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Orijinal Makale

Assessment of Insulin Resistance, HOMA-IR, and QUICKI Levels in Patients with Endometrial Cancer and Hyperplasia

Endometrium Kanseri ve Hiperplazisi Olan Hastalarda İnsülin Direnci, HOMA-IR ve QUICKI Düzeylerinin Değerlendirilmesi

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Abstract

Aim: To analyze insulin resistance and related parameters in patients with endometrial cancer and hyperplasia.

Methods: The study included 102 patients in 3 groups. Group I and II included patients with a histologic diagnosis of endometrial cancer (n=41, 40.2%) and endometrial hyperplasia (n=31, 30.4%) based on the final pathology report. Group III was the control group and included patients who had undergone surgery for a benign indication other than endometrial hyperplasia (n=30, 29.4%). Age, body mass index (BMI), menarcheal age, menopausal status, gravidity, parity score, diabetes, oral contraceptive status, fasting glucose levels, insulin levels, endometrial thickness, HOMA-IR and QUICKI scores were assessed.

Results: The mean age of group I was statistically higher than that of group II (55.3±9.5 vs. 48.8±7.1, p=0.002). The average BMI of the two groups was similar (p=0.076). When fasting glucose values were evaluated, group I showed significantly higher values compared to group II. The mean insulin and HOMA-IR values in the control group were significantly higher than those in group I (p<0.001) and the QUICKI value was significantly higher in group I than in the control group (p=0.026).

Conclusion: Insulin resistance appears to be associated with endometrial cancer.

Keywords: insulin resistance; endometrial cancer; hyperplasia

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Öz

Amaç: Endometriyal kanser ve hiperplazi hastalarında insülin direncini ve ilgili parametreleri analiz etmek.

Yöntemler: Çalışmaya 3 grupta 102 hasta dahil edildi. Grup I ve II, nihai patoloji raporuna göre histolojik tanısı endometriyal kanser (n=41, %40.2) ve endometriyal hiperplazi (n=31, %30.4) olan hastaları içermekteydi. Grup III kontrol grubuydu ve endometriyal hiperplazi dışında iyi huylu bir endikasyon nedeniyle ameliyat geçiren hastaları içeriyordu (n=30, %29,4). Yaş, vücut kitle indeksi (VKİ), menarş yaşı, menopoz durumu, gravidite, parite skoru, diyabet, oral kontraseptif durumu, açlık glukoz düzeyleri, insülin düzeyleri, endometriyal kalınlık, HOMA-IR ve QUICKI skorları değerlendirildi.

Bulgular: Grup I'in yaş ortalaması grup II'den istatistiksel olarak daha yüksekti (55.3±9.5 vs. 48.8±7.1, p=0.002). İki grubun VKİ ortalaması benzerdi (p=0.076). Açlık glukoz değerleri değerlendirildiğinde, grup I, grup II'ye kıyasla anlamlı derecede daha yüksek değerler göstermiştir. Kontrol grubundaki ortalama insülin ve HOMA-IR değerleri grup I'dekilerden anlamlı derecede yüksekti (p<0.001) ve QUICKI değeri grup I'de kontrol grubundan anlamlı derecede yüksekti (p=0.026).

Sonuç: İnsülin direnci endometriyal kanser ile ilişkili görünmektedir.

Anahtar Kelimeler: insülin direnci; endometrial kanser; hiperplazi

1. Introduction

Uninhibited estrogen forms the basis of the pathophysiology of endometrial cancer (EC), and any condition that leads to uncontrolled hyperestrogenism may play a role in the development of EC. However, metabolic abnormalities such as obesity, polycystic ovary syndrome (PCOS), type II diabetes, and components of the metabolic syndrome that lead to hyperestrogenism are often associated with insulin resistance (IR) and hyperinsulinemia (1-5). In addition, 33% of non-diabetic EC patients have IR, and hyperinsulinemia has also been shown to be associated with endometrial hyperplasia and endometrial proliferative disorders (6-9).

Elevated insulin plays a role in the pathogenesis of endometriosis in several ways. Via the endometrial cancer cell lines ECC-1 and USPC-1, it may play a direct role in stimulating cell proliferation and anti-apoptotic effects on the endometrium (7). In addition, elevated insulin levels can lead to cervical cancer due to increased insulin-like growth factor 1, decrease in sex hormone-binding globulin and inflammation, which can stimulate signaling pathways such as PI3K/Akt, Ras/MAPK and insulin-like growth factor receptor (8-10).

