Relation of red cell distribution width to the presence and severity of endometriosis

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Summary

Aim: Although the exact pathogenesis of endometriosis is not known, it is proposed to be a chronic inflammatory disease. The association between red cell distribution width (RDW) and inflammation is well established. Therefore, in the present study, the authors aimed to investigate the association between presence and severity of endometriosis and RDW. *Materials and Methods:* Fifty endometriosis patients and 48 controls were included in the study. The endometriosis group was categorized in two subgroups as mild-to-moderate (n=35) and moderate-to-severe disease (n=15). CA-125 and RDW values of all participants were measured. *Results:* Both RDW (17.7 ± 2.2 vs 14.9 ± 1.5, $p < 0.001$) and CA-125 (50.6 ± 35.1 vs 27.9 ± 4.8) levels were significantly higher in the endometriosis patients when compared to the control group. Moreover the authors found a significant positive correlation between RDW and CA-125 levels (r: 0.495, $p < 0.001$). *Conclusion:* The present study results demonstrated that RDW levels were significantly increased in endometriosis patients and associated with the severity of endometriosis.

Key words: Red cell distribution width; Endometriosis.

Introduction

Endometriosis is classically defined as the extrauterine proliferation of endometrial tissue. It is a common benign gynecologic disease seen in 10% of women at reproductive age which is also observed in 35-50% of infertility patients [1, 2]. Despite the advances in imaging and biomarker technologies, endometriosis is still diagnosed via surgical exploration and histological examination [3]. Although there is no reliable non-invasive test, CA-125 is the most commonly preferred marker [4]. CA-125 is elevated in advanced endometriosis; however, it has a low sensitivity for minimal and mild endometriosis [5]. Although the exact etiopathogenesis of endometriosis is not known, it is regarded as a chronic inflammatory disease [6]. Studies have shown elevated inflammatory markers in the serum and peritoneal fluid of endometriosis patients [7].

Red cell distribution width (RDW) is a hematologic parameter indicating variations in erythrocyte volume. Recently, it has been shown to have a prognostic value in acute and chronic cardiac cases and healthy individuals [8-10]. There appears to be a relationship between chronic inflammation and elevated RDW, although the underlying association is not fully known [11]. In the present study, the authors aimed to investigate the association between endometriosis and RDW.

Materials and Methods

The study population consisted of 98 patients who underwent surgical exploration for primary infertility between February 2010 and December 2012. Out of these, 50 patients were diagnosed with endometriosis by histopathological examination and 48 healthy individuals without endometriosis or other pathology in the laparoscopy were enrolled as the control group. The patients with a history of an operation within the past six months as well as those with hormonal therapy, anemia, or systemic disease (eg, diabetes or hypertension), inflammatory diseases, kidney disorders, and signs of other concurrent medical complications were excluded from the study. The endometriosis group was classified according to the *American Society of Reproductive Medicine* as follows: minimal-to-mild disease (Stage 1-2; n=35) and moderate-to-severe disease (Stage 3-4; n=15) [12]. This study was approved by the local ethics committee and informed consents were obtained from all participants.

All participants underwent blood collection before surgical exploration via antecubital vein puncture. Hemoglobin (Hb), RDW and white blood cell count, and other hematological indices were measured as part of the automated complete blood count (CBC) using a LH 780 hematology analyzer. CA-125 was measured by using electrochemiluminescence immunoassay (ECLIA) and cut off values of CA125 were determined as 35 U/ml.

Statistics

Continuous variables are expressed as mean ±SD. Categorical variables are expressed as percentages. To compare parametric continuous variables, the Student's t test was used; to compare nonparametric continuous variables, the Mann-Whitney U was used. To compare categorical variables, the chi-square test was used. To assess differences in RDW and CA125 in between the control group, mild to moderate and moderate to severe endometriosis groups, analysis of variance (ANOVA) and Tukey's Honestly Significant Difference (HSD) as a post hoc test were used. Two-tailed p values < 0.05 were considered to indicate statistical significance. Correlation analyses between variables were performed using Pearson or Spearman correlation. Statistical analyses were performed using SPSS, version 15.0 for Windows.

