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The relationship between oxidative stress markers and endometrial hyperplasia: A case-control study

Oksidatif stres belirteçleri ile endometriyal hiperplazi arasındaki ilişki: Bir olgu kontrol çalışması

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Abstract

Objective: Endometrial hyperplasia (EH) is considered an endometrial cancer precursor. This study aimed to determine the role of oxidative stress and thiol groups with antioxidant properties in EH pathogenesis.

Materials and Methods: In our prospective case-control study, participants were washed with 5 mL of saline before the endometrial biopsy. Endometrial washing fluid was taken into microtubules, and thiol and disulfide levels were analyzed using the Ellman reagent.

Results: A total of 108 patients were in the EH group and 84 patients in the control group. The total and native thiol levels were higher values in the control group (p<0.001, for both). Disulfide levels were higher in the EH group (p<0.001). Native/total thiol ratio and disulfide/total thiol ratio were higher in the EH group (p<0.001, for both). The analysis performed in the control group revealed a significant positive correlation between estradiol and disulfide levels (r=0.322, p=0.033). No significant correlation was found between estradiol and disulfide in the EH group.

Conclusion: Oxidative stress level was higher in the washing fluids of patients with EH and this stress plays a role in the EH etiology.

Keywords: Endometrial hyperplasia, oxidative stress, thiol, disulfide

Öz

Amaç: Endometriyal hiperplazi (EH) endometriyum kanseri prekürsörü olarak kabul edilir. EH patogenezinde oksidatif stresin rolünü ve antioksidan özelliği olan tiyol gruplarının rolünü saptamayı hedefledik.

Gereç ve Yöntemler: Prospektif olgu kontrol çalışmamızda katılımcılara endometriyal biyopsi yapılmadan önce 5 mL salin ile endometriyal yıkama yapıldı. Endometriyal yıkama sıvısı mikrotübüllere alındı, Ellman reagent kullanılarak tiyol ve disulfid düzeyleri analiz edildi.

Bulgular: EH grubunda 108, kontrol grubunda 84 hasta vardı. Toplam tiyol ve doğal tiyol seviyeleri kontrol grubunda daha yüksekti (her ikisi için p<0,001). Disulfid düzeyleri ise EH grubunda daha yüksekti (p<0,001). EH grubunda native/total tiyol oranı ve disulfid/total tiyol oranı daha yüksekti (her ikisi için p<0,001). Kontrol grubunda yapılan analizde estradiol düzeyleri ile disulfid düzeyleri arasında anlamlı pozitif ilişki saptandı (r=0,322, p=0,033). EH grubunda estriol ile disulfid arasında anlamlı korelasyon bulunamadı.

Sonuç: EH hastaların yıkama sıvılarında oksidatif stres düzeyi daha yüksek bulundu ve EH etiyolojisinde bu stres rol oynayabilir.

Anahtar Kelimeler: Endometriyal hiperplazi, oksidatif stress, tiol, disülfid

PRECIS: Oxidative stress level was found higher in the washing fluids of patients with endometrial hyperplasia and may play a role in the etiology of endometrial hyperplasia.

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Introduction

As a component of the PALM-COEIN classification, endometrial hyperplasia (EH) is one of the important pathological diagnoses in females with abnormal uterine bleeding (AUB) symptoms[1,2]. Its clinical importance is derived from its potential as an endometrial adenocarcinoma precursor[3]. EH is mainly caused by continuous and high estrogen exposure that was imbalanced with progesterone[4]. Endometrial estrogen exposure effects are not explained only with cellular proliferation. An example of this issue is the increased nitric oxide synthase activity in patients with endometriosis and adenomyosis with estrogen exposure in the etiology[5,6]. Previous studies showed that estrogens and estrogen metabolites play a prooxidant role and cause reactive oxidative species (ROS) formation[7]. ROS with estrogen stimulus cause cell genetic instability. Redox reactions formed by ROS stimulate intracellular signaling pathways and cause cell proliferation, cell migration, invasion, and malignant transformation[8].

