^{**}P < 0.01$. $^{****}P < 0.0001$.