Clinical Investigation / Araştırma

DOI: 10.4274/tjod.galenos.2021.12080

Turk J Obstet Gynecol 2021;18:175-180

The role of adropin, salusin-α, netrin-1, and nesfatin-1 in endometriosis and their association with insulin resistance

Endometriozisde adropin, salusin-α, netrin-1 ve nesfatin-1'in rolü ve bunların insülin direnci ile ilişkisi

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Abstract

Objective: The pathogenesis of endometriosis has not been clearly explained. Inflammatory factors of ectopic implantation and the growth of ectopic endometrial cells have been subjects of major interest. The number of studies evaluating salusin-α and nesfatin-1 markers in patients with endometriosis is limited. No studies have evaluated the levels of anti-inflammatory markers for adropin and netrin-1 in patients with endometriosis. This study investigates how some important inflammatory regulatory markers in the inflammatory process affect the pathogenesis of endometriosis and determines whether any relationship exists between serum levels of these parameters and endometriosis and insulin resistance.

Materials and Methods: This prospective study included 73 patients with endometriosis diagnosed histopathologically after laparoscopic surgery and 75 healthy controls. Serum adropin, salusin-α, netrin-1, and nesfatin-1 levels and homeostatic model assessment of insulin resistance (HOMA-IR) values of the participants were measured.

Results: The endometriosis group had significantly lower nesfatin-1 levels than the control group (3.0±0.53 vs 9.5±0.94, p=0.005). Between the patient and control groups, there was no difference regarding serum adropin, salusin-α, and netrin-1 levels (p=0.36, p=0.34, p=0.75, respectively). Nesfatin-1 had a significant positive correlation with adropin, salusin-α, and netrin-1 (r=0.563, p<0.01; r=0.738, p<0.01; r=0.700, p<0.01, respectively), but had a negative correlation with fasting blood glucose (r=–0.343, p<0.05). HOMA-IR values were comparable between both groups.

Conclusion: The lower nesfatin-1 levels leading to increased inflammatory pathway activity in patients with endometriosis might play a role in endometriosis pathogenesis. Without causing systemic insulin resistance, decreased nesfatin-1 might contribute to endometriosis pathogenesis locally by leading to the reduced insulin susceptibility of endometriosis cells.

Keywords: Endometriosis, adropin, salusin-α, netrin-1, nesfatin-1, insulin resistance

Öz

Amaç: Endometriozisin patogenezi henüz net bir şekilde aydınlatılamamıştır. Ektopik implantasyon ve endometriyal hücrelerin ektopik büyümesine ilişkin enflamatuvar faktörler büyük ilgi konusu olmuştur. Endometriozisli hastalarda salusin-α ve nesfatin-1 belirteçlerini değerlendiren çalışma sayısı sınırlıdır. Endometriozisli hastalarda adropin ve netrin-1 düzeylerini inceleyen bir çalışma bulunmamaktadır. Bu çalışmada, enflamatuvar süreçte rol oynayan bazı önemli enflamasyon düzenleyici belirteçlerin endometriozis patogenezine etkisini araştırmayı ve bu parametrelerin serum düzeyleri ile endometriozis ve insülin direnci arasında bir ilişki olup olmadığını ortaya çıkarmayı amaçladık.

Gereç ve Yöntemler: Bu prospektif çalışmada laparoskopik cerrahi sonrası histopatolojik olarak endometriozis tanısı alan 73 hasta ve kontrol grubu olarak 75 sağlıklı kadın çalışmaya dahil edildi. Katılımcıların serum adropin, salusin-α, netrin-1 ve nesfatin-1 düzeyleri ve insülin direncinin homeostatik model değerlendirmesi (HOMA-IR) değerleri ölçüldü.

