

Association between Red Cell Distribution Width and Disease Activity in Patients with Behcet's Disease

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Abstract

Aims: we aimed to investigate whether red cell distribution width (RDW) can also be used for the assessment of disease activity in Behcet's disease (BD).

Methods and results: Forty patients with active BD and seventy patients with inactive BD were included in the study. Forty-six healthy volunteers constituted the control group. Hematological parameters, C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were analyzed by standard methods. All the individuals underwent comprehensive echocardiographic examination.

Echocardiographic parameters of the study population were similar all groups. ESR, CRP and RDW were significantly higher in active BD patients than in inactive BD patients and controls (33.6 ± 22 vs 15.7 ± 9 vs 5 ± 4.1 , 23.4 ± 21.6 vs 5.5 ± 6.2 vs 1.2 ± 0.5 and 17.2 ± 2.5 vs 14.4 ± 1.9 vs 13.2 ± 0.5 , $p < 0.0001$ for all, respectively). Moreover, we also found that ESR, CRP and RDW were significantly higher in inactive BD patients when compared with the controls (15.7 ± 9 vs 5 ± 4.1 , 5.5 ± 6.2 vs 1.2 ± 0.5 and 14.4 ± 1.9 vs 13.2 ± 0.5 , $p < 0.0001$ for all, respectively). There were modest positive correlations between RDW and disease duration ($r = 0.320$, $P = 0.001$).

Conclusion: We demonstrated that RDW significant increased in active and inactive BD patients without cardiac involvement. In addition, our study has established that RDW can be used to determine the disease activity state of BD.

Keywords: Behcet's disease; Red cell distribution; Disease activity

Introduction

Behcet's disease (BD) is a chronic, generalized, relapsing and multisystemic inflammatory disorder characterized by recurrent oral and genital ulcerations and ocular manifestations [1]. The main clinical manifestations include the involvement of the mucocutaneous, urogenital, locomotor, ocular, neurological, gastrointestinal, respiratory, and vascular systems.

Disease activity of Behcet's disease has been calculated clinically using the Behcet's Disease Current Activity Form 2006. However, because there are no novel laboratory markers that reflect disease activity in patients with Behcet's disease, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) have been used to assess disease activity and clinical responses to treatment [2]. In addition, S100A12, which is related to neutrophil hyperactivity, and anti-streptolysin O titers may reflect disease activity in Behcet's disease [3,4].

Red cell distribution width (RDW) is usually assessed as part of the hemogram to obtain information about the variability in the size of circulating erythrocytes [5], in particular it is mainly used for the differential diagnosis of anemia [6]. Recent studies have demonstrated a strong independent association between levels of high RDW and the risk of adverse outcomes in patients with cardiovascular disease [7], acute coronary syndromes [8,9], heart failure [10,11], critically ill patients and unselected population referred for coronary angiography [8,12]. Similarly, RDW was also found to be higher in patients with prehypertension and hypertension [13], inflammatory bowel disease [14], obstructive sleep apnea syndrome [15], metabolic syndrome [16] and macrovascular and microvascular complications of diabetes [17].

In the present study, we aimed to investigate whether RDW can also be used for the assessment of disease activity in Behcet's disease.

Methods

Forty patients with active BD and seventy patients with inactive BD were included in the study. Forty-six healthy volunteers constituted the control group. Patients with BD diagnosed according to the International Study Group criteria [18] were divided into two groups, active and inactive.

All the patients' demographic parameters such as age, gender, body mass index (BMI), current cigarette smoking status, cardiovascular and metabolic diseases and duration of BD were recorded.

Laboratory analysis

Blood samples were drawn from left antecubital vein after a 12-hour overnight fast. Blood glucose, CRP (Behring Nephelometer Analyzer, Germany), ESR, total cholesterol, low-density lipoprotein cholesterol, and triglyceride levels were recorded. Hematological parameters, including hemoglobin (Hb), white blood cell (WBC) count, mean corpuscular volume (MCV), and RDW were analyzed by standard methods.

