J Surg Med. 2019;3(3):242-245.
DOI: 10.28982/josam.536426

Research article
Araştırma makalesi

Journal of Surgery and Medicine
e-ISSN: 2602-2079

Evaluation of serum irisin levels in patients with endometrial hyperplasia: A controlled cross-sectional study

Endometrial hiperplazili hastalarda serum irisin düzeylerinin değerlendirilmesi: Kontrollü kesitsel çalışma

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Ethics Committee Approval: The study was approved by the Ethics Committee of Erciyes University (Decision number: 2016/466).
Etik Kurul Onayı: Çalışma Erciyes Üniversitesi Etik Kurulu tarafından onaylandı (Karar numarası: 2016/466).

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Received / Geliş Tarihi: 06.03.2019
Accepted / Kabul Tarihi: 10.03.2019
Published / Yayın Tarihi: 11.03.2019

Abstract

Aim: Irisin, which is proteolytically splited form of fibronectin type III domain containing 5 (FNDC5), is a protein with 112 amino acid. Irisin is an exercise-induced hormone excreted primarily by cardiac muscle and skeletal cells which can be described as an exercise hormone and a new potential target for the treatment of metabolic diseases and obesity. Our goal was to evaluate the serum irisin levels in patients with endometrial hyperplasia (EH).

Methods: An observational study is planned. The study population consisted of two groups: 1) the EH group (study group), consisting of participants who had been histopathologically diagnosed with simple EH without atypia and 2) the control group, consisting of healthy participants admitted to the clinic for an annual examination without any complaints or symptoms. Primary outcome of the study was evaluation irisin status. Serum irisin levels were determined by an enzyme-linked immunosorbent assay (ELISA) method.

Results: After sample size analysis, 52 participants enrolled into the study as study group (EH group) (n=26) and control group (n=26). The mean age was 39.5±3.8 years in the EH group and 40.7±2.4 years in the control group (p=0.258). Mean BMI was 28.8±2.1 kg/m^2 in the EH group and 28.5±1.2 kg/m^2 in the control group (p=0.666). Gravidity, parity, systolic blood pleasure, diastolic blood pleasure, fasting glucose levels, smoking status, alcohol use were similar for both groups (p=0.499, p=0.278, p=0.248, p=0.424, p=0.646, p=0.486 and p=0.153, respectively). In control group regular exercise rates was significantly higher than EH group (26.9%, 3.84%, respectively p<0.001). The mean serum irisin level was 1.9±0.7 µg/ml in the EH group and 3.5±2.0 µg/ml in the control group. Serum irisin levels were found to be significantly lower in the EH group compared to the control group (p<0.001).

Conclusion: The data from the current study indicate that serum irisin levels were significantly decreased in patients with endometrial hyperplasia. Serum irisin levels may open up new horizons for therapeutic targets for the treatment of patients with EH.

Keywords: Endometrial hyperplasia, Obesity, Sedentary life, Physical activity, Irisin

Öz

Amaç: Proteolitik olarak bölünmüş 5 (FNDC5) içeren fibronektin tip III alan formunda olan irisin, 112 amino asitli bir proteindir. İrisin, temel olarak kalp kası ve iskelet hücreleri tarafından salgılanan, egzersiz hormonu ve metabolik hastalıkların ve obezitenin tedavisi için yeni bir potansiyel hedef olarak tanımlanabilen, egzersiz kaynaklı bir hormondur. Amacımız endometrial hiperplazi (EH) hastalarında serum irisin düzeylerini değerlendirmektir.

Yöntemler: Çalışma popülasyonu iki gruptan oluşmaktadır: 1) histopatolojik olarak atipisiz basit EH tanısı almış EH grubu ve 2) kliniğe herhangi bir yakınması ve şikayeti olmadan yıllık muayene için başvuran kontrol grubu. Çalışmanın primer sonucu serum irisin seviyelerinin araştırılmasıdır. Serum irisin düzeyleri, enzyme-linked immunosorbent assay (ELISA) yöntemiyle belirlendi.