Bulgular: Endometriozis grubunda nesfatin-1 düzeyleri kontrol grubuna göre anlamlı olarak düşüktü (3,0±0,53'e karşı 9,5±0,94, p=0,005). Her iki grup arasında serum adropin, salusin-α ve netrin-1 düzeyleri açısından anlamlı fark saptanmadı (p=0,36, p=0,34, p=0,75, sırasıyla). Nesfatin-1, adropin, salusin-α ve netrin-1 ile anlamlı pozitif korelasyon içindeyken (sırasıyla r=0,563, p<0,01; r=0,738, p<0,01; r=0,700, p<0,01), serum açlık kan şekeri düzeyi ile negatif bir korelasyonu vardı (r=-0,343, p<0,05). HOMA-IR değerleri her iki grup arasında benzerdi.

PRECIS: Without causing systemic insulin resistance, decreased nesfatin-1 might be contributing to the endometriosis pathogenesis locally by leading to a reduced insulin susceptibility of endometriomal cells.

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Received/Geliş Tarihi: 23.04.2021 **Accepted/Kabul Tarihi:** 28.06.2021

Sonuç: Endometriozis hastalarında enflamatuvar aktivitenin artmasına neden olan düşük nesfatin-1 düzeyi endometriozis patogenezinde rol oynayabilir. Sistemik insülin direncine neden olmadan, azalmış nesfatin-1 düzeyi, endometriozis hücrelerinin azalmış insülin duyarlılığına yol açarak lokal olarak endometriozis patogenezine katkıda bulunuyor olabilir.
Anahtar Kelimeler: Endometriozis, adropin, salusin-α, netrin-1, nesfatin-1, insülin resistansı

Introduction

Endometriosis is defined as the presence of endometrial glands and stromal cells outside the endometrial cavity. It affects from 7% to 10% of reproductive-age women[1]. The pathogenesis of endometriosis has not yet been clearly explained. However, recent papers suggest that inflammation plays an underlying role[2,3].

Studies demonstrated that circulatory adropin levels had a negative correlation with various inflammatory markers[4]. According to a study investigating the effects of adropin on glucose metabolism, adropin promoted carbohydrate oxidation, especially in skeletal muscle[5]. Another study found that adropin increased glucose tolerance, improved insulin resistance, and promoted carbohydrates over fat for fuel[6].

Salusin-α is a soluble peptide hormone found in various human tissues and plasma and acts in an endocrine and/or paracrine fashion. Salusin-α has angiogenic and anti-atherosclerotic effects[7]. Serum salusin-α levels are remarkably lower in confirmed coronary artery disease patients[8]. Salusin-α suppresses gene expression and protein levels of specific pro-inflammatory cytokines IL-6,IL-8, and IL-18 and, thus, attenuates inflammation in vascular endothelial cells[9].

A recent study asserts the anti-inflammatory influence of netrin-1 on endothelial cells[10]. In a study on newly diagnosed type 2 diabetes mellitus (DM) patients, netrin-1 was negatively correlated with the homeostatic model assessment of insulin resistance (HOMA-IR) and fasting blood glucose (FBG)[11].

Nesfatin-1 is secreted by the hypothalamic nuclei, which are responsible for controlling appetite[12]. An inverse correlation of serum nesfatin-1 levels with high-sensitivity C-reactive protein and the neutrophil percentage was reported[13]. Also, nesfatin-1 can inhibit the signaling pathway associated with inflammation by decreasing human recombinant high mobility group box 1 *(HMGB1)* gene expression, reducing inflammation, and oxidative stress in epithelial cells, thereby alleviating acute organ damage[14].Angiogenesis is a critical mechanism that allows the establishment and growth of endometriotic lesions. Several cytokines can either stimulate or inhibit the process of angiogenesis[15]. Inflammation stimulates the proliferation of quiescent vascular smooth muscle cells and fibroblasts[7]. A limited number of studies have evaluated salusin-α and nesfatin-1 markers-which play important roles in inflammatory pathways-in patients with endometriosis. No studies have evaluated the levels of anti-inflammatory markers for adropin and netrin-1 in patients with endometriosis. Similarly, the inflammatory process plays a role in the pathogenesis of insulin resistance. In addition, no research study has investigated the relationship between endometriosis and insulin resistance. This study investigates how some important inflammatory regulatory markers in the inflammatory process affect the pathogenesis of endometriosis and determines whether any relationship exists between serum levels of these parameters and endometriosis and insulin resistance.

