Kocatepe Tıp Dergisi
Kocatepe Medical Journal
24:195-200 / Nisan 2023 Sayısı

ARAŞTIRMA YAZISI / RESEARCH ARTICLE

BENİGN, PRE-MALİGN VE MALİGN ENDOMETRİYAL LEZYONLARDA PROLİDAZ AKTİVİTESİ VE OKSİDATİF STRES

PROLIDASE ACTIVITY AND OXIDATIVE STRESS IN BENIGN, PRE-MALIGNANT AND MALIGNANT ENDOMETRIAL LESIONS

Mesut KÖSE[1], Ayhan VURMAZ[2], Yasemin ÇELİK[3]

[1]Afyonkarahisar Park Hayat Hastanesi Tüp Bebek Merkezi
[2]Afyonkarahisar Sağlık Bilimleri Üniversitesi Tıp Fakültesi, Tıbbi Biyokimya Ana Bilim Dalı
[3]Afyonkarahisar Sağlık Bilimleri Üniversitesi Sağlık Bilimleri Fakültesi Hemşirelik Bölümü

ÖZET

AMAÇ: Bu çalışmada benign, pre-malign ve malign endometrial patolojiler tanısı konan kadınlarda prolidaz aktivitesi, toplam oksidan durumu (TOS) ve toplam antioksidan durumu (TAS) araştırıldı.

GEREÇ VE YÖNTEM: Anormal uterin kanama nedeniyle endometriyal biyopsi yapılan doksan kadın histopatolojik bulgularına göre üç gruba ayrıldı: Benign endometrial patoloji (n=65), endometrial hiperplazi (n=12) ve endometrial kanser (n=13). Bu gruplar, serum ve endometriyal dokudaki oksidatif stres belirteçleri ve prolidaz aktivitesi açısından karşılaştırıldı.

BULGULAR: Benign endometrial patoloji grubu ile karşılaştırıldığında, endometrium kanserli grup anlamlı olarak daha yüksek yaş, daha kısa boy ve menopoz insidansı ve jinekolojik malignite açısından pozitif aile öyküsüne sahipti (p=0,001, p=0,023, p=0,001 ve p=0,001). Benign endometrial patoloji grubu ile karşılaştırıldığında, endometrium hiperplazisi ve endometrium kanseri gruplarında doku prolidaz aktivitesi anlamlı olarak daha yüksekti (her ikisi için p=0,001). Ancak doku prolidaz aktivitesi, endometriyal hiperplazi ve endometriyal kanser gruplarında istatistiksel olarak benzerdi (p=0,166). Tüm çalışma grupları istatistiksel olarak benzer serum prolidaz aktivitesi, serum ve doku TOS, serum ve doku TAS, doku malondialdehit ve glutatyon değerlerine sahipti.

SONUÇ: Endometriyal dokudaki prolidaz aktivitesi, benign endometrial lezyonlarla karşılaştırıldığında, pre-malign ve malign endometriyal lezyonlarda artmıştır. Endometriyal dokudaki prolidaz aktivitesinin değerlendirilmesi, histopatolojik özelliklerin endometriyal lezyonların ayırt edilmesi için yetersiz olması durumunda malign öncesi ve malign lezyonları ayırt etmeye yardımcı olabilir.

ANAHTAR KELİMELER: Biyopsi, Endometrium kanseri, Hiperplazi, Oksidatif stres, Prolidaz aktivitesi

ABSTRACT

OBJECTIVE: The present study aims to investigate the prolidase activity, total oxidant status (TOS) and total anti-oxidant status (TAS) in women who have been diagnosed with benign, pre-malignant and malignant endometrial pathologies.

MATERIAL AND METHODS: Ninety women who underwent endometrial biopsy due to abnormal uterine bleeding were divided into three groups according to their histopathological findings: Benign endometrial pathology (n=65), endometrial hyperplasia (n=12) and endometrial cancer (n=13). These groups were compared with respect to oxidative stress markers and prolidase activity in serum and endometrial tissue.

