

Association Between Serum Irisin Levels and ST-Segment Elevation Myocardial Infarction

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Background: An acute ST-elevation myocardial infarction (STEMI) is a serious cardiovascular condition with a high risk of morbidity and mortality. Irisin is adipomyokine that is associated with various health conditions. In post-STEMI, elevated serum irisin levels are associated with more adverse cardiovascular events.

Objective: The purpose of this study was to investigate associations between the serum irisin levels and acute MI (AMI) and whether irisin may be a useful biomarker for severity of AMI in patients with STEMI. Possible correlations between serum irisin and cardiac troponin-I (cTi) levels were investigated.

Methods: A total of 90 subjects (46 control subjects and 44 STEMI patients) were included in the study. Besides demographic data, presence of diabetes mellitus and hypertension, electrocardiography (ECG) findings, blood biochemistry, cardiac biomarkers (cTi) and serum irisin levels were examined.

Results: Significantly lower heart rate (HR) and significantly higher ST-elevation and QTc interval were detected in ECG recordings in STEMI patients ($p < 0.05$). Serum irisin levels were significantly lower in STEMI patients compared to the control subjects ($p < 0.001$). The decrease in the serum irisin levels was significantly correlated with the increase in cTi levels, as well as increased QTc ($p < 0.05$). The sensitivity and specificity of irisin were found to be 93% and 78%, respectively.

Conclusion: Decreased irisin levels were found to be highly predictive in STEMI. In patients with STEMI, the serum irisin levels were associated with cTi levels and QTc, suggesting that irisin is a promising biomarker for AMI cases.

Keywords: myocardial infarction, cardiovascular diseases, irisin, troponin-I, QT interval, biomarker

Introduction

Myocardial infarction (MI) is among the main risk factors for heart failure.^{1,2} Acute ST-elevation MI (STEMI) occurs when one or more coronary arteries are occluded that leads to transmural myocardial ischemia resulting in myocardial injury or necrosis.³ Regardless of the advances in the management of STEMI including pharmacological and surgical approaches, there are still areas to be clarified and improved.⁴

Irisin, a 112 amino acid-long peptide, is an adipomyokine that is cleaved from a plasma membrane protein, fibronectin type III domain containing protein 5 (FNDC-5).⁵ Previous studies have reported that irisin exerts beneficial effects such as exerting anti-inflammatory⁶ and anti-oxidant activities,⁷ as well as improving glucose and lipid metabolism.⁸ On the other hand, higher levels of irisin were found to be associated with obesity and metabolic syndrome, suggesting muscular resistance to irisin,^{9,10} the fact of which is similar to the conditions of leptin resistance in obesity and insulin resistance in diabetes.¹¹

Irisin has been shown to play different roles in cardiovascular conditions. Irisin was shown to be protective against pressure-overload cardiac hypertrophy via induction of autophagy.¹² Moreover, irisin is beneficial against ischemia/

reperfusion injury both in vitro and in vivo.¹³ Endothelial dysfunction and endothelial cell apoptosis were found to be alleviated by irisin.^{7,14} Infarct size was reduced, and cardiac function was improved by irisin treatment in post-MI mouse hearts via increased angiogenesis.¹⁵ Skeletal and myocardial irisin levels are elevated in rats after MI,¹⁶ while in humans, serum and saliva levels of irisin are diminished after acute MI (AMI).¹⁷

The above-mentioned effects and functions of irisin and the potential relationship between irisin and atherosclerotic cardiovascular disease are insufficient and controversial.^{12–21} Therefore, this study aimed to investigate associations between the circulating irisin levels and MI and whether irisin levels may be a useful biomarker for the severity of MI in patients with STEMI.

Materials and Methods

Subjects and Study Design

The protocol for sample collection was prospectively approved by the University of Health Sciences, Sisli Hamidiye Etfal Education and Research Hospital, Clinical Research Ethics Committee (date: 28.01.2020, no: 2648). We conducted in this single center cross-sectional study between February 2020 and June 2020. The study was performed in accordance with the 1975 Helsinki Declaration, updated in 2013. All participants were informed of the study protocol, and their written informed consents were obtained.