Bulgular. Örneklem büyüklüğü analizi sonrası toplam 52 katılımcı çalışmaya dahil edildi (EH grubu (n=26) ve kontrol grubu (n=26)). Ortalama yaş EH grubunda 39,5±3,8, kontrol grubunda 40,7±2,4 idi (p=0,262). EH grubunda ortalama VKI 28,8±2,1 kg/m2, kontrol grubunda 28,5±1,2 kg/m2 idi (p=0,666). Gravidite, parite, sistolik kan basıncı, diyastolik kan basıncı, açlık glikoz seviyeleri, sigara içme durumu, alkol kullanımı her iki grup için benzerdi (sırasıyla p=0,499, p=0,278, p=0,248, p=0,424, p=0,646, p=0,486 ve p=0,153). Kontrol grubunda düzenli egzersiz oranları EH grubundan anlamlı olarak yüksekti (sırasıyla %26,9, %3,84, p<0,001). Ortalama serum irisin düzeyi EH grubunda 1,9±0,7 µg/ml ve kontrol grubunda 3,5±2,0 µg/ml idi. Serum irisin düzeyleri EH grubunda kontrol grubuna gore anlamlı olarak düşük bulundu (p<0,001).

Sonuç. Mevcut çalışmadan elde edilen veriler, endometrial hiperplazili hastalarda serum irisin düzeylerinin anlamlı derecede azaldığını göstermektedir. Serum irisin düzeyleri, EH'li hastaların tedavisinde terapötik hedefler için yeni ufuklar açabilir.

Anahtar kelimeler: Endometrial hiperplazi, Obesite, Sedanter yaşam, Fiziksel aktivite, İrisin

Introduction

Endometrial cancer (EC) is the most common gynecological malignancies worldwide, with approximately 50,000 new cases annually identified in the United States [1]. Estrogen-dependent EC (type 1 EC) accounts for approximately 80% of cases. Endometrial hyperplasia (EH), which is a pre-cancerous lesion, occurs via abnormal proliferation of the uterine endometrial layers, characterized by an increased endometrial gland-to-stroma ratio with changing of shape and size [2]. EH and EC have similar risk factors, and the most notable factors are unopposed estrogen, obesity, inadequate physical activity and sedentary behavior [3].

Irisin, which is proteolytically splited form of fibronectin type III domain containing 5 (FNDC5), is a protein with 112 amino acid. Irisin is an exercise-induced hormone excreted primarily by cardiac muscle and skeletal cells. Small amounts of this myokine have been identified in, subcutaneous glands, adipose tissue, spleen, stomach, testis brain, and liver [4]. Irisin release increases during exercise. Irisin synthesis rises owing to the activation of peroxisome proliferator-activated receptor-γ coactivator 1α (PGC1α) in muscle cells. The primarily effects of brown fat tissue are provided by the activation of high volumes of uncoupling protein 1 (UCP1) in their mitochondria; in other words, the feature of brown fat tissue is the over-expression of PGC1α and UCP1. Because of the irisin effect, PGC1α and UCP1 levels, which are lowly expressed in white fat tissue, are stimulated, and their expression is increased. Therefore, white fat tissues phenotypically become brown fat tissues [4].

There are few studies in literature to evaluate irisin levels and irisin effect in cell proliferation and tumor progression, but results were different and irisin effect on cell proliferation is not fully illuminated today [5-7].Therefore in the present study we aimed to evaluate relationship between serum irisin levels and endometrial hyperplasia.

Materials and methods

This cross-sectional study was conducted at the Kayseri Education and Research Hospital, Kayseri, Turkey. The study was approved by the Ethics Committee of Erciyes University (Decision number: 2016/466) and was carried out in compliance with the Declaration of Helsinki. All participants gave informed consent before the study.

