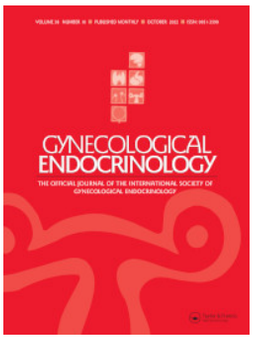

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RESEARCH ARTICLE
ENDOMETRIOSIS

The role of cytokeratin 19 levels in the determination of endometriosis stages

Caglar Yildiz[a], Armagan Caner[b], Bugra Oksasoglu[c], Sema Misir[d], İlhan Yaylim[e] and Ceylan Hepokur[e]

[a]Department of Gynecology and Obstetrics, Medical Faculty of Sivas Cumhuriyet University, Sivas, Turkey; [b]Faculty of Medicine, Department of Biophysics, Erciyes University, Kayseri, Turkey; [c]Clinic of Obstetrics and Gynecology, Sarkisla Public Hospital, Sivas, Turkey; [d]Department of Biochemistry, Faculty of Pharmacy, Sivas Cumhuriyet University, Sivas, Turkey; [e]The Institute of Experimental Medicine, Department of Molecular Medicine, Istanbul University, Istanbul, Turkey

ABSTRACT

Objective/Aim: Endometrisosis, one of the most common gynecological disease, is characterized by the presence of endometriotic tissue outside of uterine cavity. The development and the validation of a simple blood biomarker specific and sensitive for endometriosis may facilitate the rapid and the accurate diagnosis of the disease and thus early treatment. Cytokeratin expression changes during epithelial differentiation and this expression is important for the modulation and the control of cell cycle regulation, tumor cell motility and apoptosis. Cytokeratin 19 (CK-19) is expressed in most simple epithelial cells and their malignant counterparts. The aim of this study is to investigate serum CK-19 expression levels in patients with endometriosis and to determine the diagnostic role of CK-19 levels in differentiating various stage of endometriosis.

Methods: Ctytokeratin-19 expression and level were studied in 70 endometriosis patients and 50 volunteers by ELISA and RT-PCR. ROC analysis was performed by comparing all stages with each other and with the control group.

Results: The CK-19 levels were significantly higher in the endometriosis groups than that of the control group by ELISA and RT-PCR. A significant ($p < .05$) difference was observed in endometriosis patients according to the stages.

Conclusion: Based on our data, it suggests that Cytokeratin-19 may have a potential role in the development of endometriosis.

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Endometriosis; biomarker; noninvasive diagnosis; cytokeratin 19; RT-PCR

Introduction

Endometrisosis, one of the most common gynecological disease, is characterized by the presence of endometriotic tissue outside of uterine cavity [1,2]. The disease affects approximately 10% of the women in the reproductive age and the prevalence is between 20 to 50% in infertile women [3,4]. Although the prevalence of the disease is high, the diagnosis is often delayed due to its complex pathogenesis and variable symptomatology [5–7]. Inability to diagnose the disease in its early stages is one of the leading causes of treatment failure. The main diagnostic tool for endometriosis is histopathological examination and laparoscopy is the most common surgical method for tissue sampling. To minimize the number of the laparoscopic surgery, there is a huge need to establish a reliable noninvasive diagnostic method for the disease. The development and the validation of a simple blood biomarker specific and sensitive for endometriosis may facilitate the rapid and the accurate diagnosis of the disease and thus early treatment. As serum biomarkers are measured easily and simply, the serum levels of specific cytokeratin 19 can be used for endometriosis diagnosis.

Cytokeratins are expressed by all epithelial cells. Cytokeratin expression changes during epithelial differentiation and this expression is important for the modulation and the control of cell cycle regulation, tumor cell motility and apoptosis [8]. Cytocreatin 19 (CK-19) is expressed in most simple epithelial cells and their malignant counterparts. Cyfra 21-1, a CK-19 fragment which has 311-335 and 346-367 epitope series, is secreted to the serum from the cells that are proliferating during late S and G2 phases [9]. Cyfra 21-1 is considered to be a promising biomarker for many cancer types because of its differential expression in normal and malignant epithelium [10,11].

