

Original Article

Chest Pain is Associated With Decreased Irisin Serum Levels in Type 2 Diabetic Patients With Coronary Artery Disease

Taybeh Zyaddini¹, MD; Gholamreza Asadikaram², PhD;
Mohammad Masoumi^{3*}, MD

ABSTRACT

Background: This study aimed to determine irisin serum levels in type 2 diabetic patients with and without coronary artery disease (CAD).

Methods: This study was performed on 56 type 2 diabetic patients with and without CAD and 28 normal controls. The serum levels of irisin, HbA1c, and fasting blood sugar of all the participants and the severity of CAD in the diabetic patients were determined.

Results: The irisin serum level was significantly decreased in the CAD diabetic patients who were symptomatic. HbA1c had a moderate positive correlation with the SYNTAX score in the diabetic patients with CAD. The serum level of irisin was not significantly different between the evaluated groups.

Conclusions: Based on the results, decreased irisin may be considered a risk factor for type 2 diabetic patients with CAD. Accordingly, the evaluation of patients with decreased irisin serum levels regarding the prediction of heart infarcts may be valuable. (*Iranian Heart Journal 2020; 21(1): 55-66*)

KEYWORDS: Irisin, Type 2 diabetes, Cardiovascular diseases, Angiography

¹ Neuroscience Research Center, Institute of Neuropharmacology, Kerman University of Medical Sciences, Kerman, IR Iran.

² Endocrinology and Metabolism Research Center, Institute of Basic and Clinical Physiology Sciences and Department of Biochemistry, Afzalipur Faculty of Medicine, Kerman University of Medical Sciences, Kerman, IR Iran.

³ Cardiovascular Research Center, Institute of Basic and Clinical Physiology Sciences, Kerman University of Medical Sciences, Kerman, IR Iran.

*Corresponding Author: Mohammad Masoumi, MD; Cardiovascular Research Center and Department of Cardiology, Afzalipur Faculty of Medicine Kerman University of Medical Science, Kerman, IR Iran.

Email: masoomidr@yahoo.com

Tel:09131409938

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Diabetes is the most common chronic disease and affects human life world wide.¹ It has been estimated that diabetes will be raised to more than 328 million cases in the near future.² It is the fourth cause of morbidity and mortality in developed countries.³ Diabetes can be

associated with several complications including retinopathy, nephropathy, and cardiovascular diseases^{4, 5} It has been reported that diabetic patients suffer from cardiovascular diseases 2 to 5 times more than nondiabetic individuals.⁶ Diabetes can be associated with the incidence of heart

ischemia and cardiovascular disease-related complications. Therefore, the identification of new markers for the prediction of heart ischemia in diabetic patients who suffer from cardiovascular diseases is a new aim of investigators.

Recent investigations have proposed that irisin, a novel defined myokine, may be considered a potential marker for the induction of cardiovascular diseases and then heart ischemia in diabetic patients.⁷

Irisin is a novel glycoprotein produced by the proteolysis of membrane fibronectin type III domain-containing, which happens in response to the activation of PPAR- γ co-activator-1 α (PGC-1 α).⁸ It has been proposed that irisin is an important molecule that participates in the conversion of white to brown adipose tissues and, thus, decreases the risk of obesity, a critical risk factor for the induction of type 2 diabetes and cardiovascular diseases.⁹ There is some controversy regarding the serum levels of irisin in type 2 diabetic patients with and without coronary artery disease (CAD).^{9,10}

However, some investigations have reported that the serum level of irisin is associated with decreased risks of insulin resistance and glucose tolerance.^{11,12} It has also been hypothesized that the altered expression of irisin during cardiovascular diseases may be a mechanism to manipulate the ATP levels of myocardial cells, which are under ischemic conditions, to protect them from further damage.¹⁰ It appears that the altered expression of irisin may be associated with either physiological or pathological responses to heart ischemia. Due to the recent defined roles played by irisin, it has been hypothesized that the molecule may participate in the pathogenesis of type 2 diabetes and its complications. Thus, the main aim of the present study was to identify the irisin serum level in type 2 diabetic patients suffering from CAD in

comparison with type 2 diabetic patients without CAD and healthy controls. Another aim of the current study was to determine the relationship between the irisin serum level and other risk factors such as the SYNTAX score, HbA1C, and ethnic factors in the evaluated groups.

