

Received: 2016.01.02
Accepted: 2016.03.09
Published: 2016.11.05

Association of Serum Irisin Concentrations with Presence and Severity of Coronary Artery Disease

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Source of support: Departmental sources

Background: Irisin, an exercise-induced myokine, is closely correlated with obesity and body mass index. Obesity is one risk factor of coronary artery disease (CAD). Therefore, the present study aimed to determine if serum irisin concentrations are correlated with the presence and severity of CAD.





Material/Methods: Serum irisin concentrations were determined in 350 patients with CAD and in 214 healthy subjects. The severity of CAD was assessed by coronary atherosclerosis index (CAI).

Results: Serum irisin concentrations were significantly lower in CAD patients compared with healthy controls. Multivariable logistic regression analysis revealed that serum irisin concentrations were an independent determinant of the presence of CAD. In addition, Pearson correlation analysis showed that serum irisin concentrations were negatively correlated with CAI in CAD patients.

Conclusions: Decreased serum irisin concentrations may be associated with the presence and severity of CAD.

MeSH Keywords: **Coronary Artery Disease • Receptors, Cytokine • Severity of Illness Index**

Full-text PDF: <http://www.medscimonit.com/abstract/index/idArt/897376>

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Background

Coronary artery disease (CAD) is a major cause of morbidity and mortality worldwide. Diabetes, dyslipidemia, hypertension, family history, obesity, and smoking are thought to increase the risk of developing CAD [1]. In addition, genetic factors contribute to the susceptibility of developing CAD [2]. Recent studies have demonstrated various candidate genes and epigenetics in the pathogenesis of CAD [3]. However, the exact mechanism of CAD has not been fully elucidated.

Irisin, a cleaved and secreted fragment of fibronectin type III domain containing 5 (FNDC5), contributes to energy consumption in mice [4]. Irisin reversed diet-induced obesity and diabetes by inducing the browning of subcutaneous white adipocytes and up-regulating the expression of thermogenesis-related genes [5]. In humans, serum irisin concentrations are negatively correlated with body mass index (BMI) [6]. Serum irisin concentrations were significantly reduced in obese subjects compared with lean ones [7]. Obesity is a potential risk factor of developing CAD. Therefore, irisin is speculated to play a role in the pathogenesis of CAD.

We performed this cross-sectional investigation in a population of CAD patients to determine the relation of serum irisin to the development and severity of CAD.

Material and Methods

Subjects

This cross-sectional study was performed in a population of 350 patients with angiographically proven CAD and 214 healthy subjects. The case and control groups were statistically matched for age, sex, and BMI. Subjects who had angiographic evidence of stenosis $\geq 50\%$ in at least 1 major coronary artery were considered as CAD patients. Patients were excluded if they had acute coronary syndromes, history of coronary artery bypass surgery, heart failure, valvular heart disease, malignant tumor, or systemic disease. Control subjects were recruited from individuals attending routine checkups including CT angiography in our hospital. All control subjects were free of personal or family history of cardiovascular or hemorrhagic disease. The study protocol was approved by the Human Ethics Review Committee of our hospital and a signed consent form was obtained from each subject.

We used the coronary atherosclerosis index (CAI) to assess the severity of CAD. The sum of the following scores was graded as CAI: no significant stenosis, defined as a score of 0; 1–24% narrowing, defined as a score of 1; 25–49% narrowing, defined

as 2; 50–74% narrowing, defined as 3; and 75–100% narrowing, defined as 4 [8].

Laboratory methods

Serum was obtained from all subjects in a fasting state. An enzyme-linked immunosorbent assay kit (Phoenix Pharmaceuticals, Inc, USA) [coefficient of variations (CVs) for intra assay: 5–7%; CVs for inter-assay: 12–15%; detection limit range: 0.1–1000 ng/mL] was used to evaluate serum irisin concentrations.

Statistical analysis

The data are exhibited as means \pm standard errors (interquartile range). We used unpaired *t* test, chi-square tests, or Mann-Whitney U test to determine the differences in parameters between case and control groups. Univariate analysis was performed and the variables with a $P < 0.10$ were then entered into a backward stepwise multivariate logistic regression model to examine the risk factors of CAD. The correlation of serum irisin concentrations with CAI was analyzed by Pearson correlation analysis. P value < 0.05 was considered to be a statistically significant difference.

Results

Baseline clinical characteristics

CAD patients showed higher levels of triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), and smoking, and decreased high-density lipoprotein cholesterol (HDL-C), compared with the controls.

Serum irisin concentrations in CAD patients

The case group had lower serum irisin concentrations than in the control group ($P < 0.001$) (Table 1). Both simple and multivariate logistic regression analysis indicated that serum irisin concentrations were negatively associated with the presence of CAD (Table 2).