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A resting 12-lead electrocardiography was obtained. In addition, all the individuals underwent comprehensive 2-dimensional echocardiographic examination according to the recommendations by the American Society of Echocardiography [19]. The following 2-dimensional echocardiographic parameters were measured (machine; Philips Medical Systems, IE-33, Bothell, USA): left ventricular end-diastolic diameter (LVEDD, mm), left ventricular end-systolic diameter (LVESD, mm), aortic root diameter (Ao, mm), LA diameter (LAD, mm), interventricular septum thickness in diastole (IVST, mm) and posterior wall thickness in diastole (PWT, mm). The left ventricular ejection fraction (EF, %) was calculated by Simpson's biplane method.

Exclusion criteria included the presence of diabetes mellitus and hypertension, cerebral infarction, hepatic and renal diseases, BMI over 31 kg/m², anemic patients, coronary artery disease, heart failure and cardio-Behcet's disease [20]. The study was approved by the Local Research Ethics Committee.

Statistical analysis

Statistical analysis was performed using SPSS for Windows, version 17.0 software (SPSS, Chicago, IL). All continuous variables were expressed as mean ± SD, and categorical variables were defined as percentages. Differences among the groups were assessed with the chi-square test for categorical variables. Continuous variables were compared between the groups using the Student's t-test or Mann-Whitney U test, depending on whether they distributed normally or did not, as tested by the Shapiro-Wilk's test. Pearson's correlation analysis was used to estimate the relationship between the test parameters. Differences in laboratory parameters between groups were tested by one-way ANOVA followed by LSD procedure for post-hoc testing. A p value <0.05 was considered to be statistically significant.

Results

The baseline characteristics of the study groups are shown in Table 1. There were no significant differences study groups with regard to age, gender, BMI, smoking status, blood pressures, heart rate, serum glucose, total cholesterol, LDL-cholesterol, triglycerides and disease duration. Echocardiographic parameters of the study population are given in Table 2. LVEDD, LVESD, IVST, PWT, LAD, Ao and EF were similar across all groups. Complete blood count, CRP and ESR results are shown in Table 3. There was no difference in platelet and WBC counts across all groups. However, there were significant differences between active BD patients and control subjects with respect to Hb and MCV (13.7±1.2 vs 14.6±1.3, p=0.002 and 83.9±5.4 vs 87.1±3, p=0.002, respectively). ESR, CRP and RDW were significantly higher in active BD patients than in inactive BD patients and controls (33.6±22 vs 15.7±9 vs 5±4.1, 23.4±21.6 vs 5.5±6.2 vs 1.2±0.5 and 17.2±2.5 vs 14.4±1.9 vs 13.2±0.5, p<0.0001 for all, respectively). Moreover, we also found that ESR, CRP and RDW were significantly higher in inactive BD patients when compared with the controls (15.7±9 vs 5±4.1, 5.5±6.2 vs 1.2±0.5 and 14.4±1.9 vs 13.2±0.5, p<0.0001 for all, respectively). Figure 1 shows distribution of RDW values in each group. There were modest positive correlations between RDW and ESR (r=0.368, P<0.0001), and RDW and CRP (r=0.330, P<0.0001). Similarly, there were also modest positive correlations between RDW and disease duration (r=0.320, P=0.001).

Discussion

Previous studies have shown that RDW may be an important biomarker predicting adverse cardiovascular outcomes and mortality,

including all-cause mortality in adults [8,21-23]. Additionally, some studies have recently evaluated a marker to assess disease activation, such as inflammatory bowel disease [24]. Although the exact mechanisms are open to debate, several mechanisms have been suggested to determine the role of RDW in clinical settings. Among those, inflammatory, oxidative stress and neurohormonal activation has been proposed to be one of the mechanistic links between elevated RDW and worse clinical outcomes [25-27]. Although BD manifests itself as local symptoms such as recurrent oral, genital ulcerations and ocular involvement, it is characterized by a chronic, generalized, and multisystemic inflammatory disorder. Akdeniz et al. showed that higher levels of inflammation markers (interleukin-2 ,interleukin-6, tumor necrosis factor-alpha and nitrikoksit) were associated with BD [28]. The main finding of this study was that ESR and CRP levels were

