Endometrial Kanser Evresi, Hastalığın Biyokimyasal Belirteçleri ve Vücut Kitle İndeksi Arasındaki İlişki

The Association Between Endometrial Cancer Stage, Biochemical Markers of The Disease and Body Mass Index

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ÖZ

GİRİŞ ve AMAÇ: *Literatürde obezitenin endometriyal kanser evresi ve biyolojik davranış üzerindeki etkileri üzerine yapılan az sayıdaki çalışma sonuçları çelişkilidir. Bu nedenle çalışmamızda endometriyal kanserli hastalarda vücut kütle endeksi ile hastalık evresi ve hastalığın moleküler belirteçleri arasındaki ilişkinin araştırılması amaçlanmıştır.*

YÖNTEM ve GEREÇLER: *Kliniğimizde opere edilen endometriyal kanser tanılı olgularının arşiv kayıtları ve patolojik raporları retrospektif olarak incelendi. Kliniğimizde opere edilen endometriyal kanser tanılı olgularının arşiv kayıtları (patoloji ve klinik raporları) retrospektif olarak incelendi. Olguların vücut kütle endeksi değerleri dünya sağlık örgütü kriterlerine göre üç gruba ayrıldı. Sonrasında, grupların demografik, klinik, patolojik özellikleri ve moleküler belirteçleri (Östrojen reseptörleri, progesteron reseptörleri ve P53) karşılaştırıldı.*

BULGULAR: *Çalışmaya toplam 99 vaka dahil edildi. Gruplar arasında menapoz varlığı (p=0.042) ve hipertansiyon dışındaki demografik verilerde (p =0.038) anlamlı fark yoktu. Endometriyal kansere ait klinik karakteristikler karşılaştırıldığında ise tümör çapının (p=0.026) ve kanser tipinin (p=0.042) gruplar arasında istatisitiksel olarak anlamlı şekilde farklı olduğu gözlendi. Vücut kütle endeksinin en fazla olduğu grupta (≥35kg/m2) endometriyal kanserin non endometrioid alt tipi en yüksek oranda izlendi. Hastalık evresi ve hastalığa ait moleküler belirteçler ile gruplar arasında anlamlı bir ilişki bulunmadı (p>0.05).*

TARTIŞMA ve SONUÇ: *Endometriyal kanser hastaları içinde ikinci ve üçüncü derece obesitesi bulunan grupta, daha agresiv davranış gösteren non endometrioid tip tümör görülme riski artıyor görünmektedir. Ancak vücut kütle endeksi ile hastalık evresi ve hastalığa ait diğer markırlar arasında ilişki bulunamamıştır.*

Anahtar Kelimeler: *Endomitriyal kanser, vücut kitle indeksi, östrojen resepterü, progestoron reseptörü, evre*

ABSTRACT

INTRODUCTION: *The results of the few studies in literature on the effects of obesity on stage and biological behavior of the endometrial cancer are conflicting. Therefore, it was aimed to investigate the relationship between body mass index (BMI) and disease stage and molecular markers of the disease in patients with endometrial cancer in our study.*

METHODS: *Archive records (pathological and clinical reports) of patients diagnosed with endometrial cancer who were operated in our clinic were analyzed retrospectively. The BMI values of the cases were divided into three groups according to the criteria of the world health organization. Then, the demographic, clinical, pathological characteristics and molecular markers (estrogen receptors, progesterone receptors and P53) of the groups were compared.*

RESULTS: *A total of 99 cases were included in the study. There was no significant difference in demographic data (p=0.038) except for hypertension and the presence of menopause (p=0.042) between the groups. Among the clinical features, tumor diameter (p = 0.026) and cancer type (p = 0.042) were found to be statistically significant between the groups. In the group with the highest BMI (>35 kg/m2), the non-endometrioid subtype of endometrial cancer was observed with the highest rate. There was no significant relationship between stage and molecular markers of the disease with the groups (p>0.05).*

DISCUSSION AND CONCLUSION: *Endometrial cancer patients with second and third degree obesity seem to have an increased risk of endometrioid type tumors with more aggressive behavior, but there was no relationship between stage and other markers of the disease with BMI.*

