Özgün Araştırma / **Original Article**

The Effect Of Poor Glycemic Control On Stage And Grade Of Endometrial Cancer

Endometrium Kanserinde Kötü Glisemik Kontrolün Evre ve Grade Üzerine Etkisi

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ÖZ

Amaç: Endometrium kanseri en sık görülen jinekolojik kanserlerden biridir. Bu çalışmamızda kötü glisemik kontolün hastalığın evre ve derecesi üzerine etkisini incelemeyi amaçladık.

Gereç ve Yöntemler: Endometrium kanseri tanısı almış ve bu sebeple cerrahi evrelemeye tabi tutulmuş hastaların kayıtarı retrospektif olarak incelendi. Ameliyat-tan 3 ay önceki döneme kadar glikozle haemoglobin (HgA1c), açlık glikozu ve açlık insulin seviyesi ölçülmüş olanhastalar çalışmaya dahil edildi. Hastaların nihai patoloji sonuçları hastalığın evre ve derecesi için incelendi. HgA1c ve açlık glikoz ve insulin düzeyleri hastalığın evre ve dereceleri ile karşılaştırıldı.

Sonuç: Açlık glikoz seviyeleri ile hastalığın evresi arasında istatistiksel olarak anlamlı bir fark saptandı. Ayrıca HgA1c seviyeleri ve hastalığınderecesi arasında da istatistiksel olarak anlamlı bir fark saptandı. HgA1c seviyeleri grade 3 tümörlerde daha yüksek bulundu. (p<0,05)

Tartışma: Grade I endometrium kanserinde plasma glukoz değerleri daha yüksek gözükse de ileri evre ve grade açısından istatistiksel bir anlam saptanamamıştır. Ancak grade ve kötü glisemik control arasındaki istatistiksel olarak anlamlı ilişki yüksek gradeli endometrial tümörler ve kötü glisemik kontrol arasındaki bağlantıya işaret ediyor olabilir. Bu çalışma kötü glisemik kontrol süresi ve hastalık prognozu ile ilgili ilişkinin incelenmesi açısından yol gösterici olabilir.

Anahtar Kelimeler: Hiperglisemi, endometrium kanseri-HbA1c

ABSTRACT

Aim: Endometrium cancer is one of the most common gynecological malignancies. In this study we aim to examine the effect of poor glycaemic control on stage and grade of endometrial carcinoma.

Material and Methods: Hospital records of patients who had a diagnosis of endometrium cancer and underwent a surgical staging for endometrial cancer were retrospectively reviewed. The patients who had examined forgly cosylated hemoglobin (HgA1c) within 3 months preoperatively, fasting plasma glucose and fasting insulin levels were included to the study. Final pathology results were examined to determine the FIGO stage and grade of tumour. HbA1c fasting insulin levels and fasting glucose levels of the patients were compared according to stage and grade.

Results: There was a significant difference among the stage of tumours according to fasting plasma glucose levels. There was a significant difference in terms of HgA1c levels among grade of tumours. HgA1c levels were found to be higher in favour of grade III tumours (p<0,05).

Discussion: Alt hough there was a significant higher level of fasting plasma glucose in favour of grade I endometrial cancer, no significant correlation between both advanced stage and grade of tumours was found. No significant difference among four stages of endometrial cancer was found in this study. On the other hand HgA1c levels were found to be higher in grade III endometrial cancers. It can be postulated that poor glycaemic control is associated with advanced grade of endometrial cancer. This study can be defined as a guiding study for investigating the relationship between the duration of poor glycemic control and prognosis of the disease

Keywords: Hyperglycemia, endometrial cancer-HbA1c

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Introduction

Endometrium cancer is one of the most common gynecological malignancies with 280,000 new cases per year worldwide.(1) Insulin resistance and hyperinsulinemia are widely hypothesized to play a role in the etiology of endometrial cancer.(2) Excess weight gain, hypertension and impaired glucose tolerance, which are known risk factors for endometrial cancer, are all associated with insulin resistance and hyperinsulinemia.(3) Insulin may influence endometrial cancer risk by a number of mechanisms. As a growth factor,it can stimulate cell proliferation and inhibit apoptosis directly through insulin receptors. On the other hand, it may increase IGF-I bioactivity in many tissues, including the endometrium, by down-regulating the synthesis of IGFBP-1(4).

Fasting plasma glucose and glycosylated hemoglobin levelscan be used for determining glycemic control. The most widely used clinical test for glycemic control is glycated hemoglobin (HgA1c). HgA1c reflects the entire 120 day life span of red blood cell; it correlates best with mean blood glucose over the previous 8 to 12 weeks.

There are several reports in literature about the relationship with poor glycemic control and neoplastic cell formation. (5,6)However, there are few reports on association between poor glycemic control and stage or grade of endometrial cancer. The goal of the present study was to examine the effect of poor glycemic control and stage and grade of endometrial carcinoma.