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Table 1. — *Main clinical and laboratory characteristics of the patient and control groups.*

	Endometriosis (n:50)	Control group (n:48)	*p* value
Age (years)	33±3.7	32±3.3	0.386
Infertility duration	3.8±0.7	3.7±0.8	0.606
RDW,%	17.7±2.2	14.9±1.5	<0.001
Ca-125	50.6±35.1	27.9±4.8	0.004
Hemoglobin (g/dl)	11.2±1.5	11.6±1.6	0.176
Platelet (x10^3 µl)	269±86	264±78	0.907
WBC (x10^3 µl)	8.5±1.9	8.2±1.9	0.377

RDW: red cell distribution width; WBC: white blood cell.

Table 2. — *Main clinical and laboratory characteristics of the endometriosis subgroups and controls.*

	Stage 1-2 (n:35)	Stage 3-4 (n:15)	Control (n:48)	*p* value
Age (years)	33±4	32±2.9	32±3.3	0.514
Infertility duration	3.7±0.8	3.9±0.4	3.7±0.8	0.512
RDW,%	17.2±2.1	19±2	14.9±1.5	<0.001
Ca-125	28.2±5.5	103±6.9	27.9±4.8	<0.001
Hemoglobin (g/dl)	11.2±1.5	11.2±1.4	11.6±1.6	0.403
Platelet (x10^3 µl)	260±79	289±101	264±78	0.509
WBC (x10^3 µl)	8.4±1.6	8.8±2.4	8.2±1.9	0.482

RDW: red cell distribution width; WBC: white blood cell.

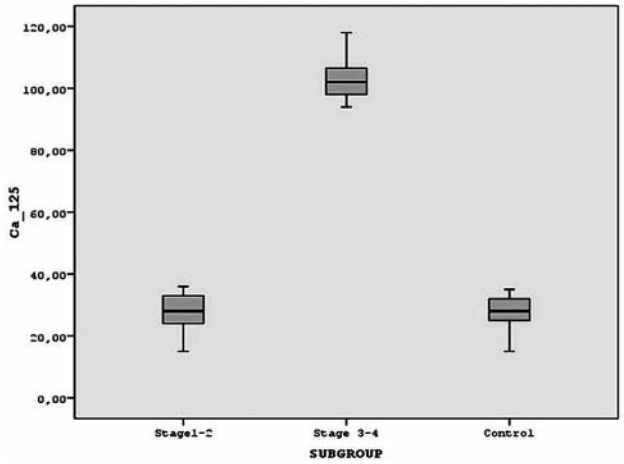

Figure 1. — Comparison of CA-125 levels in the control and endometriosis subgroups.

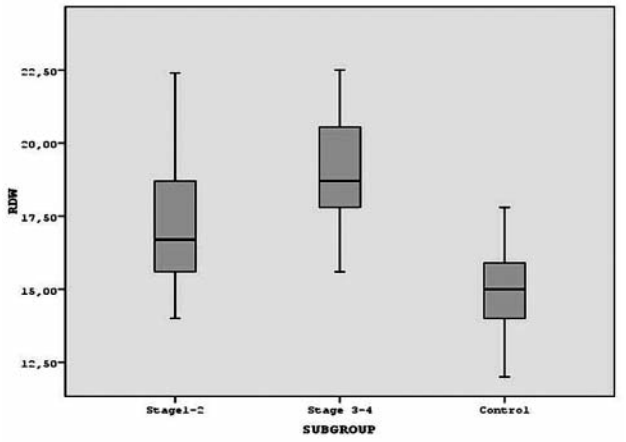

Figure 2. — Comparison of RDW levels in the control and endometriosis subgroups.

Results

The mean age of the study population was 32 ± 3.5 years (33 ± 3.7 in the endometriosis group vs 32 ± 3.3 in the control group; $p = 0.386$). The general characteristics of the study population are shown in Table 1.

In the endometriosis group, RDW ranged from 14.0% to 22.5% (mean 17.7 ± 2.2%), whereas in the control group it ranged from 12.0% to 17.8% (mean 14.9 ± 1.5%, $p < 0.001$). Similarly, CA-125 levels were significantly higher in the endometriosis group than in the control group (50.6 ± 35.1 vs 27.9 ± 4.8; $p = 0.004$). Regarding the endometriosis subgroup analysis, CA-125 level was significantly higher in the moderate-to-severe subgroup than in the mild-to-moderate subgroup (Figure 1, Table 2). However, no significant difference relative to CA-125 level was observed between the control and mild-to-moderate endometriosis groups (27.9 ± 4.8 vs 28 ± 5.5, $p = 0.930$). In addition, the subgroup analysis revealed that RDW level was significantly higher in the moderate-to-severe endometriosis subgroup as compared to the mild-to-moderate endometriosis subgroup (19 ± 2 *vs* 17.2 ± 2.1, $p = 0.007$) and the control group (19 ± 2 *vs* 14.9 ± 1.5, $p < 0.001$) (Figure 2). Moreover,