A total of 90 subjects (healthy control = 46 and STEMI = 44) were included in the study. STEMI diagnosis was made according to the third universal definition of MI document.²²

Inclusion Criteria

Patients with STEMI were admitted to the emergency room and healthy volunteers who were 18 years old or older were included. The healthy volunteers consisted of hospital personnel who were subjected to annual routine control examinations. Patients with STEMI were required to have (1) continuous chest pain upon presentation, refractory to nitrates, and lasting >30 min; (2) ST-segment elevation of >0.2 mV in >2 contiguous precordial leads, or >0.1 mV in >2 contiguous limb leads, or new (or presumably new) left bundle branch block on admission electrocardiogram; (3) presentation within the first 12 h from index pain. Patients with NSTEMI were required to have angina-like chest pain at rest in the last 24 h lasting >5 min, with associated ST-segment depression of >0.1 mV in >2 contiguous leads upon presentation.

Exclusion Criteria

Patients were younger than 18 years, with a known history of heart failure or left ventricular diastolic dysfunction, coronary artery disease, atrial fibrillation and/or cerebrovascular disease, peripheral artery disease, chronic renal failure, and malignancy, and had ongoing infectious disease, and chronic inflammatory disease were excluded from the study.

Demographic data (age, gender and body weight), presence of diabetes mellitus (DM), hypertension (HT), and smoking status of the subjects were recorded on admission. Blood pressure (BP), heart rate (HR), time to onset of chest pain, elevation in electrocardiography (ECG), QT interval was measured. The vein that was involved and angiography were performed on were also recorded in STEMI patients.

Laboratory Tests

Venous blood was drawn from each patient in the biochemistry tube within the first 24 hours of the emergency department admission. Serum samples were obtained after at least 30 min of clotting by centrifugation at 2.500g for 15 min and were stored at -80 C until assayed for determination of irisin concentrations. All icteric or hemolyzed blood samples were discarded. All parameters were analyzed in all samples together in a single batch.

Fasting blood sugar, urea, creatinine, cardiac troponin-I (cTi), total cholesterol (TC), high-density lipoprotein (HDL), low-density lipoprotein (LDL), total glyceride (TG), levels were measured with an automated analyzer (COBAS 8000, ROCHE-2007, Tokyo, Japan).

Measurement of Serum Irisin Levels

Serum irisin levels were measured according to manufacturer's instructions (Human Irisin ELISA Kit, Cat. No: YLA1361HU; YL Biont). The coefficients of intra and inter-assay variation were 7.6% ($n = 25$) and 9.5% ($n = 25$), respectively.

Statistical Analysis

The Statistical Package for Social Sciences (SPSS) for Windows, Version 22 (IBM, Armonk, NY, USA) was used for the statistical analyses. The Kolmogorov–Smirnov test was used to analyze the distribution of the variables. Data with were either expressed as mean \pm standard deviation (SD) or median, minimum and maximum. Unpaired Student's *t*-test was used for parameters that were normally distributed and the data without normal distribution were evaluated with Mann–Whitney *U*-test. Associations between the groups were investigated by Fisher's exact test. Correlations between numerical data were investigated by using Pearson correlation coefficient test for parameters that were normally distributed, while Spearman correlation coefficient test was used for the analysis of the data that were not normally distributed. The diagnostic values of irisin, cTi and QTc variables in diagnosing AMI were determined by ROC analysis. Logistic regression analysis was performed for clinical factors and biochemical parameters thought to be associated with STEMI, and the OR and 95% confidence interval were calculated. A $p < 0.05$ was considered statistically significant.

Results

Age, gender, body weights and smoking status of the subjects did not differ between the STEMI patients and control subjects (Table 1). There were no differences in the number of patients with systemic HT between the groups, while the number of patients with DM was higher in STEMI patients ($p = 0.034$; Table 1). The number of patients who developed angina pectoris was significantly higher in STEMI patients ($p = 0.031$) Table 1). Most of the patients underwent prior percutaneous coronary intervention in STEMI group (Table 1). On the other hand, none of the subjects had a history of coronary artery bypass graft.