RESULTS: When compared to the benign endometrial pathology group, the endometrium cancer group had significantly higher age, shorter height and higher incidences of menopause and positive family history for gynecological malignancy (p=0.001, p=0.023, p=0.001 and p=0.001). When compared to the benign endometrial pathology group, tissue prolidase activity was significantly higher in the endometrium hyperplasia and endometrium cancer groups (p=0.001 for both). However, tissue prolidase activity was statistically similar in the endometrial hyperplasia and endometrial cancer groups (p=0.166). All study groups had statistically similar serum prolidase activity, serum and tissue TOS, serum and tissue TAS, tissue malondialdehyde and glutathione values.

CONCLUSIONS: Prolidase activity in endometrial tissue has enhanced in pre-malignant and malignant endometrial lesions when compared to benign endometrial lesions. The assessment of prolidase activity in endometrial tissue might help to distinguish pre-malignant and malignant lesions in case histopathological characteristics are insufficient for the differentiation of endometrial lesions.

KEYWORDS: Biopsy, Endometrium cancer, Hhyperplasia, Oxidative stress, Prolidase activity

Geliş Tarihi / Received:19.04.2022
Kabul Tarihi / Accepted:22.06.2022
Yazışma Adresi / Correspondence: Doç. Dr. Ayhan VURMAZ
Afyonkarahisar Sağlık Bilimleri Üniversitesi Tıp Fakültesi, Tıbbi Biyokimya Ana Bilim Dalı
E-mail: ayhan.vurmaz@gmail.com
Orcid No (Sırasıyla): 0000-0002-5840-138X, 0000-0002-1840-2900, 0000-0002-8134-3026
Etik Kurul / Ethical Committee: Afyonkarahisar Sağlık Bilimleri Üniversitesi Klinik Araştırmalar Etik Kurulu (10.09.2015/314).

INTRODUCTION

Abnormal uterine bleeding is irregular uterine bleeding that occurs in the absence of recognizable pelvic pathology, general medical disease, or pregnancy. It reflects a disruption in the normal cyclic pattern of ovulatory hormonal stimulation to the endometrial lining. Endometrial sampling could be effectively used to determine the underlying endometrial pathology and rule out endometrium cancer (1, 2). In vivo and in vitro studies report that oxidative stress is enhanced in malignant cells when compared with normal cells (3, 4). Oxidative stress can directly induce genetic alterations including DNA chain rupture, base modifications, DNA-DNA cross-linking and DNA-protein cross-linking and trigger epigenetic alterations such as DNA methylation. Both genetic alterations and epigenetic changes participate significantly in the pathogenesis of cancer (5, 6). Antioxidant defense systems such as glutathione can provide protection from the harmful effects of increased oxidative stress (7). Prolidase is a cytosolic exopeptidase which degrades iminodipeptides including C-terminal proline or hydroxyproline (8, 9). It has been shown that prolidase activity is maintained in plasma, erythrocytes, leukocytes, dermal fibroblasts, and in various organs, such as the kidneys, brain, heart, thymus, liver, and uterus (10). It is well known that prolidase activity plays an important role in collagen metabolism, matrix remodeling, and cell growth (8, 9). Moreover, tissue collagen in the microenvironment undergoes extensive degradation during carcinogenesis and a large quantity of peptides containing proline and hydroxyproline were released (11). That's why; it would be prudent to expect significantly increased prolidase activity in various malignancies (12 - 15). The present study aims to investigate the prolidase activity, total oxidant status (TOS) and total anti-oxidant status (TAS) in women who have been diagnosed with benign, pre-malignant and malignant endometrial pathologies.

MATERIALS AND METHODS

A total of 117 women who were to undergo endometrial biopsy due to abnormal uterine bleeding were eligible. Ten patients who were taking drugs that might affect collagen turnover (such as angiotensin converting enzyme inhibitors, angiotensin receptor blockers, aldosteron antagonists or statins), seven patients who had a concurrent or previous diagnosis of malignant disease, five patients with cardiac insufficiency, three patients with renal dysfunction and two patients with hepatic dysfunction were excluded. Then, the remaining 90 patients were recruited into the study.

