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Clinical Significance of Serum Bilirubin in Behçet's Disease

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ABSTRACT

Background and Objective: Bilirubin (Bb) is the product of the intravascular compartment of catabolic pathway. In a small number of clinical trials, it has been shown that Bb molecules are associated with cardiovascular diseases, diabetes, cancer, autoimmune (lupus, rheumatoid arthritis) diseases and schizophrenia. Behçet's disease is a chronic, multisystemic, inflammatory vasculitis that was first described by Hulusi Behçet in 1937, which affects almost all organs and systems without any known aetiology. Here, we investigated the clinical significance of serum Bb as a biomarker in the patients with Behçet's disease. **Methods**: Seventy-one (N = 71) patients with Behcet's diagnosis within the last 1 year were included retrospectively. Control group consisted of 75 subjects with similar age and sex distribution. Serum Bb, indirect Bb, total Bb, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP) and erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) data were recorded from the hospital records. **Results**: In the Behçet group, direct Bb was significantly lower (P = 0.011), ESR and CRP were significantly higher (P = 0.00). No significant differences were observed in other parameters. In the whole group, total Bb and indirect Bb were negatively correlated with ESR (P = 0.025, P = 0.01). Direct Bb was negatively correlated with CRP (P = 0.002). For the diagnosis of Behçet, direct Bb with a threshold of < 0.14 can be used as a diagnostic test (P = 0.000) with 70% sensitivity, 68% specificity (area under the curve = 0.69; 95% confidence interval 0.59–0.80) in ROC curve analysis. **Conclusion**: According to our study, we found that inflammatory markers were high and direct Bb values were low in patients with Behcet's disease. In addition, Bb parameters were negatively associated with acute phase reactants. As a practical biomarker with anti-oxidative properties, the direct Bb can be used to diagnose and clinical follow-up in cases with Behçet's disease.

Key words: Behcet's disease, bilirubin, biomarker

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INTRODUCTION

Behçet's disease is a rare vasculitic disorder characterized by recurrent oral aphthous ulcers, genital ulcers and uveitis, a triple symptom complex.[1] Bb is a heme degradation product with anti-inflammatory, antioxidative, and immunosuppressive features.[2] Studies conducted in the previous two decades showed a strong antioxidative feature of Bb, in addition to its being a degradation product. Many hypotheses were put forth concerning the mechanism of action of Bb. The most well-known is the immunomodulatory effect that suppresses inflammation through its redox (antioxidative) capacity.[3,4]

Here, we investigated the clinical significance of serum Bb as a biomarker in patients with Behçet's disease. To the best of our knowledge, there is no other study in the literature that analyzes serum Bb levels in patients with Behcet's disease.

METHODS

Seventy-one (N = 71) patients with Behcet's diagnosis within the last 1 year were included retrospectively. Control group consisted of 75 patients of similar age and sex. Behçet's diagnosis was based on the criteria of international study group.

Serum direct Bb, indirect Bb, total Bb, aspartate aminotransferase (AST), alanine

aminotransferase (ALT), alkaline phosphatase (ALP) and erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) data were recorded from the hospital records. The acute phase reactants (ESR and CRP) were used for disease activity. Patients with known inflammatory rheumatism disease, malignancy, infection and primary liver disease were not included in the study.

Statistical Analysis

Continuous variables were shown as means ± standard deviation, and categorical variables were presented as percentages. We used the Kolmogorov-Smirnov test to identify data normality. The *t* test and Mann–Whitney *U* test were used to analyze the data according to their distribution. The correlation between two continuous variables was analyzed using the Spearman approach. Statistical analysis was performed using SPSS 16.0 (SPSS Inc., Chicago, IL, USA); $P < 0.05$ was designated as statistically significant.

RESULTS

The Behçet group consisted of 40 male and 31 female patients. The mean age was 42 ± 9.5 years. Mean direct Bb = 0.016 ± 0.08, Indirect Bb = 0.39 ± 0.2, total Bb = 0.5 ± 0.25, CRP = 8.1 ± 10.7 mg/dL, ESR = 14.9 ± 12.9 mm / h, AST = 23.5 ± 5.3, ALT = 24.4 ± 10.1, ALP = 79.2 ± 24.1.

The control group consisted of 44 males and 31 females. The mean age was 46 ± 10.5 years. The mean direct Bb = 0.19 ± 0.61, Indirect Bb = 0.33 ± 0.17, total Bb = 0.53 ± 0.17, CRP = 1.1 ± 1.6 mg / dL, ESR = 9± 8.3 mm / h. Sociodemographic and laboratory data of the groups are listed at Table1.

In the Behçet group, direct Bb was significantly lower ($P = 0.011$) (Figure 1), ESR and CRP were significantly higher ($P = 0.00$). No significant differences were observed in the other parameters. In the whole group, total Bb and indirect Bb were negatively correlated with ESR ($P = 0.025$, $P = 0.01$) (Figure 2). Direct Bb was negatively correlated with CRP ($P = 0.002$). ALP were not related with any parameters (Bb and CRP, ESR) in the study group.

