Türk Kadın Sağlığı ve Neonatoloji Dergisi

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Original Article

Does Obestatin Level Change in Endometrial Pathologies? A Case-Control Study in A Tertiary Care Hospital

Endometrial Patolojilerde Obestatin Düzeyi Değişir Mi? Üçüncü Basamak Hastanede Bir Vaka Kontrol Çalışması

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Abstract

Background: The rising incidence of endometrial cancer has been associated with increases in obesity and physical inactivity. We investigated the clinical significance of serum obestatin levels in women with endometrial cancer, endometrial hyperplasia, and age-matched healthy controls.

Material and Methods: The present study was a case-control study conducted at a single center between May 2014 and July 2015. The medical records of 90 patients with a final histopathologic diagnosis after therapeutic curettage for abnormal uterine bleeding were reviewed and categorized by diagnosis. The study population included women with adenocarcinoma of the endometrium (n= 33), hyperplasia of the endometrium (n= 27), and proliferative endometrium (n=30) according to histopathological diagnosis. The women with proliferative endometrium formed the control group.

Results: Endometrial cancer was diagnosed in 33 (36.6%) of the patients who presented to our clinic for abnormal uterine bleeding. In the group with endometrial cancer, the mean age was 55.2 ± 8.6 years. There were no differences in obestatin levels between groups ($p > 0.05$). In the ROC curve analysis, the area under the curve value was 0.574, and obestatin did not prove to be a significant marker for cancer prediction in the population involved in the study.

Conclusion: This study did not demonstrate a clear association between circulating levels of obestatin and endometrial pathologies.

Keywords: Obestatin; endometrial cancer; endometrial hyperplasia; obesity

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Öz

Amaç: Artan endometriyal kanser insidansı, obezite ve fiziksel hareketsizlikteki artışlarla ilişkilendirilmiştir. Bu bilgiden yola çıkarak, endometriyal kanserli, endometriyal hiperplazili kadınlarda ve aynı yaştaki sağlıklı kontrollerde serum obestatin düzeylerinin klinik önemini araştırdık.

Gereç ve Yöntem: Bu çalışma Mayıs 2014-Temmuz 2015 tarihleri arasında tek merkezde yürütülen bir vaka-kontrol çalışmasıdır. Anormal uterin kanamaya yönelik terapötik küretaj sonrası kesin histopatolojik tanısı konulan 90 hastanın tıbbi kayıtları incelenmiş ve tanılarına göre kategorize edilmiştir. Çalışma popülasyonu, histopatolojik tanıya göre endometrium adenokarsinomu (n= 33), endometrium hiperplazisi (n=27) ve proliferatif endometrium (n=30) olan kadınları içermiştir. Kontrol grubunu ise proliferatif endometriumlu kadınlar oluşturdu.

Bulgular: Kliniğimize anormal uterin kanama ile başvuran hastaların 33'ünde (%36,6) endometrium kanseri tanısı konuldu. Endometrium kanserli grupta yaş ortalaması 55.2 ± 8.6 yıl idi. Gruplar arasında obestatin seviyelerinde fark yoktu ($p > 0.05$). ROC eğrisi analizinde, eğrinin altında kalan alan değeri 0,574 idi ve obestatin, çalışmaya dahil edilen popülasyonda kanser tahmini için önemli bir belirteç olduğunu kanıtlamadı.

Sonuç: Bu çalışma, dolaşımdaki obestatin seviyeleri ile endometriyal patolojiler arasında net bir ilişki göstermedi.

Anahtar Kelimeler: Obestatin; endometriyal kanser; endometriyal hiperplazi; obezite

1. Introduction

Endometrial cancer (EC) is one of the most common cancers of the female reproductive system. Endometrial hyperplasia (EH) is a precancerous, nonphysiologic, noninvasive proliferation of the endometrium that can progress to EC if left untreated. Most cases of EH and EC occur with chronic estrogen exposure that is not counterbalanced by progesterone (1,2). Obesity, a condition in which women are exposed to higher levels of estrogen produced in adipose tissue. The rising incidence of endometrial cancer has been associated with increases in obesity and physical inactivity (3). Although the incidence rate is steadily increasing, the mortality rate for endometrial cancer is low (4). This is because the prognosis for endometrial cancer is favorable in early stages. However, it has been shown that patients diagnosed with advanced stage disease have a significantly worse outcome (5). Therefore, it is important to understand the underlying mechanisms.

