Evaluation of Irisin Levels and Epicardial Fat Thickness in Metabolic Syndrome

Metabolik Sendromda İrisin Düzeylerinin ve Epikardiyal Yağ Kalınlığının Değerlendirilmesi

Irisin Levels and Epicardial Fat Thickness in Metabolic Syndrome

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Özet

Amaç: Metabolik sendrom (MetS), santral şişmanlık, hiperlipidemi, hipertansiyon ve insülin direnci dahil olmak üzere birçok kardiyovasküler risk faktörleri ile karakterizedir. Visseral karın ve epikardiyal yağ (EY) dokularının aynı ontojenetik kökene sahip oldugu ve çok sayıda proinflamatuar ve pro-aterojenik sitokinleri üretmekte olduğu bildirilmiştir. Irisin obesite, insülin direnci, tip 2 diyabet gibi metabolik bozukluklarda önemli bir rol oynamaktadır. Bu çalışmanın temel amacı, MetS hastalarında serum irisin düzeylerini ve ayrıca irisin ile insülin direnci ve hastalık şiddeti arasindaki ilişkisiyi değerlendirmekti. Aynı zamanda metabolik sendromlu hastalarda irisin seviyeleri ve EY kalınlığı arasındaki ilişki de araştırıldı. Gereç ve Yöntem: Diyabeti olmayan 43 MetS'lu hasta ve 45 sağlıklı birey çalışmaya alındı. Serum irisin düzeyleri ve ekokardiyografik EY kalınlığı gruplar arasında karşılaştırıldı. Bulgular: Serum irisin düzeyleri ve EY değerleri MetS grubunda kontrol grubuna gore anlamlı olarak yüksek bulundu (sırasıyla p <0.001, p = 0.01). Irisin düzeyleri ile insülin direnci (r = 0.33, p <0.01) ve obezite ile ilişkili diger antropometrik ölçümler arasında pozitif korelasyon bulundu. Tartışma: Artmış irisin düzeyleri MetS'e ait karakteristik metabolik bozuklukları iyileştirmek için adaptif veya kompanzatuar bir yanıtı temsil ediyor olabilir. Yüksek irisin düzeylerinin önemini ve altında yatan mekanizmaları açıklığa kavuşturmak için ve insanlarda irisinin tam rolünü aydınlatmak için ileri çalışmalara gereklidir.

Anahtar Kelimeler

İnsülin Rezistansı; İrisin; Epikaryal Yag; Metabolik Sendrom

Abstract

Aim: Metabolic syndrome (MetS) is characterized by a combination of several cardiovascular risk factors, including central obesity, hyperlipidaemia, hypertension, and insulin resistance. It has been reported that visceral abdominal and epicardial fat tissues have the same ontogenic origin and produce many proinflammatory and proatherogenic cytokines. Irisin is a newly-discovered myokine that plays an important role in metabolic disorders such as obesity, insulin resistance, and type 2 diabetes. The primary aim of this study is to evaluate serum levels of irisin in MetS patients, as well as its association with insulin resistance and disease severity. We also investigated the association between irisin levels and EFT in patients with MetS. Material and Method: Forty-three patients who had MetS without diabetes and 45 healthy individuals were enrolled into the study. Serum irisin levels and echocardiographic EFT values were compared between the groups. Results: Serum irisin levels and EFT values were significantly higher in the MetS group than in the control group (p<0.001, p=0.01, respectively). Irisin levels were positively correlated with insulin resistance (r= 0.33, p<0.01) and other obesity-related anthropometric measurements. Discussion: Elevated irisin levels may represent an adaptive or compensatory response to prevent and ameliorate the metabolic disturbances characteristic of MetS. Further studies are needed to clarify the significance and underlying mechanisms of the elevated irisin levels, and direct evidence is needed to elucidate irisin's exact role in humans.