Serum irisin concentrations in smoking cases and controls

As shown in Figure 1, serum irisin concentrations were not significantly different between smoking and non-smoking CAD patients, or between smoking and non-smoking controls. Furthermore, both smoking and non-smoking CAD patients showed lower serum irisin concentrations than in smoking and non-smoking controls.

Table 1. Clinical and biochemical characteristics of the case and control groups.

	The controls	CAD patients	P value
N	214	350	
Age (years)	59.29±10.41	60.33±9.95	0.239
Gender (M/F)	118/96	190/160	0.843
BMI (Kg/m ²)	24.43±2.65	24.82±3.17	0.129
SBP (mmHg)	138.44±26.20	141.10±16.95	0.145
DBP (mmHg)	82.04±12.73	83.19±10.06	0.238
TC (mmol/L)	5.09±0.87	5.18±1.11	0.301
TG (mmol/L)	1.21±0.71	1.78±1.16	<0.001
LDL-C (mmol/L)	3.18±0.51	3.42±0.81	<0.001
HDL-C (mmol/L)	1.41±0.24	1.18±0.28	<0.001
Irisin (ng/mL)	146.22 (112.34–179.52)	119.55 (99.53–139.27)	<0.001
Smoking, n (%)	33 (15.42%)	82 (23.43%)	0.022

CAD – coronary artery disease; BMI – body mass index; SBP – systolic blood pressure; DBP – diastolic blood pressure; TC – total cholesterol; TG – triglycerides; LDL-C – low-density lipoprotein cholesterol; HDL-C – high-density lipoprotein cholesterol.

Table 2. Logistic regression Analysis for the presence of CAD.

	Simple regression		Multiple regression	
	OR (95%CI)	P	OR (95%CI)	P
Age (years)	1.010 (0.993–1.027)	0.239		
Gender (M/F)	1.035 (0.735–1.457)	0.843		
BMI (Kg/m ²)	1.046 (0.987–1.108)	0.130		
SBP (mmHg)	1.006 (0.998–1.015)	0.145		
DBP (mmHg)	1.009 (0.994–1.025)	0.238		
TC (mmol/L)	1.093 (0.924–1.292)	0.301		
TG (mmol/L)	2.388 (1.810–3.151)	<0.001	2.507 (1.820–3.455)	<0.001
LDL-C (mmol/L)	1.643 (1.278–2.113)	<0.001	1.974 (1.432–2.723)	<0.001
HDL-C (mmol/L)	0.046 (0.023–0.095)	<0.001	0.035 (0.015–0.081)	<0.001
Irisin (ng/mL)	0.972 (0.966–0.978)	<0.001	0.974 (0.967–0.981)	<0.001
Smoking, n (%)	1.678 (1.074–2.621)	0.023	1.687 (0.980–2.903)	0.059

BMI – body mass index; SBP – systolic blood pressure; DBP – diastolic blood pressure; TC – total cholesterol; TG – triglycerides; LDL-C – low-density lipoprotein cholesterol; HDL-C – high-density lipoprotein cholesterol.

Correlation of serum irisin concentrations with the severity of CAD

Pearson correlation analysis revealed that serum irisin concentrations were negatively correlated with CAI score, which is a characteristic for evaluating the severity of CAD ($r=-0.340$, $P<0.001$) (Figure 2).

Discussion

To investigate whether serum irisin concentrations are correlated with the presence and severity of CAD, we performed this study. The current study demonstrated that serum irisin concentrations are negatively associated with the presence and severity of CAD.

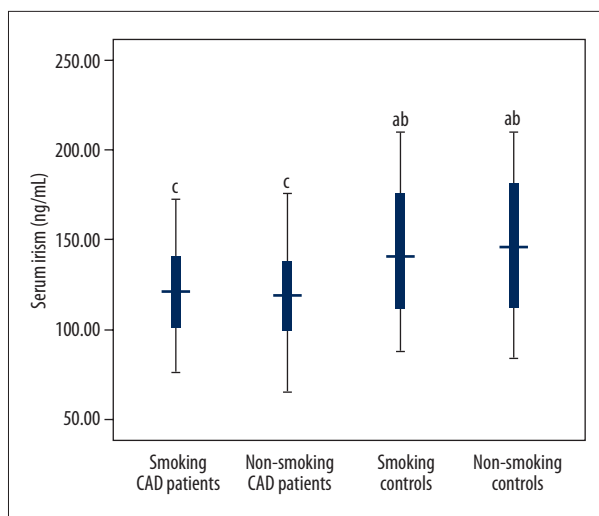


Figure 1. Serum irisin concentrations in smoking cases and controls. Both smoking and non-smoking CAD patients showed lower serum irisin concentrations than in smoking and non-smoking controls.

