Türk Kadın Sağlığı ve Neonatoloji Dergisi

To cite this article: Kaplan A, Tatac N. Circulating Obestatin levels in women with uterine leiomyoma. Turk J Womens Health Neonatol 2023; 5(4): 80-84.

Original Article

Circulating Obestatin levels in women with uterine leiomyoma

Leiyomiyomu olan kadınlarda dolaşımdaki obestatin düzeyleri

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Abstract

Objective: Uterine leiomyomas are the most common benign tumors of reproductive age women with symptoms of bleeding, pain, pressure and consequences on reproduction. Obestatin is a recently discovered secreted peptide encoded by the preproghrelin gene. The role of obestatin in the regulation of metabolism is still under debate. In this article, we investigate the use of biomarker in patients with uterine leiomyoma. Our goal is to study the obestatin as a biomarker for the diagnosis and monitoring of uterine leiomyoma.

Methods: This cross-sectional observational study was conducted between January 2015–June 2015 in outpatient gynecology clinic of Zekai Tahir Burak Women's Health Education and Research Hospital, Ankara. A total of 82 women were recruited as 48 with uterine leiomyoma and 34 healthy controls.The obestatin levels were reviewed prospectively.

Results: The obestatin levels of study group was lower than the control group (1.91±2.64 pg/mL vs. 3.58±4.81 pg/mL, p =.009). The obestatin levels without normal distribution, Mann–Whitney U-test was performed for two independent groups.

Conclusion: Increased obestatin characterized obesity in women, supporting the hypothesis that the imbalance of obestatin may have a role in the pathophysiology of leiomyoma due to obesity. On the other hand, some relevant differences between our data on circulating blood levels of obestatin in normal-weight women who had leiomyoma subjects and those reported in the few studies published so far imply that further extensive research in this new area is needed.

Keywords: obestatin; peptide hormone; premenopausal women; uterine leiomyoma

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DOI: 10.46969/EZH.1399590
Received: 3.12.2023 Accepted: 6.12.2023

Öz

Amaç: Uterin leiomyomlar üreme çağındaki kadınlarda kanama, ağrı, baskı ve üreme üzerine etkileri gibi semptomlarla en sık görülen iyi huylu tümörlerdir. Obestatin, preproghrelin geni tarafından kodlanan, yakın zamanda keşfedilen salgılanan bir peptiddir. Obestatinin metabolizmanın düzenlenmesindeki rolü halen tartışılmaktadır. Bu yazıda uterin leiyomiyomlu hastalarda biyobelirteçlerin kullanımını araştırdık. Amacımız obestatin'i uterus leiomyomunun tanısı ve takibi için bir biyobelirteç olarak incelemektir.

Gereç ve Yöntem: Bu kesitsel gözlemsel çalışma Ocak 2015-Haziran 2015 tarihleri arasında Ankara Zekai Tahir Burak Kadın Sağlığı Eğitim ve Araştırma Hastanesi Kadın Hastalıkları Polikliniği'nde gerçekleştirildi. Çalışmaya 48'i uterin leiyomiyomlu ve 34'ü sağlıklı kontrol olmak üzere toplam 82 kadın dahil edildi. Obestatin düzeyleri prospektif olarak incelendi.

Bulgular: Normal dağılım göstermeyen obestatin düzeyleri için iki bağımsız gruba Mann-Whitney U-testi uygulandı. Sonuçlar bu istatistik metod sonrası elde edilmiştir. Çalışma grubunun obestatin düzeyleri kontrol grubuna göre daha düşüktü (1.91±2.64 pg/mL vs. 3.58±4.81 pg/mL, p = 0.009).

Sonuç: Kadınlarda obestatin ile karakterize obezitenin artması, obestatin dengesizliğinin obeziteye bağlı leiomyomun patofizyolojisinde rol oynayabileceği hipotezini desteklemektedir. Öte yandan, leiomyoma hastası olan normal kilolu kadınlarda dolaşımdaki obestatin düzeylerine ilişkin verilerimizle şu ana kadar yayınlanan birkaç çalışmada bildirilenler arasındaki bazı anlamlı farklılıklar, bu yeni alanda daha kapsamlı araştırmalara ihtiyaç olduğunu ima etmektedir.

Anahtar Kelimeler: obestatin; peptid hormonlar; pre-menapoz; uterin leimyoma

1. Introduction

Obestatin is a 23 amino acid peptide hormone produced in the stomach. It is encoded by the recently discovered preproghrelin gene and has been shown to be produced in many other tissues of the body (1). Obestatin is thought to have an opposite effect to ghrelin. However, obestatin is not an endogenous ghrelin antagonist but a multifunctional compound (1,2). The role of obestatin in the regulation of food intake, body weight control, energy expenditure, or growth is not fully understood (3). Studies have found a positive association between basal obestatin levels and body mass index (BMI). The role of obestatin in regulating metabolism remains controversial. Vicenatti et al. have shown that women with obesity have higher circulating obestatin levels than normal individuals (4). Obestatin is also thought to play a role in adipogenesis, pancreatic homeostasis, and cancer (5).