Keywords

Insulin Resistance; Irisin; Epicardial Fat; Metabolic Syndrome

DOI: 10.4328/JCAM.4443 Received: 28.02.2016 Accepted: 08.03.2016 Printed: 01.07.2016 J Clin Anal Med 2016;7(4): 497-500
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Introduction

Metabolic syndrome (MetS) is characterized by a combination of several cardiovascular risk factors, including central obesity, hyperlipidaemia, hypertension, and insulin resistance. Although multiple mechanisms and factors have long been recognized, including increased oxidative stress and inflammation, the understanding of the exact pathophysiology of MetS has been elusive [1,2]. Early recognition of premature atherosclerosis is important as subclinical atherosclerosis precedes the clinical manifestations of cardiovascular disease by many years. Epicardial fat thickness (EFT) has been associated with left ventricular dysfunction and subclinical atherosclerosis in patients with MetS [3-5].

Irisin, a newly-discovered myokine, has autocrine, paracrine, and endocrine effects and is able to regulate glucose and lipid levels, improving insulin sensitivity [5-10].

The primary aim of this study is to evaluate serum levels of irisin in MetS patients, as well as their association with insulin resistance and disease severity. We also investigated the association between irisin levels and EFT in patients with MetS.

Material and Method

This case–control study was conducted at the Yuksek Ihtisas Education and Research Hospital, Ankara, Turkey between May and December 2015. The local Institutional Review Board approved the study and the universal principles of the Helsinki Declaration were applied. Informed consent was obtained from each participant.

Forty-three consecutive women diagnosed with MetS and 45 age and body mass index (BMI) matched consecutive healthy women (as the control group) were recruited into the study.

The diagnosis of MetS was based on the National Cholesterol Education Program Adult Treatment Panel III update criteria [11] of 3 or more of the 5 features of 1) central obesity (waist circumference [WC] ≥88 cm for women); 2) elevated triglycerides (≥150 mg/dl); 3) diminished high-density lipoprotein (HDL) cholesterol (<50 mg/dl for women); 4) systemic hypertension (systolic blood pressure ≥130 or diastolic blood pressure ≥85 mm Hg); and 5) elevated fasting glucose (≥110 mg/dl).

Exclusion criteria were as following: chronic lung diseases (chronic obstructive lung disease, asthma), any autoimmune disease or connective tissue disease, chronic kidney and/or liver disease, peripheral vascular disease, and known diabetes mellitus, coronary artery disease, cardiomyopathy or decompensated heart failure, and any malignancy.

Anthropometric Measurements

All subjects underwent comprehensive anthropometric measurements. Height, weight, and WC were measured, and body mass index (BMI) was calculated. WC was measured to the nearest 0.5 cm on bare skin during mid-respiration at the natural indentation between the tenth rib and the iliac crest. All cases and controls underwent standard ECG and transthoracic echocardiography using a Vivid 7 (GE Pro/Expert) machine with a 3.5 MHz transducer. Epicardial fat thickness was measured on the right ventricular free wall in at least two locations, from both parasternal longitudinal and transverse parasternal views in systole [12].

Biochemical Measurements

The patients in both groups were asked not to consume caffeinated beverages within eight hours prior to the procedure. Level of physical activity was not standardized, but the patients were asked not to exercise on the assessment day. Blood samples were obtained from the antecubital vein early in the morning, following ten hours of fasting. Within five to ten minutes after taking the blood samples, the samples were centrifuged at 5000 revolutions/minute for ten minutes and cryopreserved at -80°C until the measurements were performed.

Serum concentrations of irisin were measured with a commercially available Irisin ELISA Kit (USCN Life Science Inc., Wuhan, China) according to the protocols provided by the manufacturer. All samples were assessed in duplicate. The measurement range for irisin was 15.6–1000 pg/mL. The intra-assay and interassay coefficients of variation were both <10%.

Homeostatic model assessment of insulin resistance (HOMA-IR) index was calculated using the following formula: FG (mg/dl) × FI level (μU/ml) / 405 [13].

Serum concentrations of hs-CRP were determined by a Tinaquant CRP (Latex) high-sensitive particle-enhanced immuno turbidimetric assay on a Roche Modular P analyzer (Roche kit, Roche Diagnostics, GmbH, Marburg, Germany) according to manufacturer instructions. Minimum detectable concentration was 1x10−5 mg/L for hs-CRP. All of the other blood analyses were carried out within two hours of blood sampling, using a hematology analyzer (GEN-S; Beckman-Coulter Inc., Brea, CA) at the central laboratories of the hospital.