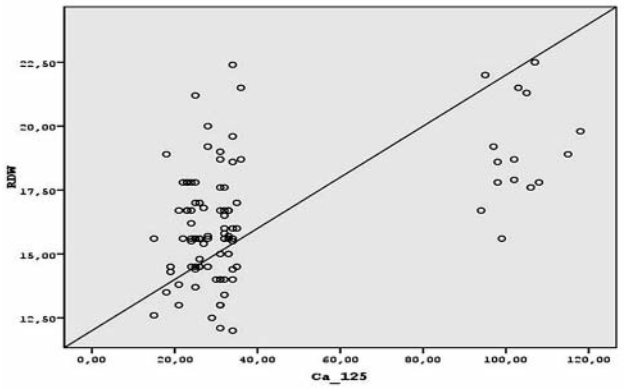

Figure 3. — The correlation of RDW and CA-125 in the whole population.

a significant difference regarding to the RDW level was also observed in between the mild to moderate endometriosis subgroup and the control group (17.2 ± 2.1 vs 14.9 ± 1.5, $p < 0.001$). Moreover, the authors found a significant positive correlation between RDW and CA-125 levels ($r = 0.495$, $p < 0.001$) (Figure 3).

Discussion

The present study results indicate that endometriosis patients had significantly increased RDW levels when compared to the control group. Furthermore, RDW levels were associated with the severity of endometriosis. This study documents, for the first time in the literature, that RDW was associated with both presence and severity of endometriosis.

Although RDW was initially used as a parameter in the diagnosis of anemia, recently it has been shown to be related to long-term adverse effects in cases of acute and chronic events such as acute myocardial infarction and heart failure and in healthy individuals [11, 13-15]. Tonelli *et al.* hypothesized that as a cause of cardiovascular diseases, chronic inflammation might lead to elevated RDW [11]. Lippi *et al.* also revealed that RDW had a significant correlation with hsCRP and sedimentation which is supportive of the mentioned hypothesis [16]. Accordingly, in the present study, the authors observed increased RDW levels in endometriosis, a chronic inflammatory disease.

Although endometriosis is a common gynecologic disease, the exact underlying etiopathogenesis is not yet clearly known. Many hypotheses have been proposed to explain the etiology. First, retrograde menstruation theory gained recognition [17]. However in a study, while 90% of women exhibited retrograde menstruation, only a small percent exhibited endometriosis [18], suggesting that factors other than retrograde menstruation may be involved, as well. Recently, particularly inflammation is investigated in this regard. Cytokine profile and active macrophages in the peritoneal fluid have been shown to rise in endometriosis [19]. Moreover, peritoneal macrophage migration inhibitory factor [20], TNF-± alpha [21], IL-1 BETA, IL-6 [7], and IL-8 have also been observed to be increased in endometriosis. HsCRP, an inflammatory marker, has been shown to be increased in endometriosis patients, as well [22]. Nonetheless, CA-125 is the most commonly studied marker despite its low sensitivity. In the present study, CA-125 level was found to be increased in endometriosis cases, while being positively correlated to RDW.

The association between RDW and endometriosis can be explained with the increased inflammatory markers in endometriosis. Previous studies have shown elevated inflammatory markers in endometriosis patients and also a close relationship between RDW and inflammation [23]. Inflammation increases RDW levels by reducing the life span of erythrocytes via impairing iron metabolism and response to erythropoietin [24]. Moreover, RDW has been shown to have a strong graded relationship with hsCRP and sedimentation [16].

There is a need for further large scale studies in order to completely understand the pathophysiologic relationship between RDW and endometriosis. Nonetheless, the present authors believe that activation of inflammation, which is thought to be closely related to endometriosis, increases RDW levels through its impact on erythropoiesis.

Limitations

One of the most important limitations of the present study was the small number of patients enrolled. Second, since this study was of cross-sectional design, the prognostic value of RDW in endometriosis patients was not investigated. Moreover, lack of data concerning the exact day of menstruation (CA-125 levels are higher in the proliferative phase) [25] may be regarded as the limitations of this study.

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