| | Patients with Behcet's disease | | | p |
|--------------------------------------|--------------------------------|----------------|---------------|-----|
| | Active, n=40 | Inactive, n=70 | Control, n=46 | |
| Age (year) | 38.8 ± 10 | 39 ± 11.3 | 38 ± 10 | NS |
| Female / Male (n) | 25/15 | 44/26 | 26/20 | NS |
| Body mass index (kg/m ²) | 25.4 ± 3.4 | 24.6 ± 6.8 | 26 ± 5.4 | NS |
| Smoker (n,%) | 9(22.5) | 11(23.9) | 17(24.3) | NS |
| SBP (mmHg) | 115.4 ± 2.8 | 113.5 ± 6.4 | 110.8 ± 7.5 | NS |
| DBP (mmHg) | 78 ± 6.4 | 76.3 ± 5.5 | 74.6 ± 8.6 | NS |
| Heart rate (beat/min) | 78.2 ± 8.4 | 76.6 ± 4.8 | 75.7 ± 6.6 | NS |
| Blood glucose (mg/dl) | 91.2 ± 6 | 85.7 ± 10 | 88.9 ± 8 | NS |
| Total cholesterol(mg/dL) | 173.2 ± 39 | 178.7 ± 53 | 182.4 ± 35 | NS |
| LDL cholesterol(mg/dL) | 105.9 ± 34.8 | 110.7 ± 25 | 120.4 ± 42 | NS |
| Triglycerides (mg/dL) | 152 ± 76 | 146 ± 52 | 166 ± 64 | NS |
| Disease duration (years) | 6.8 ± 4.9 | 6.1 ± 4.6 | | 0.5 |

DBP, diastolic blood pressure; LDL, low-density lipoprotein; NS, not significant; SBP, Systolic blood pressure

Table 1: Baseline characteristics of the patients and controls.

| | Active BD (n=40) | Inactive BD (n=70) | Control (n=46) | p |
|-------------------------------|------------------|--------------------|----------------|----|
| LVEDD (mm) | 47.5 ± 2 | 46.5 ± 2.1 | 46.9 ± 2.4 | NS |
| LVESD (mm) | 28.3 ± 2 | 28.1 ± 2 | 29.1 ± 2 | NS |
| IVST (mm) | 10.4 ± 0.5 | 10.8 ± 0.4 | 10.1 ± 0.6 | NS |
| Posterior wall thickness (mm) | 9.8 ± 0.2 | 9.4 ± 0.7 | 9.6 ± 0.4 | NS |
| Left atrial diameter (mm) | 34.6 ± 1.1 | 33.2 ± 2.1 | 32.5 ± 1.8 | NS |
| Aortic diameter (mm) | 32.1 ± 1.4 | 32.4 ± 2.6 | 31.2 ± 2.3 | NS |
| Ejection fraction (%) | 66.4 ± 3 | 65.8 ± 6 | 68 ± 2 | NS |

BD, behcet's disease; IVST, interventricular septal thickness; LVEDD, left ventricular end-diastolic dimension; LVESD, left ventricular end-systolic dimension; NS, not significant

Table 2: Echocardiographic parameters of the study population.

| | Active BD (n=40) | Inactive BD (n=70) | Control (n=46) | p |
|--|------------------|--------------------|----------------|----------|
| White blood cell count (10 ⁹ /mm ³) | 8.3±3.2 | 7.7±2.5 | 7.7±2.1 | 0.3 |
| Hemoglobin (g/dl) | 13.7±1.2 | 14±1.1 | 14.6±1.3 | 0.002* |
| Platelet (10 ⁹ /mm ³) | 244±54 | 234±43 | 229±45 | 0.6 |
| Mean corpuscular volume (fl) | 83.9±5.4 | 84.7±5 | 87.1±3 | 0.002* |
| ESR (mm/hr) | 33.6±22 | 15.7±9 | 5±4.1 | <0.0001# |
| C-reactive protein (mg/dL) | 23.4±21.6 | 5.5±6.2 | 1.2±0.5 | <0.0001# |
| RDW (%) | 17.2±2.5 | 14.4±1.9 | 13.2±0.5 | <0.0001# |