The aim of this study is to investigate serum CK-19 expression levels in patients with endometriosis and to determine the diagnostic role of CK-19 levels in differentiating various stage of endometriosis.

Materials and method

Patients and preparation of samples

In this study, all volunteer patients who were operated or examined in the Gynecology and Obstetrics Clinic of Sivas Cumhuriyet University Faculty of Medicine and who were diagnosed with endometriosis as a result of histopathological of the biopsy material taken with the pre-diagnosis of endometriosis were included in the study. Patients with concomitant malignancies and chronic inflammatory diseases were excluded. The control group comprised fifty volunteers who have undergone surgery for benign reasons, have no endometriosis or any other systemic disease

CONTACT Ceylan Hepokur cozsoya@gmail.com Department of Biochemistry, Faculty of Pharmacy, Sivas Cumhuriyet University, Sivas, 58140, Turkey.

and have a similar age distribution with patient group. The participants of the study and the control groups were between 15 and 45 ages (reproductive period).

The study was performed in accordance with the tenets of the Helsinki Declaration. The Ethics Committee of Sivas Cumhuriyet University, School of Medicine approved the study (Decision number 2019-03/34).

A total of 5 cc of blood were taken from the patients and the controls. After the blood samples were centrifuged at 4000 rpm for 10 min, the serum samples obtained were taken into eppendorf tubes and stored at −80 °C until the relevant parameters are studied.

Measurement of cancer antigen 125 (CA-125)

Serum CA-125 levels, serum marker for endometriosis in clinical practice, were analyzed with Roche Cobas e802 autoanalyzer, USA.

Sitokeratin-19 studies by RT-PCR

The total RNA was extracted from whole blood collected by using the RNA Isolation Kit (GeneAll, Cat no:106-101) according to the manufacturer's recommendations. cDNA synthesis using a HyperScript cDNA synthesis kit (GeneAll Cat no: 601-710), according to manufacturer's protocols. Reaction mixtures were incubated at 25 °C, 10 min; 55 °C, 60 min; and 85 °C, 5 min. cDNAs were measured using a qubit ssDNA Assay Kit (Molecular probes, Life Technologies).

qRT-PCR was performed using REALAMP SYBR Green Master Mix (HIGH ROX DYE) (Cat no:801-051), according to manufacturer's protocols. About 20 ml PCR reaction included 4 µL RT product, 1 µL (10 pm) forward primer, 1 µL (10 pm) reverse primer, 1 µL ROX, 3 µL steril water, and 10 µL (2X) SYBR master mix. The following primers were used: CK-19 forward primer 5′-GACTACAGCCACTACTACACGA-3′, CK-19 revers primer 5′- GAATCCACCTCCACACTGAC-3′; GAPDH-forward primer 5′- GTCAAGGCTGAGAACGGGAA-3′, GAPDH-revers primer 5′-AAATGAGCCCCAGCCTTCTC −3′. CK-19 expression levels were normalized to the amount of GAPDH in the same sample. The PCR reaction mixtures were incubated in at 95 °C for 10 min, followed by 40 cycles of 95 °C for 15 s and 60 °C for 40 s. Relative increases in mRNA expression were processed using the 2-ΔΔCp Ct method [12].

Determination of sitokeratin-19 levels by ELISA

Serum CK-19 levels were determined by Enzyme-linked immunosorbent assay (ELISA method) by applying ready-made commercial kit (Elabscience Cat No: E-EL-H2075).

Statistical analysis

Kolmogorov–Smirnov test was used to test compatibility with normal distribution. All statistical analysis was performed by SPSS 22.0, and significant difference was set at $p < .05$ [($\alpha = 0.05$, $\beta = 0.10$, $(1-\beta) = 0.90$ (R:Sample Allection Ratio:1,7) $p = .90064$].

ROC analysis

Receiver operating characteristic (ROC) analysis was performed to determine the specifity and sensitivity of CK-19. Statistical significant difference was set at $p < .05$.

Table 1. The clinical characteristics of participants collected for the study of serum CK-19.

