

Hemoglobin A1c Level is Associated with Lymphovascular Space Invasion in Diabetic Endometrial Cancer Patients

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ABSTRACT

OBJECTIVE: Our aim in this study is to examine the relationship of hemoglobin A1c (HbA1c) and fasting glucose with the stage, grade, and histological type of cancer and its value in predicting the prognosis of endometrial cancer in diabetic endometrial cancer patients.

STUDY DESIGN: The data of 138 endometrial cancer patients with diabetes who met the study criteria were analyzed. Hemoglobin A1c levels and fasting glucose were compared with cancer stage, grade, histological type, lymphovascular invasion, chemotherapy, and radiotherapy data.

RESULTS: A statistically significant difference was found between the groups in terms of HbA1c values only according to the lymphovascular invasion ($p=0.02$). While there was no significant correlation between endometrial thickness and HbA1c, a low positive correlation was found between the fasting glucose value ($r=0.191$, $p=0.025$)

CONCLUSIONS: The higher rate of lymphovascular invasion in patients with high HbA1c values alone is insufficient in determining the prognosis when other parameters are considered.

Keywords: Diabetes mellitus, Endometrial neoplasms, Glycated hemoglobin A

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Introduction

Endometrial cancer is frequent gynecological cancer and ranks second after breast cancer among malignancies seen in women in developed countries (1). Estrogen-dependent type 1, also known as endometrioid type, and more rarely estrogen-

independent type 2 have been defined. Type 1 endometrial cancer is associated with unstable and excess estrogen exposure of the endometrium and a mutation in the PTEN tumor suppressor gene (2). In addition, diabetes, obesity, hypertension, nulliparity, and anovulation are defined risk factors (3).

It has been hypothesized that there is a relationship between hyperinsulinemia and impaired glucose metabolism and many cancer types, including the genitourinary and gastrointestinal system and breast (4-6).

Cancers have similar characteristics to diabetes, such as leptin/adiponectin secretion or high insulin and insulin-like growth factor 1 (IGF-1) and immune abnormalities. Cancer cells need glucose to provide high proliferation. More glucose need and impaired metabolic change in cancer cells induce metabolic adaptations in neighboring non-cancerous cells (7).

Hemoglobin A1c (HbA1c) is a marker used to evaluate the glycemic status of patients and reflects the average glucose level of the last three months (8).

In endometrial cancer, impaired glucose tolerance and HbA1c were found to be significantly increased compared to the patient with other cancers (9). There are very few studies in the literature examining the relationship between HbA1c and endometrial cancer stage, grade, and histological type. There was no consensus on its results either (10,11).

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In this study, our aim is to examine the relationship between HbA1c and fasting glucose with cancer stage, grade, and histological type, and the value in predicting the prognosis of endometrial cancer in patients with endometrial cancer diagnosed with diabetes.

Material and Method

This retrospective study was conducted by examining the files of 154 patients who were operated on for endometrial cancer between January 2015 and December 2020 in our clinic. Patients with no preoperative HbA1c results, patients with other primary malignancies, a history of additional diseases other than diabetes, taking hormone therapy, and those with positive pregnancy tests were excluded from the study. There was a total of 138 patients meeting the study criteria. The diagnosis of diabetes was made according to the American Diabetes Association guideline. The last patient diagnosed with diabetes was diagnosed 3 years ago (12). Demographic data of the patients including age, body mass index (BMI), gravida and parity, laboratory and examination findings including fasting blood glucose, hemoglobin, HbA1c, and endometrial thickness measurement, surgery notes, and pathology results including cancer stage, grade, histological type and lymphovascular area invasion, postoperative chemotherapy, and radiotherapy histories were recorded.

Statistical Analysis

The study was started with the data of 20 patients. Patients with and without lymphovascular space invasion were compared in terms of HbA1c values. The mean HbA1c was 8 ± 1.9 in the group with lymphovascular space invasion. In the group without lymphovascular space invasion, the mean HbA1c was 7.1 ± 1.6 . In the G Power analysis, at least 40 individuals in both groups had to be included in the study with a power of 80% and an alpha error of 0.05. The compliance of the variables to normal distribution was examined by visual (histogram) and analytical methods (Kolmogorov - Smirnov test). The numerical ones among the data collected in the study are mean, median, standard deviation, and minimum-maximum values; categorical data were expressed with descriptive methods such as numbers and percentages. Mann-Whitney U and Kruskal Wallis tests were used for intergroup comparisons of numerical variables. The Spearman correlation test was used to examine the relationship between endometrial thickness with glucose and HbA1c. Values with a p-value below 0.05 were considered statistically significant. SPSS Statistics Ver. 22.0 was used for all statistical analyses and calculations.

The study was approved by the ethics committee of the University of Health Sciences Tepecik Training and Research Hospital. Approval number 2021/04-30. Consent was obtained to use patient data. The study was conducted in accordance with the Declaration of Helsinki.