Keywords: *Endometrial cancer, body mass index, estrogen receptor, progestorene receptor, stage*

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INTRODUCTION

Endometrial cancer (EC) is the most common gynecological cancer in developed countries. Incidence peaks between the ages of 60 and 70. Patients under 50 years of age who develop EC are generally at risk due to chronic anovulation or obesity (1). The main risk factor for EC is endogenous or exogenous unopposed estrogen. In obese patients, there is high levels of endogenous estrogen that occurs in peripheral adipose tissue due to the conversion of androgens to estrogens (2). Obese patients also have lower circulating levels of sex hormone binding globulin. This leads to increased steroid hormone activity. In addition, obese patients have a high risk of having insulin resistance. It was shown in a study that estrogen enhances the malignant biological behavior of EC via the estrogen receptors (ER) (3). All of these contribute to the increased risk of EC (4).

In obese women, low-grade and low-stage EC appear to be more common than normal weight women (5), although somehow endometrial cancer in obese women appears to have a higher mortality (6). The mechanism for this remains unclear. We designed our study to investigate the relationship between body mass index (BMI) of EC cases operated in our clinic with both stage and molecular prognostic markers such as ER/progesterone receptors (PR) positivity and p53.

MATERIALS AND METHODS

99 patients who were operated with the diagnosis of EC in our clinic between January 2015 and January 2019 and their pathological materials were retrospectively screened from our clinical records and included in our study. Age at diagnosis, body mass index, parity, histological subtypes, lympho-vascular invasion (LVI), FIGO stages and comorbidities (diabetes mellitus, hypertension) and tumor diameters of the patients were recorded. All pathological material (formalin-fixed, paraffin-embedded tissue blocks) were analyzed by a pathologist at the department of pathology.

BMI was calculated using the formula [BMI= weight (kg)/height (m)2] and categorized according to World Health Organization definitions (7). Accordingly, three groups were formed as normal and overweight (BMI of <30), grade 1 obesity (BMI of 30-<35), and grades 2 and 3 obesity (BMI of ≥35) (8).

ER, PR and P53 expression in hysterectomy materials were determined by immunohistochemical staining method. We used the FIGO 2009 staging guideline for EC (9). The effects of BMI on disease stage and molecular markers were investigated by comparing the data of clinical, demographic and molecular markers of endometrial cancer between the groups. The study was approved by the local Ethics Committee.

Statistical analysis

Obtained data were analyzed with IBM SPSS Statistics 21.0. Kolmogorov-Smirnov and Shapiro Wilk tests were utilized to evaluate whether the data were normally distributed. In addition to descriptive statistics were expressed as mean and standard deviation, Student's t test was employed to compare parameters with a normal distribution between two groups and Mann-Whitney U test was used to compare parameters without a normal distribution between two groups. Spearman's rank order correlation coefficients were calculated to determine degrees of association BMI and other parameters. The statistical significance was set at $p<0.05$.

RESULTS

Descriptive statistics of the patients were shown in Table 1.

Table 1 Demographic and clinical characteristics of cases (n=99)

Age (years), [mean ± SD]		58.1±9.9
Body mass index (kg/m2), [mean ± SD]		33.5±5.3
Parity, [mean ± SD]		2.6±1.7
Menopausal status	Post menopause (n, %)	74, (74.7)
	Pre menopause (n, %)	25, (25.3)
Smoking status	Smoker (n, %)	3, (3)
	Non-smoker (n, %)	96, (97)
Presence of hypertension (n, %)		39, (39.4)
Presence of diabetes (n, %)		26, (26.3)
Biopsy method	Pipelle biopsy (n, %)	11, (11.1)
	Probe curettage (n, %)	88, (88.9)
Endometrial cancer type	Endometrioid (n, %)	92, (92.9)
	Non Endometrioid (n, %)	7, (7.1)
n: number of patients; SD: standard deviation		

The comparison of demographic data between groups formed according to BMI values was shown in Table 2. Among the groups; except for hypertension (p=0.038) and menopausal status (0.042), there was no statistically significant difference in terms of years, parity, diabetes mellitus, and smoking history (p> 0.05).