Material and Methods

This retrospective study was conducted at tertiary care hospital which is a referral center for gynecologic oncology cases in Turkey with approximately 300 new cases of endometrial cancer operation per year. Hospital records for patients who had a diagnosis of endometrial cancer preoperatively and underwent a surgical staging for endometrial cancer were retrospectively reviewed for this study. The patients who had a blood sample for HgA1c within 3 months preoperatively, fasting plasma glucose and fasting insulin levels were included to the study. Blood samples for insulin and glucose were collected from patients during routine preoperative testing for the measurement of plasma glucose levels (mg/dl). The patients fasted for 12 hours before sample collection as a routine protocol of the hospital. Patients who had a history of corticosteroids use during the period of the disease, and those who had been diagnosed with diabetes mellitus in their history were excluded from the study. FIGO staging system for endometrial cancer was used to determine the clinical stage. Pathologic grade of tumor was determined by standard FIGO pathologic criteria. Demographic features of the patients including age, weight, height, body mass index and clinical features of the patients including fasting glucose levels, insulin levels, CA-125 levels, final pathology, FIGO stage and grade of tumor were collected from medical records. Statistical analyses were performed with IBM SPSS 20.0 (SPSS Inc., Chicago, IL, USA) software. Continuous variables were expressed as mean ± standard deviation (SD), discrete variables as median (range) and categorical variables as number and percentage. Kolmogorov-Smirnov test was used to assess normal data distribution. Differences were considered significant at the $P = 0.05$ level (two tailed). Differences among groups were analyzed using a one –way ANOVA test. A Tukey's post hoc test was used when a significant difference seen with ANOVAs test for comparing the significance between groups.

Results

A total of 60 patients who underwent a surgical staging for endometrial cancer and had a measurement of HbA1c, within 3 months preoperatively and fasting plasma glucose and insulin levels preoperative day 1 was encountered during the study period. Mean age in the study population was 56,5±9. The study population was obese on average that mean BMI was 31,1±4,1 kg/m². Mean fasting glucose levels and insulin levels were 102,1±13,5 gr/dl and 12,7±5,8 IU/ml respectively. Mean CA-125 levels were found to be 28,9±56,0 kU/L. The distribution of stages of endometrial cancers were as follows; stage I: 51 patients (%85), stage II: 2 patients (3,3%), stage III 6 patients (10%), stage IV: 1 patients (1,7%). Table-1 shows clinical stages of the patients with endometrial cancer. The distribution of tumor grades were as follows; grade I: 30 patients (50%), grade II: 26 patients (43,3%), gradeIII: 4 patients (6,7%). Tumor grades are presented on Table-2. The most common pathologic subtype of endometrial cancer was endometrioid subtype with the rate of % 50 and the other subtypes and their percentages were as follows, mixed type 7%, serous subtype 2% and was clear cell subtype 1%. Pathologic subtypes of tumors are presented on Table-3.Grades and stages of tumors are presented together on Table-4.

Table.1. Clinical stages of the patients with endometrial cancer

Stage (FIGO)	Frequency(number of patients)	Percentage(%)
Stage I	51	85
IA	37	61,7
IB	14	23,3
Stage II	2	3,3
Stage III	6	10
IIIA	1	1,7
IIIC	5	8,3
Stage IV	1	1,7
IV A	1	1,7

Table 2: Pathologic grades of endometrial tumors

Grade	Frequency(number of patients)	Percentage(%)
I	30	50
II	26	43,3
III	4	6,7

Table 3: Distribution of pathologic subtypes of the patients

Pathologic subtype	Frequency(number of patients)	Percentage(%)
Endometriod	50	83,3
Mixed	7	11,7
Serous	2	3,3
Clear cell	1	1,7

Table 4: Stages and grades of endometrial cancer patients

	stageI	stageII	stageIII	stageIV	total
Grade I	28 (54,9%)	0 (0%)	2 (33,3%)	0 (0%)	30 (50%)
Grade II	21 (41,2%)	0 (0%)	4 (15,4%)	1 (3,8%)	26 (43,3%)
Grade III	2 (3,9%)	2(2,8%)	0 (0%)	0 (0%)	4 (6,7%)
Total	51 (85%)	2 (3,3%)	6 (10%)	1 (1,7%)	60 (100%)