ECG findings revealed significantly lower HR and significantly higher ST-elevation and QTc interval in STEMI patients ($p < 0.05$) (Table 1). Most of the infarct-related artery was found as left anterior descending artery (LAD) followed by right coronary artery (RAC) (Table 1).

Table 1 Baseline Demographics, Characteristics, and Comorbidities of the Subjects

	Control (n = 46)	STEMI (n = 44)	P value
Age (years; mean \pm SD (range))	55 \pm 10 (22–82)	59 \pm 12 (32–88)	0.151 ^c
Gender (male; n (%))	30 (65)	32 (72)	0.499 [#]
Body weight (kg; mean \pm SD)	76.1 \pm 16.9	75.1 \pm 13.7	0.818 ^m
Systemic HT (n (%))	26 (59.1)	22 (47.8)	0.300 [#]
DM, n, (%)	8 (17.4)	17 (38.6)	0.034 [#]
Current smoker (n (%))	30 (65.2)	27 (61.4)	0.827 [#]
Systolic BP (mmHg; mean \pm SD)	130 \pm 20	120 \pm 32	0.103 ^m
Angina pectoris (1 hour; n (%))	13 (28.2)	22 (50)	0.034 [#]
Prior PCI (n (%))	–	39 (88.6)	
Prior coronary artery bypass graft (n (%))	–	–	
Prior thrombectomy (n (%))	–	5 (11.3)	
ECG findings			
HR (mm/seconds; mean \pm SD)	72.8 \pm 16.2	63.9 \pm 18.7	0.020 ^m
ST-elevation (mV)	–	0.3 \pm 0.11	<0.001 ^m
QTc interval (msec; mean \pm SD)	306.5 \pm 9.2	360.3 \pm 9.1	<0.001 ^c

(Continued)

Table 1 (Continued).

	Control (n = 46)	STEMI (n = 44)	P value
Infarct-related artery (n (%))			
LAD	-	22 (50)	
CX	-	1 (2.2)	
RCA	-	17 (38.6)	
CX and RCA	-	4 (9.1)	
Biochemical analysis at admission (mean \pm SD)			
Urea (mg/dL)	39 \pm 16.1	50.3 \pm 19.8	0.004 ^m
Creatinine (mg/dL)	0.93 \pm 0.82	1.0 \pm 0.8	0.198 ^m
Total cholesterol (mg/dL)	186 \pm 46	201.1 \pm 52.9	0.154 ^t
TG (mg/dL)	166.1 \pm 100.3	100.7 \pm 32.7	<0.001 ^m
LDL (mg/dL)	181.3 \pm 50.5	157.6 \pm 44.9	0.021 ^t
HDL (mg/dL)	44.3 \pm 11.9	43.6 \pm 10.3	0.824 ^m
Fasting glucose (mg/dL)	107 \pm 37.1	144 \pm 48.8	<0.001 ^m
Peak cTi (ng/L)	4.9 \pm 1.6	4132.1 \pm 1080.9	<0.001 ^m
Irisin	12.5 \pm 8.9	4.95 \pm 2	<0.001 ^m

Notes: “-”Denotes no value/number. ^tt-test, [#]Chi-square test, ^mMann–Whitney U-test.

Abbreviations: BP, blood pressure; CX, circumflex artery; cTi, cardiac troponin-I; DM, diabetes mellitus; HDL, high-density lipoprotein; HR, heart rate; HT, hypertension; LAD, left anterior descending artery; LDL, low-density lipoprotein; PCI, percutaneous coronary intervention; RCA, right coronary artery; TG, triglyceride.

Urea, fasting glucose and peak cTi levels were significantly higher ($p < 0.01$), while TG, LDL levels were significantly lower in STEMI patients compared to control subjects ($p < 0.05$) (Table 1).