Ghrelin and obestatin are two peptides associated with appetite control and regulation of energy balance in adults. Obestatin is a 23-amino acid peptide derived from the C-terminal portion of the preproghrelin precursor (6,7). Both ghrelin and obestatin decrease markedly in response to food intake (8,9). Fasting plasma concentrations of obestatin have been found to decrease in insulin resistance and to be positively related to whole-body insulin sensitivity in nondiabetic subjects (8). Therefore, obestatin could be a nutritional marker reflecting body adiposity and insulin resistance (9,10). On the other hand, ghrelin is known to have proliferative and antiapoptic properties (11). Studies have shown that downregulation of its receptor is associated with endometrial hyperplasia and cancer (12,13).

Based on this information, we sought to determine whether obestatin is effective in endometrial hyperplasia and cancer. We examined the clinical significance of obestatin serum levels in women with endometrial cancer, endometrial hyperplasia, and age-matched healthy controls. We also investigated the possible associations between obestatin levels and the stage and grade of endometrial cancer.

2. Materials and Methods

The study protocol was approved by the Ethics Committee of Zekai Tahir Burak Women Health Education and Research Hospital (28/04/2014 #44/2014), and the principles of the Declaration of Helsinki were followed. All female patients signed an informed consent form to participate in the study.

In this cohort study, the medical records of 90 patients with a final histopathological diagnosis after therapeutic curettage for abnormal uterine bleeding between May 2014 and July 2015 were reviewed and categorized by diagnosis. Blood samples were obtained from patients with abnormal uterine bleeding at enrollment, and histopathologic results were subsequently followed. The study population included women with adenocarcinoma of the endometrium (n= 33), hyperplasia of the endometrium (n=27), and proliferative endometrium (n=30) according to histopathological diagnosis. The women with proliferative endometrium formed the control group.

Venous blood was drawn from all patients in the morning after a fasting night. Ten ml of blood was collected for determination of total obestatin. After centrifugation at 4000 g for 10 minutes, serum samples were stored at -80 °C until further analysis. Plasma obestatin levels were measured by enzyme-linked immunosorbent assay (ELISA) using a commercial kit (Eastbiopharm Human OB), and all samples were analyzed according to the manufacturer's recommendations.

Transvaginal ultrasonography was performed in all patients to examine the endometrium. We collected data on patients' descriptive demographic and clinical characteristics, including age, parity, body mass index, smoking, history of systemic comorbidities and medications, previous surgery, screening for known risk factors for endometrial cancer and hyperplasia (32), and history of infertility. We also retrieved clinical outcome data from the hospital information system: 5-year survival rate, recurrence-free survival, presence of recurrence, date of recurrence, site of recurrence, treatment of recurrence, date of last follow-up, and presence of mortality. We also evaluated the histopathologic findings: Probe/curettage, histopathologic diagnosis, type of carcinoma, stage of disease. All histological sections were examined by two experienced pathologists in our hospital. Endometrial lesions were interpreted and reported according to the latest guidelines.

Statistical analysis

Statistical Package for the Social Sciences-SPSS 22 (SPSS Inc, Chicago, IL) was used for statistical analysis. The distribution of parameters was tested with the Shapiro-Wilk normality test. Data were expressed as mean ± standard deviation and median (min-max). For the normally distributed data, the independent-samples t test was used, and for the non-normally distributed variables, the Mann Whitney U test was used. For analysis of categorical variables, the chi-square test or the Fisher extract test was used. A Type-I error level of 5% overall was used to derive statistical significance.