Based on this point of view, in this study we investigated hyperinsulinemia and insulin resistance in patients with endometrial hyperplasia and endometrial cancer compared to a control group using the very well accepted homeostasis model for assessing insulin resistance (HOMA-IR) and the quantitative index for testing insulin sensitivity (QUICKI) (11).

2. Materials and Methods

This study was conducted at Zekai Tahir Burak Women's Health Education and Research Hospital and was approved by the institutional review board of the hospital with the number (approval number:10). The study group included patients with endometrial cancer and endometrial hyperplasia compared to the control group, which included patients who had undergone hysterectomy for non-endometrial reasons. Over a period of five months (01.11.2014-01.04.2015), 102 patients were included in the study. All groups were informed about the study and voluntary informed consent was obtained. Our study was conducted in accordance with the latest principles of the Declaration of Helsinki. The study was designed as a retrospective case-control study.

All patients underwent hysterectomy and/or unilateral/bilateral salpingo-oophorectomy. However, patients who did not fulfill the Mayo criteria[12] underwent staging surgery (additional omentectomy and bilateral pelvic para-aortic lymphadenectomy).

The patients were divided into 3 groups: Group I and II included patients with a histologic diagnosis of endometrial carcinoma (n=41) and endometrial hyperplasia (n=31) based on the final pathology report. Group III was the control group and included patients who had undergone surgery for non-endometrial benign indications (n=30).

Age, age at menarche, menopausal status, body mass index (BMI (kg/m^2)), previous use of oral contraceptives, endometrial thickness (mm), fasting glucose level (mg/dL) were recorded. Fasting insulin and glucose levels were used to calculate the QUICKI value (1/(log(insulin))+ (log(plasma glucose(mg/dL)) and the HOMA value (insulin(mU/L)x(glucose (mmol/L)/22.5). There is no clear significance threshold for the detection of insulin resistance based on HOMA IR and QUICKI values. However, it is known that an increase in HOMA-IR and a decrease in QUICKI indicate insulin resistance.

Statistical analysis

The Statistical Package for Social Sciences (SPSS Inc, Chicago, IL) for Windows ® 22.0 was used to analyze the data. Pearson's chi-square test was used for categorical variables. The Kruskal-Wallis test was used to analyze three groups that were not normally distributed. Post-hoc analysis was performed using the Mann-Whitney U test after Bonferroni correction for the comparison of two groups. Logistic regression was also used to analyze the variables. The power analysis showed that the power for the difference in QUICKI score between patients with endometrial cancer or vice versa and patients with diagnosed or undiagnosed endometrial hyperplasia was 98.23% and 97.01%, respectively.

3. Results

A total of 102 patients were evaluated. Most patients with endometrial carcinoma had stage 1A (n=30, 73.2%) and grade 1 (n=22, 53.6%). Myometrial invasion > ½ was found in 10 (24.4%) patients and lymph node involvement in 5 (12.1%) patients. Among the patients with endometrial hyperplasia, 12 (38.7%) had complex atypical hyperplasia.

The mean age of the groups was 55.29±9.57, 48.84±7.06 and 54.77±8.75, respectively, and the difference between patients with endometrial cancer and patients with endometrial hyperplasia was statistically significant (p=0.002). When comparing the mean number of gravidities, the patients in the control group had significantly higher gravidities than those in group I (p=0.015). The mean BMI of the two groups was similar (p=0.076). The presence of postmenopausal status and diabetes was significantly more common in group I than in the other groups (p<0.001 and =0.017, respectively). The demographic data of the groups are shown in Table 1.

When fasting glucose values were evaluated, group I had significantly higher values compared to group II. The mean insulin and HOMA-IR values in the control group were significantly higher than those in group I (p<0.001) (Table 2).

4. Discussion

In our study, we investigated insulin resistance, HOMA-IR and QUICKI levels in patients with endometrial cancer and endometrial hyperplasia compared to a control group. Our results showed an association between endometrial cancer or hyperplasia and increased insulin resistance.

There are many risk factors for the development of endometrial cancer, but the exact cellular and molecular mechanism of carcinogenesis is still under investigation. Since EC is a hormone-dependent carcinoma, the risk increases with unbalanced estrogen levels and diseases that cause elevated estrogen levels (8).