Before endometrial biopsy was performed, venous blood samples of all participants were obtained in the morning following an overnight fast before endometrial biopsy. After the blood samples were drawn into tubes and they were immediately centrifuged at 3000 rpm for 10 min and stored at -80°C. The participants were allocated into three groups according to their endometrial biopsy findings. The first group included 65 patients with benign endometrial pathologies which were proliferative endometrium (n=32), endometrial polyp (n=20) and secretory endometrium (n=13). The second group consisted of 12 patients with endometrial hyperplasia and the third group included 13 patients with endometrium cancer. Data related with age, height, body weight, gravidity, parity, menopause, concurrent chronic diseases, previous oral contraceptive use and family history were acquired from the hospital records. Body mass index was calculated according to the following formula:

Body mass index (kg/m^2) = Body weight (kg) / Height^2 (m^2)

Measurement of prolidase activity: Prolidase activity in serum and endometrial tissue was determined by a photometric method based on the measurement of proline levels produced by prolidase (16-18). Serum and tissue Xaa-Pro dipeptidase or peptidase (PEPD) levels were studied with the kit provided by SunRed (Shanghai Sunred Biological Technology). Absorbance readings were made with a ChemWell brand (ChemWell Awareness Technology Inc. ELISA Reaer) reader. The results are given as ng/ml for serum samples and ng/g tissue for tissue samples.

Measurement of total oxidant status (TOS): Total oxidant status (TOS) levels in serum and endometrial tissue was measured using the Erel method

(19). Absorbance readings were made with a ChemWell brand (ChemWell Awareness Technology Inc. ELISA Reaer) reader. Results are given as µmol H2O2 equiv./L for serum and µmol H2O2 equiv./mg for tissue samples.

Measurement of total anti-oxidant status (TAS): Total antioxidant status (TAS) levels in serum and endometrial tissue was also measured using a novel automated measurement method developed by Erel (20). Serum and tissue TAS levels Rel Assay brand (Mega Medicine Industry and Trade Limited Company Gaziantep) worked with kits. Absorbance readings were made with a ChemWell brand (ChemWell Awareness Technology Inc. ELISA Reaer) reader. Results are given as mmol trolox equiv/L for serum and µmol Trolox Equiv./g for tissue samples.

Measurement of Tissue Reduced Glutathione and Malondialdehyde Levels: Reduced glutathione (GSH) and malondialdehyde (MDA) levels in endometrium tissue samples were studied with kits from Cayman Chemical (1180 E. Ellsworth Rd. Ann Arbor, MI.USA). Absorbance readings were made with a ChemWell brand (ChemWell Awareness Technology Inc. ELISA Reaer) reader. Results are given as nmol/g tissue for MDA levels and as nmol/g tissue for GSH.

Ethical Committe

Afyonkarahisar Health Sciences University, where this prospective study was conducted between January 2017 and June 2017, was approved by the ethics committee (10.09.2015/314). Written informed consent was obtained from all participants in accordance with the principles of the Declaration of Helsinki.

Statistical Analysis

Collected data were analyzed by Statistical Package for Social Sciences version 16.0 (SPSS IBM, Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation and categorical variables were denoted as numbers and percentages. The normality of data distribution was assessed by Smirnov-Kolmogorov test. In order to avoid type 1 error in multiple comparisons, alpha levels were adjusted using the conservative Bonferroni method. Two-tailed p values < 0.05 were accepted to be statistically significant.

RESULTS

Table 1 demonstrates the demographic and clinical characteristics of the study groups. When compared to the patients with benign endometrial pathologies, the women with endometrium cancer were significantly older and shorter (p=0.001 and p=0.023 respectively). Menopause and positive family history for gynecological malignancy were significantly more frequent in women with endometrium cancer than in women with benign endometrial pathologies (p=0.001 for both). All study groups were statistically similar with respect to body weight, BMI, parity, previous oral contraceptive use, hypertension, diabetes mellitus and other chronic diseases (p>0.05 for all).