The study population consisted of two groups: 1) the EH group, consisting of participants who had been histopathologically diagnosed with simple EH without atypia who were from 35 to 50years of age, and 2) the control group, consisting of healthy participants admitted to the clinic for an annual examination without any complaints or symptoms. Patients were excluded from the study in the presence of malignancy or pregnancy and also liver, cardiovascular, metabolic or kidney disease, type 1 or 2 diabetes mellitus, hypertension, immune suppressive drug usage or extreme exercise in previous months. Demographic parameters, including age, gravidity, parity, ethnicity, body mass index (BMI), smoking status, alcohol use, regular exercise and systolic and diastolic blood pressure were recorded.

Three 3 cc peripheral venous blood samples were drawn from each participant into serum separating tubes for the measurement of serum irisin levels. Blood samples were collected from the participants with EH during a control visit after endometrial sampling and from the control group during regular clinic visits in a follicular menstrual phase. Until analysis, blood samples were stored at –80oC in a freezer after which they were centrifuged at 4,000 rpm for 10 min. All blood samples were analyzed on the same day at the Kayseri Education and Research Hospital of Medicine Biochemical clinics after four months of storage from the time of the first blood sample. Serum irisin levels were determined by an enzyme-linked immunosorbent assay method (ELISA) (Biovision K4761-100).

Statistical analysis

The Shapiro-Wilk test was used to test the normality assumption of the data. Levene's test was used to test the variance homogeneity assumption. Values are expressed as mean ± standard deviation, median (25th–75th percentile), or n (%). Parametric comparisons were made using a t-test or a z-test, and nonparametric comparisons were made using the Mann-Whitney U test. All comparisons were made with the PASW Statistics 18 program and a p-value of <0.05 was considered statistically significant.

Results

Overall, 52 participants enrolled in the study: 26 were in the EH group, and 26 were in the healthy control group. The mean age was 39.5±3.8 years in the EH group and 40.7±2.4 years in the control group (p=0.258). Mean BMI was 28.8±2.1 kg/m2 in the EH group and 28.5±1.2 kg/m2 in the control group (p=0.666). Gravidity, parity, systolic blood pleasure, diastolic blood pleasure, fasting glucose levels, smoking status, alcohol use were similar for both groups (p=0.499, p=0.278, p=0.248, p=0.424, p=0.646, p=0.486 and p=0.153, respectively). In control group regular exercise rates was significantly higher than EH group (26.9%, 3.84%, respectively, p<0.001). A comparison of the patients' characteristics is shown in Table 1.

Table 1: Comparison of patients' characteristics between groups

Characteristic	Study group n=26	Control group n=26	p
Age (year)	39.5±3.8	40.7±2.4	0.258
Gravity (min-max)	(1-5)	(1-5)	0.499
Parity (min-max)	(1-4)	(1-4)	0.278
BMI (kg/m^2)	28.8±2.1	28,5±1,2	0.666
SBP (mmHg)	120.7±10.5	118,4±7,8	0.248
DBP (mmHg)	79.2±8.1	77,6±8,9	0.424
Fasting blood glucose (mg/mL)	82.0±5.6	82,6±3,6	0.646
Smoking status (n%)	4 (15.3%)	6 (23.0%)	0.486
Alcohol use (n%)	2 (7.6%)	0 (0%)	0.153
Exercise regularly (n%)	1 (3.84%)	7 (26,9%)	<0.001
Serum irisin (µg/mL)	1.9±0.7	3.5±2.0	<0.001

BMI: Body mass index, SBP: Systolic blood pleasure, DBP: Diastolic blood pleasure

A comparison of the serum irisin levels is shown in Figure 1. The mean serum irisin level was 1,9±0,7µg/ml in the EH group and 3.5±2.0 µg/ml in the control group. Serum irisin levels were found to be significantly lower in the EH group compared to the control group (p<0.001).

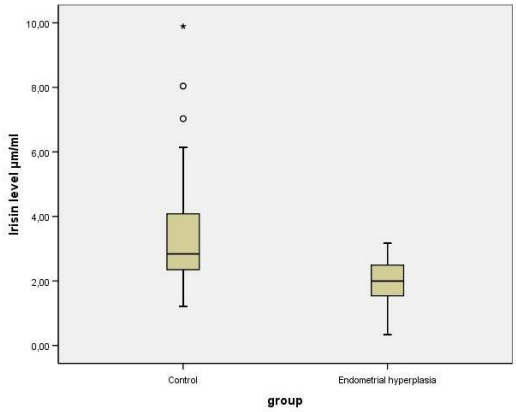

Figure 1: Comparison of serum irisin levels between groups.