		Endometriosis	Control	*p*-value
	(years, mean ± SD)	39.63 ± 9.826	37.96 ± 12.7	.419
Ages		Endometriosis (N, %)	Control (N, %)	*p*-value
Family history of endometriosis	No Family History	57 (81.4)	47 (94)	.086
	First degree relative	13 (18.6)	3 (6)	
Infertility	Yes	15 (21.4)	8 (16)	.456
	No	55 (78.6)	42 (84)	
Infertility type	Primary	15 (100)	7 (87.5)	.161
	Secondary	0 (0)	1 (12.5)	
Dysmenorrhea symptoms	Yes	52 (74.3)	28 (56)	.001*
	No	18 (25.7)	22 (44)	
Dyspareunia symptoms	Yes	34 (48.6)	13 (26)	.013*
	No	36 (51.4.)	37 (74)	
Cronic pelvic pain	Yes	34 (48.6)	14 (28)	.023*
	No	36 (51.4)	36 (72)	
Ca-125 levels	Normal	29 (41.4)	40 (80)	.001*
	High	41 (58.6)	10 (20)	

N; number, ($p < .05$), compared to control group.

Table 2. Endometriosis stages after laparoscopy and laparotomy in the study groups.

		Endometriosis (N, %)
Diagnosis	Primary Diagnosis	47 (67.1)
	Incidental	23 (32.8)
All Endometriosis Stages	Stage 1	38 (54.3)
	Stage 2	11 (15.7)
	Stage 3	10 (14.3)
	Stage 4	11 (15.7)
Presence of Endometrioma	Yes	53 (75.7)
	No	17 (24.3)
Surgery	Laparotomy	53 (75.7)
	Laparoscopy	17 (24.3)

N; number.
Serum CK-19 levels of the patient and the control groups were measured with ELISA assay.

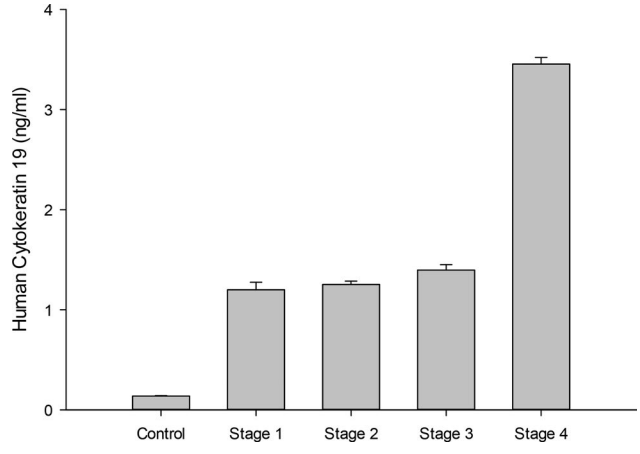

Figure 1. Cytokeratin 19 levels of the patient and the control groups.

Result

The clinical characteristics of the participants are shown in Table 1. Endometriosis stages after laparoscopy and laparotomy in the study groups are shown in Table 2. As expected, dysmenorrhea and dyspareunia symptoms were more common in the patient group. In terms of the infertility type, primary

infertility was more common and secondary infertility was less common in the endometriosis group. Also, chronic pelvic pain was more common in the patients with endometriosis than the control group, the difference reached statistical significance (Table 1).

Serum CK-19 levels were 0.1382 ± 4.5000e-3 in the control group, 1.1991 ± 0.0760 in the stage 1, 1.2522 ± 0.0340 in the stage 2, 1.3964 ± 0.0540 in the stage 3, and 3.4547 ± 0.0650 in the stage 4 endometriosis groups (Figure 1). The CK-19 levels were significantly higher in the endometriosis groups than that of the control group (Figure 2).

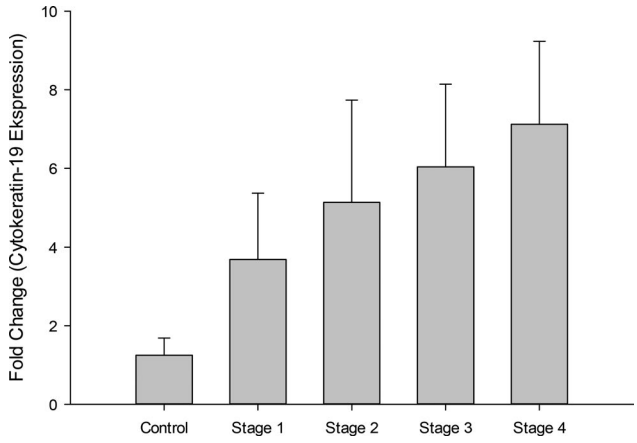

Figure 2. CK-19 level fold change in the patient and the control groups.