METHODS

Subjects

This cross-sectional study was performed between 2016 and 2017 on type 2 diabetic patients who referred to Shafa Hospital, Kerman University of Medical Sciences, Kerman, Iran. Fifty-six type 2 diabetic patients with angiography criteria, based on clinical presentations and paraclinical indications, and 28 healthy controls without diabetes and CAD were introduced to the study. Blood samples were collected in both groups pre-treated and without anticoagulant agents to evaluate HbA1C and irisin serum levels, respectively. Healthy controls were comprised of individuals who had angiography criteria but who did not suffer from diabetes and CAD. The type 2 diabetic patients were divided into 2 groups consisting of patients with and without CAD. The demographic data including age and sex, as well as other information regarding the history of familial CAD, smoking, blood hypertension, drug consumption, dyslipidemia, and obesity, were collected from the participants. Angiography was performed by an expert cardiologist via the Judkins method and interpreted by another cardiologist blinded to the study aims. The severity of CAD was determined using the SYNTAX scoring method.¹³ The exclusion criteria were as follows: type 2 diabetes of less than 1 year's duration, age < 30 years and > 60 years, and regular exercise in the recent 12 months (due

to the effects of exercise on the irisin serum level).

Determination of the Irisin Serum Level

The irisin serum level was determined using commercial kits from BioCompare Company (New York, USA).

Evaluation of HbA1C

The status of HbA1C was evaluated using a commercial kit according to the manufacturer's guidelines.

Statistical Analysis

SPSS software, version 18, was used to analyze raw data. Based on the normality in the data distribution, one-way ANOVA was employed to analyze the differences in irisin, HbA1C, fasting blood glucose (FBG), age, and weight between the groups. The χ^2 test was applied to analyze the differences between the groups regarding gender; smoking; opium consumption; regular exercise; chest pain; chronic diarrhea; a history of diabetes; elevated triglyceride and cholesterol; heart diseases; familial heart diseases; hospitalization; and liver, kidney, and infectious diseases. The independent *t*-test was also used to analyze the differences in the variables within each group between the male and female patients, between the participants residing in urban and rural areas, between the smokers and nonsmokers, between the opium users and non-users, and finally between the patients with and without chest pain. The Pearson correlation test was also utilized to calculate the correlation between irisin, FBG, weight, age, HbA1C, and the SYNTAX score.

RESULTS

The results showed that the serum level of irisin was not significantly altered ($P = 0.097$) in the type 2 diabetic patients with (3.16 ± 0.44 ng/mL) and without ($3.35 \pm$

0.38 ng/mL) CAD and the normal controls (2.25 ± 0.27 ng/mL) (Fig. 1).

The data analysis revealed that there were no significant differences between the groups regarding age ($P = 0.08$); sex ($P = 0.168$); smoking ($P = 0.210$); opium addiction ($P = 0.199$); a history of kidney ($P = 0.350$), liver ($P = 0.376$), and familial heart ($P = 0.103$) diseases; weight ($P = 0.370$); regular exercise ($P = 0.304$), and chronic diarrhea ($P = 0.583$). However, the levels of FBG and HbA1C were significantly higher in the type 2 diabetic patients (with and without CAD) than in the normal controls, while there were no significant differences between the 2 diabetic groups regarding FBG ($P = 0.938$) and HbA1C ($P = 0.202$) (Fig. 1).

The diabetic patients (with and without CAD) had significantly higher scores of a history of increased triglyceride ($P = 0.012$) and cholesterol ($P = 0.027$) levels as well as chest pain ($P < 0.001$).

The results also showed that the serum levels of irisin, FBG, and HbA1c were not changed between the male and female (Fig. 2), between the smoking and nonsmoking (Fig. 3), and between opium-addicted and nonaddicted (Fig. 4) type 2 diabetic patients with and without CAD.

The statistical analysis also revealed that the serum level of irisin significantly decreased in the type 2 diabetic patients with CAD who suffered from chest pain in comparison with the patients without chest pain ($P = 0.039$) (Fig. 5). Nonetheless, there were no significant associations regarding FBG and HbA1c between the type 2 diabetic patients with and without CAD who were suffering from chest pain in comparison with those without chest pain. The irisin serum level also was not changed between the type 2 diabetic patients without CAD with chest pain in comparison with those without chest pain ($P = 0.342$).