Serum irisin levels were found to be significantly lower in the AMI patients compared to control subjects ($p < 0.001$; Figure 1). Moreover, when there are correlations between irisin levels, peak cTi levels and QTc intervals, there is a moderately negative correlation between serum irisin levels with cTi levels ($p < 0.001$) and QTc interval ($p < 0.05$) in AMI patients (Table 2).

In the ROC analysis of peak cTi level for STEMI and control groups, the AUC value of 0.98 (95% CI 0.969–0.1000 and Cut off >16.5) was found to be statistically significant ($p < 0.05$). In the ROC analysis of QTc interval for STEMI and control groups, the AUC value of 0.71 (95% CI 0.609–0.820 and Cut off >16.5) was found to be statistically significant ($p < 0.05$). In the ROC analysis of the irisin level for STEMI and control groups, the AUC value of 0.93 (95% CI 0.881–0.980 and Cut off <6.71) was found to be statistically significant ($p < 0.05$). Decreased irisin levels were found to be highly predictive in STEMI. The sensitivity and specificity were found to be 93% and 78%, respectively (Figure 2, Table 3).

In the regression analysis of independent variables for the STEMI patient group, irisin, peak cTi, urea, LDL and TG variables showed significant differences in the univariate model. However, no parameter showed significant difference in

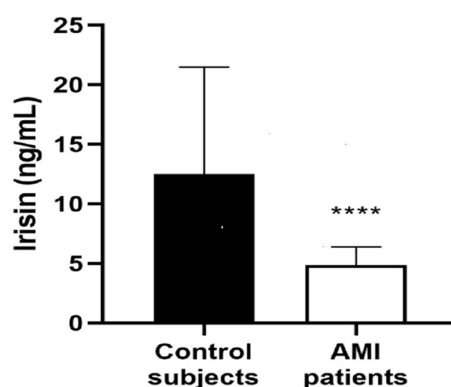


Figure 1 Serum irisin levels in control subjects and AMI patients (**** $p < 0.0001^m$).

Table 2 Correlations Between Serum Irisin, cTi Levels and QTc Interval

Parameters	Serum Irisin	
	Spearman's <i>r</i>	<i>p</i> value
cTi (ng/mL)	−0.595	<0.001
QTc interval (msec)	−0.250	<0.05

Note: *p* values lower than 0.05 were considered significant.

Abbreviation: cTi, cardiac troponin-I.

the multivariate model (Table 4). cTi peaked at 0.283 (0.627–0.905). In univariate regression analysis; irisin (odds ratio [OR]: 1.047; 95% confidence interval [CI]: 1.756–4.619; $p < 0.001$), urea (OR: 0.037; 95% CI: 0.940–0.990; $p = 0.008$), LDL (OR: 0.011, 95% CI: 1.001–1.020; $p = 0.011$), and TG (OR: 0.022; 95% CI: 1.010–1.035; $p = 0.001$) were found to be factors associated with a peak cTi (STEMI patient group).

Discussion

In this study, we demonstrated that serum irisin levels are significantly lower in STEMI patients compared to healthy control subjects and reduced irisin levels are significantly correlated with increased AMI biomarkers and cTi levels, as well as with increased QTc interval. In the differential diagnosis of AMI, cTi and irisin were found to have high sensitivity and specificity. There was also a moderate relationship between cTi and irisin in patients with STEMI. This study demonstrated a potential relationship between irisin levels and prognostic markers in patients with STEMI.

Irisin was discovered as a muscle derived hormone in response to exercise,²¹ while further studies reported several other tissues also produce irisin.^{23–25} Although irisin has been reported to be beneficial against cardiovascular events,^{7,12–15}