CK-19 level fold change was 1.2482 ± 0.4400 in the control group, 3.6832 ± 1.6818 in stage 1, 5.1322 ± 2.6000 in stage 2, 6.0350 ± 2.1025 in stage 3 and 7.1188 ± 2.1102 in the stage 4 endometriosis groups. ROC analysis results are shown in Figures 3 and 4.

ROC analysis showed that AUC was 0.922 between the control and the stage 1 endometriosis groups ($p < .001$), 0.982 between the control and the stage 2 endometriosis groups ($p < .003$); 1.000 between the control and the stage 3 endrometriosis groups ($p < .003$); 1,000 between the control and the stage 3 endrometriosis groups ($p < .003$). The differences between the control groups and the endometriosis groups were statistically significant (Table 3).

When the endometriosis stages groups were compared to each other using ROC analysis, the AUC was 1,000 between the stage 1 and the stage 2 ($p < .009$), 0.644 between the stage 1 and the stage 3 ($p < .175$), 0.813 between the stage 1 and the stage 4 ($p < .006$), 0.626 between the stage 2 and the stage 3 ($p < .342$), 0.904 between the stage 2 and the stage 4 ($p < .005$), and 0.333 between the stage 3 and the stage 4 ($p < .317$) endometriosis groups. The differences between the stage 1 and the stage 2, the stage 1 and the stage 4 and the stage 2 and the stage 4 were statistically significant.