The Pearson test demonstrated that HbA1c had a moderate positive correlation with the SYNTAX score and a significant correlation with FBG in the type 2 diabetic patients with CAD (Table 1 Section A). The evaluation of the type 2 diabetic patients with CAD (Table 1 Section A) showed that there was a poor

negative correlation between the SYNTAX score and weight in the patients. HbA1c also had a significant correlation with FBG in the type 2 diabetic patients without CAD (Table 1 Section B). Table 1 Section C reveals no correlation between the variables in the normal controls.

Table 1. Correlation analysis regarding irisin, FBG, age, HbA1c, the SYNTAX score, and weight in the type 2 diabetic patients with CAD (A), without CAD (B), and normal controls (C)

A		Irisin	HbA1C	SYNTAX score	Age	Weight	FBG
Irisin	Pearson Correlation	1	0.017	-0.113	-0.085	-0.190	-0.081
	P value		0.933	0.567	0.667	0.332	0.682
HbA1C	Pearson Correlation	0.017	1	0.646*	0.176	-0.239	0.885**
	P value	0.933		>0.001	0.371	0.220	0.000
SYNTAX score	Pearson Correlation	-0.113	0.646*	1	0.268	-0.375***	0.521
	P value	0.567	>0.001		0.168	0.050	0.004

B		Irisin	HbA1C	Age	Weight	FBG
Irisin	Pearson Correlation	1	0.361	0.082	0.044	0.267
	P value		0.054	0.674	0.820	0.162
HbA1C	Pearson Correlation	0.361****	1	0.125	-0.116	0.816*****
	P value	0.054		0.518	0.549	>0.001

C		Irisin	HbA1C	Age	Weight	FBG
Irisin	Pearson Correlation	1	0.161	-0.328	.081	-0.05
	P value		0.254	.095	.687	.980
HbA1C	Pearson Correlation	0.161	1	0.225	-0.216	0.416
	P value	0.254		0.438	0.849	0.095

Data analysis revealed that HbA1c had a moderate positive correlation with the SYNTAX score (*) and a significant correlation with FBG (**) in the type 2 diabetic patients with CAD (A).

Evaluation of the type 2 diabetic patients with CAD (A) revealed that there was a poor negative correlation between the SYNTAX score and weight in the patients (***). HbA1c also had a poor and significant correlation with irisin (****) and FBG (*****). The variables had no significant correlation with each other in the normal controls.