Leiomyomas of the uterus are the most common benign tumors in women of childbearing age, presenting symptoms such as bleeding, pain, pressure, and reproductive effects (6). The main treatment for leiomyomas, which pose a serious economic burden and a high risk of morbidity and mortality, is surgery. Biomarkers are biological compounds that are readily available and reflect normal physiology or pathology. They are useful in a variety of clinical situations, including detection of subclinical disease, risk stratification, preoperative planning, and treatment monitoring. For a biomarker to be an effective tool, a useful intervention must be present. Many compounds have been investigated as potential biomarkers for the diagnosis and monitoring of uterine leiomyomas. Many of these compounds show subtle differences between patients when leiomyomas are compared with controls.

Recent in vivo and in vitro studies have hypothesized that obestatin may influence the endogenous growth and pathophysiology of cancer (7). In this article, we investigated the use of biomarkers in patients with uterine leiomyomas. Our aim is to investigate obestatin as a biomarker for the diagnosis and follow-up of uterine leiomyomas.

2. Material and method

This cross-sectional observational study was conducted between December 2014–June 2015 in outpatient gynecology clinic of Zekai Tahir Burak Women's Health Education and Research Hospital, Ankara. Reproductive age women (30–45 years) with at least one uterine fibroid with a diameter ≥10 mm detected with transvaginal ultrasound formed the study group and control group included women with normal uterine examination. History of previous myomectomy, chronic systemic disease, malignancy, adenomyosis; menopausal women, pregnants; oral contraceptive/hormonal agents use in the past 3 months were excluded. Eighty-two patients who consulted to single investigator's outpatient clinic and met the inclusion were recruited.

The study was approved by local institutional ethical committee and; a verbal and written informed consent was obtained from participants.

Transvaginal ultrasound was performed by a single investigator using Aloka SSD-5500 PHD (Aloka, Tokyo, Japan) with 6.5 MHz

probe. Volume of leiomyomas were calculated by ellipsoid volume formula (V ¼ D1 D2 D3 0.52) (8). Blood samples were collected after at least 8 h fasting, and kept in -80o until assessment. Obestatin levels were analyzed in Obestatin ELISA Kit (Human) (OKEH01443).

Aviva Systems Biology OB ELISA Kit (Human) (OKEH01443) is based on a competitive enzyme immuno assay technique. The microtiter well-plate in this kit has been pre-coated with an anti-human obestatin(OB) antibody. Sample or standards are added to the wells along with a fixed quantity of biotinylated OB and incubated. ELISA kit range is 15.6 – 1000 pg/mL. and sensitivity is 10 pg/mL.

Statistical analysis was performed out by SPSS (Statistical Package for the Social Sciences) for Windows 22 (SPSS Inc., Chicago, IL). Pearson's Chi square test was performed for analysis of categorical variables. Normal distribution was analyzed by both visual (histograms and probability graphics) and statistical (Shapiro–Wilk Tests) methods. For the variables with normal distribution, Student's t-test; for the variables normal distribution, Mann–Whitney U-test was performed for two independent groups. p values < 0.05 were considered significant. The sample size was calculated by power analysis based on the previous study by Markowska A et al. (8). In the independent sample's t-test, with an impact power of 1.2932795 and α-value set at 0,05; power (1-β) was calculated as 0,95 with 28 participants.

3. Results

A total of 82 women were recruited as 48 with uterine leiomyoma and 34 healthy controls. The clinical characteristics of the study are summarized in Table 1. No significant differences were found between the groups in body mass index, gravidity, parity, age (p>0.05). In the study group, the average diameter of the fibroids was 45.24±34.85 mm and the average number of fibroids was 1.18±1.24.

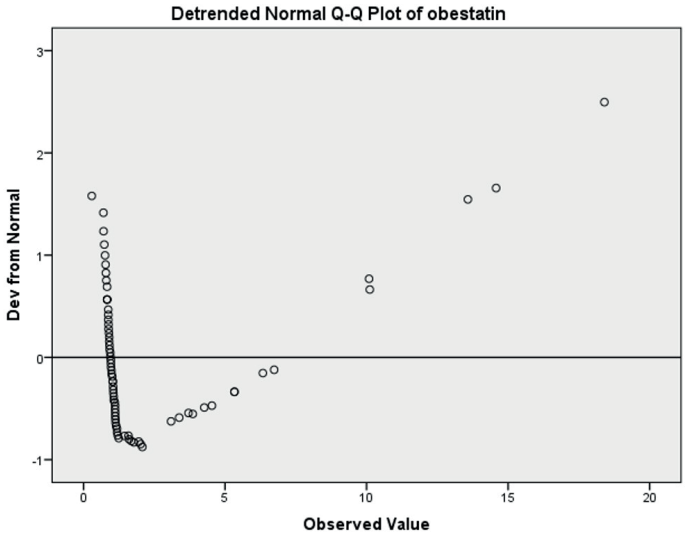

Figure 1. The obestatin levels without normal distribution

The obestatin levels of study group was lower than the control group (1.91±2.64 pg/mL vs. 3.58±4.81 pg/mL, p =.009). Figure1 shows the obestatin levels without normal distribution, Mann–Whitney U-test was performed for two independent groups.