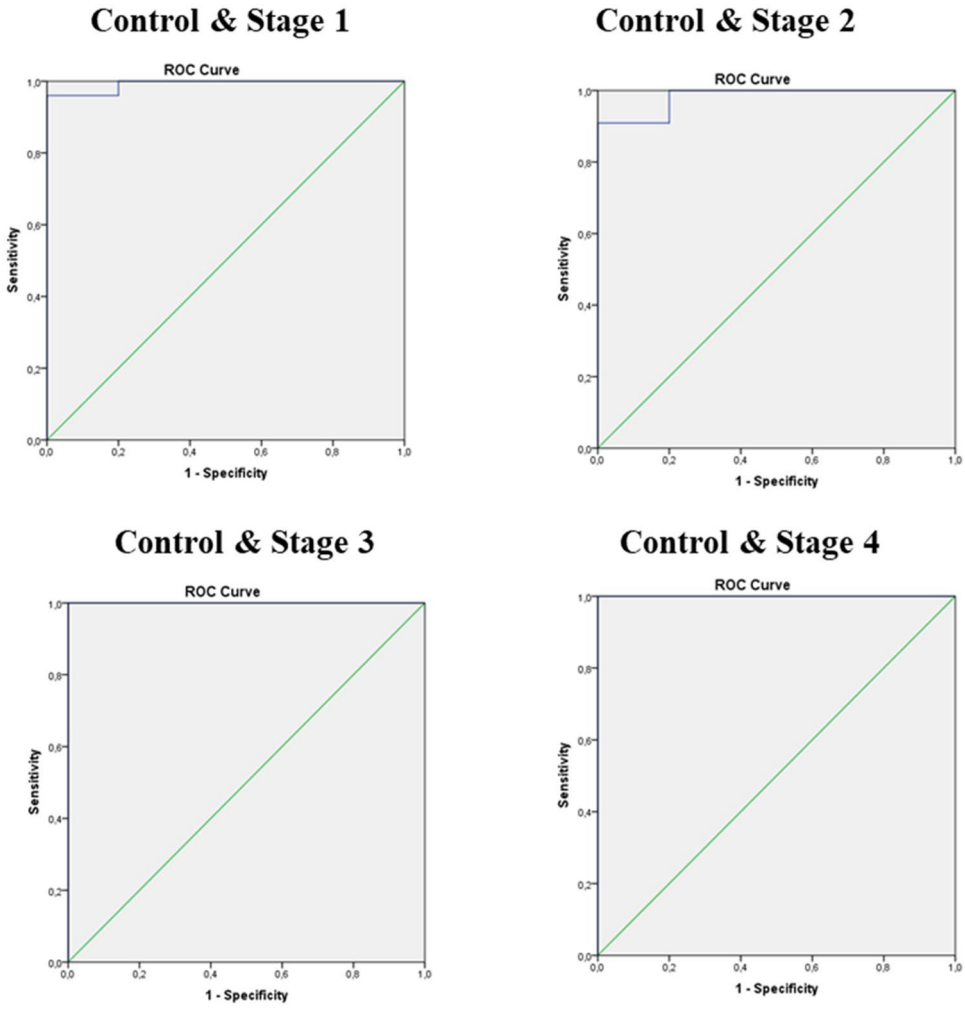

Figure 3. ROC curves analysis of expression levels of CK-19 for all endometriosis stages.

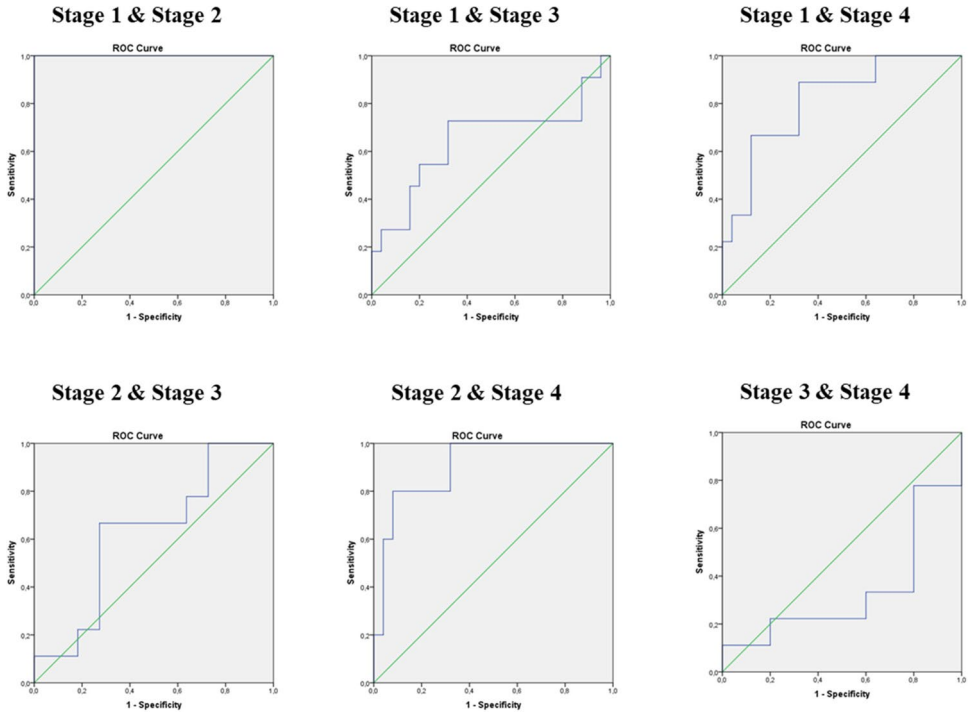

Figure 4. ROC curves analysis of expression levels of CK-19 for different endometriosis stages.

Table 3. ROC curves analysis of CK-19 in endometriosis.

	AUC	Cut-off (<value)	Sensitivity (%)	Specificity (%)	*p* value
Control & Stage 1	0.992	1.721	96	80	$p < .001$
Control & Stage 2	0.982	1.732	90	80	$p < .003$
Control & Stage 3	1.000	3.407	88	99	$p < .003$
Control & Stage 4	1.000	5.518	80	99	$p < .003$
Stage 1 & Stage 2	1.000	3.957	72	68	$p < .009$
Stage 1& Stage 3	0.644	3.952	88	68	$p < .175$
Stage 1 & Stage 4	0.813	6.578	80	92	$p < .006$
Stage 2 & Stage 3	0.626	6.159	80	73	$p < .342$
Stage 2 & Stage 4	0.904	5.772	66	73	$p < .005$
Stage 3 & Stage 4	0.333	6.858	30	40	$p < .317$

ROC; receiver operating characteristic, AUC; Area under the ROC Curve.