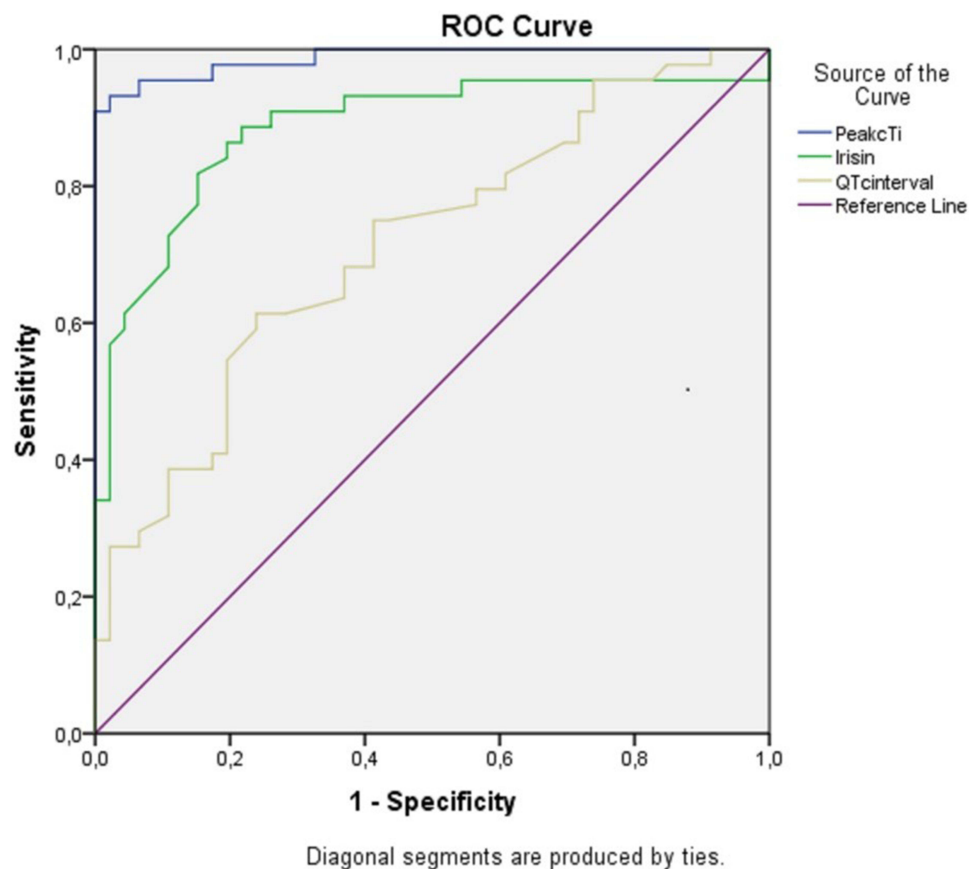


Figure 2 ROC analysis of irisin, peak cTi and QTc interval for STEMI variables and control groups.

Table 3 Diagnostic Values of Irisin and Other Variables in All Groups

Variables	Cut-Off	AUC	Sensitivity	Specificity	p
Peak cTi	> 16.5	0.98	93%	98%	<0.001
Irisin	< 6.71	0.93	93%	78%	<0.001
QTc interval	> 16.5	0.71	61%	76%	<0.001

Abbreviations: cTi, cardiac troponin I; AUC, area under the curve.

Table 4 Regression Analysis of Variables for STEMI

	Univariate			Multivariate		
	Odds Ratio	95% C.I.for EXP(B)	p	Odds Ratio	95% C.I. for EXP(B)	p
		Lower–Upper			Lower–Upper	
Peak cTi	0.283	0.627–0.905	0.002	0.290	0.525–1.066	0.108
Irisin	1.047	1.756–4.619	0.000	1.472	0.304–62.423	0.278
Urea	0.037	0.940–0.990	0.008	0.096	0.806–1.503	0.548
LDL	0.011	1.001–1.020	0.011	0.015	0.952–1.083	0.639
TG	0.022	1.010–1.035	0.001	0.048	0.98–1.124	0.170

elevated irisin levels were reported to be associated with adverse cardiovascular events in patients.^{18–20} A study reported that circulating irisin levels are not associated with acute coronary syndrome (ACS) development in healthy individuals, while elevated irisin levels are associated with major adverse cardiovascular events in patients with established coronary artery disease (CAD).¹⁸ Moreover, an inverse relation between serum irisin levels in CAD patients with stable angina was found.¹⁹ In post-STEMI patients, elevated serum irisin levels are found to be associated with adverse cardiovascular events.²⁰ Another recent study reported reduced serum irisin levels after AMI.¹⁷