CAD, Coronary artery disease; FBG, Fasting blood glucose

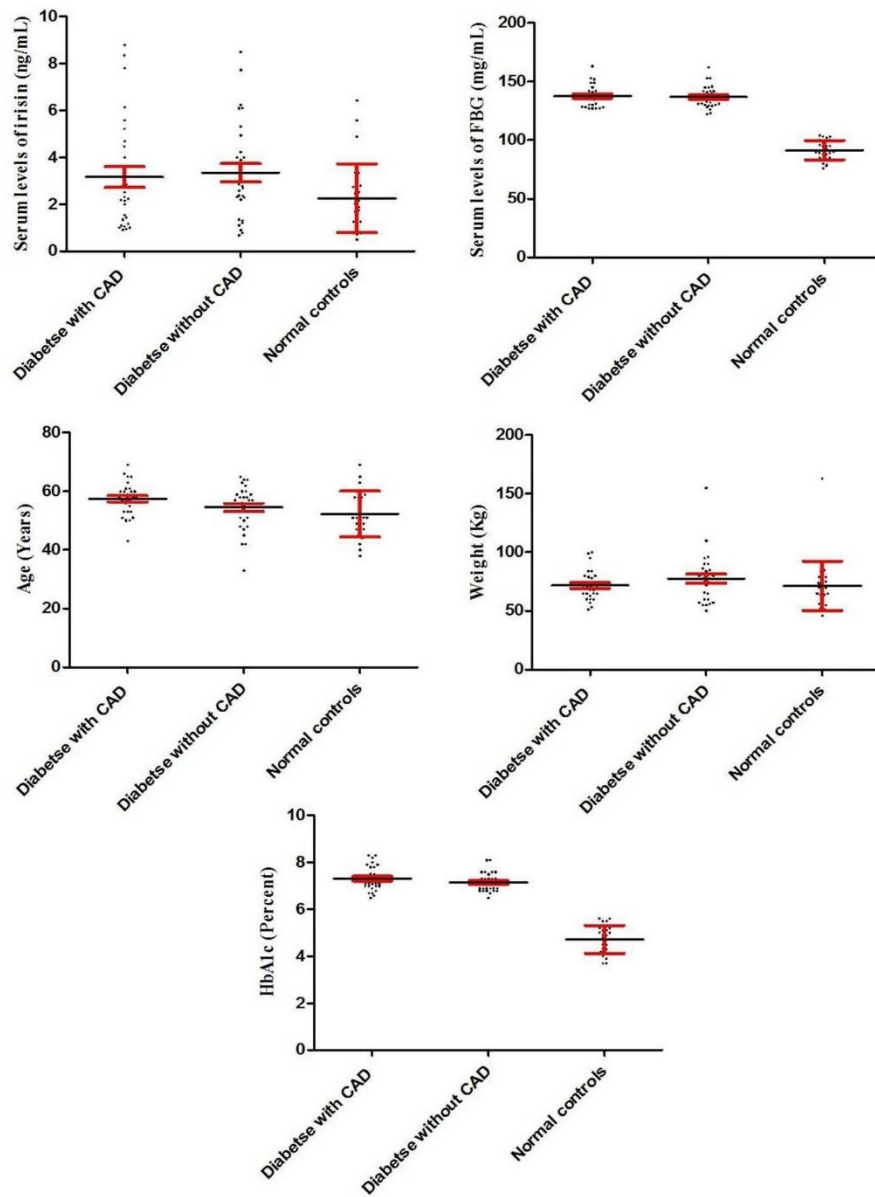


Figure 1. Serum levels of irisin and fasting blood glucose (FBG) as well as the HbA1c percentage, age, and weight values in the type 2 diabetic patients with and without coronary artery disease (CAD) as well as the healthy controls. The figure demonstrates that there were no significant differences between the groups regarding irisin, age, and weight. However, the serum level of FBG and the HbA1c percentage were significantly higher in the diabetic patients than in the normal controls.

343 x 412 mm (96 x 96 DPI)