Scatter dot plots of serum irisin levels in patients with cases of endometrial hyperplasia and controls. Mean values ± standard deviation are also denoted. Serum irisin levels were significantly lower in the endometrial hyperplasia patients compared to controls (1.9±0.7 vs. 3.5±2.0 µg/ml, p<0.001)

Discussion

Obesity and lifestyle factors are increasingly being studied for their associations with cancer. Sedentary behavior and inadequate physical activity are related with an increased risk of various cancers especially endometrial cancer. The goal of present study was to examine serum irisin levels that can be described as an exercise hormone in patients with EH. Our results indicated that serum irisin levels were significantly decreased in patients with EH.

In the present study we found that serum irisin levels were significantly decreased in patients with EH. In the literature, there are a few studies which evaluated the role of irisin in regulating cell proliferation and malign potential of mouse and human cancer cell lines. Gannon et al. suggested that irisin was a potential therapeutic agent for cancer and had a suppressive effect on the cell number and migratory characteristics in malignant breast cancer cells and induced apoptotic cell death in malignant breast cells [5]. In another study, Provatopoulou et al. [6] reported that irisin could be potentially used as an adipokine and a new diagnostic indicator of breast cancer. Irisin is crucial in early detection of breast cancer because it can efficiently differentiate between diseased and healthy individuals with 62.7% sensitivity and 91.1% specificity with a cut-off value of 3.21 µg/mL [6]. In contrast, Moon and Mantzoros declared irisin did not affect the malign potential of obesity-associated cancer cell lines in vitro at physiological and high physiological and/or high pharmacological concentrations [7].

In the current study we found that BMI was similar between groups and regularly exercise rates was significantly higher in control group. Considering that BMI is equal in both groups, it is possible to explain this difference in serum irisin levels with regular exercise rates. It is declared that exercise increases circulating irisin levels [8-10]. We may be able to explain our results with physical activity and changes in circulating concentrations of insulin, insulin-related pathways, and inflammation [11]. It is well documented that exercise has beneficial changes in circulating concentrations of insulin, insulin-related pathways, and inflammation [12]. The effects of sedentary behavior and physical activity on the immune system that related to cancer development are well documented [13,14].Additionally, it is showed that time spent sitting was associated with an increased risk of metabolic syndrome, increased insulin resistance, and higher levels of C-reactive protein [15,16].

Various risk factors that are associated with EH and EC are addressed. In a study of Beavis et al. [3] it is reported that physical activity was inversely associated with EC. In another cohort study Borch KB et al. [17] declared that 21.9% of endometrial cancers could be avoided if women with low levels of physical activity increased their physical activity level. In addition it is reported that higher levels of sedentary behavior were associated with increased risk of EC incidence [18-20]. Therefore, managing obesity is warranted in these patients. Diet, exercise, and weight loss are the preventive measures recommended for obese women diagnosed with EH [21]. Similar lifestyle modifications can help to treat diabetes or metabolic syndrome, but effective management requires pharmacologic interventions. It is clear that irisin levels can be a therapeutic target for obesity, diabetes, insulin resistance and metabolism regulation [22-27]. No studies have quantified the magnitude of therapeutic benefit. However, morbidity and mortality are significantly alleviated through lifestyle modifications than using temporary pharmacologic therapies. Thus, lifestyle modifications have a pivotal role in a comprehensive management plan. Of course, prospective studies with a greater number of patients are required in this area. There are several limitations of study. Small sample size and cross sectional design are major limitations. Additionally new further prospective studies that included patients with atypical EH and EC can be explain mechanisms more clearly.

Conclusion

The data from the current study indicate that serum irisin levels were significantly decreased in patients with endometrial hyperplasia. Serum irisin levels may open up new horizons for therapeutic targets for the treatment of patients with EH.

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