Table1: Demographic and Clinical Characteristics of the Study Groups

	Benign endometrial pathology (p=65)	Endometrial hyperplasia (n=12)	Endometrium cancer (n=13)	p
Age (years)	45.9±11.7	46.8±11.7	63.2±11.5	0.001†↓
Height (cm)	163.1±5.4	161.1±4.5	159.1±2.7	0. 23
Body weight (kg)	71.9±11.5	74.6±11.2	73.9±6.5	0.649
Body mass index (kg/m^2)	28.25±5.54	30.75±4.16	30.0±4.1	0.217
Gravidity	5.3±1.6	4.3±1.8	4.0±1.4	0.049
Parity	2.6±1.2	3.2±1.3	3.2±0.9	0.147
Previous oral contraceptive use	6 (9.2%)	1 (8.3%)	0 (0.0%)	0.524
Menopause	7 (10.7%)	4 (33.3%)	12 (92.3%)	0.001↓
Hypertension	14 (21.5%)	4 (33.3%)	6 (46.2%)	0.160
Diabetes mellitus	15 (23.1%)	2 (16.7%)	5 (38.5%)	0.398
Other chronic diseases	7 (10.8%)	3 (25.0%)	3 (23.1%)	0.276
Family history for malignancy	0 (0.0%)	0 (0.0%)	5 (38.5%)	0.001†↓

†There was statistical significance between the benign endometrial pathology and endometrium cancer groups.

↓There was statistical significance between endometrial hyperplasia and endometrium cancer groups.

Table 2 shows the laboratory findings of the study groups. All study groups had statistically similar serum prolidase activity, serum and tissue TOS, serum and tissue TAS, tissue malondialdehyde and glutathione values.

Table 2: Laboratory Findings of the Study Groups

	Benign endometrial pathology (p=65)	Endometrial hyperplasia (n=12)	Endometrium cancer (n=13)	p
Serum prolidase activity (U/l)	17.3±16.7	15.1±4.6	27.5±25.6	0.443
Tissue prolidase activity (U/g)	142.5±29.2	276.1±50.4	287.2±24.2	0.001‡†
Serum total oxidant status (µmolH_2O_2 equiv./L)	32.1±19.9	32.4±15.8	28.7±16.6	0.825
Tissue total oxidant status (µmolH_2O_2 equiv./mg)	173.2±108.3	141.1±40.1	129.0±82.0	0.376
Serum total anti-oxidant status (mmol Trolox equiv./L)	1.25±0.51	1.05±0.59	1.22±0.49	0.462
Tissue total anti-oxidant status(mmol Trolox equiv./mg)	4.48±4.16	3.69±3.64	3.86±3.33	0.913
Tissue malondialdehyde (nmol/g)	90.3±79.8	89.6±58.8	137.7±128.7	0.190
Tissue glutathione (nmol/mg)	198.0±162.6	152.5±111.9	206.0±153.2	0.617

†There was statistical significance between the benign endometrial pathology and endometrium cancer groups.

‡There was statistical significance between the benign endometrial pathology and endometrial hyperplasia groups.

Tissue prolidase activity was significantly higher in the endometrium hyperplasia and endometrium cancer groups than the benign endometrial pathology group (p=0.001 for both). However, tissue prolidase activity was statistically similar in the endometrial hyperplasia and endometrial cancer groups (p=0.166) **(Figure 1)**.