3. Results

Endometrial cancer was diagnosed in 33 (36.6%) of the patients who presented to our clinic for abnormal uterine bleeding. Baseline data and metabolic parameters of the entire study population are shown in Table 1. In the endometrial cancer group, the mean age was 55.2 ± 8.6 years, which was higher than in the other groups ($p < 0.05$). The time since onset of menopause 6.6 ± 6.4 years in the cancer group which was significantly longer than in the hyperplasia group ($p < 0.05$). There were more patients in the cancer group with DM, and significantly more than in the other groups ($p < 0.05$). The thickness of the endometrium was significantly thicker in the cancer group than in the other groups ($p < 0.05$). There was no difference in obestatin levels ($p > 0.05$).

Cancer type was classified as endometrioid in all patients. Twenty-seven patients were stage 1, only one patient was stage 2, and a total of 5 patients were stage 3. Most patients were in grade 1 (n=19), 10 patients were in grade 2, and 4 patients were in grade 3. Myometrial invasion was noted in 90.9% of patients (Table 2).

When the cancer patients were divided into two groups, an early stage (6.1±5.8 µg/ml) and a late stage (4.1±1.4 µg/ml), no significant difference was found between the obestatin levels of the two groups ($p > 0.05$). Obestatin level was found to

Table 1. Baseline characteristics of the total study population

	Control n=30	Endometrial Hyperplasia n= 27	Endometrial Cancer n=33	p- value
Age (years)	47,2±3,6	47,6±6,9	55,2±8,6	0.005
BMI (kg/m^2)	31,8±5	31,1±5,5	35,2±7	0.010
Time since the onset of menopause (years)	0	1,7± 4,0	6,6 ± 6,4	0.000
Endometrial thickness (mm)	10,5±5,3	10,5±5,7	14,5±8,8	0.030
Diabetes mellitus (%)	10	22.2	45.4	0.005
PCOS (%)	0	1 (3.7%)	0	0.300
Obestatin (µg/ml)	6,9±7,9	4,2±3,9	5,8±5,4	0.200

Table 2. Clinical disease characteristics of the adenocancer group	
	Cancer group (n=33)
Grade	
Grade 1	19 (57.6%)
Grade 2	10(30.3%)
Grade 3	4 (12.1%)
Stage	
I	27(81.8%)
II	1(3.0%)
III	5 (15.1%)
VI	- (0%)
Myometrial invasion	
No	3 (9.0%)
≤%50	24 (72.7%)
>%50	6 (18.1%)
Serosal involvement	- (0%)
Cervical involvement	
Yes	6 (18.1%)
No	27 (81.8%)
Lymphovascular space invasion	
Yes	8 (24.2%)
No	25 (75.7%)
Lymph node involvement	
Yes	4 (12.1%)
No	29 (87.8%)

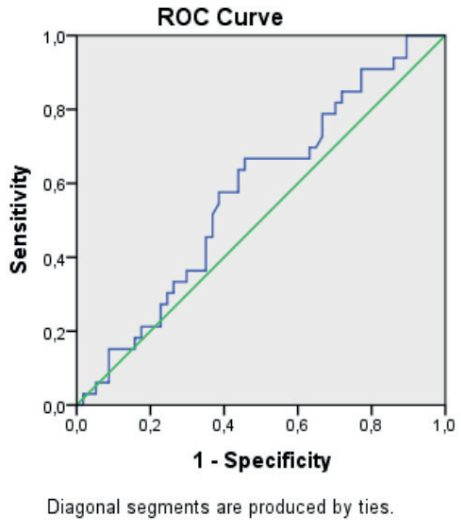

Figure 1. ROC curve for obestatin in endometrial cancer

have no effect on myometrial invasion by grade and lymphatic invasion ($p > 0.05$). In the ROC curve analysis, the value of the area under the curve was 0.574, and obestatin was not found to be a significant marker for cancer prediction in the population involved in the study (Figure 1).

4. Discussion

To date, there are no studies on obestatin levels in patients with endometrial cancer. In our study, it was found that there was no difference between serum obestatin levels in the endometrial cancer, atypical hyperplasia, and control groups.