Tablo 2. Comparison of demographic data between BMI groups

	Normal/ Overweight (BMI of <30, n=25)	Grade 1 obesity (BMI of 30-<35, n=29)	Grade 2 and 3 obesity (BMI of ≥35, n=41)	P value
Age (years) [mean ± SD]	59.0±17.75	58.1±12.1	58.1±8.8	0.988
Post Menopause (n, %)	16 (57.1)	23 (79.3)	34 (82.9)	**0,042***
Smoker [n, %]	0	2 (6.9)	1 (2.4)	0.297
Parity [mean ± SD]	2.6±2.0	2.3±1.2	2.7±1.9	0.767
Presence of hypertension [n, %]	17 (58.6)	10 (34.5)	12 (29.3)	**0.038***
Presence of diabetes [n, %]	3 (10.3)	10 (34.5)	13 (31.7)	0.066

n: number of patients; SD: Standard deviation; *: p<0.05

The comparison of clinical characteristics between groups formed according to BMI values is shown in Table 3. While there was no statistical difference between the groups in terms of stage, tumor grade, LVI and malignant intraperitoneal fluid, there was a significant difference with tumor diameter (p=0.026) and cancer type (p=0.042).

Table 4 shows the correlation coefficients and significance levels among stage, tumor diameter, hypertension and molecular markers with BMI. Accordingly, there is a negative correlation stage, tumor diameter, presence of ER, PR, P53 and a positive correlation with grade and hypertension, but only hypertension correlations with BMI were statistically significant (p=0.043, r=0.204) In addition, there was no significant correlation between other demographic, clinical and molecular parameters with BMI.

Comparison of molecular markers between groups formed according to BMI values is shown in Table 5. Among the groups; there was no significant difference in terms of p53 expression, ER, PR positivity (p> 0.05).

Table 3: Comparison of clinical findings between BMI groups

		Normal and overweight (BMI of <30, n=25)	Grade 1 obesity (BMI of 30-<35, n=29)	Grade 2 and 3 obesity (BMI of ≥35, n=41)	P value
Type of endometrial cancer (n, %)	Endometrioid (n=92)	28 (96.6)	29 (100)	35 (85.4)	**0.042***
	Non endometrioid (n=7)	1 (3.1)	0	6 (14.6)	
Stage (n, %)	IA	16 (55)	23 (79.3)	30 (73.2)	0.366
	IB	6 (20.7)	5 (17.2)	7 (17.1)	
	IIA	2 (6.9)	1 (3.4)	2 (4.9)	
	IIB	1 (3.4)	0	0	
	IIIA	2 (6.9)	0	2 (4.9)	
	IIIC	2 (6.9)	0	0	
Grade (n, %)	1	4 (13.8)	10 (34.4)	11 (26.8)	0.322
	2	21 (75.9)	18 (62.1)	25 (61.0)	
	3	3 (10.3)	1 (3.4)	5 (12.2)	
Mean tumor diameter [mean ± SD]		3.9±2.2	2.5±1.7	3.5±2.2	**0.026***
Presence of LVI (n, %)		10 (34.5)	6 (20.7)	10 (24.4)	0.460
Presence of malignant cells in peritoneal fluid (n, %)		4 (13.7)	4 (13.7)	4 (13.7)	0.833

LVI: lenfo vasküler invazyon; n: number of patients; SD: Standard deviation; *: p<0.05

Table 4. Correlation coefficients and significance levels among tumor diameter, stage, hypertension and molecular markers with BMI value

	Correlation coefficients	p-value †
Stage	-0.168	0.097
Diameter of tumor	-0.031	0.760
Hypertension	0.204	0.043*
ER +	-0.076	0.406
PR +	-0.014	0.889
P53	-0.037	0.716

†Spearman's rank order correlation analysis. *: p<0.05ER: Estrogen receptor; PR: Progesteron receptor