Mean HgA1c in the study population was 5,9±0,54. The correlation between

stage of tumor and HgA1c levels and plasma insulin levels were investigated but there was no statistically significant difference among stage of tumors according to HgA1c and insulin levels (p values were 0,241 and 0,482 respectively) (Table- 5).On the other hand there was a significant difference among the stage of tumors according to fasting plasma glucose levels on one-way ANOVAs test ($p < 0,05$). A Tukey's post hoc test was performed and fasting plasma glucose levels were found to be higher in favor of grade 1 tumors compared to others ($p = 0,04$). There was also no difference between grade of tumor and fasting plasma glucose levels and plasma insulin levels respectively (p values: 0,084 and 0,669). There was a significant difference in terms of HgA1c levels among grade of tumors on one-way ANOVAs test. A Tukey's post hoc test was conducted and HgA1c levels were found to be higher in favor of grade III tumors ($p = 0,04$) (Table-6). A comparison between endometrioid and non-endometrioid subtypes of endometrial cancer according to HgA1c, fasting plasma glucose levels and insulin levels was performed but no significant difference was found between the groups. (Table-7)

Table 5: Correlation of stage of cancer and HgA1c and fasting plasma glucose levels

Stage	Frequency	HgA1c (mean±SD)	FPG (mean±SD)	Insulin (mean±SD)
I	51	5,8±0,54	104±11,1	13,1±6,0
II	2	6,4±0,7	103,4±0,8	13,6±0,74
III and IV	7	6,0±0,56	91,1±21	8,2±3,6
P values		0,241	0,03	0,482

FPG:fasting plasma glucose

Table 6.: Correlation of grade of cancer and HgA1c and fasting plasma glucose levels

Grade	Frequency	HgA1c (mean±SD)	FPG (mean±SD)	Insulin (mean±SD)
I	30	5,9±0,51	100±13,3	12,01±5,4
II	26	5,8±0,51	102±12,5	13,4±6,7
III	4	6,6±0,57	116,4±17,3	13,0±3,9
P value		0,021	0,084	0,669

FPG:fasting plasma glucose

Table 7: Correlation of pathology subtype of tumor HgA1c, FPG and insulin levels

Pathology	Frequency	HgA1c (mean±SD)	FPG (mean±SD)	Insulin (mean±SD)
endometriod	30	5,9±0,53	102±13,2	12,9±6,2
Non-endometrioid	26	6,0±0,59	98,2±18,9	11,4±3,8
P value(t test)		0,588	0,075	0,063

FPG:fasting plasma glucose

Discussion

Endometrial cancer is reported to be associated with obesity, diabetes and polycystic ovary syndrome, all conditions directly associated with hyperinsulinemia.(7) It has beenshown that obese women, who tend to have raised peripheralestrogens, have a higher frequency of endometrial cancer.(8)In the current study we investigated the association of markers of poor glycemic control and endometrial cancer in our non- diabetic obese study population.

The increased risk of endometrial cancer due to obesity has been reported. A threshold of BMI of 30 kg/m² or higher was associated with increased risk of endometrial cancer.(9) Our study population was obese that mean BMI was 31,1±4,1 kg/m². Insulin resistance is a common accompaniment of obesity. Hyperinsulinemia has been shown to increase ovarian steroid production, to stimulate conversion of testosterone into estradiol, and to suppress sexhormone binding globulin (SHBG) thereby increasing estradiol bioavailability.(10) The association between fasting plasma insulin levels and grade and stage of endometrial cancer has not been investigated previously in literature. Although our study population was obese on average no significant association was found between both stage and grade of tumor and fasting plasma insulin levels.

The relationship between stage of uterine cervical cancer and fasting plasma glucose levels were studied but the relationship between stage and grade of endometrial cancer and fasting plasma glucose levels has not been previously investigated. Although there was a significant higher level of fasting plasma glucose in favor of grade I endometrial cancer, no significant correlation between both advanced stage and grade of tumors was found. This may be due to more number of patients in low grade and stage of tumors and restricted number of patients in advanced grade and stage of tumors.

Increased HgA1c levels has been reported to be associated with aggressive colorectal cancers.(11) HgA1c are used to determine poor and good diabetic control. Augustinet. al. studied the association with HgA1c levels and grade and stage of endometrial cancer in their survival analysis study and found no relationship between stage and grade of endometrial cancer.(12) No significant difference among four stages of endometrial cancer was found in this study. On the other hand HgA1c levels were found to be higher in grade III endometrial cancers. It can be postulated that poor glycemic control is associated with advanced grade of endometrial cancer.

We also investigated the relationship between pathologic subtypes of endometrial cancer. The most common pathologic subtype was endometrioid subtype and comprised 83.3% of the study population. There was no relationship between pathologic subtypes and insulin, fasting plasma glucose levels and HgA1c levels. The relationship has not been explored previously.

The main limitation of our study can be defined as the small sample size with a few number of advanced stage patients. The distributionof patient characteristicscan be a reason for unexpected bias for the study.However the main aim of this study can be defined as first steps for defining the exact relationship between glycemic control and the prognosis of endometrial cancer. The further studies should be focused on the relationship between duration of poor glycemic control and stage, grade of endometrial cancer.

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