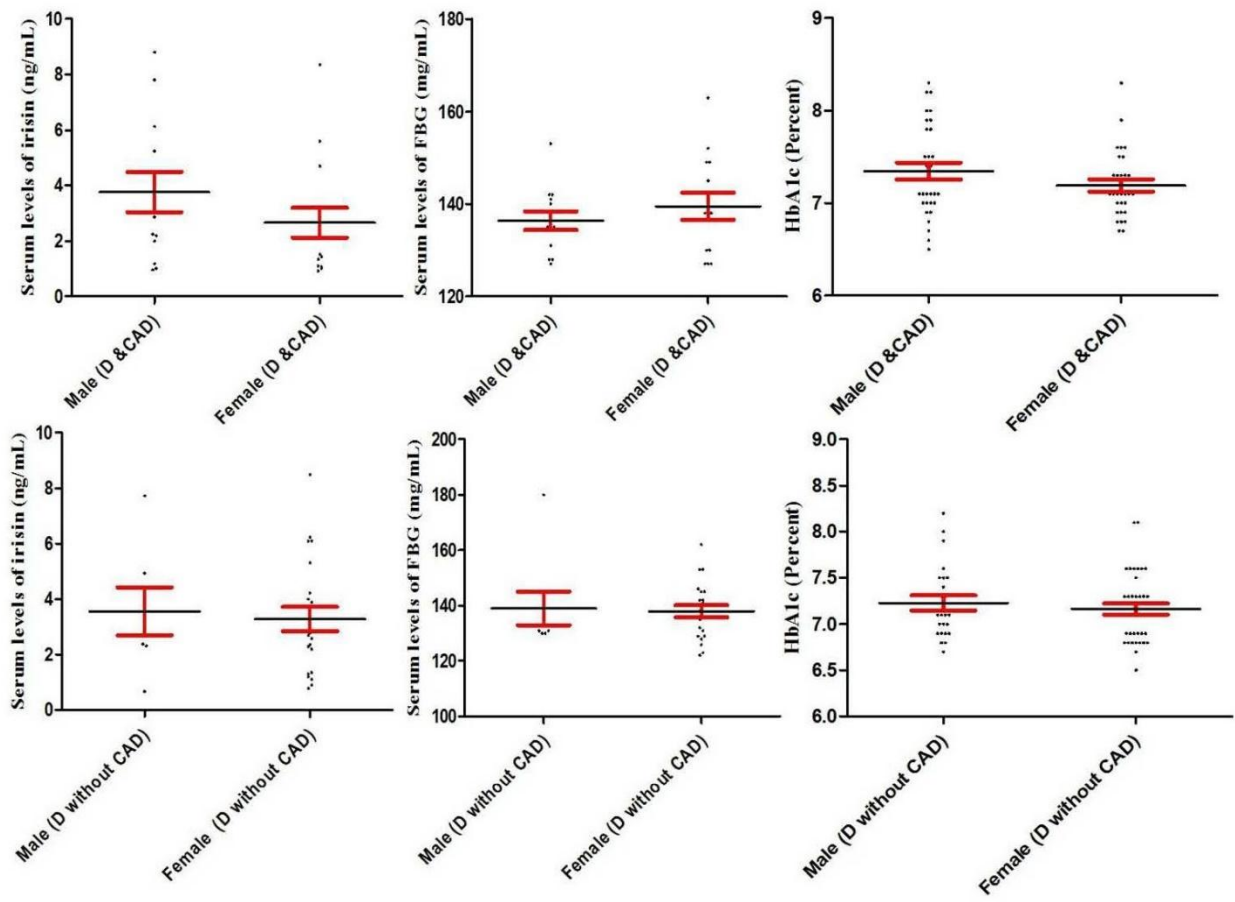


Figure 2. Serum levels of irisin and fasting blood glucose (FBG) as well as the HbA1c percentage in the male and female type 2 diabetic patients with and without coronary artery disease (CAD). The figure demonstrates that there were no significant differences between the male and female patients in both groups regarding irisin, FBG, and the HbA1c percentage.

405 x 293 mm (96 x 96 DPI)