Previous studies have also shown that the potential relationship between irisin and atherosclerotic cardiovascular disease is insufficient and controversial.^{12–21} In current study, serum irisin levels were significantly lower in AMI patients. Irisin is also produced by cardiomyocytes at a higher amount than muscles.¹⁷ Reduced irisin levels may be explained by the fact that irisin is released into the circulation after cardiomyocyte damage from the intracellular pool, similar to the CK-MB and cTi.²⁶ However, why irisin levels decrease after AMI still remains elusive. Another reason might be that irisin levels are decreased to limit the heat production and increase ATP synthesis in the damaged tissue. In order to repair the damaged tissue, cells require more energy than the steady state conditions.¹⁶ Irisin was previously found to induce mitochondrial thermogenesis via heat production²⁷ and reduce ATP production.²⁸ Heat is associated with elevated incidence of various cardiovascular diseases and may worsen the conditions related to AMI.^{29,30} Therefore, it is suggested that limiting irisin production may provide more energy in the damaged tissue. Moreover, reduced levels of irisin might be a protective mechanism against additional myocardial damage. Results of the experimental study of Bashar et al³¹ revealed a significant decrease in serum irisin in the infarct rats as compared to the control rats. Their results also showed a significant positive correlation between serum irisin level and QRS duration. Similarly, to our study, there is a negative correlation between serum irisin and troponin. They recommend regular exercise or taking recombinant irisin as a supplement to protect at-risk individuals against AMI. However, additional studies are required to clarify this issue.

cTi and CK-MB are two well-known biomarkers for the AMI diagnosis.³² Higher CK-MB levels are associated with adverse outcomes after MI.³³ Elevation in cTi is also associated with adverse outcomes after MI.^{34,35} In our study, cTi levels were found to be significantly higher in STEMI patients compared to control subjects. Moreover, the increase in the serum irisin levels was associated with the decrease in serum cTi levels in STEMI patients. Similar to our study, decreased levels of irisin were found in association with cTi in AMI models of animals^{16,31} and AMI patients.¹⁷

The sensitivity of peak cTi was 93%, and the specificity was 98%; the sensitivity of irisin was 93%, specificity 78%; QTc had a sensitivity of 61% and a specificity of 76%. It was determined that serum irisin could statistically significantly distinguish patients with AMI from healthy individuals. QTc are not valuable in the diagnosis of AMI. Serum irisin performed well in distinguishing AMI from healthy volunteers, even in patients with normal QTc. The serum irisin level also appears to be a statistically strong and independent protective factor against STEMI risk and severity, according to univariate regression analysis.

Smoking is an important risk factor for heart diseases. The current study found that smoking was not statistically significant between the two groups. It is well known that smoking is an important risk factor for heart attacks. Many prospective studies show that both male and female smokers have a higher risk of myocardial infarction, recurrent heart attacks, and sudden death due to coronary artery disease. The incidence of coronary artery disease is 2–4 times higher in smokers. The risk of death from coronary artery disease is related to the number of cigarettes smoked per day, depth of inhalation, age at onset of smoking, and number of years smoked. In addition, smoking greatly affects other risk factors of coronary artery disease such as hypercholesterolemia and diabetes.³⁶

Our study also had some limitations. First of all, the sample size was small, and studies investigating the associations between serum irisin levels in with a larger population of STEMI patients are relevant. Moreover, the patients were not followed up after discharge, and their baseline irisin levels and their association with other cardiac biomarkers were investigated.

In conclusion, this study provides evidence of a reduction in serum irisin levels in patients with STEMI. Serum irisin also maintained a higher discriminatory ability for AMI. Circulating irisin levels were found to be correlated with cTi levels. Our data indicate that irisin may be a good candidate as a biomarker for STEMI besides cTi levels.

Data Sharing Statement

The primary author must be contacted with a valid request in order to provide the data sets used in this study. The email address is drmustafacalik@yahoo.com.

Funding

There is no funding to report.

Disclosure

No potential conflict of interest relevant to this article was reported.

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