Materials and Methods

Patient Selection

This prospective study was conducted in the infertility department of the Muğla Sıtkı Koçman University Faculty of Medicine between September 2019 and January 2021. The study included 73 patients with endometriosis diagnosed histopathologically after laparoscopic surgery and 75 healthy controls without endometriosis. Our study was approved by the Local Ethics Committee of Muğla Sıtkı Koçman University Faculty of Medicine (protocol ID: 22/08/2019-05). It was registered at Clinical Trials.gov (ID: NCT04371133). The study was conducted in accordance with the provisions of the Declaration of Helsinki. Informed consent forms were signed by all patients who participated in the study. Any patients with DM (2), chronic kidney disease (1), coronary artery disease (1), cerebrovascular accident (1), malignancy (0), rheumatoid disorder (2), liver disease (1), or active infections (3) were excluded from the study (Figure 1).

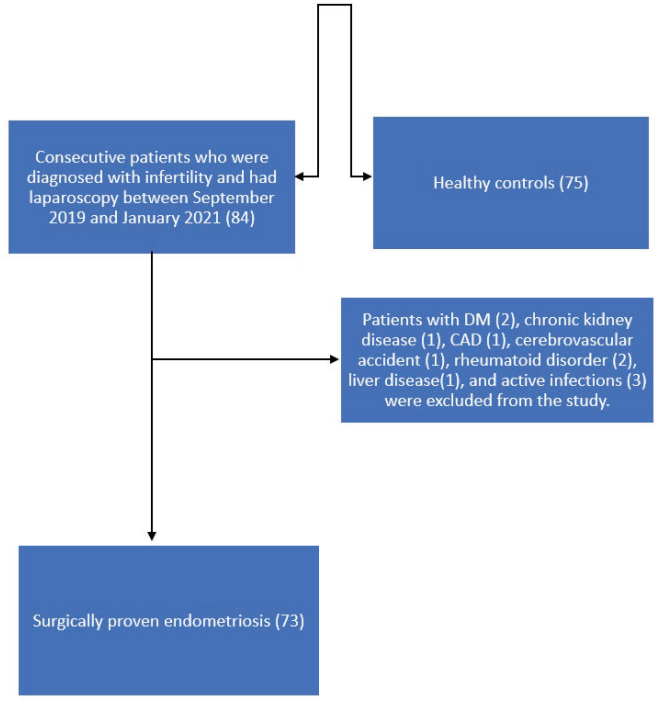

Figure 1. Flowchart for selecting the study population

Anthropometric Measurements

Body mass index (BMI) was calculated using the following formula: BMI: weight/(height)^2 (kg/m^2). Waist circumference measurements, in cm, were taken in parallel along the midpoint in between the lower edge of the 12th rib and the greater ischiadic (sciatic) notch. Hip circumference was measured at the maximum measurement of the buttocks in cm. The waist-to-hip ratio was calculated by dividing the waist circumference by the hip circumference.

Biochemical Analyses

After approximately eight hours of fasting, 4 cc of venous blood was drawn into a biochemistry tube from each patient during the preoperative period. Once collected, samples were left at room temperature for 30 min. The samples were then centrifuged for 5 min at 4000 rpm. Then, the serum were allocated into Eppendorf tubes and stored at -80 °C until the time of assay. When a sufficient number of patients and controls were reached, the Eppendorf tubes were taken out and thawed at room temperature to test for serum adropin, salusin-α, netrin-1, and nesfatin-1 levels. Thawed samples were measured on a Molecular Devices SpectraMax i3 Multi-Mode, Microplate Reader (batch number: SER 35 370-1448, Molecular Devices, LLC. made in Austria) using enzyme-linked immunosorbent assay (ELISA). Manufacturer instructions were followed to perform the tests. Serum adropin levels were measured using an adropin ELISA kit with article number: YLA0019HU; serum salusin-α levels were measured using a salusin-α ELISA kit with article number: YLA1761HU; serum netrin-1 levels were measured using a netrin-1 ELISA kit with article number: YLA1764HU; and finally, serum nesfatin-1 levels were measured using a nesfatin-1 ELISA kit with article number: YLA0715HU-all of which were commercially available under brand YL Biont. Measurements were recorded in ng/L for serum adropin levels, in pg/mL for salusin-α and netrin-1 levels, and in ng/mL for nesfatin-1 levels. Kits were stored at -20 °C until the time of use. Thyroid function and antibody testing were performed with a Cobas® c 8000 e602-3 series device (Roche, Switzerland) using the electrochemiluminescence method. Serum glucose and lipid values were determined spectrophotometrically using a Cobas® c 8000 c702 series device (Roche, Switzerland).