Table 5. Comparison of biochemical markers between groups

	Normal/ Overweight (BMI of <30, n=25)	Grade 1 obesity (BMI of 30-<35, n=29)	Grade 2 and 3 obesity (BMI of ≥35, n=41)	P value
Progesterone receptor positivity (n, %)	20 (69.0)	22 (75.9)	27 (65.9)	0.665
Estrogen receptor positivity (n, %)	19 (65.5)	23 (79.3)	24 (58.5)	0.190
Presence of P53 Expression (n, %)	10 (34.5)	10 (34.5)	12 (29.3)	0.861

n: number of patient

DISCUSSION

In our study, most patients presented with early stage of EC (93.9%, stage I, II) and endometrioid histology (92.9%). Among the groups we formed according to BMI; although there was no significant relationship between the EC stage, the presence of ER, PR and the p53, the risk of non-endometrioid type of EC was increased in the group with excessively high BMI (>35kg/m2). Nowadays, it is known that obesity is a risk factor for both metabolic diseases and many types of cancer (10, 11). There are many studies in the literature about the role of obesity in the etiology of EC (12-15).

The main risk factor for EC is endogenous or exogenous unopposed estrogen. In obese individuals, high endogenous estrogen serum levels are encountered due to the conversion of androgens to estrogens in adipose tissue (2). In a previous study, it was reported that estrogen enhances the malignant biological behavior of endometrial carcinoma via the estrogen receptor (3). Cases with p53 mutations have a worse prognosis than patients with positive ER and PR. Nuclear receptors ER and PR regulate gene expression and their decreased expression is associated with the poor prognosis of malignant tumors. (16). In our study, high ER / PR receptor levels were found in all groups (Table 5). It was thought that this may be due to the fact that most of the patients included in the study had type 1 endometrioid adenocarcinoma histology and this type is associated with the presence of high levels of hormone receptors (17).

P53 protein, which inhibits cell proliferation, is a transcription factor. Mutation of the P53 gene, increases the proliferation of cancer cells and causes aggressive tumor behavior. (189. ER, PR and P53 should be considered as disease-related indicators. Because all these markers are known to be closely related to the prognosis of EC. In addition, these markers can be demonstrated by immunohistochemical methods. (19, 20). In our study, no significant relationship was found between BMI and p53 mutation. Busch et al. (21) emphasized that those who are obese may be associated with greater hormone receptor expression in endometrial tumors compared to non-obese. Busch et al. (21) emphasized that hormone receptor expression seen in obese patients with endometrial cancer may be higher than in non-obese patients. Contrary to this data, no similar relationship was found between ER and PR and obesity in our study.

There are numerous conditions that increase the risk of obesity EC, including increased endogenous estrogen, insulin resistance, chronic inflammation, and adipokines. Data between obesity and disease stage in the literature is conflicting. Although high BMI was found to be significantly associated with low stage and non-aggressive markers in a previous study (22), in another study, it was reported that neither BMI was associated with the stage or degree of the disease (23). In our study, while there was no significant relationship between disease stage and obesity, we observed that tumor diameter and cancer subtypes were significantly different between BMI groups. The largest mean tumor diameter was observed in the patient group classified as normal / overweight. Sollberger et al. (24) reported that obesity is associated with both type 1 and type 2 EC, but this relationship is greater with type 1. In our study, unlike this study, non-endometrioid type EC was more common in groups with morbid obesity and BMI>35 kg/m2. The small number of patients diagnosed with non-endometrioid subtype might have affected this result. There is a need for studies on this issue with larger case series.

In studies conducted to determine the relationship between obesity and increased mortality risk in women with endometrial cancer, it was reported that hypertension, diabetes mellitus and increased surgical difficulty were

recommended as parameters in this regard (25, 26). In our study, among the additional medical risk factors (27), only a positive significant correlation was found between hypertension and BMI, while no significant relationship was found between diabetes mellitus, age and parity among other risk factors. It was thought that this situation might be related with the relatively low number of our patient population.

Study Limitations

The relatively low number of cases can be considered as a limitation of our study.

Conclusion

In conclusion, it was observed that the risk of non-endometrioid type of EC with aggressive course was increased especially in the second and third degree obesity group but no relationship was found between the disease stage and disease-related markers (ER, PR, p53) and BMI. This issue should be supported by studies to be conducted with larger case series. The awareness of patients about the effects of obesity on endometrial cancer type should be increased.

Conflict of Interest: No conflict of interest was declared by the authors.

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