For the diagnosis of Behçet, direct Bb with a threshold of < 0.14 can be used as a diagnostic test ($P = 0.00$) with 70% sensitivity, 68% specificity (area under the curve = 0.69; 95% confidence interval 0.59–0.80) in ROC curve analysis (Figure 3).

DISCUSSION

Behçet's disease is a chronic, multisystemic, inflammatory vasculitis that was first described by Hulusi Behçet in 1937, which affects almost all organs and systems without any known aetiology. Behçet's is most common along the Silk Road. It is particularly common among persons who have the HLA-B51 major histocompatibility type It is thought that exposure to infectious agents plays a role

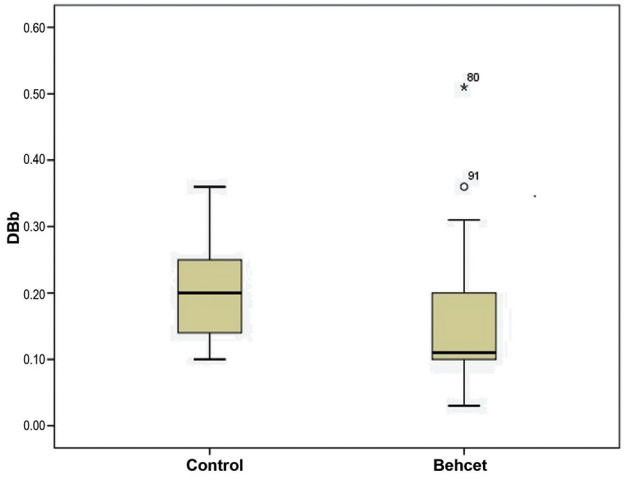

Figure 1: The distribution of direct bilirubin (DBb) according to the groups

Table 1: Sociodemographic and laboratory data of the groups

	Behçet group	Control group	*P*
Age (Year)	42.0 ± 9.5	46.0 ± 10.5	0.45
Gender (M/F)	40/31	44/31	0.06
TBb (0–1.9; mg/dL)	0.50 ± 0.25	0.53 ± 0.17	0.58
DBb*(0–0.3; mg/dL)	0.016 ± 0.008	0.19 ± 0.61	0.011
İnBb	0.39 ± 0.2	0.33 ± 0.17	0.085
CRP* (mg/dL; 0-5)	8.1 ± 10.7	1.1 ± 1.6	0.00
ESR* (mm/h; 0-20)	14.9 ± 12.9	9.0 ± 8.3	0.00
AST (0-40 IU/L)	23.5 ± 5.3	-	
ALT (0-56 IU/L)	24.4 ± 10.1	-	
ALP (25–100 IU/L)	79.2 ± 24.1	-	

TBb: total bilirubin; InBb: indirect bilirubin; DBb: Direct bilirubin; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; AST: aspartate aminotransferase; ALT: alanine aminotransferase; ALP: alkaline phosphatase. *statistically significant.

in the genetically susceptible person in the pathogenesis of the disease. There is no pathognomonic laboratory test, but there are clinical criteria to assist in establishing the diagnosis.[1,5,6] Mortality may occur as a result of neurologic or vascular disease or gastrointestinal perforation.[5,6]

Clinical findings of Behçet's disease show great differences from one patient to another. In addition, there are also changes in organ involvement and clinical course of the disease, exacerbation and recovery periods. Clinical manifestations tend to decline as age progresses.[5,6]

The diagnosis of Behçet's disease is based on clinical findings, and there are no specific laboratory findings of the disease.[6-8] The ESR and CRP are mostly moderately increased, but do not directly correlate with disease activity. Main routine laboratory tests give information about organ functions and helps in differential diagnosis. It should be remembered that drugs may have high toxic effects on liver. Rarely amyloidosis, glomerulonephritis, interstitial nephritis, renal vein thrombosis proteinuria, hematuria, pyuria, renal failure laboratory findings can be detected. There is no autoantibody specific for Behcet's disease (rheumatoid factor, antinuclear antibody, anticardiolipin, and antineutrophil cytoplasmic antibody, anti-endothelial antibodies and antibodies against the oral mucosa may be positive).[6-8]

In Behcet's disease, gastrointestinal tract involvement is known as intestinal Behçet's disease or entero-Behçet. Gastrointestinal system involvement of Behcet's disease differs between countries. Oral aphthous, gastric, duodenal ulcer, esophagitis, small and large intestine ulcers.