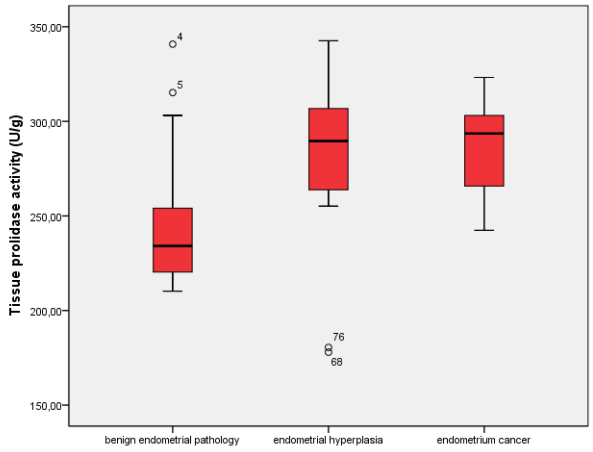

Figure 1: Tissue prolidase activity in the benign endometrial pathology, endometrial hyperplasia and endometrium cancer groups

DISCUSSION

As a soft tissue tumor invades the neighboring areas, natural barriers such as basement membrane and interstitial tissue should undergo degradation. Therefore, it has been hypothesized that these natural barriers are overcome by the proteolytic enzymes synthesized by the soft tissue tumor. Metalloproteinases are one of the most important enzymes for the destruction of extracellular matrix proteins. As their name implies, these enzymes need calcium and zinc ions for their activity (21).

Prolidase acts primarily in the collagen turnover and extracellular matrix remodeling by generating proline from dipeptides for collagen synthesis and breaking down the collagen degradation products. It has been suggested that prolidase activity may be a step-limiting factor in collagen biosynthesis (9). Jussila et al. observed that collagen synthesis was significantly enhanced and collagen maturation was significantly accelerated in fibroblasts located within well-differentiated endometrial adenocarcinomas. Additionally, newly synthesized type 1 and type 3 procollagens were significantly increased in extracellular matrix found in endometrial adenocarcinomas. These findings were interpreted as an evidence for the local invasion of an endometrial tumor which triggers the degradation of extracellular matrix. Increased collagen synthesis was also attributed to the fibroproliferative response of the surrounding uterine tissues which attempt to limit the growth of an endometrial tumor (22).

In case of endometrium cancer, it could be expected that prolidase activity would be increased due to the enhancement in collagen synthesis, collagen turnover or both. Accordingly, serum prolidase activity was found to be significantly elevated in patients with stage 1 endometrium cancer than healthy controls (23). However, this study failed to detect any significant change in serum prolidase activity of endometrium cancer patients when compared to patients with benign endometrial pathologies and endometrial hyperplasia. Such discrepancy may be due to the relatively small study cohort and variations in techniques adopted for the measurement of serum prolidase activity. On the other hand, the patients with endometrium cancer were found to have significantly increased prolidase activity within endometrium in this study. The concurrence of enhanced endometrial prolidase activity and unaltered serum prolidase activity might suggest that the increase in prolidase activity has been confined to the endometrium and this increase was not sufficient enough to cause a significant change in peripheral circulation.

Another explanation might be the regulation of prolidase activity by the interaction of extracellular proteins in normal fibroblasts. That is, prolidase activity is mainly regulated by β1-integrin-dependent signaling pathway which allows type 1 collagen to interact with β1-integrin receptor (13, 24). It has been shown that transcriptional activity of β1 integrin gene is significantly reduced in endometrial adenocarcinoma while transcriptional activity of β1 integrin gene is significantly increased in endometrial hyperplasia. A decrease in β1 integrin expression may cause an augmentation in prolidase activity (25, 26). Previously published studies have concluded that the activation in oxidative stress

mechanisms such as lipid peroxidation and the attenuation in anti-oxidant defense molecules such as glutathione are associated with carcinogenesis. The disruption in oxidant-antioxidant balance system has also been specified in cervical, endometrial and ovarian cancers. It has been suggested that weakened activity of antioxidant enzymes in gynecological tumors could be a result of the disturbance in oxidant-antioxidant balance system whereas augmentation in lipid peroxidation seems to be a consequence of gynecological tumors rather than being their cause (27 - 30). On the contrary, the present study was unable to detect significantly altered TOS and TAS levels in serum and endometrial tissue as well as significant changes in malondialdehyde and glutathione concentrations of endometrial tissue. These contradictory results might be attributed to the characteristics of the study cohort such as relatively small cohort size, relatively small number of patients with endometrial cancer and the existence of early stage endometrial cancer in recruited patients. The heterogeneity in the amounts of acquired endometrial tissue specimens and the variations in the techniques utilized for the measurement of oxidant and anti-oxidant molecules might have also caused the inadequacy to detect significant alterations in laboratory data.