Endometrial ROS balance is maintained with enzymatic and nonenzymatic antioxidative systems. Among these systems, thioredoxins are one of the disulfide-reducing proteins found in human endometrium, and its relationship with implantation was reported[9]. Thiol/disulfide homeostasis moves in the disulfide direction and binds to oxidant radicals in the first stage of oxidative damage. Oxidative products, such as reactive oxygen species formed in the organism, are reduced by transferring their excess electrons to compounds containing thiol while thiol groups are oxidized. Thiol group oxidation forms disulfide bonds. However, the reaction is reversible and the disulfide bonds formed are reduced back to thiol groups. Thus, dynamic thiol-disulfide homeostasis is achieved. Comparing the native thiol levels to the ratio of total thiol will show the changing dynamic -SH redox reactions more clearly[10].

Thiols are secreted as a response to oxygen radicals and protect the tissue against oxidative stress[11]. The amount of total thiol is free, protein-dependent, or reduced by glutathione. Thiol level is used as a marker that shows oxidative defense; Thiol/disulfide homeostasis plays an important role in maintaining many physiological processes and the disulfide balance form shifting is expected to be associated with oxidative stress[12]. As the association of oxidative stress and endometrium cancer was proven, increased cancer precursor lesions are expected[7]. Therefore, this study aimed to investigate the relationship of oxidative stress markers in females with EH and healthy females.

Materials and Methods

Study Design and Population

The present study was designed as a prospective case-control in nature and conducted at the Hitit University Hospital between March 2019 and April 2020. The study was approved by the Erzincan Binali Yıldırım University Clinical Research Ethics Committee and conducted following the Helsinki Declaration (approval number: 33216249-604.01.02-E.24314). Informed consent was obtained from all participants at the beginning of the study.

Females admitted to the hospital with AUB complaints were enrolled in the study. Firstly, detailed demographic data and medical history were recorded. The same clinician evaluated all participants using a pelvic examination and transvaginal sonography (Logiq P5, GE Healthcare, Milwaukee, USA).

The exclusion criteria included the presence of any reproductive tract structural abnormality leading to vaginal bleeding, any coexisting disease or drug usage affecting the reproductive tract, smoking, pregnancy, lactation, body mass index of >30 kg/m^2. Participants were between the ages of 18-55 years with any type of AUB pattern (<24 or >37-day interval, >7-day duration, or intermenstrual bleeding). The main indication for endometrial biopsy was determined as AUB. Endometrial biopsies were performed in cases where sonographically polypoid appearance, heterogeneous-cystic endometrial appearance, anemia, and AUB were long and severe. Thereafter, participants were classified into two main groups based on histopathological reports: (i) EH group composed of participants with histological EH diagnoses without atypia (n=108) and (ii) control group composed of women with normal histological diagnoses (n=84).

Specimen Collection and Analyses

The venous samples obtained from all participants in their early follicular phases of the menstrual cycle on days 2-4 after overnight fasting were collected into 5 mL serum separator tubes (BD Vacutainer, Becton Dickinson, New Jersey, USA). After 30 min for blood samples to clot, the samples were centrifuged at 1000×g for 20 min. The serum analyses for estradiol (E2), follicle-stimulating hormone (FSH), luteinizing hormone (LH), thyroid-stimulating hormone (TSH), and free thyroxine (fT4) were performed by an electro-chemiluminescence immunoassay method using an autoanalyzer (Cobas 6000, E 601 Roche Diagnostics, GmbH, Mannheim, Germany) on daily basis. The analyses of hematological parameters, including hemoglobin (Hb), neutrophil, lymphocyte, and platelet concentrations, were performed using an analyzer (Sysmex XE2100, TOA Medical Electronics, Kobe, Japan).

Participants were placed in a lithotomy position to obtain an endometrial sample. After a plastic flexible catheter (Medlab, Izmir, Turkey) passes through the cervical canal and fundal touch feeling was taken, a volume of 5 mL of saline solution was flushed into the uterine cavity[13,14]. Gentle suction was applied to recover the fluid back, and then approximately equal amounts of aspired solution were poured into microtubules to analyze the thiol and disulfide levels. Ellman reagent (5,5'-dithio-bis-2-nitrobenzoic acid, also known as DTNB) was used for spectrophotometric analysis to detect endometrial thiol and disulfide levels reacted with thiol molecules and formed a yellow complex with a maximum absorbance at 421 nm wavelength (Evolution™ 201 Bio, Thermo Scientific Inc., USA)[15,16]. Oxidative stress markers, including thiol, native

thiol, disulfide concentrations, and native thiol-to-total thiol, disulfide-to-total thiol, and disulfide-to-native thiol ratios, were calculated in each group.