The age, BMI, blood pressure, and hs-CRP, basal hematological and biochemical profile, fasting blood glucose (FBG), fasting insulin (FI), hemoglobin (Hb) A1c, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and irisin levels of each participant were recorded.

Statistical Analysis

Statistical analysis was performed using SPSS version 18 (Statistical Package for the Social Sciences, Chicago, IL). The data were summarized as mean ± standard deviation and median (minimum–maximum). Comparisons of parametric variables between the groups with a normal distribution were made by one-way analysis of variance. The Kruskal–Wallis test was performed to compare continuous variables that did not have a normal distribution. A chi-square test was performed for nominal or ordinal variables between groups, where appropriate. Independent parameters associated with EFT and irisin were assessed by a standard multiple linear regression analysis. Results were considered significant when the p value was <0.05.

Results

Forty-three consecutive women who had MetS without diabetes and met all inclusion criteria were enrolled into the study as study group. For the control group, 45 healthy, consecutive women matched for age and BMI were recruited within the same time interval.

The demographic and laboratory characteristics of the groups are shown in Table 1. The mean systolic and diastolic blood pressure levels were significantly higher in the MetS group than in the control group (p<0.001). The WC, HbA1c, FB, FI, HOMA-

Table 1. Comparison of parameters in patient with and without metabolic syndrome.

	MetS - group (n= 45)	MetS + group (n= 43)	p value
Age, years	53.6± 7.6	54.0± 5.5	NS
BMI, kg/m2	27.9± 3.9	283 ± 3.4	NS
Systolic BP, mmHg	130± 12	140± 26	<0.001
Diastolic BP, mmHg	75± 10	81± 15	<0.001
WC, cm	90± 6	107± 6	<0.001
Hemoglobin, g/dl	14.1± 2.4	13.6± 3.6	NS
WBC, 103/ uL	7.7± 2.1	7.1± 2.4	NS
HbA1c, %	5,6± 1,5	6 ± 1,3	0.01
FBG, mg/dl	88.6± 6.3	105.8± 10	<0.001
Fasting insulin, µU/ml	8.81±2.02	14.59±2.51	<0.001
Serum Creatinine, mg/dl	0.81± 0.43	0.82± 0.37	NS
HOMA-IR	1.1± 0.5	3.16± 0.8	<0.001
Triglyceride, mg/dl (range)	84 (79-110)	143 (105-155)	<0.001
LDL-cholesterol , mg/dl	113.3 ± 28.9	131.3 ± 28.9	NS
HDL-cholesterol, mg/dl	53± 8.9	41± 14.1	<0.001
Total Cholesterol, mg/dl	197.2 ± 33.2	215.2 ± 33.2	<0.001
C-reactive protein, mg/L	2.5± 1.9	3.8± 2.7	0.05
Irisin, ng/ml (range)	141 (121-223)	224 (188-286)	<0.001
EFT, mm	4.1± 1.0	5.6± 1.6	0.01

Data expressed as mean ± SD, The mean difference is significant at the 0.05 level. NS: Non-significant.
BP: Blood pressure, BMI: body mass index, EFT: Epicardial Fat Thickness, FPG, fasting plasma glucose; HbA1c: hemoglobin A1c; HDL: high density lipoprotein; LDL: low density lipoprotein; WC, waist circumference;WBC: white blood cell

IR, triglyceride, and CRP levels of the patients with MetS were higher than those of the control group (Table1).

Serum irisin levels and EFT values were significantly higher in the MetS group than in the control group (p<0.001 and p=0.01, respectively). In correlation analysis there was a positive correlation between irisin levels and EFT (r = 0.25, p=0.04). Irisin levels were also positively correlated with BMI, WC, and HOMA-IR (Table 2).

Table 2. Correlations of irisin levels and epicardial fat thickness with Insulin Resistance (Evaluated by Homeostasis Model Assessment), and BMI in the MetS + group.