This study points out that prolidase activity in endometrial tissue has been enhanced in pre-malignant and malignant endometrial lesions when compared to benign endometrial lesions. The assessment of prolidase activity in endometrial tissue might help to distinguish pre-malignant and malignant lesions in case histopathological characteristics are insufficient for the differentiation of endometrial lesions.

Relatively small study cohort, relatively small number of patients with endometrial and hyperplasia as well as lack of blinding for the biochemists limit the power of this study. Further research is required to clarify how prolidase activity in serum and endometrial tissue is altered in benign, pre-malignant and malignant endometrial lesions.

REFERENCES

1. Matthews ML. Abnormal uterine bleeding in reproductive-aged women. Obstet Gynecol Clin North. 2015;42(1): 103-15.

2. Singh S, Best C, Dunn S, Leyland N, Wolfman WL; Clinical Practice – Gynaecology Committee. Abnormal uterine bleeding in pre-menopausal women. J Obstet Gynaecol. 2013;35(5):473-5.

3. Kawanishi S, Hiraku Y, Pinlaor S, Ma N. Oxidative and nitrative DNA damage in animals and patients with inflammatory diseases in relation to inflammation-related carcinogenesis. Biol Chem. 2006;387(4):365–72.

4. Martinez-Outschoorn UE, Balliet RM, Lin Z, Whitaker-Menezes D, Howell A et al. Hereditary ovarian cancer and two-compartment tumor metabolism: epithelial loss of BRCA1 induces hydrogen peroxide production, driving oxidative stress and NFκB activation in the tumorstroma. Cell Cycle. 2012;11(22):4152-66.

5. Federico A, Morgillo F, Tuccillo C, Ciardiello F, Loguercio C. Chronic inflammation and oxidative stress in human carcinogenesis. Int J Cancer. 2007;121(11):2381–6.

6. Ziech D, Franco R, Pappa A, Panayiotidis M. I. Reactive Oxygen Species (ROS)-Induced genetic and epigenetic alterations in human carcinogenesis. Mutat Res. 2011;711(1-2):167–73.

7. Comini MA. Measurement and meaning of cellular thiol:disufhide redox status. Free Radic Res. 2016;50(2):246-71.

8. Zareba I, Palka J. Prolidase-proline dehydrogenase/proline oxidase-collagen biosynthesis axis as a potential interface of apoptosis/autophagy. Biofactors. 2016;42(4):341-8.

9. Surazynski A, Miltyk W, Palka J, Phang JM. Prolidase-dependent regulation of collagen biosynthesis. Amino Acids. 2008;35(4):731–8.

10. Yildiz A, Demirbag R, Yilmaz R, Gur M, Altiparmak IH, Akyol S. The association of serum prolidase activity with the presence and severity of coronary artery disease. Coronary Artery Dis. 2008;19(5):319–25.

11. Surazynski A, Donald SP, Cooper SK, Whiteside MA, Salnikow K, Liu Y, et al. Extracellular matrix and HIF-1 signaling: the role of prolidase. Int J Cancer. 2008;122(6):1435–40.

12. Palka J, Surazynski A, Karna E, Orlowski K, Puchalski Z, Pruszynski K, et al. Prolidase activity disregulation in chronic pancreatitis and pancreatic cancer. Hepatogastroenterology. 2002;49(48):1699–703.

13. Cechowska-Pasko M, Pakła J, Wojtukiewicz MZ. Enhanced prolidase activity and decreased collagen content in breast cancer tissue. Int J Exp Pathol. 2006;87(4):289–96.