Discussion

In this study, we investigated serum CK-19 expression levels in patients with all stages of endometriosis and we showed that serum CK-19 levels can serve as a diagnostic biomarker for endometriosis. Our results indicate that serum CK-19 levels are increased in patients with endometriosis. In addition, ROC analysis revealed that CK-19 levels can be used for endometriosis diagnosis with high sensitivity and specificity.

Cytokeratins are intermediate filaments forming cell skeleton and divided into subtypes according to their molecular weights [13]. Generally, low molecular weight cytokeratins belong to simple and glandular epithelium, whereas high molecular weight cytokeratins belong to multilayered and epidermal epithelium [14]. The lowest molecular weight cytokeratin, CK-19 has a molecular weight of 40 kDa and it is present in simple epithelial cells. In complex and multilayered epithelial cells, it could be present in only basal layer [15]. Because carcinoma cells maintain cytokeratin profiles in epithelium they originated from, analysis of cytokeratin type in metastatic foci could serve for primary malignant site detection [16–19]. In some instances, cytokeratin profiles can change during carcinogenesis, new cytokeratin types can be synthesized or existent cytokeratins can be expressed more intensely; these are associated with neoplasm type and malignancy stage [20]. Therefore, cytokeratins have been tried to be used for both primary site detection in metastatic carcinomas and benign and malignant tumor differentiation in primary sites [21,22]. Focal and week CK-19 presence was shown in various benign thyroid lesions and normal thyroid tissue. It has been reported that malignant transformation is associated with a diffuse and severe CK-19 expression and this can be used to differentiate benign lesions from malignant ones, especially in diagnosis of papillary thyroid carcinoma [23–25].

Endometriosis is a benign, chronic inflammatory and estrogen-dependent disease [1,2]. Therefore, most of the proposed endometriosis biomarkers are glycoproteins, hormones, growth and adhesion factors and proteins involved in immunology and angiogenesis [26–29]. The most known and widely used blood biomarker is CA125 [28,30]. Some authors have reported that serum CA125 level is significantly correlated with disease severity in especially ovarian endometrioma and thus it is an useful biomarker for endometriosis diagnosis [28,31,32]. However, CA125 is not specific for endometriosis and its serum levels can be elevated in ovarian cancer and many other benign diseases such as uterine fibroids, adenomyosis and pelvic

inflammatory disease [33]. Moreover, CA125 has a low sensitivity for early stage endometriosis [13].

To date, many studies have been performed to determine blood or urine biomarkers for diagnosis or exclusion of endometriosis [27,28]. A reliable, noninvasive diagnostic test is needed to minimize the number of diagnostic laparoscopic procedures. The development of a simple blood test specific for endometriosis providing rapid and accurate diagnosis could facilitate early therapeutic intervention. The role of CK-19 in endometriosis has not been understood yet. CK-19 can be detected in endometrium endothelium and endometriotic tissue in women with and without endometriosis [34]. Tokushige *et al.* [35] reported that urine CK-19 level was different between the endometriosis and the control groups. Lessey *et al.* [36] showed that urine CYFRA 21-1 levels have a limited clinical value as a diagnostic biomarker for endometriosis.

Although the results of our study are promising, there are some limitations. First of all, the endometriosis and the control groups in our study are small to determine the diagnostic performance of the serum biomarkers. Future studies with higher participant numbers and homogeneously distributed patients across endometriosis stage groups are warranted.

Conclusion

In conclusion, CK-19 protein expression and CK-19 serum levels can serve as a diagnostic biomarker for endometriosis. Also, it can be used to determine disease severity. More studies are needed.

Author contributions

Authors contributed to the manuscript equally. All authors read and approved the final version of this manuscript.

Disclosure statement

The authors declare no conflict of interest in regard to this study.

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ORCID

Sema Misir http://orcid.org/0000-0002-5919-3295
Ilhan Yaylim http://orcid.org/0000-0003-2615-0202
Ceylan Hepokur http://orcid.org/0000-0001-6397-1291

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