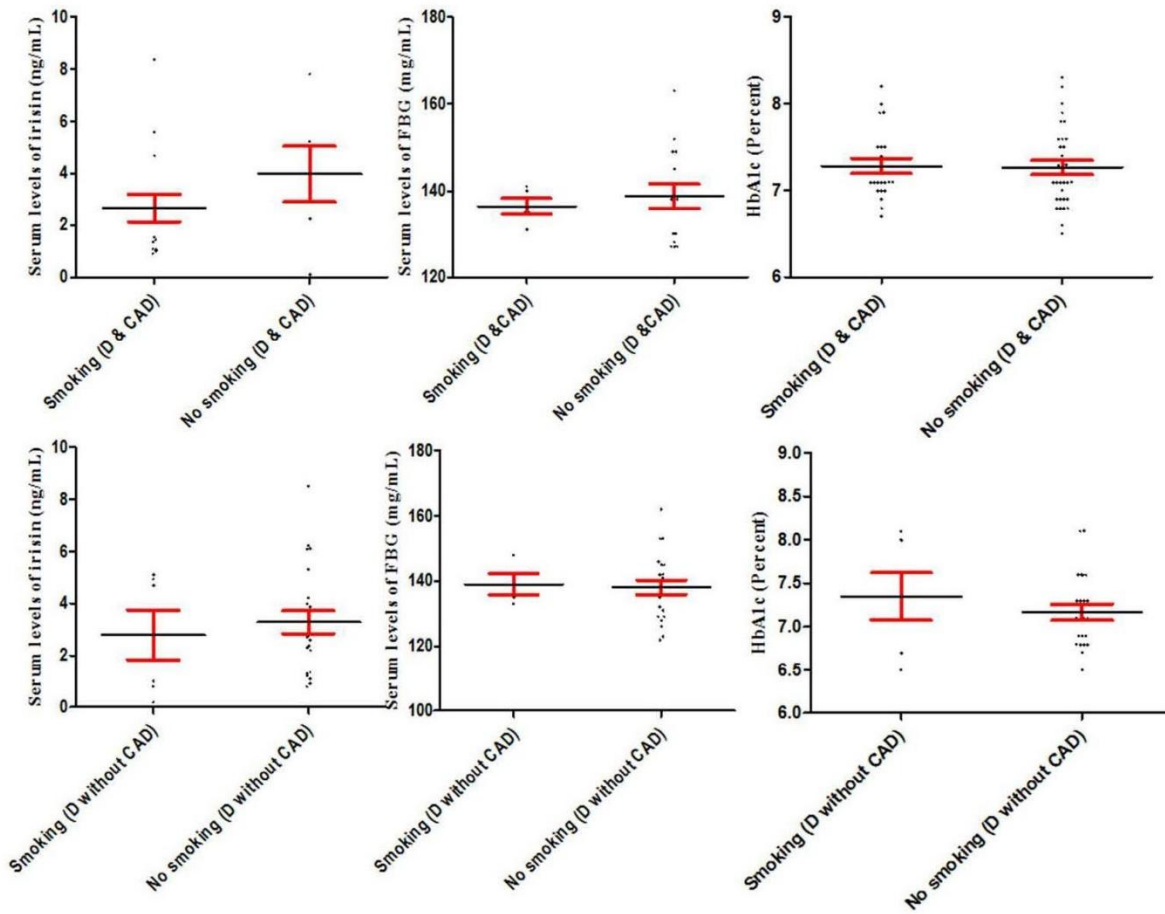


Figure 3. Serum levels of irisin and fasting blood glucose (FBG) as well as the HbA1c percentage in the smoking and nonsmoking type2 diabetic patients with and without coronary artery disease (CAD). The figure demonstrates that there were no significant differences between the smoking and nonsmoking patients in both groups regarding irisin, FBG, and the HbA1c percentage.

264 x 205 mm (96 x 96 DPI)