HOMA-IR

The HOMA-IR was determined using the following formula:
HOMA-IR: Fasting insulin (mU/L) × Fasting plasma glucose (mg/dL)/405.
Patients with a HOMA-IR value of 2.7 and above were considered to have insulin resistance[16].

Statistical Analysis

The authors determined the sample size for this study based on a preliminary evaluation[17]. From the differences, a two-tailed α value of 0.05 and a β value of 0.50 (study power: 95%), they ruled that at least 45 women in each group would be mandatory for an analysis comparing the two groups (G-Power 3 power analysis program). Therefore, assuming likely dropouts, it was determined that a minimum of 73 women should be included in each group.
The data were analyzed using the Statistical Package for Social Science (SPSS) 20.0 for Windows (SPSS Inc, Chicago, Illinois, USA). The distribution of the continuous variables was investigated using the Kolmogorov-Smirnov test. The significance of differences between the groups was determined using the Mann-Whitney U test (for non-normally distributed data) and the independent sample t-test (for normally distributed data). For the statistical evaluation of the categorical data, the chi-square test was used. The correlation of nesfatin-1 with adropin, salusin-α, netrin-1, and FBG was performed using Spearman's correlation analysis. Logistic regression analysis was performed. Statistical significance levels of the obtained data were interpreted using p-values. A p-value of <0.05 was considered statistically significant.

Results

A comparison of the clinical features of the patient and control group is provided in Table 1. On average, the group with endometriosis was significantly older than the control group (38.8±6.2 vs 35.0±5.2 years, p=0.02). Infertility and dyspareunia were more common in the endometriosis group than in the control group (36.4% vs 9.1%, p=0.03; 57.1% vs 20%, p=0.01, respectively).

Table 1. Clinical characteristics of endometriosis and control groups

Variables	Endometriosis (n=73)	Control (n=75)	p
Age (years)	38.8±6.2	35.0±5.2	0.02*
Gravidy (n)	1.6±0.4	1.6±0.5	0.97*
Parity (n)	1.3±0.5	1.2±0.4	0.68*
Abortus (n)	0.7±0.1	0.6±0.1	0.84*
Infertility, n (%)	8 (34.8)	2 (8)	0.03¥
Dysmenorrhea, n (%)	18 (78.3)	16 (64)	0.35¥
Dyspareunia, n (%)	12 (57.0)	5 (20)	0.01¥
Pelvic pain, n (%)	12 (52.2)	8 (32)	0.24¥
Menorrhagia, n (%)	7 (30.4)	3 (12)	0.12¥
GDM, n (%)	2 (11.8)	0	0.13¥
Gestational HT (%)	0	0	NS¥
Preeclampsia (%)	0	0	NS¥
BMI (kg/m^2)	25.0±4.7	24.9±4.0	0.27*
Waist-to-hip ratio	0.86±0.05	0.82±0.11	0.14*

GDM: Gestational diabetes mellitus, BMI: Body mass index, HT: Hypertension
*Independent samples t-test. ¥ Chi-square test

A comparison of the biochemical results of the patient and control group is shown in Table 2. In the endometriosis group, FBG was significantly higher (90.4±8.1 vs 82.1±6.7, p<0.01), although HDL-C and nesfatin-1 levels were significantly lower (52.6±9.0 vs 62.1±11.8, p=0.02; 3.0±0.53 vs 9.5±0.94, p=0.005, respectively). The patient and control groups did not differ regarding serum adropin, salusin-α, and netrin-1 levels (p=0.36, p=0.34, p=0.75, respectively).