The clinical significance of the association between obesity and endometrial cancer and its impact on prognosis have long been a hot topic. In studying the pathophysiology of endometrial carcinoma, many mechanisms that are also seen in obesity stand out (14). Obesity is a known risk factor for endometrial cancer in both premenopausal and postmenopausal women. Obestatin initially attracted attention for its anorexic effect and acts through the G-protein-coupled receptor (15). Interestingly, obestatin and ghrelin derive from the same peptide precursor (preprogrelin), and obestatin has opposite effects than ghrelin (15). In studies conducted to date, obestatin has been shown to be particularly effective in disorders of energy homeostasis such as obesity (16,17). In gynecological studies, many different subjects have been studied, but the most marked changes have been observed in PCOS, which is thought to be associated with obesity (18,19). However, the effect here is thought to be mainly related to gluconeogenesis and insulin secretion. Ghrelin has been studied in the context of endometrial pathologies (20). Differentiation between atypical endometrial hyperplasia and well-differentiated endometrial carcinoma is difficult, especially with small biopsy specimens. The gold standard for the diagnosis of endometrial carcinoma is invasion of the myometrium (21). In the studies, ghrelin was considered as a peptide that helps in this differentiation (22). It has been observed that ghrelin expression decreases when endometrial tissue is harvested, however this is not the case in the bloodstream. The role of ghrelin in the pathogenesis of carcinomas in various organs has also been studied. Changes in the antiproliferative effect of ghrelin have been observed in thyroid, breast, and testicular cancer cells (23). Ghrelin and obestatin were found in ovarian tissues. Gaytan et al. demonstrated increased expression of ghrelin in benign and malignant serous ovarian tumors (24). In addition, ghrelin was observed to circulate more in serous tumors resembling fallopian epithelium (25). The expression of obestatin and ghrelin is increased in benign tissues (25). It was observed that the expression of ghrelin and obestatin increased with the degree of malignancy. However, in our study, we did

not find any difference between obestatin in the circulation of patients with benign and malignant endometrial lesions.

It has been reported in the literature that the risk of endometrial cancer is higher in patients with abnormal uterine bleeding than with other symptoms (26, 27). In our study, the risk of endometrial carcinoma was found to be high in this group. However, these data are influenced by the fact that the hospital, where the study was conducted, was a tertiary maternity, education, and research hospital, and the suspected patients were also referred from the surrounding hospitals. However, consistent with these data, the association between gynecologic cancers and these markers can also be demonstrated in patients with abnormal uterine bleeding. Moreover, patients with this symptom, typical of endometrial cancer, are known to be associated with obesity, polycystic ovary syndrome (PCOS), and metabolic syndrome as additional morbidity. In particular, this group consists of patients with endometrial cancer type 1. Because typing was not performed in our study, the difference between these two types could not be clearly demonstrated. It is instructive that previous studies have shown that ghrelin decreases and obestatin increases in DM and PCOS. Since this is the first study on this topic, it would be appropriate to make this distinction in future studies.

One of the limitations of the study is that it is difficult to obtain sufficient data with a limited number of patients and that some confounding factors cannot be excluded. Another limitation is that the histopathological examination was not repeated in detail and the obestatin marker in the tissue was not evaluated.

In conclusion, the association between circulating levels of obestatin and endometrial pathologies has not been clearly demonstrated. However, there is a need for larger studies that are better standardized and examined in tissue samples. To elucidate the pathophysiology, the subject needs to be explored in greater depth by molecular studies, and the relationship between these diseases needs to be more clearly established.

Author contribution

Study conception and design: TM, NO; data collection: CT; analysis and interpretation of results: BSO and MCI; draft manuscript preparation: TM and TG. All authors reviewed the results and approved the final version of the manuscript.

Ethical approval

The study was approved by the Ethics Committee for Noninterventional Studies of Zekai Tahir Burak Women Health Education Research Hospital (Protocol no. 44/28.04.2014).

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Conflict of interest

The authors declare that there is no conflict of interest.

Yazar katkısı

Araştırma fikri ve tasarımı: TM ve NO; veri toplama: CT; sonuçların analizi ve yorumlanması: BSO ve MCI; araştırma metnini hazırlama: TM ve TG. Tüm yazarlar araştırma sonuçlarını gözden geçirdi ve araştırmanın son halini onayladı.

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