14. Guszczyn T, Sobolewski K. Deregulation of collagen metabolism in human stomach cancer. Pathobiology. 2004;71(6):308–13.

15. Karna E, Surazynski A, Palka J. Collagen metabolism disturbances are accompanied by an increase in prolidase activity in lung carcinoma planoepitheliale. Int J Exp Pathol. 2000;81(5):341–7.

16. Kayadibi H, Gültepe M, Yasar B, Ince AT, Ozcan O, Ipcioglu OM, et al. Diagnostic value of serum prolidase enzyme activity to predict the liver histological lesions in non-alcoholic fatty liver disease: a surrogate marker to distinguish steatohepatitis from simple steatosis. Dig Dis Sci. 2009;54(8):1764-71.

17. Myara I, Charpentier C, Lemonnier A. Optimal conditions for prolidase assay by proline colorimetric determination: application to imidodipeptiduria. Clinica Chimica Acta. 1982;125(2):193 – 205.

18. Chinard FP. Photometric estimation of proline and ornithine. J Biol Chem. 1952;199(1):91–5.

19. Erel O. A new automated colorimetric method for measuring total oxidant status. Clin Biochem. 2005;38(12):1103–11.

20. Erel O. A novel automated method to measure total antioxidant response against potent free radical reactions. Clin Biochem. 2004;37(2):112–9.

21. Camuzcuoglu H, Arioz DT, Toy H, Kurt S, Celik H, Aksoy N. Assessment of preoperative serum prolidase activity in epithelial ovarian cancer. Eur J Obstet Gynecol Reprod Biol. 2009;147(1):97-100.

22. Jussila T, Kauppila S, Bode M, Tapanainen J, Risteli J, Risteli L et al. Synthesis and maturation of type I and type III collagens in endometrial adenocarcinoma. Eur J Obstet Gynecol Reprod Biol. 2004;115(1):66-74.

23. Arioz DT, Camuzcuoglu H, Toy H, Kurt S, Celik H, Aksoy N. Serum prolidase activity in patients with stage I endometrial cancer. Int J Gynecol Cancer. 2009;19(7):1244-7.

24. Surazynski A, Sienkiewicz P, Wolczynski S, Palka J. Differential effects of echistatin and thrombin on collagen production and prolidase activity in human dermal fibroblasts and their possible implication in beta1-integrin mediated signaling. Pharmacol Res. 2005;51(3):217–21.

25. Wójcik-Krowiranda K, Forma E, Zaczek A, Bryś M, Anna MK, Bieńkiewicz A. Expression of E-cadherin and beta1-integrin mRNA in endometrial cancer. Ginekol Pol. 2013;84(11):910-4.

26. Moro L, Greco M, Maiorano E, Selvaggi L, Marra E, Perlino E. Transcriptional regulation of beta1 integrin expression in the physio/pathological states of human endometrial tissues. Int J Oncol. 2005;26(2):457-65.

27. Manoharan S, Kolanjiappan K, Kayalvizhi M. Enhanced lipid peroxidation and impaired enzymic antioxidant activities in the erythrocytes of patients with cervical carcinoma. Cell Mol Biol Lett. 2004;9(4A):699-707.

28. Pejić S, Kasapović J, Todorović A, Stojiljković V, Pajović SB. Lipid peroxidation and antioxidant status in blood of patients with uterine myoma, endometrial polypus, hyperplastic and malignant endometrium. Biol Res. 2006;39(4):619-29.

29. Camuzcuoglu H, Arioz DT, Toy H, Kurt S, Celik H, Erel O. Serum paraoxonase and arylesterase activities in patients with epithelial ovarian cancer. Gynecol Oncol. 2009;112(3):481-5.

30. Vural M, Camuzcuoglu H, Toy H, Camuzcuoglu A, Aksoy N. Oxidative stress and prolidase activity in women with uterine fibroids. J Obstet Gynaecol. 2012;32(1):68-72.