Irisin was shown to regulate endothelial function in recent investigations [9–12]. Irisin treatment in obese mice and human umbilical vein endothelial cells (HUVEC) both led to NO secretion and phosphorylation of adenosine 5'-monophosphate (AMP)-activated protein kinase (AMPK), Akt, and endothelial nitric oxide synthase (eNOS) [9]. This demonstrates the important role of irisin in improving endothelial function [9]. In another study, diabetic aortic segments showed endothelium-dependent vasorelaxation and decreased overproduction of superoxide and peroxynitrite after irisin incubation, which suggests that irisin alleviates endothelial dysfunction through inhibiting oxidative/nitrative stresses [10]. Wu et al. reported that irisin promoted angiogenesis in human umbilical vein endothelial cells [11]. Irisin alleviated endothelial injury by inhibiting inflammation and oxidative stress in apolipoprotein E-null diabetic mice [12].

Recently, irisin has recently been implicated in the development of atherosclerosis [12]. Irisin treatment improved endothelial dysfunction, inhibited endothelial apoptosis, and decreased atherosclerotic plaque area in apoE(–/–) diabetic mice [12]. In addition, serum irisin concentrations are closely correlated with exercise [4]. Therefore, exercise should be encouraged to elevate irisin levels. Serum irisin was negatively correlated with carotid intima-media thickness (cIMT) [13]. Serum irisin was an independent predictor for carotid atherosclerosis in peritoneal dialysis patients [13]. In a study performed by Sesti et al., circulating irisin levels were associated with vascular atherosclerosis as assessed by cIMT in a cohort of white adults [14].

In this study, we found that serum irisin concentrations were negatively correlated with the occurrence and severity of

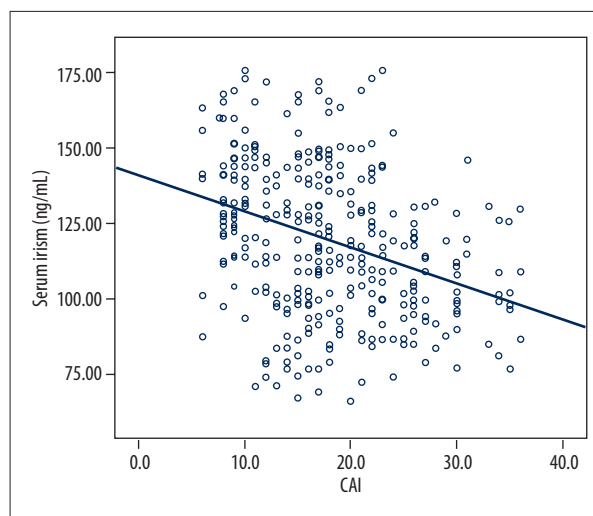


Figure 2. The correlation of serum irisin concentrations and CAI. Pearson correlation analysis revealed a negative correlation of serum irisin concentrations with CAI score ($r=-0.340$, $P<0.001$).

CAD, supporting the potential role of irisin in the pathogenesis of CAD.

However, Aronis et al. reported that there is no association of circulating irisin levels with acute coronary syndromes [15], and serum irisin was associated with major adverse cardiovascular events in CAD patients after receiving percutaneous coronary interventions [15]. These conflicting results may be attributable to differences in disease advancement, different populations, or assays used. Therefore, irisin could serve as a therapeutic drug for ameliorating or preventing atherosclerosis and CAD.

The exact mechanism by which irisin is involved in CAD is unclear. Obesity is one of risk factors of CAD, and irisin is closely correlated with obesity. Irisin acts on white adipose cells in culture and to stimulate UCP1 expression and a broad program of brown-fat-like development [4]. Irisin stimulates browning of white adipocytes through mitogen-activated protein kinase p38 MAP kinase and ERK MAP kinase signaling [16]. In humans, serum irisin concentrations were found to be negatively correlated with body mass index (BMI) [6]. Considering the close correlation of irisin with obesity, we speculate that irisin may contribute to the development of CAD by a cross-link with obesity.

CAD patients had relatively higher LDL-C and TG, lower HDL-C, and decreased serum irisin, but it is unclear if these are related. Irisin has an effect on lipid metabolism. Irisin was reported to regulate the expression of lipolysis-related genes and contributed to increased secretion of glycerol and decreased lipid accumulation in 3T3-L1 adipocytes [17]. In obese mice,

FNDC5 overexpression led to enhanced lipolysis and reduced hyperlipidemia [18]. These results indicate the important role of irisin in lipid metabolism. This may explain the hyperlipidemia and decreased serum irisin in CAD patients.

This study has several potential limitations. First, the sample size was not large enough to reach definitive conclusions. Secondly, our study had a cross-sectional design, and the causative relation must be confirmed by future longitudinal studies.

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Conclusions

Our results suggest that decreased serum irisin concentrations is associated with the presence and severity of CAD.

Conflict of interests

Author have no conflict of interests to declare.