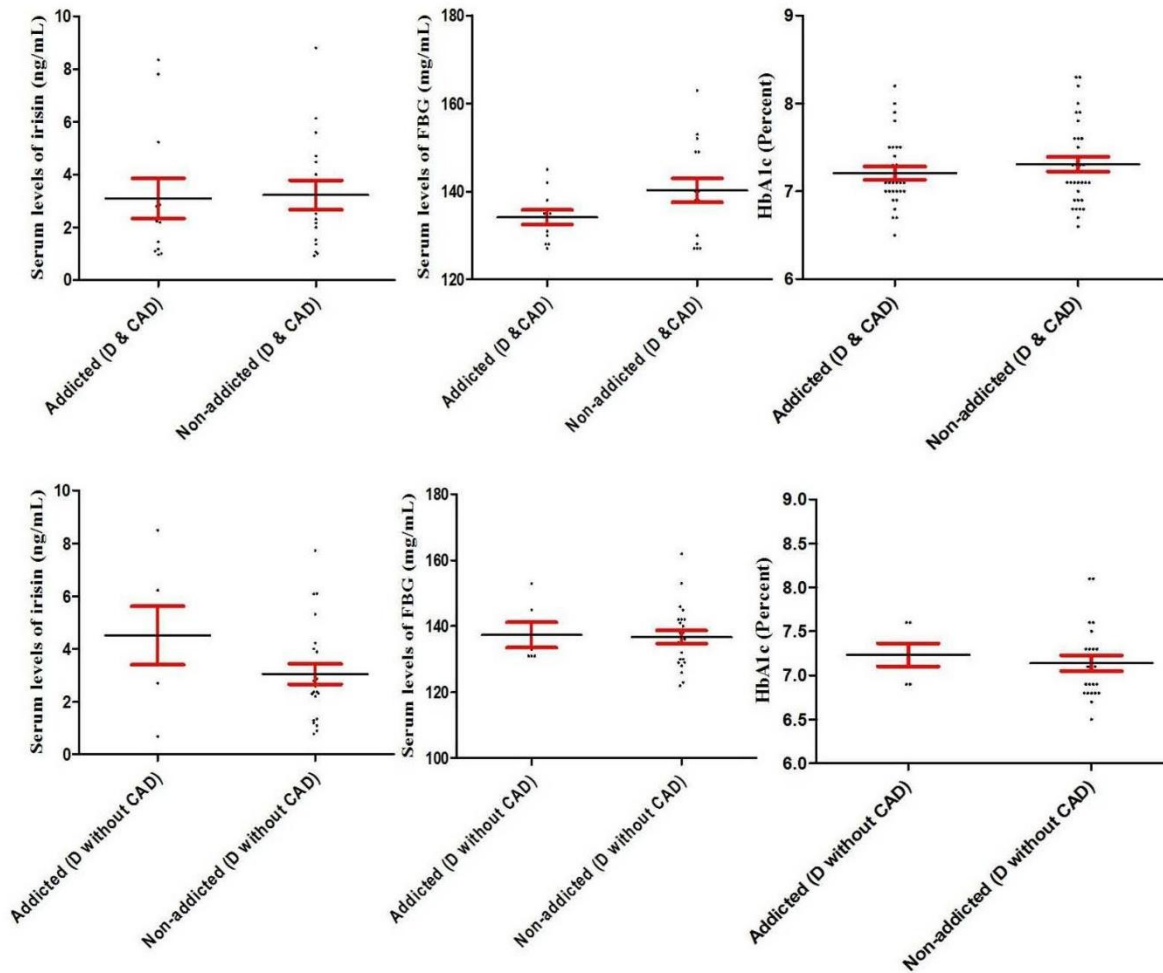


Figure 4. Serum levels of irisin and fasting blood glucose (FBG) as well as the HbA1c percentage in the opium-addicted and nonaddicted type 2 diabetic patients with and without coronary artery disease (CAD). The figure demonstrates that there were no significant differences among the opium-addicted and nonaddicted patients in both groups regarding irisin, FBG, and the HbA1c percentage.

411 x 350 mm (96 x 96 DPI)