Results

The mean age of 138 patients participating in the study was 59.4 ± 9.22 years, and the average BMI was 30.9 ± 5.2 kg/m². One hundred and three (74.6%) of the patients had diabetes (Table I).

Table I: Demographic characteristics of the patients

	Mean±SD
Age (year)	59.4±9.22
BMI (kg/m ²)	30.9±5.2
Gravidity	3.5±1.9
Parity	2.8±1.7

BMI: Body mass index

The mean blood glucose level values of the patients were 165.6 ± 65 mg/dL, the mean HbA1c was $7.5\pm 1.8\%$ and the mean endometrial thickness was 14.1 ± 7.04 mm. The most common histological type was the endometrioid type with 85.5%, while clear cell, serous, and mixed types were in second place with a frequency of 4.3%. When cancer staging frequencies were examined, Stage 1A in 73 patients (52.9%), Stage 1B in 32 patients (23.2%), and Stage 3 in 19 patients (13.8%) were the most frequently detected stages. The most frequently detected histological grade in patients was 52.2% (n=72) Grade 2. Lymphovascular invasion was present in 46 (33.3%) patients. Fifty-four (39.1%) of the patients had received radiotherapy and 36 (26.1%) had received chemotherapy treatment (Table II).

Table II: Clinical characteristics and laboratory parameters of the patients

Variables	Mean±SD
Glucose (mg/dL)	165.6±65.9
HbA1c (%)	7.5±1.8
Hemoglobin (g/dL)	12.05±1.57
Endometrial thickness (mm)	14.1±7.04
	n (%)
STAGE	
IA	73 (52.9)
IB	32 (23.2)
II	11(8)
III	19 (13.8)
IV	3 (2.2)
GRADE	
1	51(37)
2	72 (52.2)
3	15 (10.9)
Histological type	
Endometrioid	118 (85.5)
Clear cell	6 (4.3)
Serous	6 (4.3)
Mix	6 (4.3)

Villoglandular	1 (0.7)
Undifferentiated	1 (0.7)
Radiotherapy	
No	84 (60.9)
Yes	54 (39.1)
Chemotherapy	
No	102 (73.9)
Yes	36 (26.1)
Lymphovascular invasion	
No	92 (66.7)
Yes	46 (33.3)

HbA1c: Hemoglobin A1c

When the relationship between the HbA1c and fasting glucose values of the patients and the disease stage, grade, histological type, chemotherapy, radiotherapy, and lymphovascular invasion were examined, a statistically significant difference was found between the groups in terms of HbA1c values only according to the lymphovascular invasion ($p=0.02$). While there was no significant correlation between endometrial thickness and HbA1c, a low positive correlation was found between the fasting glucose value ($r=0.191$, $p=0.025$) (Table III).

When the distribution of cancer stages of the patients by

cancer level is examined, it is noteworthy that the most common cancer grade in each stage is 2 (Table IV).

Discussion

The most common gynecological cancer in developed countries is endometrial cancer. The specified risk factors for endometrial cancer are diabetes, hypertension, obesity, anovulation, and nulliparity (13). It has been suggested in some studies that diabetes is an independent risk factor for endometrial cancer (14). In addition, the presence of diabetes has also been shown to increase some types of cancer (15).

Prognostic factors for endometrial cancer include clinical, surgical, pathological, biological, and molecular factors. Advanced age, high tumor grade, non-endometrioid histological type, deep myometrial invasion, lymphovascular area involvement, and oncogene amplification, especially HER-2, are poor prognostic factors (13). Except for age, all these factors are determined after endometrial cancer surgery. However, there are studies claiming that high HbA1c values are preoperative poor prognostic factors (10).

The question we sought an answer to before starting this study was whether there was a significant relationship between HbA1c and fasting blood glucose in endometrial cancer

Table III: Comparison of HbA1c and fasting glucose values according to grade, stage and histological type, lymphovascular invasion, radiotherapy and chemotherapy

Variables	HbA1c	p	Glucose	p
STAGE	Mean±SD		Mean±SD	
Stage I	7.4±1.7		163.1±60.8	
Stage II	7.8±2.0	0.830	164.7±62.5	0.987
Stage III-IV	7.8±2.1		178±89.7	
GRADE				
Grade 1	7.6±1.8		162.5±66.3	
Grade 2	7.6±1.9	0.759	169.4±68.1	0.918
Grade 3	7.1±1.5		158.1±56.1	
Histological type				
Endometrioid	7.5±1.8		164.4±68	
Non-endometrioid	7.7±1.9	0.405	173.1±53.3	0.280
Radiotherapy				
No	7.5±1.8	0.389	164.4±62.1	0.924
Yes	7.6±1.7		167.5±72	
Chemotherapy				
No	7.5±1.8	0.528	165.3±66.4	0.810
Yes	7.7±1.8		166.6±65.6	
Lymphovascular invasion				
No	7.3±1.8	0.02	160.9±64.4	0.209
Yes	7.9±1.8		175.2±68.9	
Endometrial Thickness (mm)	r		r	
	0.124	0.146	0.191	0.025