4. Discussion

Obestatin originates from the ghrelin prohormone and is secreted by the stomach. In contrast to ghrelin, obestatin acts as an anorectic hormone, has been implicated in cellular proliferation, and exhibits other proliferative effects, such as increasing phosphorylation of certain response elements and activation of growth factors(5). Obestatin binds and activates a G-protein coupled receptor, ultimately stimulating extracellular signal-regulated kinase (ERK 1/2)(6).

Although the majority of obestatin is produced by the stomach, the obestatin peptide has been reported to be expressed in a

Table 1. Sociodemographic characteristics of patients

	Leiomyoma group (n:48)		Control Group (n:34)		p*
	Mean±SD	Median(Min-Max)	Mean±SD	Median (Min-Max)	
Age (years)	40.06±3.75	41(32-45)	39.73±3.81	40(31-42)	.685
BMI (kg/m^2)	26.48±4.19	26(18-35)	25.60±2.95	25(19-34)	.605
Gravidy	2.64±1.68	3(0-8)	2.32±1.22	2(1-4)	.451
Parity	1.97 number of myomas 1.06	2(0-5)	1.73±0.79	2(1-3)	.241
Myoma diameter (mm)	45.24±34.85	31.50(10.00-160.00)	0	-	-
Number of myomas	1.18±1.24	1(1-5)	0	-	-
Obestatin (pg/ml)	1.91±2.64	1.06(0.29-18.40)	3.58±4.81	1.04(0.70-13.58)	.009

p <.05 significant. SD: Standard deviation

range of peripheral tissues, including the pancreas, liver, testis, mammary gland, thyroid, and lung (7, 9). This may indicate that obestatin has local autocrine/paracrine roles in addition to its actions as an endocrine hormone. Obestatin is an orphan ligand and the search for the obestatin receptor is still ongoing, however, binding sites for the obestatin peptide have been identified in the pancreas, heart, white adipose tissue and other tissues (10). Exogenous obestatin stimulates proliferation of pancreatic β-cells and isolated human pancreatic islet cells and promotes adipogenesis (11).

It is clear that much research is needed to clearly define the role of obestatin as a hormone involved in body weight regulation and gastrointestinal motility.

Serum concentrations of active ghrelin in uterine leiomyoma were significantly higher compared to women in the control group (86 +/- 3 vs 56 +/- 9 pg/ml, respectively; $p < 0.02$). On the other hand, serum concentrations of total ghrelin and obestatin in uterine leiomyoma did not differ from those in the control group (8).

In contrast to early suggestions, obestatin is not an endogenous antagonist of ghrelin, but recent studies indicate that obestatin is a multi-functional peptide hormone in its own right. Obestatin may have important endocrine, autocrine or paracrine roles in a number of tissues including pancreas, and adipose tissue and it may play a role in cancer progression.

Increased obestatin characterized obesity in women, supporting the hypothesis that the imbalance of obestatin may have a role in the pathophysiology of leiomyoma due to obesity. On the other hand, some relevant differences between our data on circulating blood levels of obestatin in normal-weight women who had leiomyoma subjects and those reported in the few studies published so far imply that further extensive research in this new area is needed.

Author contribution

All of the authors, AK, NT have contributed to project development, data collection, data analysis, and writing of the manuscript. All authors reviewed the results and approved the final version of the manuscript.

Ethical approval

Approval was obtained by the institutional review board from Ankara Zekai Tahir Burak Women's Health Training and Research Hospital on 26.11.2014 # 2014/37.

Funding

The authors declare that the study received no funding.

Conflict of interest

The authors declare that there is no conflict of interest.

Yazar katkısı

AK, NT tüm yazarlar proje geliştirme, veri toplama, veri analizi ve makalenin yazılmasına katkıda bulunmuşlardır.Tüm yazarlar araştırma sonuçlarını gözden geçirdi ve araştırmanın son halini onayladı.

Etik kurul onayı

Ankara Zekai Tahir Burak Kadın Sağlığı Eğitim ve Araştırma Hastanesi kurumsal inceleme kurulundan 26.11.2014 tarih ve 2014/37 sayılı onay alındı.

Finansal destek

Yazarlar araştırma için finansal bir destek almadıklarını beyan etmiştir.

Çıkar çatışması

Yazarlar herhangi bir çıkar çatışması olmadığını beyan etmiştir.

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