Endometrial biopsies were evaluated in Hitit University Medical Faculty, Central Pathology Laboratory. Especially, the pathologists who specialized in gynecopathology were blinded from the pathological specimens of the study group.

Statistical Analysis

All statistical analyses were performed using the Statistical Package for Social Sciences (SPSS version 23.0, IBM SPSS Inc. Chicago, IL, USA). Continuous variables were firstly assessed by the Shapiro-Wilks normality test for the statistical distribution normality. Eventually, no normally distributed data was found, and Mann-Whitney U test was used to compare the data in two study groups. According to the data distribution pattern, the descriptive statistics were presented as median (minimum-maximum). The nominal variables were presented as the number of cases and percentages. The correlation of oxidative stress markers was performed using Spearman's correlation test. A p-value of <0.05 was considered statistically significant.

Results

A total of 192 females were recruited for the study population. Demographic and biochemical characteristic comparisons in EH and control groups are presented in Table 1. The ages of the EH and control groups were statistically similar (p=0.360). No difference was found regarding the body mass index in both study groups, (p=0.068). As expected, the mean serum E2 level was higher in the EH group (p<0.001). FSH and LH levels did not statistically differ from each other (p=0.690 and p=0.441). The median serum TSH level was elevated in the EH group (p=0.002). In both groups, hematological parameters including Hb, lymphocyte, and platelet concentrations did not statistically differ from each other. In addition, no statistical difference was found between the neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio as inflammatory markers in the two groups (p=0.125 and p=0.435, respectively).

Oxidative stress markers, including thiol, native thiol, disulfide concentrations, and native thiol-to-total thiol, disulfide-to-total thiol, and disulfide-to-native thiol ratios, were compared in both study groups, as presented in Table 2. The serum and

Table 1. Comparison of demographic and biochemical characteristics in endometrial hyperplasia and control groups

	EH Group (n=108, 55.9%) (Median. min-max)	Control Group (n=84, 44.1%) (Median. min-max)	p
Age (years)	45.0 (34.0-54.0)	44.0 (32.0-5.0)	0.360
BMI (kg/m²)	23.3 (20.3-28.7)	22.3 (18.3-29.4)	0.068
Gravida	3.0 (1-6.0)	3.0 (2-6.0)	0.05
Parity	3.0 (0-5.0)	3.0 (0-5.0)	0.833
Live	2.0 (0-5.0)	2.0 (0-4.0)	0.713
Abortus	0 (0-4.0)	0 (0-2.0)	**0.001**
Termination	0 (0-2.0)	0 (0-3.0)	**0.011**
Endometrial thickness (mm)	9.2 (5.6-10.3)	6.2 (4.9-8.3)	**<0.001**
E2 (pg/mL)	121.5 (80.5-169.7)	95.4 (71.8-141.3)	**<0.001**
FSH (IU/L)	9.3 (4.9-17.8)	9.4 (4.4-18.3)	0.690
LH (IU/L)	8.2 (3.7-13.6)	7.6 (3.9-13.6)	0.441
TSH (µIU/mL)	2.2 (0.9-4.1)	1.8 (0.8-3.2)	**0.002**
fT4 (ng/dL)	1.3 (0.7-2.4)	1.4 (0.7-2.4)	0.599
Hb (g/dL)	12.4 (7.7-14.7)	12.0 (8.6-14.6)	0.436
Neutrophil (10^3/µL)	3.3 (2.2-10.3)	4.4 (1.9-9.3)	**0.001**
Lymphocyte (10^3/µL)	2.4 (1.1-4.2)	2.4 (1.8-4.2)	0.198
Platelet (10^3/µL)	261.0 (119.0-429.0)	260.0 (152.0-373.0)	0.324
NLR	1.5 (0.8-6.8)	1.6 (0.6-3.9)	0.125
PLR	105.4 (401-231.4)	107.2 (66.9-1784)	0.435

EH: Endometrial hyperplasia, BMI: Body mass index, E2: Estradiol, FSH: Follicle-stimulating hormone, LH: Luteinizing hormone, TSH: Thyroid-stimulating hormone, fT4: Free thyroxine, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, Min: Minimum, Max: Maximum

native thiol levels were significantly decreased in the EH group (p<0.001, for both). However, serum disulfide level was higher in the EH group (p<0.001). Native thiol-to-total thiol, disulfide-to-total thiol and disulfide-to-native thiol ratios were elevated in EH group (p<0.001, p<0.001, and p<0.001, respectively).