HbA1c: Hemoglobin A1c

patients with a previous diabetes diagnosis in terms of cancer stage, grade, histological type, lymphovascular area invasion, and the frequency of receiving chemotherapy or radiotherapy. As a result of our study, we found that there was no statistically significant relationship when HbA1c and fasting blood glucose were examined in terms of cancer stage, grade, histological type, and the frequency of receiving chemotherapy or radiotherapy. There was only a statistically significant relationship between lymphovascular area involvement and HbA1c. The presence of lymphovascular area invasion was higher in patients with higher HbA1c.

In studies, the average age of endometrial cancer patients ranges from 56 to 62 years (10,11,14). In our study, the mean age of the patients was found to be 59.4 ± 9.22 years and it was consistent with the literature.

According to a review reviewing 127 cohort studies conducted in 2018, among endometrial cancer risk factors, increased BMI was stated as the primary risk factor (16). According to the results of our study, the patients' mean BMI was 30.9 ± 5.2 and they had an important risk factor.

According to a meta-analysis conducted in 2018, the risk of endometrial malignant pathologies was increased in postmenopausal women when the endometrial thickness was > 11 mm (17). According to our study, the mean endometrial thickness of the patients was found to be 14.1 ± 7.04 mm, and this was another risk factor that these patients had. In our study, there was no significant correlation between endometrial thickness and HbA1c, but a low positive correlation was found between glucose values.

The most common histological type was specified as the endometrioid type according to literature data. In our study, 85.5% of our patient population was of the endometrioid type (10,11).

Some studies show that high HbA1c levels increase the risk of some types of cancer (18,19). In a population-based controlled study conducted by Chen et al., they concluded that diabetes may increase the risk of breast and endometrial cancer to a great extent (20). According to the study conducted by Travier et al., high fasting glucose levels increase the risk of cancer in the genitourinary system, especially endometrial cancer (21). One study showed that impaired glucose tolerance measured by HgA1c is significantly increased in endometrial cancer compared to other types of cancer (9). However, studies examining the relationship between HbA1c and glucose levels in endometrial cancer in diabetic patient population and cancer stage, grade, and histological type are limited in the literature. As a result of the study conducted by Karaman et al. in 2015, HbA1c levels were found to be statistically significantly higher in endometrial cancer patients compared to the normal patient group. However, they did not find a significant relationship between cancer stage, grade, his-

tological type, and HbA1c (11). Similar to the results of this study, there was no statistically significant relationship between HbA1c and fasting glucose levels of the patients and endometrial cancer stage, grade, and histological type in our study. There was only a statistically significant relationship between lymphovascular area involvement and HbA1c. According to this result, although a high HbA1c value increases the risk of endometrial cancer, it was thought that HbA1c was insufficient in predicting the prognosis of endometrial cancer.

In their study, Stevens et al. concluded that in patients with high HbA1c, the cancer stage is more advanced at the time of diagnosis, but HbA1c is weak in determining the prognosis (10). In our study, there was no evidence to show that patients with high HbA1c had a worse cancer prognosis. There was no significant difference between the HbA1c and fasting glucose levels of the patients and the rates of chemotherapy and radiotherapy.

The retrospective nature of our study is a limitation of the study. However, since our center is a referral hospital, the sufficient number of patients is the advantage of our study. In addition, the presence of patients in our patient group not only at an early stage but also at advanced grade and stage is another advantageous aspect of the study.

Although increased HbA1c and high fasting glucose levels increase the risk of developing endometrial cancer, there was no statistically significant relationship between these parameters and the cancer stage, grade, histological type, chemotherapy, and radiotherapy rates in terms of the course of the disease. The higher rate of lymphovascular invasion in patients with high HbA1c values alone is insufficient in determining the prognosis when other parameters are considered. Studies involving more patient series are needed to better explain the relationship on this topic.

Declarations

Availability of data and materials: The data supporting this study is available through the corresponding author upon reasonable request. / The datasets and code used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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Authors' Contributions Statement: ARS, and MS. Raised the presented idea. ARS, SYK. and SK. designed the study. ARS. conducted the analyses. ARS. and SYK. developed the first draft of the manuscript. All authors contributed to the writing of the paper, and have read and approved the final manuscript. SK. conducted the population study, analyzed and interpreted the data, and drafted the manuscript. ARS. participated in data analysis, interpretation, and draft revision. SYK. and SK. participated in data collection and result interpretation. SK. SYK. and ARS. assisted with data collection and analysis. MS. designed the study and critically revised the manuscript. All

authors read and approved the final manuscript.

Competing interests: The authors declare that they have no competing interests.

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