Nesfatin-1 was positively correlated with adropin, salusin-α, and netrin-1, whereas it was negatively correlated with FBG (Table 3). No significant correlation between nesfatin-1 and any other parameters was detected (data not shown).

The multivariate analysis revealed that nesfatin-1 levels were associated with endometriosis. Individuals with decreased levels of nesfatin-1 had a 1.209-fold greater chance of exhibiting endometriosis (Table 4).

Table 2. Biochemical results of endometriosis and control groups

Variables	Endometriosis (n=73)	Control (n=75)	p
FBG (mg/dL)	90.4±8.1	82.1±6.7	**<0.01***
Insulin (μIU/mL)	1.8±0.32	1.4±0.28	0.53*
HOMA-IR	2.01±0.4	2.00±0.31	0.98*
Triglyceride (mg/dL)	131.7±24.3	109.3±19.1	0.25*
LDL-C (mg/dL)	112.2±21.7	98.6±18.9	0.13*
VLDL-C (mg/dL)	26.3±4.9	21.9±3.6	0.26*
HDL-C (mg/dL)	52.6±9.0	62.1±11.8	**0.02***
CRP	3.04±0.4	1.8±0.3	0.20*
Adropin (ng/L)	93.6±17.6	107.5±19.6	0.36**
Salusin-α (pg/mL)	415.9±83.1	511.8±92.2	0.34**
Netrin-1 (pg/mL)	441.8±74.2	472.2±84.0	0.75**
Nesfatin-1 (ng/mL)	3.0±0.53	9.5±0.94	**0.005****

FBG: Fasting blood glucose, HOMA-IR: Homeostatic model of assessment insulin resistance, LDL-C: Low-density lipoprotein cholesterol, VLDL-C: Very low-density lipoprotein cholesterol, HDL-C: High-density lipoprotein cholesterol, CRP: C-reactive protein *Independent samples t-test. **Mann-Whitney U test

Discussion

In our cohort of patients with endometriosis, nesfatin-1 levels were decreased, but they positively correlated with adropin, salusin-α, and netrin-1 levels. In addition, we identified a negative correlation of nesfatin-1 with FBG and comparable levels of HOMA-IR in patients with endometriosis. Our results corroborate the hypothesis that inflammatory pathways may play a role in the pathogenesis of endometriosis.

Activation of nuclear factor kappa-B (NF-κB) contributes to the pathogenesis of endometriosis by stimulating inflammation and proliferation and inhibiting apoptosis in endometriosis cells[18]. A rat study has implied an anti-inflammatory and anti-apoptotic effect of nesfatin-1 after brain injury by inhibiting an NF-κB-related inflammatory response[19]. The above-mentioned data suggest that the lower nesfatin-1 levels detected in patients with endometriosis might be involved in the pathogenesis of endometriosis, causing enhanced activity of NF-κB-dependent inflammatory pathways. A prior study measured significantly lower nesfatin-1 levels in patients with endometriosis than controls, regardless of disease stage[20]. Our findings are consistent with the results of this study. This consistency suggests that decreased nesfatin-1 levels in patients with endometriosis may be related to decreased anti-inflammatory and anti-apoptotic effects of nesfatin-1, contributing to the etiopathogenesis of endometriosis.

Adropin decreases the mRNA expression of pro-inflammatory cytokines[21]. Our literature search revealed no studies that

Table 3. Correlation analysis for Nesfatin-1

Variables	Nesfatin-1 (ng/mL)	
	r	p
Adropin (ng/L)	0.563	**<0.01**
Salusin-α (pg/mL)	0.738	**<0.01**
Netrin-1 (pg/mL)	0.700	**<0.01**
FBG	-0.343	**<0.05**
HOMA-IR	0.117	**>0.05**

FBG: Fasting blood glucose, HOMA-IR: Homeostatic model of assessment-insulin resistance