The correlation analyses between oxidative stress markers and other study parameters were separately performed in both groups. Thiol levels were inversely correlated with TSH levels in the EH group (r=-0,288, p=0.023). Disulfide levels were positively correlated with TSH and inversely correlated with FSH and LH levels (r=0.375, p<0.001; and r=-0.206, p=0.032; r=-0.194, p=0.044, respectively). Disulfide/native thiol and disulfide/total thiol ratios were also positively correlated with TSH levels (r=0.398, p=<0.001; r=0,444 p=<0.001, respectively) (Table 3).

The correlation analysis of study parameters in the control group revealed that thiol levels were positively correlated with E2 levels and inversely correlated with TSH levels (r=0.322, p=0.033; r=-0.548, p<0.001, respectively). Native thiol levels were also inversely correlated with TSH levels (r=-0.533, p<0.001). Disulfide levels were positively correlated with E2 levels, but inversely correlated with TSH levels (r=0.399, p=<0.001; r=-0.259, p=0.011 respectively), as demonstrated in Table 4.

Discussion

Revealing the relationship was focused on between serum levels of oxidative stress markers and EH status in females with AUB complaints. In brief, native and total thiol levels of endometrial washing fluids were higher in the control group. Disulfide levels, native/total thiol levels, disulfide/total thiol levels, and disulfide/native thiol ratios were higher in the EH group.

This study also examined the correlation between the biochemical data and oxidative stress markers, which found a positive relationship between rising TSH levels and oxidative stress. Previous studies, parallel to our study results, revealed low disulfide and native thiol levels in patients with subclinical

Table 2. Comparison of oxidative stress markers in endometrial hyperplasia and control groups

	EH group (n=108, 55.9%) (Median. min-max)	Control group (n=84, 44.1%) (Median. min-max)	p
Thiol (mmol/L)	465 (336-1065)	696 (449-1218)	**<0.001**
Native thiol (mmol/L)	402 (302-991)	569 (212-1056)	**<0.001**
Disulfide (mmol/L)	87.6 (13.4-133.0)	31.5 (13.0-84.5)	**<0.001**
Native thiol/total thiol	92.9 (67.3-98.4)	84.2 (47.2-98.5)	**<0.001**
Disulfide/total thiol	16.9 (2.0-30.3)	4.2 (2.0-9.9)	**<0.001**
Disulfide/native thiol	20.3 (2.2-32.6)	5.04 (2.1-17.9)	**<0.001**

EH: Endometrial hyperplasia, Min: Minimum, Max: Maximum

Table 3. Correlation analysis of oxidative stress markers in endometrial hyperplasia group (n=108)

		E2	TSH	FSH	LH	NLR	PLR
Thiol (mmol/L)	**p**	**0.003**	**0.023**	0.579	0.295	0.749	0.947
	r	0.284	-0.288	0.054	0.102	0.031	0.006
Native thiol (mmol/L)	**p**	**0.001**	0.505	0.232	0.392	0.008	0.019
	r	0.306	0.065	-0.116	-0.096	0.253	0.226
Disulfide (mmol/L)	**p**	0.671	**<0.001**	**0.032**	**0.044**	0.673	0.212
	r	0.041	0.375	-0.206	-0.194	0.041	-0.120
Native thiol/total thiol	**p**	0.192	<0.001	0.169	**0.026**	**<0.001**	**<0.001**
	r	-0.127	0.433	-0.133	-0.214	0.459	0.441
Disulfide/total thiol	**p**	0.082	**<0.001**	0.475	0.076	0.771	0.681
	r	-0.169	0.444	-0.070	-0.171	0.028	-0.041
Disulfide/native thiol	**p**	0.117	**<0.001**	0.584	0.172	0.398	0.087
	r	-0.152	0.398	-0.053	-0.132	-0.082	-0.165

E2: Estradiol, FSH: Follicle-stimulating hormone, LH: Luteinizing hormone, TSH: Thyroid-stimulating hormone, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio

Table 4. Correlation analysis of oxidative stress markers in the control group (n=84)