MetS + group (n=43)	Irisin	EFT	BMI	WC	HOMA-IR	
Irisin	r	1	0.25	0.28	0.52	0.33
	p	-	0.04	0.02	0.01	<0.01
EFT	r	0.25	1	0.33	0.17	0.29
	p	0.04	-	<0.01	0.01	0.43

r: correlation coefficient. P<0.05 is considered statistically significant.
BMI: body mass index, EFT: Epicardial Fat Thickness, HOMA-IR: homeostatic model assessment of insulin resistance, WC: waist circumference.

Discussion

In this study irisin and EFT levels were significantly higher in women with MetS compared with women without MetS. There was a significant positive correlation between serum irisin levels and EFT, BMI, WC, and HOMA-IR index.

Epicardial fat tissue is the visceral fat deposit of the heart that is localized on the myocardium, in the atrioventricular and interventricular sulci, extends to the apex, and surrounds the coronary arteries. It is considered to be abnormal if exceeds 5 mm in thickness [14]. It is well evidenced that epicardial fat tissue can produce several vasoactive factors, growth factors, and pro-inflammatory and proatherogenic adipokines, and cytokines (i.e. interleukin-6, TNF-α, leptin, omentin and visfatin). Furthermore, it can potentially influence the myocardium and the coronary arteries adversely [14,15]. It has been reported that measuring of EFT by echocardiography is a simple, reliable, and cheap method [16]. Measurement of the EFT has been proposed as a marker of cardiovascular risk that seems to change with age, BMI, and gender; and excess epicardial adipose tissue has been associated with the prevalence and severity of several heart diseases [3-5]. In this study, patients with MetS had higher values of EFT compared with healthy subjects. These results are consistent with those from several previous studies regarding MetS and EFT values.

In recent years, it has been shown that the interaction between adipose and muscle tissues plays a critical role in body weight regulation. Both adipose and muscle tissues produce some cytokines and other peptides (adipokines and myokines) that contribute to tissue communication that is essential to maintain metabolic homeostasis. Irisin—a recently discovered insulin resistance-related hormone—regulates exercise-mediated adipocyte browning; however, the systematic effects of irisin on the metabolism of glucose and lipids are largely unknown [9]. In rat models, it has been shown that irisin treatment reduced FBG and FI levels [17]. Given that irisin is involved in glucose uptake and lipid metabolism, it has been speculated that it plays an important and beneficial role in the regulation of glucose and lipid metabolism. Thus, irisin might play a protective role against insulin resistance, making it a potential new target for the treatment of metabolic disorders [17]. Consistent with this idea, recent studies have reported significantly reduced levels of maternal irisin levels in gestational diabetes cases [18, 19]. In addition, a significant reduction in serum irisin levels has been reported in patients with type 2 diabetes, suggesting that either the diabetic state itself or the metabolic condition that caused the progression to type 2 diabetes is accompanied by lower circulating irisin levels [20]. (In this study, we did not include women who were diagnosed with diabetes.) We demonstrated that serum irisin levels were significantly higher in patients with MetS than in patients without MetS. Irisin levels were correlated positively with obesity related measurements (BMI, WC, and EFT). Although it is difficult to infer whether the high irisin level is a cause or effect of MetS, we could speculate that the effects of irisin represent an adaptive or compensatory response to prevent and ameliorate the metabolic disturbances characteristic of MetS. Further studies are needed to clarify the significance and underlying mechanisms of the elevated irisin levels, and direct evidence is needed to elucidate irisin's exact role in humans.

The strength of our study is that this is the first study to evaluate the relationship of irisin, MetS, and insulin resistance in women and to provide a more detailed analysis including MetS components and regression models adjusted for various anthropometric measurements such as BMI, WC, and EFT. Data presented herein demonstrate consistency in terms of the association between irisin and metabolic parameters. Also, anthropometric measurements provide internal validity to the study.

Competing interests

The authors declare that they have no competing interests.

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How to cite this article:
Kırbaş Ö, Ertem AO, Yayla Ç, Akboğa MK, Kirbas A, Özeke Ö. Evaluation of Irisin Levels and Epicardial Fat Thickness in Metabolic Syndrome. J Clin Anal Med 2016;7(4): 497-500.