BD, Behcet's disease; ESR, erythrocyte sedimentation rate; RDW, red cell distribution width; WBC, white blood cell count; *Significant difference is between active BD and control groups. #Significant difference is between active BD- control and inactive BD-control groups.

Table 3: Laboratory parameters of the patients and controls.

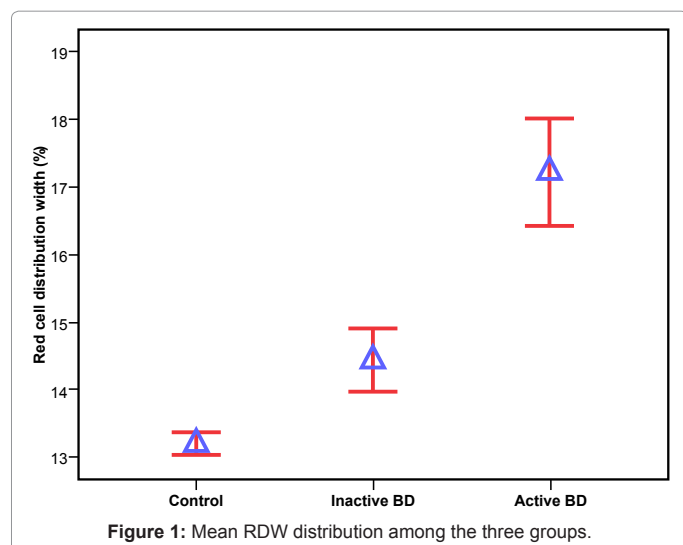


Figure 1: Mean RDW distribution among the three groups.

found to be higher in active and inactive BD patients when compared with control subjects. Moreover, RDW was correlated modestly with ESR and CRP levels. All these results, higher RDW may arise from ineffective erythropoiesis due to chronic inflammation. Inflammatory cytokines have been found to suppress the maturation of erythrocytes, which enable juvenile red cells to enter into circulation and results in increased heterogeneity in size.

Another mechanism may be that higher levels of RDW may reflect enhanced erythropoiesis resulting from circulating levels of neurohormonal mediators, which lead to an increase in the heterogeneity of circulating red cells. There is scant clinical data demonstrating neurohormonal disorders in BD [29,30]. However, most of the publications on this regard are limited to case reports [30,31].

Finally, oxidative stress has been suggested to be another indicator of the prognostic value of RDW [25,27]. Red blood cells have powerful antioxidant capacity and serve as a primary oxidative sink. So, they are prone to oxidative damage, which reduces cell survival and induces the release of juvenile erythrocytes into blood circulation. There are several studies available in the literature regarding this subject [32-34], in which oxidative response was found to be disrupted in both active and inactive BD patients.

There are potential limitations regarding the interpretation of our data. Any information regarding the nutritional status or serum folic acid, iron or vitamin B12 levels is lacking. Deficiency of these vitamins and/or minerals may result in anemia, thus affecting RDW levels. Although patients with anemia were excluded from the study, there was a significant difference in hemoglobin levels between active BD patients and control subjects. We think that this difference is due to a decrease in hemoglobin levels as a result of chronic disease.

In conclusion, there are many studies that show the predictive value of RDW for adverse cardiac events and its increase in many inflammatory situations. We demonstrated that RDW increased in active and inactive BD patients without cardiac involvement. We also observed a significant increase in RDW, ESR and CRP in the active disease periods of BD compared to inactive BD group. This finding suggests that RDW may be an important parameter in determining disease activation in BD patients.

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