Hepatobiliary complications of Behcet's disease are fatty liver, acute or chronic hepatitis, cholelithiasis, cholecystitis, primary biliary cirrhosis, hepatic abscess. In 11% of patients with Behçet's disease, liver ALP levels were increased and correlated with the disease activity.[9]

Several biomarkers have been studied in early stage vascular involvement in Behçet's disease.[10] In the study of Balta *et al.*, mean platelet volume (MPV) was significantly associated with increased arterial stiffness in Behçet disease[11]; besides, there were found no significant difference in the study of Şenel *et al.*; and Balkarli *et al.* found that neutrophil/lymphocyte ratio may be a simple, inexpensive, and convenient diagnostic marker for activity in Behçet disease.[12,13]

Bilirubin (Bb) is the major product of intravascular compartment of hem catabolic pathways. Research in the last few decades has revealed a strong antioxidant. There are a number of hypotheses about the mechanism of action of Bb. The most known is redox (antioxidative) capacity with

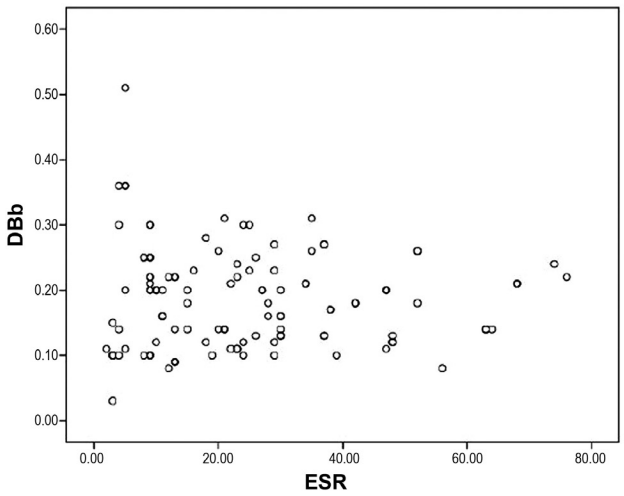

Figure 2: The distribution of direct bilirubin (DBb) according to erythrocyte sedimentation rate (ESR)

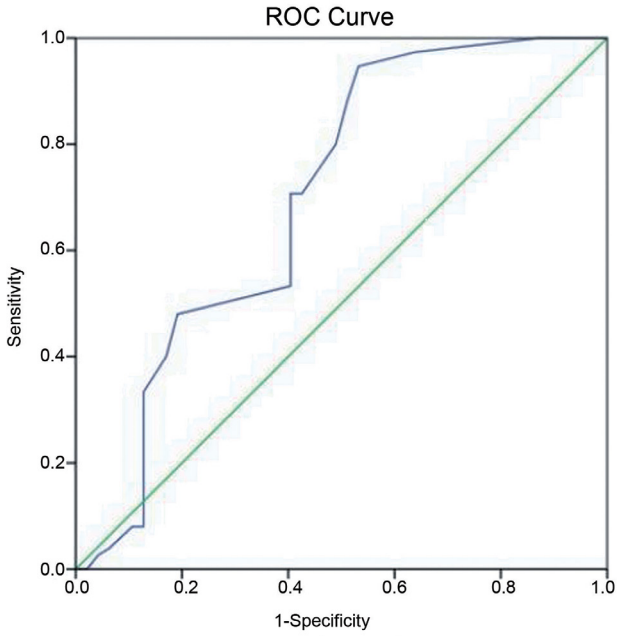

Figure 3: Direct bilirubin with a threshold of < 0.14 can be used as a diagnostic test (P = 0,00) for Behçet disease with 70% sensitivity, 68% specificity (area under the curve = 0,69; 95% confidence interval:0.59–0.80). Diagonal segments are produced by ties

immunomodulatory effect by suppressing inflammation. In a few clinical trials, Bb molecule has been shown to be associated with cardiovascular diseases, diabetes, cancer, autoimmune (lupus, rheumatoid arthritis) diseases and schizophrenia.[2,3]

Peng *et al.* found lower serum Bb values in all patients with polymyositis than in a healthy control group; a possible relationship with disease activity was also detected.[14] Zheng *et al.* found higher serum CRP values

and lower TBb values in diabetic patients and in patients with impaired insulin tolerance.[15] For the patients with psoriasis, a negative relation was found between TBb values and inflammatory parameters.[16] Peng *et al.* detected lower DBb values and higher CRP values when assessing neurogenic inflammation in patients with migraine.[17] CRP and DBb were found negatively correlated. In recent years, simple, cheap and practical biomarkers as indicators of inflammation have been the subject of various investigations.[18] Firstly, in the literature, we found that direct Bb values were low in patients with Behcet's disease and correlated negatively with acute phase reactants.

LIMITATION OF THE STUDY

Because the study data were collected retrospectively, those with high ESR and CRP values were evaluated as active disease. However, as we have already mentioned, these parameters mostly increase in Behçet's disease but are not always correlated with disease activity.

Bilirubin levels reflected hepatic and gall bladder involvement in pathology. It would be appropriate to analyze bilirubin shifts in association with venous thrombosis. The timing of the laboratory studies and the presence of venous thrombosis weren't taken into account. Direct bilirubin being low may be secondary to chronic inflammation, so it may not be specific to Behçet's disease, but it is necessary to investigate it in other inflammatory rheumatic diseases.

Behçet's disease has a heterogeneous clinical manifestation, but there is no information on disease involvement in the patient group, for example, mucocutaneous Behçet and neurobehçet.

CONCLUSION

Bilirubin values decrease as the inflammation increases in the serum. As a practical biomarker, serum direct Bb levels can be used for diagnosis and clinical follow-up in Behçet's disease.

Conflict of Interest

The authors have no conflicts of interest to declare.

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