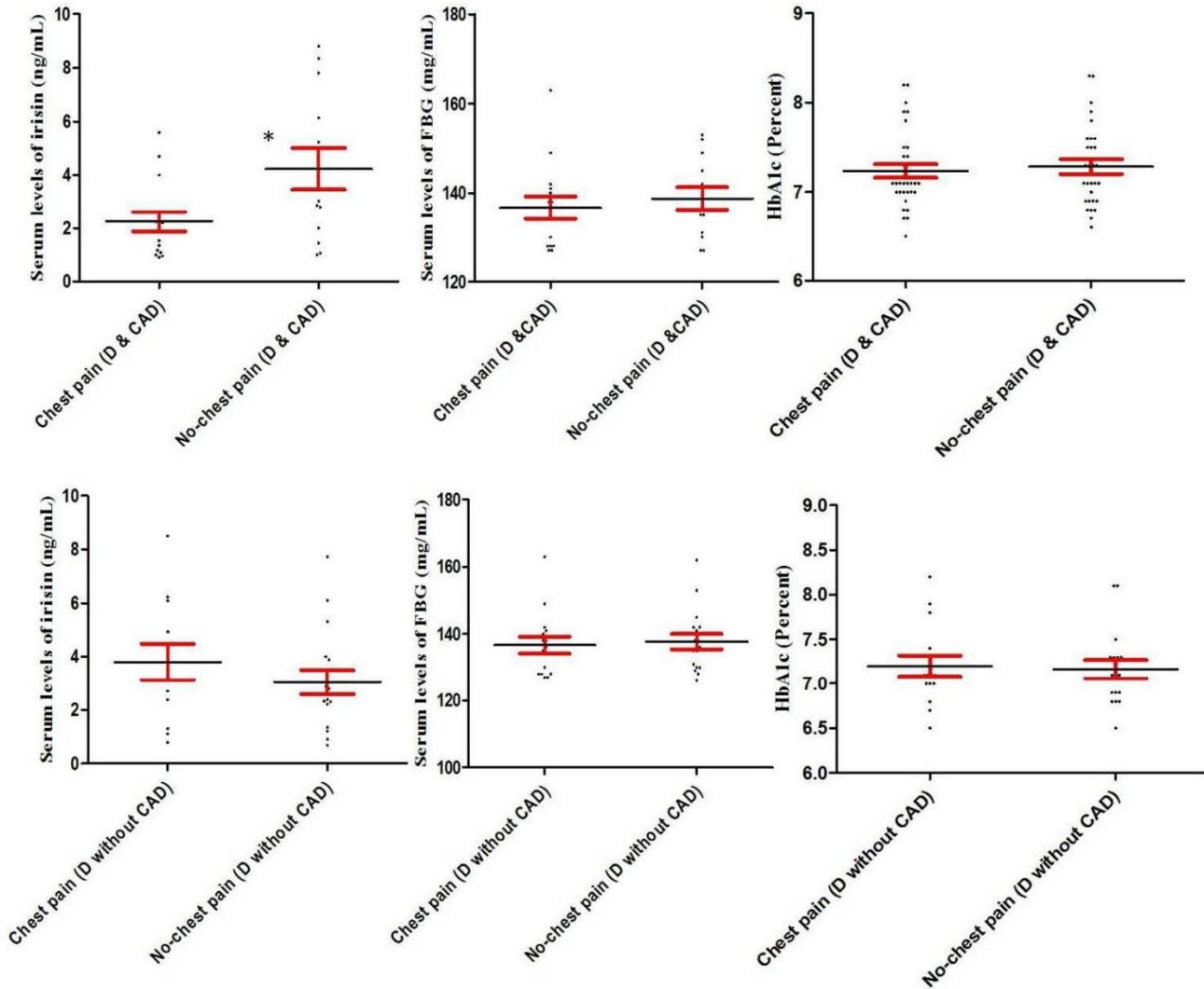


Figure 5. Serum levels of irisin and FBG as well as HbA1c percent in the type 2 diabetic patients with and without CAD who were suffered from chest pain in comparison to without chest pain. The figure shows that irisin significantly decreased in the type 2 diabetic patients with CAD who were suffered from chest pain in comparison to the patients without chest pain (* $P = 0.049$). There were no significant differences among the type 2 diabetic patients with and without CAD who were suffered from chest pain in comparison to without chest pain.

405 x 341 mm (96 x 96 DPI)

DISCUSSION

In the present study, the results revealed no significant differences between the 2 groups regarding the serum level of irisin; nevertheless, the statistical analysis demonstrated that the irisin serum level in the type 2 diabetic patients with CAD suffering from chest pain was significantly decreased when compared with the type 2 diabetic patients with CAD but without chest pain. Given that chest pain in patients with CAD is a major criterion in the induction of heart ischemia, it may be hypothesized that decreased serum levels of irisin in patients with chest pain may be considered a predicting factor for the onset of heart ischemia. Chiming in with this notion, Wang et al¹⁴ reported that irisin played a key role in protecting the mitochondria function, the myocardial infarct size, and finally the heart against ischemia and reperfusion injuries in their study population. The role played by irisin in the protection of the mitochondria function during ischemia was also documented by Chen and colleagues.¹⁵ Thus, decreased irisin levels following chest pain in type 2 diabetic patients with CAD may be a risk factor for susceptibility to cardiac infarction. Additionally, Aydin et al¹⁶ demonstrated that using iloprost and sildenafil, 2 pharmaceutical factors to mediate the resumption of reperfusion, played a significant role in increasing the expression of irisin in the heart, liver, and kidney blood tissues and that it was associated with improved cardiovascular diseases. The significant roles played by irisin in the protection of the cell system following ischemia via the downregulation of the ROS-NLRP3 inflammatory signaling pathway¹⁷ and the induction of the Akt and ERK1/2 signaling pathways have also been demonstrated previously.

We also found that the serum level of irisin had a poor positive correlation with the HbA1c percentage in our type 2 diabetic patients without CAD. It has been documented that obesity is a risk factor for the development of type 2 diabetes. Bonfante et al¹⁸ reported that obesity had a positive association with increased serum levels of irisin. Rana and colleagues¹⁹ also showed that increased irisin serum levels was a major marker for type 2 diabetes, associated with the increased expression of pro-inflammatory molecules such as E-selectins. It has also been reported that irisin induces glucose metabolism in the p38 MAPK signaling dependent manner.²⁰ Another investigation reported that, although the serum level of irisin increased in type 2 diabetic patients, its serum levels decreased in type 2 diabetic patients who suffered from nephropathy.²¹ Moreover, Shelbaya et al²¹ demonstrated that the serum level of irisin had a negative correlation with advanced glycation end-products, a factor for the worsening of type 2 diabetic patients. Collectively, it appears that irisin is a normal body response to increased FBG to minimize the side effects of diabetes. Our results also showed that the irisin serum level significantly increased in parallel with the increased percentage of HbA1c in our type 2 diabetic patients without CAD. Thus, it may be hypothesized that irisin is a response to increased HbA1c to protect the human cell system from type 2 diabetes complications.

Our results also showed that the SYNTAX score had a moderate correlation with HbA1c, which is a risk factor for the induction of cardiovascular diseases in type 2 diabetic patients.

We also found no significant differences between the male and female, smoking and nonsmoking, and opium-addicted and nonaddicted type 2 diabetic patients. Thus, it

appears that although the factors were the risk factors for the development of type 2 diabetes, they were unable to alter irisin expression. Further research can elucidate in more detail the roles played by these variables in the expression and function of irisin.

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Conflict of Interest

The authors have no conflict of interest to declare.

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