		E2	TSH	FSH	LH	NLR	PLR
Thiol (mmol/L)	**p**	**0.033**	**<0.001**	**0.012**	**0.008**	0.592	0.332
	r	0.322	-0,548	0.273	0.288	-0.059	0.107
Native thiol (mmol/L)	**p**	0.099	**<0.001**	0.371	0.207	0.194	0.827
	r	0.181	-0.533	0.099	0.139	-0.143	-0.024
Disulfide (mmol/L)	**p**	**<0.001**	**0.011**	**<0.001**	**<0.001**	0.101	0.697
	r	0.399	-0.259	0.410	0.347	0.186	-0.043
Native thiol/total thiol	**p**	**0.002**	0.913	**0.002**	**0.001**	0.385	0.473
	r	-0.340	0.012	-0.326	-0.351	0.099	-0.079
Disulfide/total thiol	**p**	0.063	0.488	**0.027**	0.135	**0.005**	0.876
	r	0.204	0.077	0.242	0.166	0.305	-0.017
Disulfide/native thiol	**p**	**0.021**	0.279	**0.014**	0.062	**0.042**	0.772
	r	0.257	0.119	0.268	0.206	0.223	-0.032

E2: Estradiol, FSH: Follicle-stimulating hormone, LH: Luteinizing hormone, TSH: Thyroid-stimulating hormone, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio

hypothyroidism having high TSH values[17]. An inverse correlation was also found between the serum FSH, LH, and native/total thiol levels, and our results were consistent with similar negative correlations in previous studies[18].

Serum E2 level was demonstrated to have a positive correlation with disulfide, disulfide/total thiol, and disulfide/native thiol levels. In addition, E2 was negatively correlated with native to total thiol ratios. Previous studies had different implications for the relationship of E2 to oxidative markers. A study evaluating the 17b-E2 levels and oxidative balance revealed no significant correlation[19]. A study investigating pubertal gynecomastia revealed a negative correlation between E2 and thiol-disulfide[20]. The present study revealed lower total and native thiol levels in the endometrial washing fluid of females with EH. Disulfide, disulfide/total thiol, and disulfide/native thiol ratios were found higher in the EH group. These findings indicated that females with EH were exposed to high levels of oxidative stress. A previous study stated that EH and endometrial cancer is developed due to obesity-related oxidative stress[21]. Similar findings were found in other studies in females with uterine fibroids reporting high oxidative stress levels and decreased antioxidant capacity[22].

Impaired oxidative balance was reported in other gynecological pathologies. Total thiol levels were reported to decrease total thiol levels in endometriosis pathogenesis, which was concluded to reflect the decreased antioxidant capacity[23]. Antioxidant treatments are beneficial in endometriosis and endometrioid tumor treatments. Experimental animal studies reported that thiol-containing ligand and dinitrosyl iron complexes cease endometriosis-associated endometrioid tumors[24]. Other studies revealed the relationship between oxidative stress markers and endometrial polyps. One of these studies revealed that catalase, xanthine oxidase, and malondialdehyde levels were higher in patients with endometrial polyp[25].

Study Limitations

The main strength of our study was the assessment of the oxidative status in direct tissues, as it conducted examinations of tissue washing fluids in the EH group with healthy volunteers. To the best of our knowledge, no other study has evaluated the status of oxidative stress in endometrial wash fluid in the existing literature other than our study. Direct evaluation of the tissues or oxidative balance, especially in precancerous pathological changes, will accurately illuminate the etiopathogenesis. The present study possesses several limitations.

Conclusion

The present study found that total and native thiol levels were lower in patients with EH compared to that of the control group. Disulfide, disulfide/native thiol, and disulfide/total thiol levels were higher in the EH group. The oxidative stress level was higher in the endometrial washing fluids of patients with hyperplasia. Oxidative levels of patients with EH could be compared to patients with endometrial cancer, and studies could be conducted with more patients that could be more beneficial for clinical use. Therefore, our results need further validation in larger-sized studies to develop an accurate predictive test.

Ethics

Ethics Committee Approval: The study was approved by the Erzincan Binali Yıldırım University Clinical Research Ethics Committee and conducted following the Helsinki Declaration (approval number: 33216249-604.01.02-E.24314).

Informed Consent: Informed consent was obtained from all participants at the beginning of the study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: E.Y., Design: C.T., Data Collection or Processing: Ü.G., Ö.Y.Ş., H.A., Analysis or Interpretation: E.Yılm., Literature Search: E.Yılm., Writing: E.Y.

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