Table 1. Demographic analysis of study groups

	Group I	Group II	Group III	P value
Age	55.29±9.57	48.84±7.06	54.77±8.75	0.002
Body Mass Index (BMI) (kg/m^2)	35.39±7.43	32.48±4,7	31.49±4.28	0.076
Menarche age	13.93±1.21	12.65±1.02	12.63±0.56	0.359
Gravida (n)	3±1	3±1	4±2	0.015
Parity	2±1	3±1	3±1	0.075
Menopause (patient n/%)	28/68.3%	7/22.6%	17/56.7%	<0.001
Diabetes (patient n/%)	18/43.9%	5/16.1%	6/20%	0.017
Using oral contraceptive history (patient n/%)	6/14.6%	7/22.6%	0	0.576

Table 2. Insulin, fasting glucose, HOMA-IR and QUICKI values between study groups

	Group I	Group II	Group III	P value
Fasting glucose level (mg/dL)	133.05±52.5	101.68±18.06	109.6±24.1	**0.002**
Insulin	8.1±12.2	8.73±11	19.46±16.4	**<0.001**
QUICKI (mg/dL)	0.35±0.14	0.34±0.13	0.32±0.05	**0.026**
HOMA-IR (µmol/L)	3.23±7.23	2.06±2.67	5.34±5.26	**<0.001**

The incidence of IR in the general population increases day by day with increasing obesity and is around 10-25% (11-19). Obesity and elevated insulin levels are associated with more severe endometrial pathology. However, weight loss increases insulin sensitivity and decreases mortality (19-20). Shan et al. have shown that BMI greater than 25 kg/m2 and menopausal status are risk factors for type 1 diabetes; in addition, abnormal metabolic changes have been demonstrated in the very early stages of endometrial hyperplasia (9). Type II diabetes and obesity are closely associated with an increased risk of EC (18). There are published data on decreased insulin response and increased fasting insulin levels, which are positively correlated with EC. In addition, hyperinsulinemia can also be found in non-obese women (11). Thus, hyperinsulinemia appears to be an independent risk factor for EC, in addition to non-opposed estrogen (17). There are published data on decreased insulin responsiveness and increased fasting insulin levels that positively correlate with EC, and hyperinsulinemia can also be found in non-obese women (11). In addition, fasting glucose levels was significantly higher in the endometrial cancer group than in the endometrial hyperplasia group and insulin resistance was more common in the endometrial cancer group.

Many different signaling pathways such as PI3K7Akt, Ras/MAPK and mediators such as insulin-like growth factor-1 (IGF-1) and sex hormone-binding globulin (SHBG) are involved in the complex mechanism of endometrial carcinogenesis through the action of insulin. Despite the role of insulin, the measurement of insulin resistance is quite difficult. Epidemiologic studies have produced some models such as HOMA-IR and QUICKI. However, it is not possible to establish a clear threshold for insulin resistance to establish a relationship with EC. HOMA-IR values are strong indicators of risk of EC, and they are significantly higher in patients with endometrial carcinoma (21). QUICKI assesses insulin sensitivity rather than insulin resistance and is the inverse of HOMA-IR. In a study by Burzawa et al. low QUICKI values were found in patients with endometrial cancer (<0.357) (10,21). Furthermore, it is clear that insulin resistance is higher in the endometrial cancer group (21-27).

The strengths of our study are the prospective structure, the selection of patients and the use of multiple methods to assess insulin resistance. The small number of cases was considered a limitation of the study.

In conclusion, we found a strong association between insulin resistance and endometrial cancer and hyperplasia in our study. Further studies on the severity of insulin resistance and endometrial disease will contribute to the literature.

Author contribution

Study conception and design: CT, TG; Data collection: CT, TG, BSO; analysis and interpretation of results: CT, TG, BSO; draft manuscript preparation: CT, TG, BSO. 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's Health Education and Research Hospital (Approval date: 24/03/2014 Issue No.: 03/10).

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Conflict of interest

The authors declare that there is no conflict of interest.

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Araştırma fikri ve tasarımı: CT, TG; veri toplama: CT, TG, BSÖ; sonuçların analizi ve yorumlanması: CT, TG, BSÖ; araştırma metnini hazırlama: CT, TG, BSÖ. Tüm yazarlar araştırma sonuçlarını gözden geçirdi ve araştırmanın son halini onayladı.

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