Table 4. Logistic regression analysis

Variables	B	S.E.	Wald	df	Sig.	Exp (B)	95% CI for EXP (B)	
							Lower	Upper
Adropin	0.005	0.009	0.273	1	0.601	1.005	0.987	1.023
Salusin-α	-0.002	0.002	0.904	1	0.342	0.998	0.995	1.002
Netrin-1	0.000	0.002	0.031	1	0.860	1.000	0.997	1.003
Nesfatin-1	0.190	0.084	5.162	1	0.023	1.209	1.026	1.424
Constant	-0.517	0.741	0.487	1	0.485	0.596		

CI: Confidence interval

explore serum adropin levels in patients with endometriosis. On the other hand, there was no intergroup difference in our study. The disturbance of physiological angiogenesis mechanisms plays a role in the pathogenesis of some diseases in blood vessel over-proliferation, including endometriosis[22]. Increased plasma levels of salusin-α can promote the pro-angiogenic activity of some endothelial cells[17]. These findings suggest that salusin-α may play an essential role in inducing the development and progression of endometriosis. There were no significant correlations between plasma salusin-α levels with age, size of endometriotic cysts, bilaterality, or endometriotic focal number[17]. Our study also measured the salusin-α levels pre-operatively, which tended to be lower in the endometriosis group, and had a significant positive correlation with nesfatin-1 levels.

Netrin-1 results in an anti-inflammatory effect by inhibiting TNF-α-induced NF-κB activation and suppresses TNF-α-induced production of inflammatory cytokines[12]. Our literature search did not reveal any studies assessing serum netrin-1 levels of patients with endometriosis. There was no difference regarding serum netrin-1 levels between the two groups in our study. However, nesfatin-1 was positively correlated with netrin-1. A further and more extensive study that also measures adropin and netrin-1 levels of the follicular fluid might provide useful information about this topic.

Existing studies have identified favorable effects of nesfatin-1 on glucose metabolism that occurred with increased sensitivity to insulin in the brain[23]. In another study, patients with type 2 DM had lower nesfatin-1 levels than the control group, but no significant correlation was determined between nesftain-1 and HOMA-IR[24]. Similar to the existing data, nesfatin-1 was negatively correlated with FBG and comparable levels of HOMA-IR in the endometriosis and the control groups. However, we did not find a significant correlation of nesfatin-1 with HOMA-IR, which is a marker of systemic insulin resistance. To the best of our knowledge, insulin resistance of patients with endometriosis has not been previously investigated. The currently available data indicate increased glycolytic pathways in endometriosis cells, followed by elevated levels of lactate in follicular fluid. Elevated lactate levels, in turn, induce inflammation, angiogenesis, and cell proliferation[25,26]. Reduced nesfatin-1 levels may play a local role in endometriosis cells causing impaired insulin sensitivity and increased glycolytic pathways.

Study Limitations

The limitations of our study include the relatively small number of patients were enrolled, and only serum measurements of the molecules (adropin, salusin-α, netrin-1, and nesfatin-1) were performed.

Conclusion

Our study is the first of its kind to investigate adropin and netrin-1 levels in patients with endometriosis. Decreased nesfatin-1 levels and a positive correlation of nesfatin-1 with adropin, salusin-α, and netrin-1 in patients with endometriosis may have a combined effect on the inflammatory pathways that are believed to act in the multifactorial pathogenesis of endometriosis. More studies with larger sample sizes need to be performed to determine the levels of adropin, salusin-α, nesfatin-1, and netrin-1 in follicular fluid. Their roles in the pathogenesis of endometriosis can be clarified.

Ethics

Ethics Committee Approval: Our study was approved by the Local Ethics Committee of Muğla Sıtkı Koçman University Faculty of Medicine (protocol ID: 22/08/2019-05).

Informed Consent: Informed consent forms were signed by all patients who participated in the study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: E.A., Design: E.A., Data Collection or Processing: B.S., Analysis or Interpretation: T.E., Literature Search: E.A., Writing: E.A., T.E.

Conflict of Interest:

Financial Disclosure: The authors declared that this study received no financial support.

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